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 appropriate volumes of 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 / 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 effect.**
- **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, 09/11/2019

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).**
  - **Midodrine can be used as an adjunct to wean IV vasopressors in patients on persistent low-doses of vasopressors.**
- **Level 3**
  - **Initiation of vasopressin may be considered in euvolemic patients receiving norepinephrine at a dose ≥ 0.3 mcg/kg/min.**
  - **Upon resolution of shock, vasopressin should be tapered / discontinued prior to norepinephrine.**

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 the 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).**

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 may be added if necessary**
- **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. 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 non-adrenergic 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 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 affect 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

The 2013 ACCF/AHA guidelines for the management of heart failure do not support a recommendation for specific vasopressor usage in the presence of cardiogenic shock (20,21). A 2019 review in CHEST cautions against the excessive use of vasopressors as first line agents (22). A multifaceted algorithmic approach is proposed that would optimize cardiac output and end organ perfusion while attempting to maintain a reasonable blood pressure. The diverse etiologies of cardiogenic shock should not be oversimplified, and a multimodal approach is recommended.

The 2004 ACC/AHA guidelines for ST-elevation myocardial infarction (STEMI) recommended 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 an SBP of 70-100 mmHg, dobutamine was recommended in the absence of shock and dopamine if shock was present. Norepinephrine was recommended when SBP is < 70 mmHg. (Class II) However, the 2013 updated guideline no longer has this algorithm listed. The current recommendation is individualization of inotropic and vasopressor therapy with invasive hemodynamic monitoring. Norepinephrine is still considered first line for cardiogenic shock. The use of dopamine may have unacceptably high risk (23).

The results of a 2010 multicenter, randomized trial challenged 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 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) (24). 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)

A 2018 meta-analysis of 2583 patients in both published and unpublished data was evaluated to determine the association between epinephrine and short-term mortality in cardiogenic shock patients. 37% of patients (all cohorts) were given epinephrine. The short-term mortality rate was 47%. The adjusted mortality risk in the epinephrine group had an adjusted OR of 4.7 (3.4-6.4) (n=1227) (25).

Additionally, inotropic therapy is only recommended as a temporizing measure to maintain end organ perfusion until definitive treatment. Examples include milrinone, dobutamine, and dopamine (21). A 2018 Cochrane Review on the utility of inotropic agents in cardiogenic shock demonstrated a paucity of quality data. No conclusion could be made supporting a specific inotropic agent (26).

Ultimately, the increased utilization of temporary mechanical circulatory support systems may have an added survival benefit. Examples include extracorporeal membrane oxygenation (ECMO), the Impella and ventricular assist devices (VAD). Rigorous clinical trials need to be performed to ascertain the true utility of these devices, including cost-benefit analysis and additional complications specific to these modalities of treatment (27).

Neurogenic Shock

AANS/CNS Joint Guidelines recommend a MAP >85 mmHg with avoidance of a systolic <90 mmHg for the first 5-7 days after spinal cord injury (Level III) (28). In 2018, Sabit, et al., performed a systematic review on the literature related to functional outcomes in traumatic acute spinal cord injury and mean arterial blood pressure. Ultimately only 9 studies were included, of which 2 were prospective. Only 4 studies suggested an improvement in functional outcome in relation to a higher MAP (29). The Consortium for Spinal Cord Medicine recommends vasopressors depending on the level of injury. Patients with SCI at cervical and high thoracic levels are at risk for bradycardia due to unopposed vagal tone and should be placed on both alpha and beta agonist support such as dopamine or levophed. Lower thoracic injuries are more susceptible to isolated vasodilation and can be placed on a pure alpha agonist such as phenylephrine (28). There still remains a paucity of evidence indicating a need for further investigation to define optimal MAP and the role of pharmacological treatment of hypotension in patients with acute SCI (12).

Septic Shock

The 2016 Surviving Sepsis Guidelines recommends norepinephrine as a first line vasopressor for septic shock (strong recommendation, moderate quality of evidence). Secondarily, epinephrine or vasopressin is recommended as a second line agent for the purpose of raising MAP. Dopamine is now only recommended in a very select patient population (low risk for tachyarrhythmias, absolute/relative bradycardia). Dobutamine is recommended if persistence of low flow state despite fluid resuscitation and vasopressor support (30).

In 2015 Avni, et al., performed a systematic review and meta-analysis on RCTs comparing vasopressors in adult patients diagnosed with septic shock. The primary outcome was all-cause mortality. Thirty-two trials were included. The use of norepinephrine demonstrated a risk reduction of 0.89 (95% CI 0.81-0.98) when compared to dopamine. This was an absolute risk reduction of 11%. Dopamine was associated with a higher risk of adverse events and an increase in tachyarrhythmias. When norepinephrine was compared to epinephrine, vasopressin/terlipressin or phenylephrine, there was no statistically significant difference in all-cause mortality. Norepinephrine suggested some benefit in urinary output, lactate levels and central venous pressure (31).

