VASOPRESSORS AND INOTROPES: TREATMENT OF HEMODYNAMIC IMPAIRMENT AND SHOCK

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ABSTRACT

Vasopressors and inotropes are used to treat shock, with the goal of restoring perfusion. When a critically ill patient is hemodynamically impaired, vasopressors, also known as pressors, may be used to increase the patient's vascular tone, and inotropes may be used to affect myocardial contractility. Low blood pressure associated with shock is typically treated with these agents to avoid loss of consciousness and oxygen deprivation to the heart, brain, and other vital organs. It is important that licensed pharmacists and associates understand the appropriate use of vasopressors and inotropes.

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1. **Compare** the mechanism of action of vasopressors and inotropes.
2. **Describe** the basic pharmacological profile and dosing for vasopressors and inotropes used in the treatment of shock.

3. **Identify** when to begin treatment with fluid resuscitation, vasopressors, and inotropes.
4. **Describe** the different types of shock and the clinical settings in which vasopressors and inotropes are most used.

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Introduction

Vasopressors and inotropes are used to treat critically ill patients who have hemodynamic impairment. Hemodynamic impairment causes low blood volume, decreased cardiac output, and inadequate oxygen delivery to bodily organs and tissue. Without treatment, patients with impairment will have a reduction in vital organ perfusion and possibly experience multisystem organ failure. The end result of inadequate perfusion and organ failure is shock and possibly vasoplegia or even death. Vasopressors and inotropes increase blood pressure so that the organs of the body are able to perfuse. Vasopressors and inotropes typically increase blood pressure in different ways; however, some vasopressors also have inotropic properties. Vasopressors and inotropes may be applied as first-line treatments or secondary treatments depending on the guidelines and practices; they may be administered separately or in combination. The specific drug chosen depends on a patient's particular medical condition and the guidelines regarding when a drug is indicated.

The Heart, Hemodynamic Impairment and Shock

The heart is the organ that pumps blood so that bodily tissues and organs may be adequately perfused and oxygenated for healthy function.[1] The adequacy of the heart's function can be assessed by cardiac output as determined by a patient's mean arterial pressure (MAP). When a patient's heart function is insufficient, hemodynamic impairment and shock may follow.[2]

Cardiac Output

In general terms, cardiac output refers to the quantity of blood that the heart pumps. Cardiac output is determined by heart rate, contractility, preload, and afterload. Blood is pumped out of the heart by afterload, which is mainly dependent on arterial blood pressure and vascular tone.[1]

Contractility is also referred to as inotropy; hence, the name inotropes is applied to agents that can increase or decrease contractility.[2,3] Myocardial

contractility or inotropy must be maintained at a constant level for proper cardiac function.[3] Farmakis, *et al.* (2019) indicate that inotropes can increase cardiac output by enhancing cardiac contractility;[4] however, Scheeren, *et al.* (2021) state that inotropic agents increase "myocardial contractility, lusitropy, and heart rate" but they do not primarily increase cardiac output."[5]

Mean Arterial Pressure (MAP)

Arterial blood pressure is essential for the heart to pump blood.[1] According to guidelines Surviving Sepsis Campaign (SSC), a patient's MAP should be at least 65 mmHg.[6-8] Although the SSC 2016 update acknowledged no evidence for targeting MAP values greater than 65 mm Hg in any patient group, MAP values reported in observational studies are systematically higher than 65 mm Hg.[2,9] This is possibly because clinicians also use other targets.[8] Regardless, if a patient's MAP falls below target levels, the patient is hypotensive, which can lead to shock. These patients also have an increased mortality rate.[6]

Altered Hemodynamics and Shock

There are medical conditions that can interfere with the heart's function. These conditions can change heart rate, contractility, preload, afterload, and vascular tone, resulting in altered hemodynamics.[2] Scheeren, *et al.* (2019) reports that approximately one-third of patients hospitalized in intensive care units have hemodynamic impairment and shock. Altered hemodynamics can reduce cardiac function leading to prolonged hypotension and shock.[2,6] Shock can be life-threatening if it is not treated immediately.[10,11]

Mechanisms of Action of Vasopressors and Inotropes

Vasopressors (also called pressors) and inotropes are used to treat shock, with the goal of restoring perfusion.[2,9] It is important for healthcare professionals to understand how these drugs work. A drug's mechanism of action plays an important part in determining whether the drug is appropriate for a specific patient and medical condition.

The primary mechanism of vasopressors is to target receptors in the peripheral blood vessels, thereby causing vasoconstriction sufficient to maintain circulation to the body's vital organs.[2] Vasopressors are agents that increase a patient's *vascular tone*.[2,9] An increase of blood pressure due to vasoconstriction causes a rise in systemic vascular resistance (SVR), which then leads to an increase in MAP.[10] Organs of the body are then able to receive appropriate perfusion.[10]

Inotropes affect myocardial *contractility*.[2] In the case of positive inotropes myocardial contractility is increased.[11-13] Negative inotropes decrease contractility. The distinction between positive and negative inotropes may be due to a drug's mechanism of action or it may be dose-dependent.[12] Inotropes may not only impact contractility but they can also have vasoactive properties; *i.e.*, some inotropic agents can act as a vasopressor and cause vasoconstriction.[12] In the end, when positive inotropes increase myocardial contractility (or in some cases cause vasoconstriction), cardiac output rises, which raises MAP and promotes organ perfusion.[10,11]

Vasopressors act in different ways. They may be adrenergic agonists or nonadrenergic agents.[12-15] Adrenergic agonists have a rapid onset of action, high potency, and short half-life, which allows easy dose adjustment. Alpha-adrenergic receptor stimulation increases vascular tone and blood pressure.[14] This results in "in arterial and venous vascular smooth muscle contraction and an increase in systemic and pulmonary vascular resistance and venous return."[12] Stimulation of beta-adrenergic receptors increases blood flow.[9] The nonadrenergic agents stimulate vasopressin V1 receptors causing vascular smooth muscle contraction.[13] Angiotensin II and nitric oxide inhibitors are classified as primarily nonadrenergic in their effects.[13]

Inotropic agents also differ in their mechanism of action. Positive and negative inotropes could be classified according to their mechanisms of action.[10,11] In this course they will be discussed within three categories: beta-agonists; phosphodiesterase type 3 inhibitors (PDIs); and, calcium sensitizers.[15] Beta-agonists act by stimulating myocardial beta-1 receptors.[15] Phosphodiesterase type 3 inhibitors inhibit the breakdown or degradation of

cAMP.[11,13] This mechanism of action of PDIs increase intracellular concentration of cAMP, leading to greater myocardial contractility.[12,16] Calcium sensitizers target the modulation of the myofilamental response to calcium ions.[17] For example, calcium sensitizers can cause troponin C to be sensitized to calcium ions in the cardiac muscle. This has a positive inotropic effect.[18]

These treatments are used to prevent shock in patients who are critically ill. These agents are reserved for patients who are experiencing significant hemodynamic impairment.[2]

Administration of Fluids and Vasopressors

When acute blood loss occurs, a patient may need rapid restoration of blood volume.[19] Acute blood loss may be due to trauma, infection, burns or other serious medical conditions. In these cases, plasma volume expanders are the preferred choice to restore vascular volume.[19]

Three questions arise in this clinical setting: Which fluid to use? How much fluid to administer? When should vasopressors be introduced into the treatment plan? These questions will be touched upon generally.

