Vasoactive Continuous Infusions in Adult Patients – Adult – Inpatient
Clinical Practice Guideline

Table of Contents
A. Executive Summary .............................................................................................................................. 2
B. Scope .................................................................................................................................................... 4
C. Methodology .......................................................................................................................................... 4
D. Introduction ............................................................................................................................................ 4
E. Recommendations ................................................................................................................................ 5
F. UW Implementation ............................................................................................................................. 10
G. References .......................................................................................................................................... 12

CPG Contact:
Name: Philip Trapskin, PharmD, BCPS, Drug Policy Manager
Phone Number: 608-265-0341
Email address: PTrapskin@uwhealth.org

Guideline Author(s):
Updated by Melissa Heim, PharmD and Jeff Fish, PharmD
Anna Krupp, RN, MS
Cindy Gaston, PharmD

Coordinating Team Members:
A. Alexander, CNS, MS; S. Aton, PharmD; J. Fish, PharmD, S. Kraus, MS, RN; M. Murray, CNS, MS; Critical Care Committee

Review Individuals/Bodies:
M. Heim, PharmD; C. Gaston, PharmD; J. Fish, PharmD; A. Krupp RN

Committee Approvals/Dates:
Critical Care Committee – August 2014
Original guideline approved by Pharmacy & Therapeutics Committee: May 2010
Revised guideline: October 2014

Release Date:
October 2014
A. Executive Summary

Guideline Overview

The purpose of this guideline is to provide a framework for the ordering, initiation and titration of specific vasoactive agents in critically ill adults

Practice Recommendations

1. General recommendations regarding vasopressors
   1.1. Treat the underlying cause of cardiovascular instability, hypoxia and acidosis and fluid resuscitate patients to response along with vasopressive agents (Class I, Level A)
   1.2. Consider a second vasopressor when one is not effective (Class I, Level B)

2. Norepinephrine
   2.1. Use norepinephrine as the first line agent in the treatment of hypotension due to septic shock (Class I, Level A)
   2.2. Central line preferred, however, peripheral/intraosseous access may be used when benefit outweighs risks (Class I, Level C)

3. Vasopressin
   3.1. Add vasopressin to norepinephrine in patients with septic shock and insufficient response to norepinephrine with the intent of raising mean arterial pressure to target or decreasing norepinephrine dosage (Class I, Level A)
   3.2. Central line preferred, however, peripheral/intraosseous access may be used when benefit outweighs risks (Class I, Level C)

4. Epinephrine
   4.1. Use epinephrine as the first line agent for patients with anaphylaxis (Class I, Level A)
   4.2. Epinephrine may be added to or substituted for norepinephrine when blood pressure goals are not attained in septic shock (Class 2b, Level B)
   4.3. Central line preferred, however, peripheral/intraosseous access may be used when benefit outweighs risks (Class I, Level C)

5. Dopamine
   5.1. Use dopamine as an alternative vasopressor agent to norepinephrine for the treatment of hypotension in patients with low risk of tachyarrhythmias and absolute or relative bradycardia (Class I, Level A)
   5.2. Do not use “renal dose” dopamine to preserve kidney function due to lack of evidence and potential toxicity (Class III, Level A)
   5.3. Central line preferred, however, peripheral/intraosseous access may be used when benefit outweighs risks (Class I, Level C)

6. Phenylephrine
   6.1. Do not use phenylephrine in the treatment of septic shock unless (Class 3, Level A)
   6.1.1. norepinephrine is associated with serious arrhythmias
   6.1.2. cardiac output is high and blood pressure is persistently low
   6.1.3. used as salvage therapy when combined inotrope/vasopressor drugs and low-dose vasopressin have failed to achieve mean arterial pressure target
   6.2. Use phenylephrine as the recommended agent for treatment of hypotension in patients with aortic stenosis, obstructive hypertrophic cardiomyopathy, or vagal induced hypotension caused by phosphodiesterase inhibitors or nitrates (Class I, Level A)
   6.3. Central line preferred, however, peripheral/intraosseous access may be used when benefit outweighs risks (Class I, Level C)

7. General recommendations regarding inotropes
   7.1. Until definitive therapy (e.g., coronary revascularization or heart transplantation) or resolution of the acute precipitating problem, patients with cardiogenic shock should receive temporary intravenous inotropic support to maintain systemic perfusion and preserve end-organ performance (Class I, Level C)
   7.2. Short-term, continuous intravenous inotropic support is useful in patients with severe systolic dysfunction who present with low blood pressure and significantly depressed cardiac output to maintain systemic perfusion and preserve end-organ performance (Class II, Level B)
8. Dobutamine

8.1. For patients with septic shock, a trial of dobutamine infusion should be administered in the presence of (Class I Level C)

8.1.1. Myocardial dysfunction (elevated cardiac filling pressures and low CO)

8.1.2. Ongoing signs of hypoperfusion despite achieving adequate intravascular volume and adequate mean arterial pressure

8.2. For HF patients who have systolic dysfunction with low cardiac index and systemic hypoperfusion and/or congestion refractory to fluid restriction, salt restriction, and diuretics, dobutamine should be trialed to improve end-organ perfusion (Class II, Level B)

8.3. For patients with low CO associated with myocardial infarction, dobutamine should be administered to improve cardiac output if no symptoms of shock are present (Class II, Level B)

8.4. Central line preferred, however, peripheral/intraosseous access may be used when benefit outweighs risks (Class I, Level C)

9. Milrinone

9.1. For HF patients who have systolic dysfunction with low cardiac index and systemic hypoperfusion and/or congestion refractory to fluid restriction, salt restriction, and diuretics, milrinone should be administered to improve end-organ perfusion (Class II, Level B)

9.2. Dose adjustment of milrinone is required for renal dysfunction (and is contraindicated in patients receiving continuous renal replacement therapy) due risk of elevated milrinone concentrations and life-threatening arrhythmias (Class I, Level B)

9.3. Use of milrinone should be limited in patients with myocardial ischemia (Class IIb, Level B)

10. General recommendations regarding vasodilators and antihypertensives

10.1. Treat hypertensive emergency with a continuous infusion of a short-acting, titratable antihypertensive agent to avoid rapid reduction of BP (Class I, Level A)

10.2. In hypertensive emergency, the immediate goal is to reduce diastolic BP by 10 to 15% or to approximately 110 mm Hg over a period of 30 to 60 minutes. If the patient is stable, systolic BP can be further reduced to 160 mm Hg and DBP can be reduced to 100–110 mm Hg over the ensuing 2–6 hours. A gradual reduction to the patient’s baseline “normal” BP is targeted over the initial 24–48 hours if the patient is stable.