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 (32). 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 (33). 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 VASST trial compared norepinephrine plus vasopressin to norepinephrine alone. Although no difference was found between the two groups in 28-day mortality, subgroup analysis suggested a mortality benefit in patients requiring low dose norepinephrine (5-14 mcg/minute) who received vasopressin within 12 hours of the onset of septic shock (34). (Class I)

Hammond et al. performed a retrospective cohort that compared the early addition of vasopressin within 4 hours of septic shock onset to norepinephrine vs. the addition of vasopressin > 4 hours after the onset of septic shock to norepinephrine. Patients started on early vasopressin achieved and maintained goal MAP sooner (6.2 vs. 9.9 hours, P=0.023). The early vasopressin group also had a greater reduction in SOFA score at 72 hours and shorter hospital length of stay. The author concluded vasopressin should be added to norepinephrine early in septic shock (35). (Class II) Based on the VASST trial and study by Hammond et al., the recommended threshold for initiating vasopressin is norepinephrine 0.3 mcg/kg/min.

Vasopressor Weaning and Discontinuation

Per the Surviving Sepsis Campaign guidelines, vasopressin 0.03 U/min can be added to norepinephrine to raise MAP or to decrease norepinephrine dosage (34). Its use is supported by observed endogenous vasopressin decline which can be seen as early as 6 hours from the onset of septic shock with vasopressin deficiency seen at 36 hours (36). However, it is unknown how long the vasopressin deficiency remains and whether or not discontinuation of exogenous vasopressin would result in clinically significant hypotension. The decision to wean norepinephrine or vasopressin first is largely controversial.

A retrospective cohort, by Bauer et al., observed tapering of vasopressin before norepinephrine in septic shock patients resulted in a greater incidence of clinically significant hypotension than the reverse order (37). (Class II) A second retrospective cohort, by Hammond et al., observed similar results in that septic shock patients who had vasopressin weaned first rather than norepinephrine required intervention more commonly for hypotension (38). (Class II) A third retrospective cohort by Musallam et al., observed higher rates of hypotension for patients who had vasopressin weaned before norepinephrine; however, there were similar rates of hospital length of stay and ICU mortality between patients who had vasopressin weaned first and those who had norepinephrine weaned first (39). (Class II) In contrast to these retrospective evaluations, a recent prospective randomized controlled trial, comparing norepinephrine tapering first to vasopressin tapering first in septic shock reported a higher percentage of hypotension in the group that had norepinephrine tapered first (68.4% vs. 22.5%, P<0.001) (40). (Class I)

Although the incidence and duration of vasopressin deficiency remains unclear, tapering vasopressin first is recommended for a number of reasons. First, norepinephrine can be titrated much more easily. Second, vasopressin can have significant effects on cardiac output and splanchnic perfusion. Third, the half-life of norepinephrine is 4-10 times longer than vasopressin which may help avoid rebound hypotension upon drug discontinuation (41,42). Finally, the cost of vasopressin along with the conflicting results of available literature also makes vasopressin as the more attractive agent to taper first upon septic shock resolution.

An additional consideration for vasopressor weaning is the use of midodrine. Midodrine is an oral alpha-1 agonist that can augment MAP through its ability to increase vascular tone. Levine et al., in 2013, was the first to demonstrate midodrine as an effective adjunct to wean IV vasopressors in patients whose clinical condition no longer necessitated critical care level of services but required continuation of low-level vasopressors. This prospective, observational study was performed in 20 surgical ICU patients. They compared vasopressor requirements before and after initiating midodrine and found an increased rate of vasopressor weaning after the initiation of midodrine (43). (Class II) A retrospective study by Rizvi, et al. in 2018, found that 48% of patients on IV vasopressors after 24 hours of midodrine administration were weaned off vasopressors successfully, and there was a decrease in the cumulative vasopressor dose in patients who remained on IV vasopressors after 24 hours of midodrine. This study evaluated safety outcomes and found 15% of patients receiving midodrine developed bradycardia, defined as HR < 50 bpm (44). (Class II)

With results showing the use of midodrine to facilitate faster discontinuation of IV vasopressors, other potential benefits have been proposed, including discontinuation of central venous lines, decrease risk of infection, decrease ICU length of stay, and decrease cost; however, these outcomes have not been demonstrated via a randomized controlled trial (44). Advantages of midodrine include its ease of administration and predictable dose-dependent response with > 90% bioavailability (45). The previous studies mentioned used starting doses of 10mg every 8 hours with the most common dose of 20mg every

8 hours. The most serious adverse effects include supine hypertension and reflex bradycardia (46). A multicenter, randomized, double-blind, placebo-controlled trial is currently underway evaluating midodrine vs. placebo in critically ill patients unable to wean from a single IV vasopressor for > 24 hours (47).

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	0.03 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

Strongest ⟷ Weakest

Alpha Activity

norepinephrine = epinephrine > dopamine > phenylephrine

Beta Activity

epinephrine > dopamine > norepinephrine

Approved 04/19/2011, 09/11/2019

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Last revision date: September 11, 2019

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