Choosing a Plasma Volume Expander

Intravenous fluids used as plasma volume expanders are generally classified as crystalloids or colloids.[20] Crystalloids are water solutions (balanced salt solutions) that contain electrolytes that move readily from the vascular space into the interstitium.[20,21] They are inexpensive and easy to use. They provide immediate fluid resuscitation. Commonly used crystalloids include normal saline, Hartman's solution and Ringer's solution.[22] One drawback is that they may cause edema.[21]

Colloids are solutions with large molecules that do not enter healthy capillary membranes.[20] They may provide volume expansion more quickly within intravascular spaces.[21] Colloids may cause allergic reactions, blood clots, and renal failure.[21] Some commonly used colloids include gelatins,

hetastarch, albumin, plasma protein fraction, and dextran. In a study conducted by Lewis, *et al.* (2018), a comparison was made as to the efficacy of colloids versus crystalloids for fluid resuscitation.[21] The comparison used a colloid (suspended in any crystalloid solution) versus a crystalloid (isotonic or hypertonic). Four types of colloids were used: starches, dextrans, gelatins, and albumin or fresh frozen plasma. The results showed that there was very little difference in mortality. Starches showed a slight increase in the need for blood transfusion, and albumin or fresh frozen plasma exhibited little or no difference in the need for renal replacement therapy.[21] Overall, the study concluded that the choices as to which fluid volume expander is used must be based on the individual patient's unique medical condition and response to treatment.[21] However, Perel, *et al.* (2007) concluded that given the similar outcomes from using colloids versus crystalloids shown in some studies, coupled with the reports in which colloids were shown to be less safe than crystalloids, it is difficult to justify using colloids, especially since crystalloids are less costly to administer.[22]

Dose Administration

After a clinician has chosen an intravenous solution, the clinician must decide the dose the patient should receive.[20] There are negative consequences if too much fluid is administered.[20] This involves a complex risk-benefit analysis. A clinician must consider "the patient's illness and underlying comorbidities, phase of fluid therapy, and anticipated hemodynamic response."[20] This must be evaluated after a considered review of the most current fluid management trials.[20]

When Should Vasopressors be Used?

It is common to begin treatment with fluids rather than pressors, which are typically utilized when fluid resuscitation is not successful. Shi, *et al.* (2020) report that the SSC recommends using "vasopressors within the first hour when fluid administration is not sufficient to achieve the hemodynamic resuscitation goals."[23] According to a number of experts within the European Society of Intensive Care Medicine, vasopressors should be started early,

"before full completion of fluid resuscitation;"[23] however, this recommendation is not followed by most clinicians; they continue to start vasopressors after fluid resuscitation has been completed and only if hemodynamic resuscitation goals have not been achieved.[23]

Commonly Used Vasopressors and Inotropes

As mentioned above, vasopressors may be described under two headings based on their actions: vasopressors as adrenergic agonists and nonadrenergic agents.[12-15] Inotropes act as beta-agonists, PDIs, or calcium sensitizers.[15] Many of the drugs described below have vasoconstrictive and inotropic properties, which will be discussed together.

Vasopressors that are adrenergic agonists may be further divided into catecholamines and non-catecholamines. Catecholamines include dopamine, norepinephrine, and epinephrine. Non-catecholamines include ephedrine and phenylephrine.[12] A patient's particular medical condition determines the choice of drug to use.

Adrenergic Agonists: Catecholamines

Dopamine

Dopamine was one of the first pressors.[24] It is a vasopressor with inotropic properties and it is dose-dependent/dose-specific.[25] Dopamine is a natural precursor to norepinephrine and epinephrine.[25] More precisely, dopamine causes the release of norepinephrine from nerve terminals;[26] and, norepinephrine is a precursor to epinephrine.[27] Dopamine stimulates alpha-adrenergic and beta-adrenergic receptors as well as dopaminergic receptors but the stimulation of dopaminergic receptors does not appear to prevent organ failure in shock patients.[28]

Dopamine was used to treat septic shock but its adverse events profile has limited its use.[29-31] Russell, *et al.* (2021) state that the risks from using dopamine outweigh the benefits it provides in the treatment of shock.[29] This

is due to its narrow therapeutic index and uncertain plasma levels that are caused by decreased renal excretion. Decreased renal excretion leads to a higher heart rate and it doubles the frequency of tachyarrhythmias.[29] Shi, *et al.* (2020) report that dopamine is associated with an increased risk of death when compared to other available drugs.[23] Evidence take from large randomized controlled trials reviewed the efficacy and safety of various treatments of septic shock. They found that based on the large randomized controlled trials, norepinephrine "remains the first-choice vasopressor in patients with septic shock. Vasopressin and epinephrine represent second-line vasopressor therapies and dopamine should be avoided."[23] Russell (2019) sums this up by stating that dopamine has limited indications since it is only recommended in bradycardic patients.[30]

Dopamine hydrochloride is indicated for the correction of hemodynamic imbalances present in the shock syndrome due to myocardial infarctions, trauma, endotoxic septicemia, open heart surgery, renal failure, and chronic cardiac decompensation as in congestive failure.[26] Where appropriate, restoration of blood volume with a suitable plasma expander or whole blood should be instituted or completed prior to administration of dopamine. Patients respond best to dopamine treatment when their physiological status (urine flow, myocardial function, and blood pressure) has not profoundly deteriorated. The shorter the time between initiation of dopamine therapy (with volume correction) and symptom onset, the better the prognosis. Nevertheless, in oliguric or anuric patients, the administration of dopamine has resulted in increased urine flow, which in some cases reached normal levels. Dopamine may also increase urine flow in patients whose output is within normal limits and may help to reduce pre-existing fluid accumulation. Doses above those optimal for the individual patient might result in a decrease of urine flow, necessitating a reduction of dosage. Concurrent administration of dopamine and diuretic agents may result in a potentiating effect.[26]

An increase of cardiac output is related to the direct inotropic effect of dopamine on the myocardium. Increased cardiac output at low or moderate doses of dopamine has been correlated with favorable prognosis. In many instances the renal fraction of the total cardiac output has been found to

increase.[26] The increase in cardiac output with the use of dopamine is not associated with substantial decreases in SVR, such as with the use of isoproterenol.[14]

When due to inadequate cardiac output, hypotension can be managed with the use of low to moderate doses of dopamine. At high therapeutic doses, alpha-adrenergic activity is more prominent and may correct hypotension due to diminished SVR. Trends in decreased systolic and diastolic pressures guide administration of dopamine.[26]