11. Nitroprusside

11.1. Nitroprusside is a recommended vasodilator for patients with acute congestive heart failure or acute pulmonary edema requiring rapid reduction in preload and afterload (Class I, Level A)

11.2. Do not use nitroprusside in patients with hypertension and acute myocardial infarction due to increased risk of mortality (Class III, Level A)

11.3. Administration of nitroprusside with sodium thiosulfate is recommended to prevent cyanide and thiocyanate toxicity, especially in patients with severe renal dysfunction (Class IIb, Level C)

11.4. Monitor for signs of cyanide and thiocyanate toxicity (metabolic acidosis, decreased oxygen saturation, bradycardia, confusion, convulsions) if nitroprusside is used at doses greater than 2 mcg/kg/min or for greater than three days (Class I, Level B)

12. Nitroglycerin

12.1. Nitroglycerin is used to reduce blood pressure in patients with acute congestive heart failure, acute pulmonary edema, acute myocardial infarction, or perioperative hypertension (Class I, Level A)

12.2. Do not administer nitroglycerin within 24-48 hours of phosphodiesterase inhibitors, such as sildenafil, tadalafil, or vardenafil (Class III, Level A)

12.3. Nitroglycerin is not first line therapy for hypertensive urgencies due to side effects and development of tolerance, but can be used as an adjunct agent (Class IIb, Level C)

13. Nicardipine

13.1. Use nicardipine for the treatment of hypertension associated with acute renal failure, acute ischemic stroke/intracerebral bleed, eclampsia/pre-eclampsia, hypertensive encephalopathy or sympathetic crisis/cocaine overdose (Class I, Level A)

13.2. Do not use nicardipine in patients with advanced aortic stenosis (Class III, Level A)
14. Diltiazem
   14.1. Use diltiazem as a continuous IV infusion for rate control in supraventricular tachycardia in patients without concomitant LV systolic dysfunction. (Class II, Level B)
   14.2. Use diltiazem cautiously in treatment of patients with concomitant LV systolic dysfunction because the negative inotropic effect can cause hypotension. (Class IIb, Level B)

15. Esmolol
   15.1. Use esmolol to lower blood pressure in patients with severe post-operative hypertension when there is increased CO, BP, and heart rate. (Class II, Level B)
   15.2. Use caution when administering this drug to patients previously on β-blocker therapy or with HF since these patients may be predisposed to bradycardia or precipitation of acute heart failure. (Class II, Level B)
   15.3. Loading doses should be administered with initiation of infusion and rate increases due to a very short duration of action. (Class II, Level B)

16. Labetalol
   16.1. Use labetalol continuous infusion for pregnancy-induced hypertensive crisis or uncontrolled hypertension. (Class II, Level B)
   16.2. Do not use labetalol in patients with reactive airway disease or chronic obstructive pulmonary disease or in patients with second- or third-degree atrioventricular block or bradycardia. (Class III, Level A)
   16.3. Labetalol can be administered by multiple loading doses until desired BP is attained or as a loading dose followed by a continuous infusion. (Class II, Level B)

Companion Documents
Vasoactive Continuous Infusion Titration Protocol

Pertinent UW Health Policies & Procedures
Guideline for Non-chemotherapeutic agents: Prevention and Treatment of Chemical Phlebitis and Extravasation of Peripherally Administered Non-chemotherapeutic Agents
High Alert Medication Administration
UWHC Guidelines for IV Administration of Formulary Medications in Adults

Patient Resources
None

B. Scope
The purpose of this guideline is to provide a framework for the ordering, initiation and titration of specific vasoactive agents in critically ill adults

Target Population: Adult patients receiving vasoactive continuous infusions

C. Methodology
A modified Grading of Recommendations Assessment, Development and Evaluation (GRADE) developed by the American Heart Association and American College of Cardiology has been used to assess the Quality and Strength of the Evidence in this Clinical Practice Guideline (Appendix 1).

D. Introduction
Vasopressor, inotropic, vasodilatory and antihypertensive agents serve a vital role in supporting the critical care patient and prompt titration of these agents is essential. Many vasoactive medications are administered by continuous infusion with dose titration based on heart rate (chronotropy), myocardial contractility (inotropy), and/or vascular resistance (vasoconstriction or vasodilatation). The rate and frequency of dose titration is dependent upon the patient's individual hemodynamic parameters and response to therapy. Prompt titration is best accomplished by the bedside nurse with continuous monitoring to parameters specified in medication orders by the physician or other health care provider (Table 1, Table 2).
E. Recommendations

1. General recommendations regarding vasopressors

1.1. Treat the underlying cause of cardiovascular instability, hypoxia and acidosis and fluid resuscitate patients to response along with vasoactive agents \(^2,10\) (Class I, Level A)

1.1.1. The etiology of shock can be sepsis, volume loss, brain and spinal cord injury, anaphylaxis or a combination of factors. The first step in treatment is identification and treatment of the underlying cause and fluid resuscitation. Without sufficient fluid resuscitation, vasopressors are ineffective and can even be detrimental. \(^1,10\)

1.2. Consider a second vasopressor when one is not effective \(^10,11\) (Class I, Level B)

1.2.1. Vasoactive medications such as dopamine, norepinephrine, epinephrine, phenylephrine, and vasopressin are employed to treat circulatory shock, which is generally defined as the inability to supply sufficient oxygen to tissues due to decreased vascular perfusion. In general, vasopressors maintain tissue perfusion through an increase in mean arterial pressure and cardiac output (CO). The preferred pressor for a given patient must be determined by patient physiology, cause of shock and patient response. When high doses of one vasoactive agent are insufficient to maintain blood pressure (BP), then the addition of another vasopressor with a different mechanism of action can improve BP response. \(^10,11\) These agents are standard treatment in intensive care and emergency room settings but administration of vasopressors is not without risks, which include induction or exacerbation of tachyarrhythmias and tissue necrosis.

