VASOPRESSOR AND INOTROPE USAGE IN SHOCK

SUMMARY

Shock is characterized by inadequate tissue perfusion, resulting in life-threatening impairment of oxygen and nutrient delivery. Treatment of shock consists of identifying and reversing the underlying pathogenesis and correcting hemodynamic abnormalities. Vasopressors should be initiated in refractory hypotension despite adequate fluid and/or blood product resuscitation. In low cardiac output states, the use of an inotropic agent should be considered.

RECOMMENDATIONS

All shock states
- **Level 1**
  - ➢ **Vasopressors should only be initiated with/after adequate resuscitation is provided with crystalloids, colloids, and/or blood products.**

Hemorrhagic Shock
- **Level 1**
  - ➢ **None**
- **Level 2**
  - ➢ **Vasopressors are not recommended in the initial stabilization of hemorrhagic shock.**
  - ➢ **Permissive hypotension may be employed until bleeding is controlled in patients requiring emergent surgical intervention.**
- **Level 3**
  - ➢ **If hypotension persists despite adequate blood and fluid resuscitation and surgical intervention, consider other etiologies for shock and an appropriate vasopressor.**

Septic Shock
- **Level 1**
  - ➢ **Low-dose dopamine should not be used for renal protective effects.**
- **Level 2**
  - ➢ **Maintain mean arterial pressure (MAP) ≥ 65 mmHg or as needed to achieve adequate end-organ perfusion (e.g. cerebral perfusion pressure, abdominal perfusion pressure, urinary output).**
  - ➢ **Norepinephrine is the first line agent when vasopressors are indicated. Epinephrine, phenylephrine, and vasopressin should not be used as first line agents.**
  - ➢ **If hypotension persists despite the use of norepinephrine, epinephrine should be added to current vasopressor therapy.**
  - ➢ **Vasopressin may be added to norepinephrine to optimize the therapeutic efficacy of norepinephrine.**

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EVIDENCE DEFINITIONS
- **Class I:** Prospective randomized controlled trial.
- **Class II:** Prospective clinical study or retrospective analysis of reliable data. Includes observational, cohort, prevalence, or case control studies.
- **Class III:** Retrospective study. Includes database or registry reviews, large series of case reports, expert opinion.
- **Technology assessment:** A technology study which does not lend itself to classification in the above-mentioned format. Devices are evaluated in terms of their accuracy, reliability, therapeutic potential, or cost effectiveness.

LEVEL OF RECOMMENDATION DEFINITIONS
- **Level 1:** Convincingly justifiable based on available scientific information alone. Usually based on Class I data or strong Class II evidence if randomized testing is inappropriate. Conversely, low quality or contradictory Class I data may be insufficient to support a Level I recommendation.
- **Level 2:** Reasonably justifiable based on available scientific evidence and strongly supported by expert opinion. Usually supported by Class II data or a preponderance of Class III evidence.
- **Level 3:** Supported by available data, but scientific evidence is lacking. Generally supported by Class III data. Useful for educational purposes and in guiding future clinical research.

Approved 04/19/2011

RECOMMENDATIONS (continued)

Septic Shock (continued)
- **Level 2**
  - ➤ **Dobutamine may be initiated in combination with norepinephrine in patients with myocardial dysfunction (i.e. elevated cardiac filling pressure, low cardiac output).**
- **Level 3**
  - ➤ **None**

Neurogenic Shock
- **Level 1**
  - ➤ **Due to the physiologic nature of neurogenic shock, vasopressors may be initiated earlier to avoid volume overload.**
- **Level 2**
  - ➤ **None**
- **Level 3**
  - ➤ **Norepinephrine should be first line agent once vasopressors are indicated.**
  - ➤ **Phenylephrine should be avoided in most patients due to unopposed alpha activity that can result in reflex bradycardia; further worsening spinal cord injury (SCI) associated bradycardia.**

Cardiogenic Shock
- **Level 1**
  - ➤ **Vasopressors and/or inotropes may be initiated earlier in cardiogenic shock with clinical evidence of volume overload.**
- **Level 2**
  - ➤ **In low output cardiogenic shock, dobutamine may be initiated in combination with norepinephrine.**
- **Level 3**
  - ➤ **None**