Dopamine hydrochloride is a potent drug requiring dilution before administration. Rate of Administration: After dilution, administer IV with rate of flow in controlled drops per minute and titrated for the desired hemodynamic and/or renal response. To reach the necessary systolic blood pressure, the IV rate for renal response may exceed optimal dosing; reduce once the patient is hemodynamically stabilized. Dopamine administration will require frequent urine output checks. Urine flow that decreases in the absence of hypotension may require dose reduction. Dopamine 20 mcg/kg/minute or less generally results in a good treatment response, but higher dosing may be needed for an appropriate arterial pressure and central perfusion. Dosage is adjusted according to the patient's response with reduction or temporary suspension for reduced urine flow, tachycardia or new dysrhythmias.[26]

Adverse reactions to dopamine include ventricular arrhythmia, atrial fibrillation (at very high dosages), tachycardia, angina, palpitations; dyspnea; nausea and vomiting; headache and anxiety.[26] As mentioned above, dopamine has been associated with an increased risk of death when compared to other available drugs.[23,31]

Norepinephrine

Norepinephrine, also known as noradrenaline, is used to increase MAP through vasoconstriction, while only causing a minor increase in cardiac output and stroke volume.[13] It is a powerful pressor, especially when titrated.[13] The dosage amounts will vary across a broad spectrum depending

on a variety of factors. It is especially useful in patients who are experiencing septic shock, as it does not cause deterioration of the cardiac index or organ function. Due to the lack of significant side effects and mortality, norepinephrine is often used as a first-line vasopressor in the treatment of shock.[23,31,32]

Control blood pressure in certain acute hypotensive states, such as during spinal anesthesia, myocardial infarction, septicemia, blood transfusion and medication reactions. Also, it is used during cardiac arrest and profound hypotension as an adjunct.[33] Norepinephrine bitartrate is a beta-adrenergic stimulating agent used to increase the strength and effectiveness of systolic contractions.[27]

It is necessary to correct blood volume depletion prior to administering a vasopressor; monitor intra-aortic pressures to prevent cerebral or coronary artery ischemia. Norepinephrine can be administered before and concurrently with blood volume replacement. *Average Dosage*: Norepinephrine bitartrate 4 mg/4 mL is added to 5% Dextrose 1000 mL solution (4 mcg/mL), IV administration at rate of drops per minute. *High Dosage*: titrated per patient response. Higher daily doses, as high as 68 mg base or 17 vials, if the patient remains hypotensive. Suspect occult blood volume depletion and correct if present (use central venous pressure monitoring to detect and treat) *Fluid Intake*: The degree of dilution depends on clinical fluid volume requirements. *Duration of Therapy*: continue infusion until adequate blood pressure and tissue perfusion are maintained without therapy; reduce gradually, avoiding abrupt withdrawal. *Adjunctive Treatment in Cardiac Arrest*: Begin norepinephrine bitartrate by IV administration during cardiac resuscitation to restore and maintain blood pressure once heartbeat and ventilation are stable.[27]

Adverse reactions to norepinephrine include ischemic injury due to potent vasoconstrictor action and tissue hypoxia; bradycardia (reflexive result of a rise in blood pressure); arrhythmias; anxiety, transient headache; respiratory difficulty; extravasation necrosis at injection site.[27]

Epinephrine

Epinephrine is a drug that selectively binds to and activates alpha-adrenergic receptors and beta-adrenergic receptors.[34] These actions lead to vasoconstriction and contractility.[34]

The drug is indirectly synthesized, stored and released from the chromaffin cells of the adrenal medulla: "Within the adrenal gland, glucocorticoids are transported to the medulla where chromaffin cells produce NE [norepinephrine]. Here, glucocorticoids activate the enzyme, phenylethanolamine N-methyltransferase (PNMT), which is required for the conversion of NE to [epinephrine]."[33] Epinephrine is then used to increase arterial pressure. It works by increasing the cardiac index and peripheral vascular tone.[12] Epinephrine also increases delivery of oxygen, but it is not consistent in its results. It is the most frequently utilized medication in the case of cardiac arrest, and it is the only drug recommended by the American Heart Association for all arrests, regardless of the cardiac rhythm. Epinephrine is not indicated for patients in cardiogenic shock because it increases myocardial oxygen demand. Additionally, it should not be used for patients in hemorrhagic or traumatic shock.[11,23]

Epinephrine produces significant results in the treatment of anaphylaxis;[34] it does have the potential to decrease regional blood flow.[35] This is especially common in the splanchnic circulation system, where almost one quarter of the total blood volume resides.[36] Epinephrine is quite effective in increasing blood pressure in patients who do not respond to other agents.[29] However, because epinephrine often affects gastric blood flow while increasing lactate concentrations, it is typically used as a second-line agent for patients who are unresponsive to traditional agents.[11] In the prehospital environment, hypotension may be reversed by bolus dose epinephrine but its use is also associated with an increase in mortality when transporting patients in this setting.[37]

Epinephrine (adrenaline) is an injectable adrenaline that is used primarily to treat anaphylaxis due to allergic reactions caused by multiple

agents.[12] Treatment for allergic reactions include insect stings, biting insects, foods, drugs, sera, diagnostic testing substances and other allergens, as well as idiopathic anaphylaxis or exercise-induced anaphylaxis. Signs and symptoms of anaphylaxis are flushing, apprehension, syncope, tachycardia, thready or unobtainable pulse associated with hypotension, convulsions, vomiting, diarrhea and abdominal cramps, involuntary voiding, airway swelling, laryngospasm, bronchospasm, pruritus, urticaria or angioedema, swelling of the eyelids, lips, and tongue.[34]

Epinephrine (Adrenalin®) is available as a single-use 1 mL vial and a multiple-use 30 mL vial. The 1 mL vial is for IM, SC, and intraocular use. The 30 mL vial is for IM and SC use only, and NOT for ophthalmic use. Inject Adrenalin® 1 mL IM or SC into the anterolateral aspect of the thigh. The injection may be repeated every 5 to 10 minutes as necessary.[38]

Common to systemically administered epinephrine, adverse reactions include anxiety, apprehensiveness, restlessness, tremor, weakness, dizziness, sweating, palpitations, pallor, nausea and vomiting, headache, and respiratory difficulties. Symptoms may occur in patients receiving therapeutic doses of epinephrine; however, they are more common in patients with heart disease, hypertension, or hyperthyroidism. The true incidence of adverse reactions associated with the systemic use of epinephrine has not been determined due to lack of clinical trials.[34]

Adrenergic Agonists: Non-catecholamines

Ephedrine

Ephedrine acts similar to epinephrine but with less potency.[12] It primarily activates alpha- and beta-adrenergic receptors.[12,38] Ephedrine also inhibits norepinephrine reuptake and increases the release of norepinephrine. These actions lead to vasoconstriction and inotropy,[12,38] which increases heart rate, cardiac output, and MAP.[12]