2. Norepinephrine

2.1. Use norepinephrine as the first line agent in the treatment of hypotension due to septic shock \(^10,11,12,13\) (Class I, Level A)

2.1.1. Norepinephrine is a first line vasopressor with potent \(\alpha\)-receptor and moderate \(\beta_1\) and \(\beta_2\) receptor agonist activity. It causes an increase in systolic, diastolic and pulse pressures, but can increase or decrease CO depending upon SVR, ejection fraction and reflex response. Norepinephrine is a first line agent in the treatment of hypotension related to septic shock and preservation of tissue perfusion has been demonstrated. \(^10,12,13\)

2.2. Central line preferred, however, peripheral/intraosseous access may be used when benefit outweighs risks \(^14,15\) (Class I, Level C)

2.2.1. Central line administration is preferred since extravasation results in tissue necrosis and sloughing. \(^14,15\) (See Guideline for Non-chemotherapeutic agents: Prevention and Treatment of Chemical Phlebitis and Extravasation of Peripherally Administered Non-chemotherapeutic Agents) Extravasation should be treated immediately with subcutaneous administration of diluted phenolamine, an \(\alpha\)-receptor antagonist. \(^14,15\) Ischemia of the hepatic-splanchnic tissue with subsequent end organ damage is also associated with norepinephrine administration. \(^1,13\)

3. Vasopressin

3.1. Add vasopressin to norepinephrine in patients with septic shock and insufficient response to norepinephrine with the intent of raising mean arterial pressure to target or decreasing norepinephrine dosage \(^4,10\) (Class I, Level A)

3.2. Central line preferred, however, peripheral/intraosseous access may be used when benefit outweighs risks \(^14,15\) (Class I, Level C)

3.2.1. Extravasation should be treated immediately with subcutaneous administration of diluted phenolamine, an \(\alpha\)-receptor antagonist. \(^14,15\)

3.2.2. Vasopressin or “antidiuretic hormone” is released from the pituitary gland in response to increased plasma osmolality, hypotension, pain and hypoxia causing direct stimulation of smooth muscle V1-receptors to cause peripheral vasoconstriction. \(^1\) During early shock, a patient’s vasopressin concentration increases significantly, but as shock progresses it declines to subnormal levels. Supplemental administration of vasopressin via continuous infusion has been demonstrated to be effective in norepinephrine resistant hypotension. \(^10\) The addition of low doses of vasopressin is recommended in septic shock patients with an insufficient response to norepinephrine. \(^5,10\) Acidosis and hypoxia have minimal impact on vasoconstriction mediated by vasopressin, unlike
catecholamines. Doses greater than 0.04 units per minute are associated with coronary vasoconstriction, peripheral necrosis, and splanchnic ischemia.

4. Epinephrine
4.1. Use epinephrine as the first line agent for patients with anaphylaxis (Class I, Level A)
4.2. Epinephrine may be added to or substituted for norepinephrine when blood pressure goals are not attained in septic shock (Class 2b, Level B)
4.3. Central line preferred, however, peripheral/intraosseous access may be used when benefit outweighs risks (Class I, Level C)
4.3.1. Extravasation should be treated immediately with subcutaneous administration of diluted phentolamine, an α-receptor antagonist.
4.3.2. Epinephrine is an alternative vasopressor with strong affinity for α, β1 and β2 receptors. It also exhibits potent positive inotropic and chronotropic effects in addition to peripheral vasoconstriction. Through direct pulmonary vasoconstriction and increased pulmonary blood flow, arterial and venous pulmonary pressures are increased. Epinephrine is recommended as an alternative agent for the treatment of septic shock in patients with an inadequate response to norepinephrine. High doses can provoke dysrhythmias, myocardial ischemia, and profound splanchnic vasoconstriction. Similar to norepinephrine, epinephrine is preferably administered through a central line since extravasation can cause severe tissue necrosis.

5. Dopamine
5.1. Use dopamine as an alternative vasopressor agent to norepinephrine for the treatment of hypotension in patients with low risk of tachyarrhythmias and absolute or relative bradycardia (Class I, Level A)
5.1.1. Dopamine may cause more tachycardia and may be more arrhythmogenic than norepinephrine.
5.2. Do not use “renal dose” dopamine to preserve kidney function due to lack of evidence and potential toxicity (Class III, Level A)
5.2.1. Dopamine also has a direct natriuretic effect, and for years “renal dose” dopamine was used in an effort to preserve kidney function, but this is no longer recommended due to lack of evidence and potential toxicity.
5.2.2. Extravasation of dopamine results in severe tissue necrosis and should be treated immediately with subcutaneous administration of diluted phentolamine, an α-receptor antagonist.
5.2.3. Dopamine is an endogenous neurotransmitter that stimulates both the β and α-receptors, causing vasoconstriction and raising both BP and heart rate (HR). It is an immediate precursor to norepinephrine and exhibits a dose dependent physiological effect. At low doses of 0.5 to 3 mcg/kg/min dopamine causes vasodilation in the coronary, renal mesenteric and cerebral beds. This effect increases nearby blood flow, but can result in tachycardia and hypotension in volume depleted patients. Intermediate doses of dopamine (approximately 3 to 10 mcg/kg/min) promote norepinephrine release and inhibit reuptake resulting in increased cardiac contractility and chronotropy. Doses above 10 mcg/kg/min of dopamine cause the release of norepinephrine from the nerve terminals resulting in vasoconstriction and an increase in systemic vascular resistance (SVR). In patients the pharmacological effects of various dose ranges overlaps.