Adrenal Insufficiency of Critical Illness (Distributive / Endocrine Shock)
- **See "Adrenal Insufficiency of Critical Illness" evidence-based medicine guideline.**
- **Level 1**
  - ➤ **Adrenal insufficiency of critical illness (AICI) should be suspected in high-risk critically ill patients with a random serum cortisol level < 20 mcg/dL.**
- **Level 2**
  - ➤ **Consider AICI and obtain a serum cortisol level in any critically ill patient who demonstrates hypotension, refractory shock, hypoglycemia, persistent systemic inflammation, and/or marked eosinophilia.**
  - ➤ **When AICI is present, steroid replacement should be initiated:**
    - ▪ **Hydrocortisone 50 mg IV q 6 hrs OR 100 mg IV Q 8 hrs**
    - ▪ **Fludrocortisone 50 mcg PO daily x 7 days**
- **Level 3**
  - ➤ **For patients on steroid therapy for ≤7 days, steroid weaning is not necessary.**
  - ➤ **For patients on steroid therapy >7 days, wean steroid replacement by 25-50% per day as tolerated by the patient's response.**

INTRODUCTION

Shock is characterized by inadequate tissue perfusion, resulting in life-threatening impairment of oxygen and nutrient delivery. The development of shock is associated with hypotension which ultimately results in multi-organ system failure (1). Some causes of shock in the trauma and general surgery patient population include cardiac dysfunction, blood loss, autonomic dysregulation, and sepsis. The treatment of shock consists of identifying and reversing the underlying pathogenesis and correcting hemodynamic abnormalities. Fluid and/or blood product resuscitation should be the initial management for hypotension.

Approved 04/19/2011

Vasopressors should be initiated in those patients with refractory hypotension despite adequate resuscitation. In low cardiac output states, an inotrope should be considered.

Adrenal Insufficiency of Critical Illness (Endocrine Shock)

Acute adrenal insufficiency of critical illness (AICI) is a common and largely unrecognized disorder in critically ill patients with a reported incidence of up to 77% (2). The most common features of AICI are hypotension refractory to fluids and vasopressors and/or delayed weaning from mechanical ventilation. However, other common signs and symptoms include unexplained fever, electrolyte abnormalities (e.g. hypoglycemia, hyponatremia, hyperkalemia), unexplained mental status changes, and neutropenia or mild eosinophilia. Traditionally, AICI has been diagnosed using an adrenocorticotropic hormone (ACTH) test; however, evidence suggests modifications from standard testing are needed (3). In the presence of severe endogenous stress (e.g. hypotension, shock, sepsis), obtaining a cortisol level can be considered superior to the traditional ACTH test. A random serum cortisol level < 20 mcg/dL is considered sufficient to diagnose AICI in suspected patients.

Cardiogenic Shock

Cardiogenic shock is persistent hypotension and tissue hypoperfusion due to cardiac dysfunction with adequate intravascular volume and left ventricular filling pressure (4). It is most important to recognize the development and cause of cardiogenic shock to prevent the associated high morbidity and mortality (4). The use of an intra-arterial catheter is helpful in managing patients in cardiogenic shock. Dopamine has traditionally been the drug of choice, owing to its vasopressor and inotropic activity. Norepinephrine was preferred over dopamine in patients with more severe hypotension due to its more potent vasoconstriction. However, recent literature showing a potential increase in mortality with dopamine over norepinephrine has questioned the use of dopamine as a first line agent in cardiogenic shock (5). Both dopamine and norepinephrine can cause increased myocardial oxygen demand and may aggravate ischemia. This can lead to arrhythmias making it important to titrate to the lowest dose needed to improve tissue perfusion. For patients who are in a low output cardiogenic shock dobutamine may be added to optimize cardiac output (CO). However, dobutamine can cause vasodilation; therefore, its use should be in patients with less severe hypotension or in combination with a vasopressor to improve cardiac output (CO) in severe hypotension (4, 6).