Ephedrine is not ideal for infusion because of its longer duration of action, its dependence on endogenous norepinephrine for its indirect effects and its potential to therefore deplete norepinephrine. As a result, it is rarely used to treat hemodynamic impairment or shock, and it is limited to the treatment of transient anesthesia-related hypotension.[12]

Phenylephrine

Phenylephrine is an alpha-1 receptor agonist.[39] For patients with no cardiac effects, phenylephrine is not likely to cause tachycardia but it has a potential to decrease stroke volume in the heart. As a result, SSC guidelines do not recommend phenylephrine for the treatment of septic shock, except in cases where a patient cannot tolerate norepinephrine, due to serious arrhythmias, and the patient has high cardiac output, or requires salvage therapy.[39] Reflex bradycardia can follow the pressor response of phenylephrine, which can be blocked by atropine. Large dosing of atropine can increase the heart rate slightly.[39] A recent study by Hawn, *et al.* (2021) questioned the safety of using phenylephrine as an IV push to achieve a rapid MAP increase in patients with septic shock.[40] It was concluded that phenylephrine pushes did result in an early, but not sustained, hemodynamic stability; however, there was an independent association with a higher incidence of ICU mortality. Levy, *et al.* (2018) recited a study that recounted a shortage of norepinephrine in 2011.[41] During this shortage, phenylephrine was the most chosen alternative to norepinephrine. One outcome from this use of phenylephrine was a higher rate of death of inpatients.[37] Caution is advised when considering the use of phenylephrine pushes in patients with septic shock.[40,41]

Phenylephrine injections are used to treat hypotension caused by shock or anesthesia.[42] In some instances, phenylephrine is useful in the treatment and management of spinal shock and vasoplegia (uncontrolled vasodilation).[41] It is used in instances when tachyarrhythmias limit available treatment options with other pressors.[30] There are other uses, such as the recommendation of infusing phenylephrine prophylactically in an attempt to prevent hypotension during the use of spinal anesthesia for a cesarean section

delivery.[40] Phenylephrine may be used as a second-line agent for the treatment of septic shock.[28]

Phenylephrine is generally injected SC, IM, slowly IV or in a dilute solution as a continuous IV infusion. For paroxysmal supraventricular tachycardia and in an emergency, it is administered directly intravenously. The dose should be adjusted according to the pressor response. It can be administered for mild or moderate hypotension, severe hypotension and shock (including drug-related), spinal anesthesia-hypotension, and to prolong spinal anesthesia. It can be used as a vasoconstrictor for regional analgesia, and by rapid IV injection for paroxysmal supraventricular tachycardia. Dosages and administration vary as per clinical indication.[42]

Adverse reactions to phenylephrine include headache, reflex bradycardia, excitability, restlessness and rarely arrhythmias. Overdosage may induce ventricular extrasystole and short paroxysms of ventricular tachycardia, a sensation of fullness in the head and tingling of the extremities. For excessive elevation of blood pressure, an alpha-adrenergic blocking agent (*i.e.*, phentolamine) may be used.[42]

Vasopressors as Nonadrenergic Agents

Vasopressors that are nonadrenergic agents include vasopressin, terlipressin and methylene blue.[8,43]

Vasopressin

Vasopressin is an adjuvant agent used for its catecholamine-sparing effects in shock patients.[35] Its effect on microcirculation is well established.[35] Vasopressin is primarily used to maintain blood pressure during instances of hypovolemia. It also restores impaired hemodynamic mechanisms while inhibiting pathological vascular responses during shock.[23] In its natural state, it is a pre-pro-hormone that is synthesized in the hypothalamus.[44-46] It is released by the pituitary gland in response to decreased blood volume.[45] Low doses of vasopressin are typically administered to pressor-refractory patients

as a means of raising blood pressure. "Regarding the dosage and administration of vasopressin, recent guidelines recommend continuous infusion up to 0.03 U/min (1.8 U/h) because adverse events were occasionally reported with the administration of a high dose of vasopressin."[47] In most instances, vasopressin is used as a replacement therapy to counter relative deficiency rather than as a direct vasopressor. When vasopressin is used in combination with norepinephrine, norepinephrine infusion rates may be reduced and more quickly weaned.[45]

According to SSC guidelines, vasopressin is recommended as a second or third option to treat septic shock, following the use of other vasopressors, such as noradrenaline.[47,48] It is indicated for prevention and treatment of postoperative abdominal distention, in abdominal roentgenography to dispel interfering gas shadows, and in diabetes insipidus.[48]

Vasopressin may be administered IM or SQ. Vasopressin dose determination includes the following considerations: Dosing should be large enough and no more than needed to elicit the desired physiological response. Side effects from excessive doses include skin blanching, abdominal cramps, and nausea. Spontaneous recovery from side effects is quick, within a few minutes. One or 2 glasses of water consumed with vasopressin use has been recommended.[48] It can be administered for post-surgical abdominal distension or abdominal roentgenography. Enemas can be given before the first dose of vasopressin.[48]

Local or systemic allergic reactions may occur in hypersensitive individuals. The following side effects have been reported following the administration of vasopressin: anaphylaxis (cardiac arrest and/or shock) has been observed shortly after injection of vasopressin; arrhythmias, decreased cardiac output, angina, myocardial ischemia, peripheral vasoconstriction, cutaneous gangrene; abdominal cramps, nausea, vomiting; tremor, vertigo; bronchial constriction; sweating, and urticaria.[48]

Terlipressin

Terlipressin, triglycyl lysine vasopressin, is a synthetic analogue of vasopressin.[43,49] Terlipressin acts on vasopressin receptor V1a, which brings about vasoconstriction. This action also causes liver gluconeogenesis, platelet aggregation and a release of factor VIII.[49] Terlipressin causes corticotrophin secretion from the pituitary through its action on vasopressin receptor V1b. Finally, it acts on vasopressin receptor V2. This last action controls free water reabsorption in the renal medullar.[49]

Terlipressin has a longer half-life than vasopressin.[29,43] Terlipressin's longer half-life allows it to be administered intermittently as a bolus injection, rather than through continuous infusion;[29] however, its long half-life also makes it difficult to use in clinical settings.[23]

Terlipressin is used for hepatorenal syndrome in patients who have liver failure, and for esophageal variceal bleeding.[29,43,49] Terlipressin has not received approval from the U.S. Food and Drug Administration. Its approval is still pending.[51] Terlipressin is commonly administered with albumin.[50]

Terlipressin has been considered as a treatment option for vasodilatory shock or septic shock.[29,43] Clinical trial data has not supported its use because of outcome failures and more serious adverse events in terlipressin-treated patients.[29]

In hospitals where vasopressin is not available, terlipressin may be the only option. In these cases, clinicians must take care to correct any hypovolemia before administering the drug. High doses of terlipressin should be avoided.[29]