6. Phenylephrine
6.1. Do not use phenylephrine in the treatment of septic shock unless (Class 3, Level A)
6.1.1. Norepinephrine is associated with serious arrhythmias
6.1.2. Cardiac output is high and blood pressure is persistently low
6.1.3. Used as salvage therapy when combined inotrope/vasopressor drugs and low-dose vasopressin have failed to achieve mean arterial pressure target
6.2. Use phenylephrine as the recommended agent for treatment of hypotension in patients with aortic stenosis, obstructive hypertrophic cardiomyopathy, or vagal induced hypotension caused by phosphodiesterase inhibitors or nitrates (Class I, Level A)
6.3. Central line preferred, however, peripheral/intraosseous access may be used when benefit outweighs risks.\textsuperscript{14,15} (Class IIb, Level C)

6.3.1. Extravasation should be treated immediately with subcutaneous administration of diluted phentolamine, an $\alpha$-receptor antagonist.\textsuperscript{14,15}

6.3.2. Phenylephrine exhibits potent $\alpha$ activity with virtually no $\beta$ activity, resulting in venous and arterial vasoconstriction. Hemodynamically this brings about an increase in SVR with variable effects on CO. These properties are beneficial when treating hypotension in patients with aortic stenosis, obstructive hypertrophic cardiomyopathy or vagal induced hypotension caused by phosphodiesterase inhibitors or nitrates.\textsuperscript{2} By increasing systolic, diastolic and mean arterial blood pressures, phenylephrine can cause reflex bradycardia and is not indicated for use as a sole agent in the treatment of hypotension associated with septic shock or anaphylaxis.\textsuperscript{3,10} Unlike other vasopressors, it can be administered via rapid bolus for acute, severe hypotension or via a continuous infusion.

7. General recommendations regarding inotropes

7.1. Until definitive therapy (e.g., coronary revascularization or heart transplantation) or resolution of the acute precipitating problem, patients with cardiogenic shock should receive temporary intravenous inotropic support to maintain systemic perfusion and preserve end-organ performance.\textsuperscript{5} (Class I, Level C)

7.2. Short-term, continuous intravenous inotropic support is useful in patients with severe systolic dysfunction who present with low blood pressure and significantly depressed cardiac output to maintain systemic perfusion and preserve end-organ performance.\textsuperscript{5,20-22} (Class II, Level B)

7.2.1. Dobutamine and milrinone are the most commonly used inotropes for low output cardiac conditions associated with increased ventricular filling pressure. The first line of therapy for acute heart failure (HF) is fluid and salt restriction, followed by diuretics and vasodilators.\textsuperscript{5} If response is insufficient and left ventricular filling pressure is elevated, then inotropes can be considered for symptomatic relief and improved end organ perfusion. Patients on these agents must be closely monitored for induction or exacerbation of tachyarrhythmias and hypotension. A large retrospective trial comparing dobutamine and milrinone in HF patients demonstrated no difference in hospital mortality or hospital complications.\textsuperscript{37}

8. Dobutamine

8.1. For patients with septic shock, a trial of dobutamine infusion should be administered in the presence of\textsuperscript{10,23} (Class I Level C)

8.1.1. Myocardial dysfunction (elevated cardiac filling pressures and low CO)

8.1.2. Ongoing signs of hypoperfusion despite achieving adequate intravascular volume and adequate mean arterial pressure

8.2. For HF patients who have systolic dysfunction with low cardiac index and systemic hypoperfusion and/or congestion refractory to fluid restriction, salt restriction, and diuretics, dobutamine should be trialed to improve end-organ perfusion.\textsuperscript{5,20-22} (Class II, Level B)

8.3. For patients with low CO associated with myocardial infarction, dobutamine should be administered to improve cardiac output if no symptoms of shock are present\textsuperscript{6} (Class II, Level B)

8.4. Central line preferred, however, peripheral/intraosseous access may be used when benefit outweighs risks.\textsuperscript{14,15} (Class I, Level C)

8.4.1. Extravasation should be treated immediately with subcutaneous administration of diluted phentolamine, an $\alpha$-receptor antagonist.\textsuperscript{14,15}

8.4.2. Dobutamine stimulates $\beta_1$ and $\beta_2$-receptors causing a chronotropic and strong inotropic effect resulting in increased CO. At low doses it exhibits a mild vasodilatory effect and BP can either decrease or increase when initiating therapy. Dobutamine is the first line inotrope in septic patients with decreased CO with adequate BP.\textsuperscript{10} It is also recommended to help improve HF symptoms and improve end-organ perfusion, but not mortality, in patients with HF with systolic dysfunction and low cardiac index who are refractory to other therapies and are suffering from end-organ hypoperfusion and/or congestion.\textsuperscript{5,20-22} Tachyphylaxis has been documented after several days of treatment and patients on $\beta$ blockers can exhibit an attenuated response. The most common adverse effects associated with the administration of dobutamine include an increase in
myocardial oxygen consumption and exacerbation of ventricular arrhythmias.\(^{37}\) The American College of Cardiology/American Heart Association Guidelines for the Management of ST-Elevation Myocardial Infarction recommend dobutamine for low CO associated with myocardial infarction if no symptoms of shock are present.\(^{5}\)

9. Milrinone

9.1. For HF patients who have systolic dysfunction with low cardiac index and systemic hypoperfusion and/or congestion refractory to fluid restriction, salt restriction, and diuretics, milrinone should be administered to improve end-organ perfusion\(^{5,20-22}\) (Class II, Level B)

9.2. Dose adjustment of milrinone is required for renal dysfunction (and is contraindicated in patients receiving continuous renal replacement therapy) due risk of elevated milrinone concentrations and life-threatening arrhythmias\(^{24-26}\) (Class I, Level B)