Hemorrhagic Shock

Hemorrhage, progressing to hemorrhagic shock, accounts for 30 to 40% of trauma fatalities and is the leading cause of preventable death in trauma (7). In response to significant hemorrhage, neuroendocrine axes are activated, leading to release of catecholamines and nonadrenergic stress hormones. However, as hemorrhage persists, these mechanisms are no longer able to compensate (8). A variety of treatment modalities have been suggested and evaluated in the literature, including permissive hypotension, fluid resuscitation, use of vasopressors, and damage control resuscitation. Permissive hypotension is evolving as a treatment strategy in which the goal is to keep the blood pressure low enough to avoid exsanguination but maintain perfusion of end organs (7). There is no well-defined mean arterial pressure (MAP) goal for patients with hemorrhagic shock. Overly aggressive fluid resuscitation is controversial as it has been linked to worsening of bleeding due to the dilution of coagulation factors, increase in arterial blood clots, and dislodgement of existing clots (9). Early vasopressor use within the first 24 hours in patients not appropriately resuscitated with blood products and fluids has been suggested to increase the risk of mortality (10). The mainstay of therapy for hemorrhagic shock is damage control resuscitation which, in addition to surgical intervention, focuses on a massive transfusion of equal ratios of packed red blood cells (PRBC) to fresh frozen plasma (FFP) to platelets (PLT) (11).

Neurogenic Shock

Neurogenic shock most often occurs in patients with severe spinal cord injury (SCI) at the cervical or high thoracic level (12). A shock state can occur following SCI as a result of sympathetic denervation leading to reduced sympathetic outflow to the cardiovascular system and subsequent decreased CO and systemic vascular resistance (SVR) (13). Neurogenic shock can occur at any time, from initial presentation to several weeks post injury (13). It is recommended to exclude other injuries or causes that could result in hypotension prior to determining the cause as neurogenic shock (12). The primary treatment for neurogenic shock is fluid resuscitation but there is no evidence for an appropriate

Approved 04/19/2011

resuscitation end point and optimal MAP to prevent hypotensive ischemia of the spinal cord (12). The Clinical Practice Guidelines of the Consortium for Spinal Cord Medicine recommend the prevention and treatment of hypotension [systolic blood pressure (SBP) < 90 mmHg] with early appropriate fluid resuscitation to maintain tissue perfusion and resolve shock but to avoid volume overloading (14). If there is inadequate response to fluid resuscitation, vasopressors with alpha and beta activity should be initiated to counter the loss of sympathetic tone and provide chronotropic cardiac support (12).

Septic Shock

Sepsis, the presence of infection plus a systemic inflammatory response, progresses to a shock state when there is persistent hypotension, despite adequate fluid resuscitation, that is unexplained by any other cause (15). The treatment of septic shock necessitates the initiation of a vasopressor. Since septic shock is caused by excessive vasodilation, vasopressors that target peripheral alpha receptors to cause vasoconstriction are desired. In determining the target MAP for patients with septic shock, one trial found a MAP < 65 mmHg is a predictor of mortality (16). This being consistent with other trials, the current recommendation for goal MAP in patients with septic shock is ≥ 65 mmHg (15). Literature is limited to support the safety of titrating MAP as high as 80 to 90 mmHg, with concern that a MAP this high causes excessive vasoconstriction that can adversely effect organ perfusion (17). An alternative endpoint is titrating to a MAP that provides adequate end-organ perfusion (e.g. maintaining urine output, optimizing intra-abdominal perfusion pressure)

Role of Vasopressors and Inotropes in the Management of Shock

At the point where patients are adequately resuscitated yet remain hypotensive the initiation of vasopressors may be required to achieve the desired MAP. Selection of a vasopressor is determined by the cause of shock and the desired therapeutic activity targeting the underlying pathogenesis. $Alpha_1$ receptor agonists work on arterial smooth muscle cells to cause vasoconstriction, thereby increasing SVR. $Beta_1$ receptor agonists stimulate myocardial cells enhancing myocardial contractility and chronotropy. Norepinephrine has a stronger affinity for $alpha_1$ receptors compared to $beta_1$ receptors (18). Epinephrine has similar affinity to $alpha_1$ receptors as norepinephrine but has more $beta_1$ activity. Dopamine's activity on $alpha_1$ and $beta_1$ receptors is dependent on the dose, with lower doses having more $beta_1$ activity and higher doses more $alpha_1$ activity. Phenylephrine is a pure alpha agonist; however, its activity on $alpha_1$ receptors is not a potent as norepinephrine. Vasopressin augments the effects of other vasopressor agents and is most commonly used for this mechanism at doses of 0.03 to 0.04 units/min (19). Vasopressin also targets V_1 receptors in the vascular smooth muscle leading to vasoconstriction of peripheral arterial beds. Due to the cardiac ischemia associated with higher doses, vasopressin is generally not used at doses greater than 0.04 units/min. Dobutamine is a synthetic catecholamine with strong affinity for both $beta_1$ and $beta_2$ receptors in a 3:1 ratio. It exerts its effects primarily through stimulation of cardiac $beta_1$ receptors, resulting in potent inotropic activity with weaker chronotropic activity. On vascular smooth muscles, dobutamine (at lower doses) can decrease SVR as a result of reflex vasodilation and $beta_2$ receptor activation leading to significant hypotension (18).