Initial daily doses of terlipressin have ranged from 2 mg to 6 mg in clinical trials. Doses are then "increased in a stepwise manner to a maximum dose of 6 mg to 12 mg until reaching an absolute reduction in serum creatinine of less than 1 mg/dL or less than 25% from baseline after 48 to 72 hours."[51]

There was a randomized trial that used a fixed dose of 0.5 mg every six hours.[51]

Methylene Blue

Methylene blue restores the vascular tone by inhibiting nitric oxide synthase and soluble guanylate cyclase.[43] This action decreases cyclic guanosine monophosphate levels and cancels its vasorelaxant effect.[52] When methylene blue is administered intravenously, it reaches peak concentrations in 30 min, and its onset of action occurs from 30 to 60 minutes. It has a half-life of 5–6 hours.[52]

Methylene blue has been used to treat several types of vasodilatory shock. Its use is controversial because its benefits have not been established;[43] however, Puntillo, *et al.* (2020) reported on studies and case reports in which methylene blue caused a statistically significant increase in MAP.[52]

Methylene blue has been used to treat vasodilatory shock. The initial therapeutic dose is a bolus of 1–2 mg/kg administered over 10–20 min or up to 1 hour. A continuous, intravenous dose may be beneficial after the initial bolus for 48 to 72 hours. Because of methylene blue's short-term effects, several studies have evaluated extended administration of methylene blue with doses of 0.25–2 mg/kg/h, up to 120 hours.[52]

Inotropic Beta-agonists

Dopamine

As discussed above, dopamine is a vasopressor with inotropic properties. It stimulates beta-adrenergic receptors, thereby increasing vasoconstriction, cardiac contractility, and heart rate.[28]

Dobutamine

Dobutamine is an inotrope. It increases myocardial contractility. Inotropes increase cardiac contractility, which improves cardiac output, aiding in maintaining MAP and perfusion to the body.

This synthetic catecholamine is primarily used as an agent to treat acute heart failure, especially when it is caused by cardiac surgery, septic shock, or cardiogenic shock.[53] Dobutamine is the first-line inotropic drug recommended by the Surviving Sepsis Campaign. It acts by stimulating the beta-adrenoceptors of the heart, which results in an increase in contractility and cardiac output.[54] For patients with cardiac conditions, dobutamine is used primarily for short-term situations. The long-term effects of the agent have not been reported. Treatment in end-stage heart failure may be needed to achieve short-term survival in patients with cardiogenic shock or very decreased output and significant reduction in organ perfusion. Mid- or long-term IV inotropic therapy however is associated with an increased mortality in advanced stage heart failure patients using dobutamine, a beta adrenoceptor agonist.[55] When considering the use of dobutamine, it should be remembered that its effect may be blunted if the patient is on a chronic regimen of beta blockers.[56] The effects on the long-term effects have to be part of the consideration for use.

This medication is used for the short-term treatment of adults with cardiac decompensation due to depressed contractility, due to organic heart disease or from cardiac surgical procedures. Experience with IV dobutamine in controlled trials does not extend beyond 48 hours of repeated boluses and/or continuous infusions.[57] Whether given orally, continuously or intermittently by IV, neither dobutamine nor any other cyclic-AMP-dependent inotrope has been shown in controlled trials to be safe or effective in the long-term treatment of congestive heart failure. In controlled trials, symptoms were not consistently alleviated, and the cyclic-AMP-dependent inotropes were consistently associated with increased risk of hospitalization and death. Patients with NYHA Class IV symptoms appeared to be at particular risk.[57]

Norepinephrine

Norepinephrine has inotropic action, in addition to its vasopressor status, as discussed above.[27] It stimulates the heart and dilates coronary arteries as a result of its activity at the beta-adrenergic receptors.[27]

Epinephrine

In addition to its vasoconstrictive mechanism described above, epinephrine provides positive inotropic action, especially in the skin, mucosa, and kidney, along with marked constriction of veins.[34]

Isoproterenol

Isoproterenol is a potent, nonselective, synthetic beta-adrenergic agonist. It has an extremely low affinity for alpha-adrenergic receptors. It has inotropic and vasodilatory properties.[14] van Diepen, *et al.* (2021) list isoproterenol as a vasoactive medication for patients in cardiogenic shock.[58]

Ironically, Yakabe, *et al.* (2020) reported on a case of cardiogenic shock possibly due to administration of isoproterenol for treatment of sinus bradycardia.[59] The patient developed rapid induced rapid atrial fibrillation that led to cardiogenic shock.[59] Isoproterenol has also been associated with stress-induced cardiomyopathy (Takotsubo cardiomyopathy). Clinicians administering isoproterenol should be aware of this relationship when treating patients in cardiogenic shock.[60]

Inotropic Phosphodiesterase Type 3 Inhibitors

Milrinone

This medication is used for cardiac support in patients with acute or chronic heart failure and pulmonary hypertension. Its inotropic properties improve the contractility of the heart and cause vasodilation. These effects increase cardiac output and enhance the heart's mechanical efficiency.[28]

Milrinone does cause more significant vasodilation when compared to other inotropic drugs, *e.g.*, dobutamine. This leads to a greater reduction in blood pressure and SVR, making milrinone less desirable in patients with hypotension.[28] In addition, renal impairment significantly increases the half-life of milrinone. Patients with renal impairment should be monitored carefully and dose adjustments made to prevent drug accumulation and cardiac adverse effects.[28]

Milrinone is used in the ICU and perioperative settings; however, in select populations, it has been used in outpatient therapy. Milrinone, when compared for use in patients with septic shock, is indicated less frequently when there is hypoperfusion and renal impairment. A comparison was made between dobutamine and milrinone as initial inotrope therapy in cardiogenic shock.[61] The study, looking at effectiveness and safety, was performed by Lewis, *et al.* (2019) and the conclusion showed no differences in hemodynamic changes during treatment with either drug, although dobutamine tended to show a greater cardiac index increase.[61] Both drugs caused hypotension but arrhythmias occurred more with dobutamine than milrinone. The rate of discontinuation due to some adverse reaction was the same for both, but milrinone was more frequently stopped because of hypotension, whereas dobutamine discontinuation was due to arrhythmia. Ultimately, the choice of inotropic agent may depend more on the individual patient's tolerability of adverse events.[61]

Inotropic Calcium Sensitizers

Levosimendan

Levosimendan is a positive, nonadrenergic inotropic agent.[29] It is a myofilament, calcium sensitizer that increases contractility. It increases contractility without appreciably elevating cAMP (cyclic adenosine 3′,5′-monophosphate) when used at recommended doses.[2] Levosimendan differs from other inotropes because it does not increase intracellular Ca2+to potentially harmful levels.[2] One significant aspect of levosimendan's mechanism of action is that its metabolite, OR-1896, has similar calcium-

sensitizing actions, which maintains the drug's inotropic effect after infusion ends.[2] Levosimendan is generally used for 24 hours, due to the accumulation of its metabolite, OR-1896. OR-1896 has a terminal half-life of 96 hours.[2]