9.3. Use of milrinone should be limited in patients with myocardial ischemia\(^{21}\) (Class IIb, Level B)

9.3.1. Similar to dobutamine, milrinone increases myocardial contractility and causes peripheral vasodilation, resulting in improved hemodynamics in patients with acute HF or low left ventricular output.\(^{5,20-22}\) It also decreases pulmonary vascular resistance and SVR. Unlike dobutamine, it does not have β or chronotropic effects, but acts by inhibiting the breakdown of intracellular cyclic adenosine monophosphate (cAMP) and can be useful in patients with down-regulated adrenergic receptors such as HF patients. Since the half-life is longer for milrinone than dobutamine, the time of onset and to reach steady state is longer than dobutamine (Table 2). The longer half-life of milrinone and renal elimination necessitate dose adjustment for renal dysfunction.\(^{24-26}\) Milrinone is contraindicated in patients receiving continuous renal replacement therapy. Hypotension and dysrhythmias are the most common adverse events and some clinicians omit a loading dose in an effort to minimize these events. Milrinone should be avoided in patients with myocardial ischemia since it can increase morbidity and mortality in this patient population.\(^{21}\)

10. General recommendations regarding vasodilators and antihypertensives

10.1. Treat hypertensive emergency with a continuous infusion of a short-acting, titratable antihypertensive agent to avoid rapid reduction of BP\(^{7-9}\) (Class I, Level A)

10.2. In hypertensive emergency, the immediate goal is to reduce diastolic BP by 10 to 15% or to approximately 110 mm Hg over a period of 30 to 60 minutes. If the patient is stable, systolic BP can be further reduced to 160 mm Hg and DBP can be reduced to 100–110 mm Hg over the ensuing 2–6 hours. A gradual reduction to the patient’s baseline “normal” BP is targeted over the initial 24–48 hours if the patient is stable.\(^{7,9}\) (Class I, Level A)

10.2.1. Continuous infusions of vasodilators also require close titration when used for the treatment of HF or hypertensive emergencies and when BP must be decreased in a controlled and predictable manner.\(^{5,7,9}\)

10.2.2. Patient and drug specific characteristics direct selection of the appropriate agent for treatment. Patients with a hypertensive emergency commonly exhibit symptoms of headache, shortness of breath, epistaxis or severe anxiety and can suffer end organ damage if BP is not controlled. Dangerous blood pressures can also be encountered during cardiovascular surgery, neurosurgery, renal transplantation and trauma surgery.\(^{7,9}\) Due to increased sympathetic tone and vascular resistance, the early post-operative period can also be associated with high blood pressures. A controlled decrease in blood pressure by titration of continuous infusions of short acting agents is often the most appropriate method of treatment in these patients. Vasodilating agents such as nitroglycerin, nitroprusside, and nicardipine are often used for hypertensive treatment and improve preload and/or afterload.

11. Nitroprusside

11.1. Nitroprusside is a recommended vasodilator for patients with acute congestive heart failure or acute pulmonary edema requiring rapid reduction in preload and afterload\(^{5,7,9}\) (Class I, Level A)

11.2. Do not use nitroprusside in patients with hypertension and acute myocardial infarction due to increased risk of mortality\(^{7,9,27}\) (Class III, Level A)
11.3. Administration of nitroprusside with sodium thiosulfate is recommended to prevent cyanide and thiocyanate toxicity, especially in patients with severe renal dysfunction\textsuperscript{7-9,28} (Class IIb, Level C)

11.4. Monitor for signs of cyanide and thiocyanate toxicity (metabolic acidosis, decreased oxygen saturation, bradycardia, confusion, convulsions) if nitroprusside is used at doses greater than 2 mcg/kg/min or for greater than three days\textsuperscript{7-9,28} (Class I, Level B)

11.4.1. Cyanide is a byproduct of nitroprusside metabolism, which is hepatically metabolized to thiocyanate. Thiosulfate is required for this conversion. Thiocyanate is 100 times less toxic than cyanide and is renally excreted. Cyanide can accumulate to cause cyanide toxicity, particularly in patients with hepatic and/or renal insufficiency. Patients with renal or hepatic dysfunction and on high doses of nitroprusside or receiving treatment for more than three days are at risk for cyanide or thiocyanate toxicity and must be monitored closely. Simultaneous administration of nitroprusside and sodium thiosulfate can prevent cyanide toxicity by enhancing conversion to a less toxic thiocyanate.\textsuperscript{28}

11.4.2. Nitroprusside acts on arteriolar and venous smooth muscle to reduce both preload and afterload, making it useful in patients with acute congestive heart failure and/or acute pulmonary edema. It causes a prompt reduction in BP and either an increase or no change in CO. Unpredictable shifts in BP can occur if patients are hypovolemic or exhibit diastolic dysfunction.\textsuperscript{7-9}

12. Nitroglycerin

12.1. Nitroglycerin is used to reduce blood pressure in patients with acute congestive heart failure, acute pulmonary edema, acute myocardial infarction, or perioperative hypertension\textsuperscript{5-9} (Class I, Level A)

12.2. Do not administer nitroglycerin within 24-48 hours of phosphodiesterase inhibitors, such as sildenafil, tadalafil, or vardenafil\textsuperscript{7-9} (Class III, Level A)

12.2.1. Nitroglycerin dilates primarily the venous system to decrease preload, but high doses also affect arterial smooth muscle. In volume-depleted patients, nitroglycerin may cause reduced CO, reflex tachycardia, and reduced cerebral and renal perfusion. It is recommended by the Heart Failure Society of American in the treatment of acute HF in combination with salt and fluid restriction.\textsuperscript{5}

12.2.2. The most common side effect of nitroglycerin administration is headache. Methemoglobinemia is a rare side effect caused by prolonged nitroglycerin administration.