LITERATURE REVIEW

Adrenal Insufficiency of Critical Illness (Endocrine Shock)

See "Adrenal Insufficiency of Critical Illness" evidence-based medicine guideline.

Cardiogenic Shock

Currently, the ACCF/AHA guidelines on the management of heart failure do not support a recommendation for specific vasopressor usage in the presence of cardiogenic shock (20). In contrast, the ACC/AHA guidelines for ST-elevation myocardial infarction (STEMI) recommend the selection of vasopressor and/or inotrope therapy based on SBP plus the presence or absence of signs and symptoms of shock (6). For patients with a SBP of 70-100 mmHg, dobutamine is recommended in the absence of shock and dopamine if shock is present. Norepinephrine is recommended when SBP is < 70 mmHg. (Class II) However, the results of a recent multicenter, randomized trial challenge the recommendation of dopamine as a first line vasopressor agent over norepinephrine in cardiogenic shock patients. The trial was conducted to determine if the use of norepinephrine over dopamine as the first line vasopressor

Approved 04/19/2011

agent could reduce the rate of death among patients in shock (5). Once predetermined maximum doses of the study agents were reached, open labeled vasopressor usage was permitted. If needed, inotropic agents could be initiated to increase cardiac output. Although no difference was found in the primary outcome of 28-day mortality, a subgroup analysis found a higher mortality rate in cardiogenic shock patients who received dopamine (p = 0.03). (Class II) The exact cause of this increased mortality could not be determined.

In 2011, results of an open, randomized interventional study were published comparing epinephrine and norepinephrine-dobutamine in dopamine-resistant cardiogenic shock (excluding cases due to acute ischemic events) (21). Study medications were titrated to a MAP of 65-70 mmHg with a stable or increased cardiac index. Both regimens increased global hemodynamic parameters (i.e. cardiac index, oxygen-derives parameters); however, epinephrine was associated with a transient lactic acidosis, higher heart rate and arrhythmias, and inadequate gastric mucosa perfusion. (Class II)

Neurogenic Shock
Paucity of evidence indicates the need for further investigation to define optimal MAP and the role of pharmacological treatment of hypotension in patients with acute SCI (12). Literature evaluating other aspects of SCI management have targeted a MAP > 85 mmHg. This goal was arbitrarily chosen; however, claims of improved neurological outcomes associated with aggressive management have led to acceptance of a target MAP 85-90 mmHg (28). (Class III) The duration for maintaining a MAP > 85 mmHg is unknown.

Septic Shock
Norepinephrine and dopamine are currently the initial vasopressors of choice for the management of septic shock (15). Norepinephrine is a more potent alpha$_1$ agonist than dopamine and may be more effective at treating hypotension in patients with septic shock. Dopamine may be particularly useful in patients with compromised systolic function but causes more tachycardia and may be more arrhythmogenic. Animal and human studies do suggest some advantages of norepinephrine and dopamine over epinephrine and phenylephrine. Therefore, epinephrine, phenylephrine, and vasopressin should not be administered as the initial vasopressors in septic shock. There has been no clinical evidence that epinephrine results in worse outcomes. Therefore, epinephrine should be used as the first alternative agent in septic shock when blood pressure is poorly responsive to norepinephrine or dopamine. Vasopressin (0.03-0.04 units/min only) may be added to norepinephrine to optimize the therapeutic efficacy of norepinephrine.