Levosimendan can cause increased heart rate at high-dose.[2] It has not been shown to be effective as a treatment for septic shock.[29] In randomized trials, a greater number of patients administered levosimendan had tachyarrhythmias; and, fewer patients were successfully weaned from mechanical ventilation. For these reasons, levosimendan is not recommended for patients with septic shock.[29]

Treatment of Hemodynamic Impairment and Shock

As mentioned above, vasopressors and inotropes are primarily used for the treatment of shock. There are different types of shock, and the specific type of pressor or inotrope used will depend on the type of shock and the patient's specific needs. When choosing a pressor or inotrope, consideration must be given to potential adverse consequences from a specific drug. For example, isoproterenol has been associated with a decrease in SVR.[14] Inotropes that decrease or increase cardiac contractility may decrease left ventricular ejection fraction or increased arrhythmic mortality in patients with preexisting cardiac diseases.[3]

Sometimes these drugs will be used in combination. Vasopressors and inotropes are often indicated after fluid resuscitation: they are used if fluid administration does not adequately restore the patient to a normal arterial pressure and organ perfusion. In some cases, fluid administration will be administered with these medications. Pressors and inotropes can also be used in instances when a patient is undergoing surgical procedures that may impact arterial pressure and organ perfusion. In these instances, the agents will be used in conjunction with anesthetics.

Vasopressors are typically administered over a short period of time to provide immediate, but typically not complete, recovery from life-threatening hemodynamic impairment. The three routes of delivery for vasopressors are

oral, injection or intravenous (IV), and topical administration, of which injection or IV is most common.[62] Due to the need to deliver the pressor quickly, this route is the most efficient and most effective.[62]

These agents are reserved for use in critically ill patients who are experiencing significant hemodynamic impairment. Pressors can also be used in instances when a patient is undergoing surgical procedures that may impact arterial pressure and organ perfusion. In these instances, the agents will be used in conjunction with anesthetics.[11]

The primary cause of shock is decreased blood flow. However, the type of shock is defined by the mechanism causing the blood flow to be affected. There are four major categories of shock, each of which is mainly related to one of four organ systems. They are distributive, cardiogenic, hypovolemic, and obstructive. When multiple categories of shock or multiple organ failures are involved, a syndrome known as vasodilatory shock may arise. There are other important settings in which shock may occur. Vasopressors are used in surgical settings to prevent hypotension. In addition, shock may be caused by a drug overdose, as in the case of an opioid overdose.

Distributive Shock

Distributive shock is the most common form of shock. Distributive shock results from a loss of vascular tone due to a maldistribution of blood. Subcategories of distributive shock include anaphylactic shock, neurogenic shock, and septic shock.

Anaphylactic Shock

Described as an acute and potentially fatal allergic reaction, it is usually associated with foods, medications and stinging insects, although the etiology can be idiopathic. Signs and symptoms vary between patients but may report to have experienced a feeling of impending death, "angor animi," in addition to other possible symptoms such as urticaria, angioedema, and pruritus.[43] The rapid recognition of anaphylaxis, followed by the immediate IM administration

of epinephrine is the first-line therapy. Untreated, death due to anaphylaxis most often is resultant from the collapse of the cardiovascular system, obstruction of the respiratory tract, or both. Certain medications can cause the efficacy of epinephrine to be lessened. Beta blockers, commonly used as anti-hypertensive agents, can interfere with the patient's ability to respond to the epinephrine. Angiotensin converting enzyme (ACE inhibitors) inhibitors can adversely affect the patient's normal physiologic response to anaphylaxis with a worsened outcome.[43] Given the circumstances wherein epinephrine has not been effective in the correction of arterial hypotension, arginine vasopressin has been studied to see if it could be an alternate medication. Zheng, *et al.* (2017), proposed a comparison between the effects of arginine vasopressin and epinephrine, in a rat model, on airway leakage and airflow. They concluded that epinephrine was a much better medication for use when bronchospasm and arterial hypotension were present during anaphylactic shock.[63]

Neurogenic Shock

The most common cause of neurogenic shock is an acute spinal cord injury. The manifestation of neurogenic shock is variable and can have a rapid progression causing secondary injury or death. It is categorized within the distributive forms of shock due to the loss of vasomotor tone secondary to autonomic nervous system imbalance from an injury. The parasympathetic nervous system, no longer opposed by the sympathetic nervous system balance, produces hypotension and bradycardia.[45] The autonomic system (involuntary) has an overarching influence from the brain, and the loss of the input from the brain is what leads to dysfunction of the nervous system, and ultimately to shock. Vasopressor use is dependent on the level of spinal cord injury. According to the Consortium for Spinal Cord Medicine, injuries at the cervical level and at the thoracic until T6 require a vasopressor agent with both ionotropic and vasoconstrictive properties to support vessel tone and cardiac contractility, due to the sympathetic innervation of the heart origination at the level T1–T4.[11] At this level of injury, the use of dopamine and norepinephrine would be used. The use of epinephrine and dobutamine

are not common in neurogenic shock treatment, in that the former can lead to arrhythmias and the latter may potentially lead to bradycardia.[11]

Septic Shock

Septic shock results from an infection.[64,65] It is a systemic inflammatory response that leads to a state of acute circulatory failure, which is characterized by persistent arterial hypotension. The mortality rate of hospitalized patients with sepsis is 20%, and in those who go on to develop septic shock, that percentage rises to between 60-80%.[65] There has been a reduction in the number of community patients with sepsis, however, the number of sepsis patients in the hospital has risen. There is a wide range in the rates of mortality from hospital-based sepsis, from 12% and 80%.[65] Antibiotic treatment can be started empirically until culture results are known. When the appropriate antibiotic regimen is administered, the risk of septic shock is decreased by 50% regardless of the underlying disease which caused sepsis, when it develops from gram negative bacteria.[65] In addition to antibiotic therapy, some have added corticosteroid regimens, which have not led to an increase in survival, most likely due to the immunosuppressive effects of corticosteroids, causative in some cases of the development of secondary infections. Pertinent to this discussion on vasopressors, the addition of corticosteroid to antibiotic regimens in septic shock has evidenced a reduction in mortality rates and reduced the duration of the period of shock that required the use of a vasopressor.[65] A short course of hydrocortisone (200 to 300 mg/day for up to 7 days or until the vasopressor is no longer needed) is the only immunomodulatory treatment recommended for refractory septic shock. The only immunomodulatory therapy that is currently advocated is a short course of hydrocortisone (200 to 300 mg per day for up to 7 days or until vasopressor support is no longer required) for patients with refractory septic shock.[66] There are guidelines for the use of vasopressors in septic shock. They should be started promptly in patients where septic shock persists despite fluid resuscitation, and in cases of severe hypotension, they can be co-administered with fluids.