12.3. Nitroglycerin is not first line therapy for hypertensive urgencies due to side effects and development of tolerance, but can be used as an adjunct agent. (Class IIb, Level C)

13. Nicardipine

13.1. Use nicardipine for the treatment of hypertension associated with acute renal failure, acute ischemic stroke/intracerebral bleed, eclampsia/pre-eclampsia, hypertensive encephalopathy or sympathetic crisis/cocaine overdose\textsuperscript{7-9,28} (Class I, Level A)

13.2. Do not use nicardipine in patients with advanced aortic stenosis\textsuperscript{7-9,30-32} (Class III, Level A)

13.2.1. Nicardipine is a dihydropyridine calcium channel antagonist with high vascular selectivity used for the treatment of hypertension associated with acute myocardial ischemia, acute renal failure, acute ischemic stroke/intracerebral bleed, eclampsia/pre-eclampsia, hypertensive encephalopathy and sympathetic crisis/cocaine overdose.\textsuperscript{7-9,28}

14. Diltiazem

14.1. Use diltiazem as a continuous IV infusion for rate control in supraventricular tachycardia in patients without concomitant LV systolic dysfunction\textsuperscript{33-35} (Class II, Level B)

14.1.1. Diltiazem is a non-dihydropyridine calcium channel blocker which causes a decrease in conductivity, myocardial contractility and peripheral vascular resistance. It
is indicated for rate control for atrial arrhythmias, hypertension and during non-cardiac surgery to reduce myocardial ischemia and supraventricular tachycardia. Parenteral diltiazem is beneficial for rapid rate control, but not for cardioversion of atrial fibrillation to normal sinus rhythm. Diltiazem is preferred over β-blockers for rate control in patients with chronic obstructive pulmonary disease.

14.2. Use diltiazem cautiously in treatment of patients with concomitant LV systolic dysfunction because the negative inotropic effect can cause hypotension. (Class IIb, Level B)

15. Esmolol

15.1. Use esmolol to lower blood pressure in patients with severe post-operative hypertension when there is increased CO, BP, and heart rate (Class II, Level B)

15.1.1. Esmolol is a short-acting cardioselective β1-antagonist that decreases arterial pressure by decreasing heart rate and myocardial contractility. It is also useful in the treatment of patients with hypertensive crisis with acute myocardial ischemia, acute aortic dissection, and peri-operative hypertension. Esmolol is eliminated via plasma esterases and the antihypertensive effects of esmolol will resolve within 20 minutes of discontinuation of infusion.

15.2. Use caution when administering this drug to patients previously on β-blocker therapy or with HF since these patients may be predisposed to bradycardia or precipitation of acute heart failure. (Class II, Level B)

15.3. Loading doses should be administered with initiation of infusion and rate increases due to a very short duration of action. (Class II, Level B)

16. Labetalol

16.1. Use labetalol continuous infusion for pregnancy-induced hypertensive crisis or uncontrolled hypertension (Class II, Level B)

16.2. Do not use labetalol in patients with reactive airway disease or chronic obstructive pulmonary disease or in patients with second- or third-degree atrioventricular block or bradycardia (Class III, Level A)

16.2.1. Labetalol is a combined selective α1 and nonselective β-antagonist that reduces systemic vascular resistance and either maintains or minimally decreases HR. The α to β activity is 1:7 when given intravenously and allows for decreased SVR without a decrease in total peripheral blood flow. Unlike esmolol, labetalol maintains CO and reduces SVR without decreasing total peripheral, cerebral, renal or coronary blood flow. The antihypertensive duration of labetalol will occur for 2-4 hours after drug discontinuation.

16.3. Labetalol can be administered by multiple loading doses until desired BP is attained or as a loading dose followed by a continuous infusion. (Class II, Level B)

17. General recommendations for titration of vasoactive therapies (Class II, Level B)

17.1. The rate and frequency of dose titration is dependent upon the patient's individual hemodynamic parameters, patient's response to therapy and clinical status, as assessed by the nurse.

17.2. The lowest effective dose of the vasoactive agent ordered that achieves the stated objective response is utilized.

17.3. Vasoactive infusions are weaned off as indicated in the titration columns of Table 1.

18. General recommendations for monitoring and documentation of vasoactive agents (Class II, Level B)

18.1. Vital signs are monitored and documented hourly and with each rate change, unless patient requires active titration, and then the patient will have continuous monitoring and vital signs and rate will be documented at least every 15 minutes.

18.2. An arterial line for continuous blood pressure monitoring is recommended for all patients requiring dose titration per protocol.

F. UW Implementation

Benefits/Harms of Implementation
Benefits of implementation include consistent dosing and use of vasoactive continuous infusions. Harms of implementation include risk of extravasation.

**Qualifying Statements**

Many of the recommendations included in the guideline include recommendations from national guidelines or expert opinion as much of the literature has studied impact of vasoactive medications on symptoms and not on outcomes. The recommendations in this guideline may change if more literature becomes available.