Martin et al. conducted a study identifying factors associated with outcomes in septic shock (29). From a cohort of septic shock patients it was found that the use of norepinephrine to provide hemodynamic support was strongly related to a favorable outcome and considered a protective factor leading to decreased mortality. Mortality on day 7 and 28 and at hospital discharge was statistically significantly lower in those patients who received norepinephrine. Use of high-dose dopamine and epinephrine did not significantly influence outcomes. (Class II)

A multicenter, randomized trial was conducted to evaluate whether norepinephrine or dopamine should be initiated as the first line agent in the management of shock states (5). Dopamine was titrated to a maximum dose of 20 µg/kg/min and norepinephrine to a maximum of 0.19 µg/kg/min. Once these maximum doses were achieved, open-label vasopressors could be added. There was no significant difference in 28-day mortality among the two groups. A subgroup analysis showed that in septic shock patients, specifically, there was no difference in mortality rates. There were more arrhythmic events in the dopamine group. More patients in the dopamine group did require open-label norepinephrine; however, the dose of norepinephrine used in both groups was similar. (Class II)
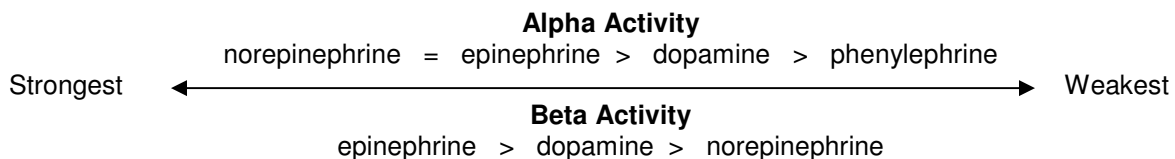
Dünser et al. randomized patients with catecholamine-resistant vasodilatory shock to norepinephrine plus vasopressin or norepinephrine alone (30). Vasopressin was infused at 4 units/hr (0.067 units/min). The vasopressin group had significantly lower heart rate, norepinephrine requirements, and incidence of new-onset tachyarrhythmias than the norepinephrine alone group. MAP, cardiac index, stroke volume index, and left ventricular stroke work index were significantly higher in the vasopressin group. (Class II) These

results support the use of the addition of vasopressin to norepinephrine in catecholamine-resistant vasodilatory shock. In 2008, the VAAST trial compared norepinephrine plus vasopressin to norepinephrine alone and found no difference in 28-day mortality rates or overall rates of serious adverse events (31). (Class II)

Appendix 1
Vasopressor and Inotropic Agents

Drug	Receptor Affinity	Dose	Adverse Events	Special Considerations
Vasopressors				
Norepinephrine (Levophed®)	$\alpha_1 > \beta_1$	0.05 – 1 mcg/kg/min	Tachycardia Peripheral/GI ischemia	
Epinephrine (Adrenalin®)	$\beta_1 > \alpha_1$ Low doses = β High doses = α	0.05 – 0.5 mcg/kg/min	Tachycardia Peripheral/GI ischemia	
Dopamine (Intropin®)	DA = <5 mcg/kg/min β_1 = 5 – 10 mcg/kg/min α_1 = 10 – 20 mcg/kg/min	5 – 20 mcg/kg/min	Tachycardia Arrhythmias	Renal protective doses of < 5 mcg/kg/min should not be used
Phenylephrine (Neosynephrine®)	α_1	0.5 – 5 mcg/kg/min	Reflex bradycardia	Tachyphylaxis
Vasopressin (Pitressin®)	V_1	0.04 units/min	Cardiac/ mesenteric ischemia Skin lesions	Do NOT titrate [doses >0.04 units/min can result in cardiac ischemia]
Inotropes				
Dobutamine (Dobutrex®)	β_1, β_2	5 – 20 mcg/kg/min	Arrhythmias Hypotension	

Relative Vasopressor Activity

Alpha Activity
norepinephrine = epinephrine > dopamine > phenylephrine

Strongest ←———————————————————————————→ Weakest

Beta Activity
epinephrine > dopamine > norepinephrine

Approved 04/19/2011

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Approved 04/19/2011

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Approved 04/19/2011