Septic Shock Pressor Guidelines set an initial goal of reaching a MAP of 65 mm Hg.[6-8] The first-line vasopressor to be provided should be norepinephrine. Vasopressin and epinephrine are the next-line agents if norepinephrine cannot maintain a MAP of 65 mm Hg.[23] Dopamine should be avoided.[23] Vasopressin can be used with norepinephrine to either improve perfusion (increase MAP) or to reduce the amount of norepinephrine; however, it is not recommended for use in septic shock as a single vasopressor. Similarly, phenylephrine is not to be used unless septic shock persists despite using 2 or more inotropes/vasopressors along with low dose vasopressin, or if cardiac output is high, or if norepinephrine has already caused serious arrhythmias.[39] Monitoring is performed by an arterial catheter whenever vasopressors are required.

Cardiogenic Shock

Loss of fluids and blood can lead to a loss of blood volume, resulting in hypovolemic shock. Distributive shock pertains to a condition leading to an inability of the vascular system to appropriately transport blood through the circulatory system. When the pump function of the heart is adversely affected, cardiogenic shock may arise. Blockages to the vessels of the circulatory system interrupting blood flow can result in obstructive shock.[67]

Cardiogenic shock is primarily caused by left ventricular failure, which often occurs as the result of ST elevation myocardial infarction (STEMI) after cardiac arrest. It is characterized by decreased cardiac output and evidence of tissue hypoxia in the presence of adequate intravascular volume. It has a mortality rate of 70 – 90% when left untreated. Acute myocardial infarctions (AMI) comprise 81% of the patients with cardiogenic shock.[68] It is an emergency that will require immediate treatment to prevent irreversible damage to the vital organs. Cardiogenic shock is a series of "maladaptive compensatory mechanisms" that brings about the mismatch between coronary and systemic perfusion.[69] Rapid diagnosis and subsequent initiation of pressors to maintain blood pressure and cardiac output is essential. Patients will require admission to the intensive care setting (if not already admitted) to obtain immediate treatment. The primary focus will be on the restoration

of coronary blood flow, with additional treatment occurring once the patient has been stabilized.[70,71] This is critical, in that new evidence has shown that if the microcirculation to the tissues is impaired, there is an association with a 30-day mortality rate.[58]

Cardiogenic shock can often be diagnosed through basic observation. Most patients will show the following signs and symptoms.[68]

- Hypotension
- Arrhythmia
- Clinical signs of poor tissue perfusion (*i.e.*, oliguria, cyanosis, cool extremities, altered mentation)
- Findings on physical examination include the following:
  - Skin is usually ashen or cyanotic and cool; extremities are mottled
  - Peripheral pulses are rapid and faint and may be irregular if arrhythmias are present
  - Jugular venous distention and crackles in the lungs are usually (but not always) present; peripheral edema also may be present; orthopnea
  - Heart sounds are usually distant, and third and fourth heart sounds may be present
  - The pulse pressure may be low, and patients are usually tachycardic
  - Patients show signs of hypoperfusion, such as altered mental status and decreased urine output
  - Ultimately, patients develop systemic hypotension (*i.e.*, systolic blood pressure below 90 mmHg or a decrease in mean blood pressure by 30 mmHg)

The final diagnosis will be confirmed using the following laboratory and imaging studies:[70]

- Biochemical profile including renal analysis
- Complete blood count (CBC)
- Cardiac enzymes (*i.e.*, creatine kinase and CK-MB, troponins, myoglobin, LDH)
- Arterial blood gases (ABGs)

- Lactate
- Brain natriuretic peptide
- Imaging studies
- Echocardiography
- Chest radiographs
- Ultrasonography
- Coronary angiography
- Electrocardiography
- Blood cultures: due to the prioritization of blood flow to the heart and brain, ischemia of the intestinal mucosa may occur. This can lead to the onset of infection. Seventy percent of patients may subsequently show positive cultures.

Hypovolemic and Hemorrhagic Shock

In instances of hypovolemic shock pressors can help temporize and maintain perfusion pressure while waiting for primary therapy to take effect.[58]

Pressors are used to treat many forms of shock, such as cardiogenic and hypovolemic, as well as subsets of the main categories of shock, such as hemorrhagic shock. This type of shock is a form of hypovolemic shock, brought about by blood loss, through trauma, coagulopathies or other mechanisms.[69]

Hemorrhagic shock occurs as a result of severe blood loss. Some will add a subcategorization to hemorrhagic shock, differentiating a traumatic etiology from non-traumatic, such as the rupture of the aortic aneurysm, as an example of the latter. The significance of this differentiation involves the additional damage caused by trauma to the soft tissues, leading to post-acute inflammatory responses. Trauma causes red blood cell adhesion to endothelial cells, which would explain the additional microvascular dysfunction after trauma.[72] This loss of blood impacts the circulating blood volume and affects lower organ perfusion pressure, which impairs delivery of oxygen to the tissues. When patients experience a massive hemorrhage, they can develop hypovolemia or isovolemic anemia. These conditions can further exacerbate

damage and early detection is necessary to prevent long-term, significant damage.

Non traumatic hemorrhagic shock can also result from gastrointestinal bleeding, postpartum bleeding, ruptured ovarian cyst or ectopic pregnancy, or other conditions that can cause sudden severe blood loss. In many instances, the blood loss will only occur internally and may not be detectable until damage has occurred.[73]

The administration of blood products and fluid are the primary means to initially begin resuscitation of a patient in hemorrhagic shock. The initiation of vasopressor therapy in this type of shock is controversial. There may be a role for vasopressors in certain circumstances, particularly if vasoplegic shock precludes the maintenance of blood pressure by using fluids alone. Fluid resuscitation, however, is not without potential adverse effects. Aggressive and continuous fluids can cause respiratory distress syndrome, which, in critically ill patients, may cause death on post-injury day 3. Fluid infusion may also cause hypothermia.[74] There is ongoing research as to the use and effectiveness of pressors in the treatment of hemorrhagic shock, and there may be implications for the future use of the agents in the management of hemorrhagic shock.