**Implementation Tools/Plan**

1. Implemented in conjunction with the Vasoactive Continuous Infusion Titration Protocol
2. Administration of vasoactive agents
   1. High alert medications require double-check (as specified in policy UWHC Policy 8.33) and must be performed directly prior to administration, with each bag change, at shift change, upon patient transfer, or when IV pump programming is outside of the established IV pump decision support software limits (Alaris Guardrails®).
   2. Upon initiation of each continuous vasoactive infusion, the compatibility of simultaneous infusions will be verified by the RN and/or pharmacist.
   3. Vasoactive continuous infusions will be infused using stopcock connectors, and will not be "y-sited" into infusion ports on the IV tubing.
   4. No continuous infusion vasoactive agents will be infused through CVP port, except when no other lines or ports are available and a vasoactive infusion is required for emergency administration. The amount of intermittent medication administration through the CVP port should be limited to avoid bolus drug administration with bolus cardiac output monitoring.
   5. Continuous infusions of vasoactive medications through the PA port of the pulmonary artery catheter can put patients at risk for pulmonary hypertension and must be approved by the provider.
   6. New IV tubing will be primed when there is a change in drug concentration.
   7. All infusions will be administered as designated in the UWHC Guidelines for IV Administration of Formulary Medications in Adults
3. Titration of vasoactive therapies
   1. If the vasoactive agent reaches the “First Notification Value,” a prescribing provider (identified as physician, advanced practice nurse prescriber or physician assistant) is notified for consideration of additional treatments or alternate agent(s).
   2. For agents without an absolute maximum dose, if the dose reaches the “Second Notification Value,” the physician is notified for consideration of additional treatments or alternate agent(s) before further titration of the current agent occurs.
   3. If the dose of the vasoactive agent reaches the “Second Notification Value,” a physician order is required to continue therapy at higher doses.
   4. Providers enter nursing communication orders to initiate weaning of vasoactive infusions.
   5. When titrating multiple vasoactive agents, providers clarify the sequence of medication titration through nursing communication orders (e.g., order of titration for weaning off for multiple agents).
   6. Initiation of weaning vasoactive mediation(s) occurs after a provider enters a nursing communication order for weaning of a specific agent with specific parameters (such as mean arterial pressure or cardiac index).
4. Monitoring and documentation of vasoactive agents
   1. The nurse will record each rate adjustment in the IV/IV MAR. If the patient requires frequent titration, the patient will have continuous monitoring and the current rate will be documented at least every 15 minutes.
   2. Notes will be documented in the electronic medical record by the RN after each provider notification for “First Notification Value” and the “Second Notification Value.”

**Disclaimer**

Copyright © 2014 University of Wisconsin Hospitals and Clinics Authority
Contact: CCKM@uwhealth.org  Last Revised: 10/2014
This Clinical Practice Guideline provides an evidence-based approach for the use of vasoactive agents. It is understood that occasionally patients will not match the conditions considered in the guideline.

G. References


# Appendix 1. Quality of Evidence and Strength of Recommendation Grading Matrix

## Size of Treatment Effect

<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
<th>Evidence</th>
<th>Recommendation</th>
<th>Additional Information</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Class I</strong></td>
<td>Benefit &gt;&gt;&gt; Risk</td>
<td>Procedure/Treatment SHOULD be performed/administered</td>
<td>Recommendation for treatment</td>
<td>Additional studies with broad objectives needed; additional registry data would be helpful</td>
</tr>
<tr>
<td><strong>Class Ia</strong></td>
<td>Benefit &gt;&gt;&gt; Risk</td>
<td>Additional studies with focused objectives needed</td>
<td>Recommendation is reasonable to perform procedure/administer treatment</td>
<td>Since it is not helpful and may be harmful</td>
</tr>
<tr>
<td><strong>Class Ib</strong></td>
<td>Benefit ≥ Risk</td>
<td>Procedure/Treatment may be considered</td>
<td>Recommendation’s usefulness/efficacy less well established</td>
<td>Greater conflicting evidence from multiple randomized trials or meta-analyses</td>
</tr>
<tr>
<td><strong>Class III</strong></td>
<td>Risk ≥ Benefit</td>
<td>Procedure/Treatment should not be performed/administered</td>
<td>Recommendation that procedure or treatment is not useful/effective and may be harmful</td>
<td>Sufficient evidence from multiple randomized trials or meta-analyses</td>
</tr>
</tbody>
</table>

## Estimate of Certainty (Precision) of Treatment Effect

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
<th>Evidence</th>
<th>Recommendation</th>
<th>Additional Information</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Level A</strong></td>
<td>Multiple populations evaluated*</td>
<td>Data derived from multiple randomized clinical trials or meta-analyses</td>
<td>Recommendation that procedure or treatment is useful/effective</td>
<td>Evidence from multiple randomized trials or meta-analyses</td>
</tr>
<tr>
<td><strong>Level B</strong></td>
<td>Limited populations evaluated*</td>
<td>Data derived from a single randomized trial or nonrandomized studies</td>
<td>Recommendation that procedure or treatment is useful/effective</td>
<td>Evidence from single randomized trial or nonrandomized studies</td>
</tr>
<tr>
<td><strong>Level C</strong></td>
<td>Very limited populations evaluated*</td>
<td>Only consensus opinion of experts, case studies, or standard of care</td>
<td>Recommendation that procedure or treatment is useful/effective</td>
<td>Only diverging expert opinion, case studies, or standard of care</td>
</tr>
</tbody>
</table>

### Suggested phrases for writing recommendations*

- Suggested phrases for writing recommendations:
  - Should
  - Is recommended
  - Is indicated
  - Is useful/effective/beneficial
  - May/might be considered
  - Is probably recommended
  - Is not recommended
  - Is not indicated
  - Should not
  - Is not useful/effective/beneficial
  - May/might be reasonable
  - Usefulness/effectiveness is unknown/unclear/uncertain or not well established
  - May/might be harmful