Obstructive Shock

In instances of obstructive shock, pressors can help temporize and maintain perfusion pressure while waiting for primary therapy to take effect.[58] Obstructive shock has an extracardiac cause, often due to insufficiency of the output of the right ventricle of the heart. Since the origin of this type of shock may not be as overt as with a trauma induced bleed, treatment initially may be for an undifferentiated form of shock, with fluid resuscitation and pressors until further testing can reveal the diagnosis. Causes of obstructive shock have been further subdivided into the categories of pulmonary vascular and mechanical obstructive shock.[75]

Pulmonary Vascular: In this category, there is a problem with blood flow from the right side of the heart to the left. This creates a hemodynamically significant impairment in blood flow. This category is responsible for most cases of obstructive shock. Causes are failure of the right ventricle from a pulmonary embolism (PE) or severe pulmonary hypertension and may also be caused by a severe stenosis or acute obstruction of the pulmonary or tricuspid valves.[76]

Mechanical: Here, the cause is not pump failure but rather a decreased preload, as seen in an impaired filling of the right side of the heart or secondary to the right side having a decreased venous return due to some type of external compression. Each of these mechanisms can present clinically as hypovolemic shock. Causative conditions of this type of mechanical obstructive shock include tension pneumothorax, pericardial tamponade, constrictive pericarditis, and restrictive cardiomyopathy.[76]

Vasodilatory Shock/Vasoplegia

Vasodilatory shock is a condition marked by multiple and diverse etiologies found with septic, cardiogenic, neurogenic, and anaphylactic shock.[43] This syndrome eventually leads to uncontrolled vasodilation known as "vasoplegia."[43] Vasodilatory shock is characterized by hypotension, tachycardia, and low systemic vascular resistance, with or without high cardiac output.[29] This syndrome is seen after cardiovascular surgery or during a heart transplant.[16,29]

Belletti, *et al.* (2015) stated that in patients with vasodilatory shock, catecholamines are associated with side effects and poor outcomes.[45] Outcomes can improve with the use of nonadrenergic vasopressors because of their catecholamine-sparing effect.[45,12,52] These include methylene blue, vasopressin, and angiotensin II.[16,23,29,45]

Vasopressor Use During Surgery

Vasopressors are often used in the operating room to help prevent surgical hypotension. In most instances, the pressor will be administered by the anesthesiologist in conjunction with anesthesia.[7] The primary function of vasopressors in surgery is maintaining patient stability. Typically, vasopressors are administered in conjunction with inotropes.[52] The two agents work together to provide a therapeutic approach to controlling cardiovascular syndromes in the operating room.

Vasopressor use is common in the intensive care unit (ICU), and the staff are specially trained to administer pressors and monitor patient response.[53] Due to the severe trauma and significant health concerns of patients in the ICU, pressors must be administered sparingly and monitored closely. ICU staff is expected to adhere to specific guidelines and monitoring protocols when treating patient with pressors.[53] The following is a list of the most important precautions and guidelines for the use of pressors in the ICU:

- Hypovolemic and septic shock patients should always be given volume resuscitation prior to vasopressors or inotropes. If preload is inadequate, vasopressors will cause further reductions in cardiac output, and inotropes will worsen tachyarrhythmias and induce ischemia.
- These agents may also aggravate outflow tract obstruction in idiopathic hypertrophic subaortic stenosis.
- Cardiac monitoring is imperative in the clinical use of these pharmacologic agents. Electrolytes (especially potassium and magnesium) should be monitored and replaced, if needed, to reduce the likelihood of arrhythmias.[54]

Opioid Overdose and Shock

An opioid overdose may lead to shock. Clinicians treating patients with shock caused by an opioid overdose outside of the hospital setting should follow a systematic approach to identify the cause of shock. Life-sustaining therapies for opioid overdose patients often differ from other shock cases

because patients tend to be younger, and they tend to have fewer comorbidities. Treating post-arrest shock is further complicated by delayed opioid onset, coingestion of other substances, or sedation metabolism.[77] Norepinephrine is a reasonable, first-line vasopressor when a patient's shock is undifferentiated.[77] Crystalloids may be used to correct hypovolemia, and norepinephrine may be administered to treat hypotension.[77]

Summary

Vasopressors (also called pressors) and inotropes are used to treat shock, with the goal of restoring perfusion. It is critical for healthcare professionals to understand how these drugs work. A drug's mechanism of action plays an important part in determining whether the drug is appropriate for a specific patient and medical condition.

When acute blood loss occurs, a patient may need rapid restoration of blood volume. Acute blood loss may be due to trauma, infection, burns or other serious medical conditions. In these cases, plasma volume expanders are the preferred choice to restore vascular volume. Three questions arise in this clinical setting: Which fluid to use? How much fluid to administer? When should vasopressors be introduced into the treatment plan?

It is common to begin treatment with fluids rather than pressors, which are typically utilized when fluid resuscitation is not successful. The SSC recommendation is to use vasopressors within the first hour when fluid administration is not sufficient. However, other medical associations recommend starting vasopressors before completion of fluid resuscitation.

Vasopressors may be described under two headings based on their actions: vasopressors as adrenergic agonists and nonadrenergic agents. Inotropes act as beta-agonists, PDIs, or calcium sensitizers. Many of the drugs described above have vasoconstrictive and inotropic properties.

Vasopressors that are adrenergic agonists may be further divided into catecholamines and non-catecholamines. Catecholamines include dopamine, norepinephrine, and epinephrine. Non-catecholamines include ephedrine and phenylephrine. Vasopressors that are nonadrenergic agents include vasopressin, terlipressin and methylene blue. A patient's particular medical condition determines the choice of drug that should be used.

The primary cause of shock is decreased blood flow. However, the type of shock is defined by the mechanism causing the blood flow to be affected. There are only four major categories of shock, each of which is mainly related to one of four organ systems. They are distributive, cardiogenic, hypovolemic, and obstructive. Vasodilatory shock is a condition marked by multiple and diverse etiologies found with septic, cardiogenic, neurogenic, and anaphylactic shock.

Course Test

1. **Blood is pumped out of the heart by afterload, which is mainly dependent on arterial blood pressure and**

    a. cardiac output.
    b. vascular tone.
    c. preload.
    d. contractility.

2. **Contractility is also referred to as**

    a. entropy.
    b. vascular tone.
    c. pressure.
    d. inotropy.

3. **The primary mechanism of vasopressors is to target receptors in**

    a. the brain.
    b. the central nervous system.
    c. the heart.
    d. the peripheral blood vessels.

4. **True or False: Inotropes can impact contractility and may have vasoactive properties that cause vasoconstriction as well.**

    a. True
    b. False

5. **_____ is an injectable adrenaline that is used primarily to treat anaphylaxis due to allergic reactions.**

    a. Dobutamine
    b. Dopamine
    c. Epinephrine
    d. Vasopressin

6. Cardiogenic shock is primarily caused by

a. right ventricular failure
b. left ventricular failure
c. an aneurysm
d. a stroke

7. Which of the following drugs is a synthetic catecholamine and inotrope that is used to treat acute heart failure?

a. Ephedrine
b. Phenylephrine
c. Methylene blue
d. Dobutamine

8. _____ is a vasopressor with inotropic properties and it is a natural precursor to norepinephrine.

a. Dobutamine
b. Dopamine
c. Epinephrine
d. Methylene blue

9. _____ are balanced salt solutions that contain electrolytes that move readily from the vascular space into the interstitium.

a. Crystalloid fluids
b. Colloid Fluids
c. Gelatins
d. Plasma protein fractions

10. According to the Septic Shock Pressor Guidelines, _____ is the first-line vasopressor.

a. vasopressin
b. dopamine
c. norepinephrine
d. epinephrine

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