---

Copyright © 2014 University of Wisconsin Hospitals and Clinics Authority
Contact: CCKM@uwhealth.org
Last Revised: 10/2014
<table>
<thead>
<tr>
<th>Drug</th>
<th>Typical Dose Range</th>
<th>Typical Starting Dose</th>
<th>Dose Titration Increment</th>
<th>Rate of Titration</th>
<th>First Notification Value</th>
<th>Second Notification Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diltiazem</td>
<td>1-15 mg/hr</td>
<td>2.5-5 mg/hr</td>
<td>2.5 mg/hr</td>
<td>30-60 min</td>
<td>15 mg/hr</td>
<td>20 mg/hr</td>
</tr>
<tr>
<td>Dobutamine</td>
<td>2-20 mcg/kg/min</td>
<td>2 mcg/kg/min</td>
<td>2.5 mcg/kg/min</td>
<td>5-15 min</td>
<td>10 mcg/kg/min</td>
<td>15 mcg/kg/min</td>
</tr>
<tr>
<td>Dopamine</td>
<td>2-20 mcg/kg/min</td>
<td>2-5 mcg/kg/min</td>
<td>1-5 mcg/kg/min</td>
<td>1-15 min</td>
<td>15 mcg/kg/min</td>
<td>20 mcg/kg/min</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>0.01 mcg/kg/min</td>
<td>0.01-0.05 mcg/kg/min</td>
<td>0.01-0.05 mcg/kg/min</td>
<td>1-15 min</td>
<td>0.4 mcg/kg/min</td>
<td>2 mcg/kg/min</td>
</tr>
<tr>
<td>Esmolol</td>
<td>50-300 mcg/kg/min</td>
<td>25-50 mcg/kg/min</td>
<td>50 mcg/kg/min</td>
<td>5-20 min</td>
<td>250 mcg/kg/min</td>
<td>300 mcg/kg/min</td>
</tr>
<tr>
<td>Labetalol</td>
<td>10-180 mg/hr</td>
<td>10 mg/hr</td>
<td>10 mg/hr</td>
<td>10-30 min</td>
<td>120 mg/hr</td>
<td>180 mg/hr</td>
</tr>
<tr>
<td>Milrinone</td>
<td>0.375-0.75 mcg/kg/min</td>
<td>0.375 mcg/kg/min</td>
<td>0.125 mcg/kg/min</td>
<td>15-30 min</td>
<td>0.5 mcg/kg/min</td>
<td>0.75 mcg/kg/min</td>
</tr>
<tr>
<td>Nicardipine</td>
<td>5-15 mg/hr</td>
<td>2.5-5 mg/hr</td>
<td>2.5 mg/hr</td>
<td>15-30 min</td>
<td>10 mg/hr</td>
<td>15 mg/hr</td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td>5-200 mcg/min</td>
<td>5-10 mcg/min</td>
<td>5-20 mcg/min</td>
<td>5-15 min</td>
<td>200 mcg/min</td>
<td>300 mcg/min</td>
</tr>
<tr>
<td>Nitroglycerin (mcg/kg/min)</td>
<td>0.2-3 mcg/kg/min</td>
<td>0.2 mcg/kg/min</td>
<td>0.2-0.5 mcg/kg/min</td>
<td>5-15 min</td>
<td>2 mcg/kg/min</td>
<td>3 mcg/kg/min</td>
</tr>
<tr>
<td>Nitroprusside</td>
<td>0.2-4 mcg/kg/min</td>
<td>0.2 mcg/kg/min</td>
<td>0.25-0.5 mcg/kg/min</td>
<td>1-15 min</td>
<td>4 mcg/kg/min</td>
<td>10 mcg/kg/min</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>0.01 mcg/kg/min</td>
<td>0.01-0.05 mcg/kg/min</td>
<td>0.01-0.05 mcg/kg/min</td>
<td>1-15 min</td>
<td>0.4 mcg/kg/min</td>
<td>2 mcg/kg/min</td>
</tr>
<tr>
<td>Phenylephrine</td>
<td>0.25 mcg/kg/min</td>
<td>0.25-0.5 mcg/kg/min</td>
<td>0.25 mcg/kg/min</td>
<td>1-15 min</td>
<td>3 mcg/kg/min</td>
<td>5 mcg/kg/min</td>
</tr>
<tr>
<td>Vasopressin (septic shock)</td>
<td>0.01-0.04 units/min</td>
<td>0.04 units/min</td>
<td>Do not increase rate without MD Order. Wean off by 0.01 unit/min</td>
<td>30-60 min</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Drug</td>
<td>Onset</td>
<td>Duration</td>
<td>T&lt;sub&gt;1/2&lt;/sub&gt;</td>
<td>Primary Route of Elimination</td>
<td>Noteworthy Adverse Effects/Comments</td>
<td></td>
</tr>
<tr>
<td>---------------</td>
<td>-------</td>
<td>----------</td>
<td>----------------</td>
<td>-------------------------------</td>
<td>------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Diltiazem</td>
<td>3 min</td>
<td>1-3 hr</td>
<td>3-6.6 hr</td>
<td>hepatic</td>
<td>AV block, bradycardia, CHF exacerbation</td>
<td></td>
</tr>
<tr>
<td>Dobutamine</td>
<td>2 min</td>
<td>10 min</td>
<td>2 min</td>
<td>hepatic</td>
<td>Hypotension, dysrhythmias</td>
<td></td>
</tr>
<tr>
<td>Dopamine</td>
<td>5 min</td>
<td>10 min</td>
<td>2 min</td>
<td>renal</td>
<td>Tissue necrosis with extravasation, dysrhythmias</td>
<td></td>
</tr>
<tr>
<td>Esmolol</td>
<td>1-2 min</td>
<td>10-30 min</td>
<td>9 min</td>
<td>hydrolyzed by RBC esterases</td>
<td>Infusion site reactions, confusion, bradycardia</td>
<td></td>
</tr>
<tr>
<td>Epinephrine</td>
<td>1-2 min</td>
<td>5-10 min</td>
<td>2 min</td>
<td>hepatic</td>
<td>Dysrhythmias, tissue necrosis, ischemia</td>
<td></td>
</tr>
<tr>
<td>Labetalol</td>
<td>5-15 min</td>
<td>2-4 hr</td>
<td>5.5 hr</td>
<td>hepatic</td>
<td>Hypotension, bradycardia</td>
<td></td>
</tr>
<tr>
<td>Milrinone</td>
<td>5-15 min</td>
<td>3-5 hr</td>
<td>1.5-2 hr</td>
<td>renal</td>
<td>Hypotension, dysrhythmias, nausea, vomiting. Clinical response may last up to 24 hours in certain patients</td>
<td></td>
</tr>
<tr>
<td>Nicardipine</td>
<td>10 min</td>
<td>2 hr</td>
<td>2-4 hr</td>
<td>hepatic</td>
<td>Peripheral edema, tachyarrhythm</td>
<td></td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td>5-10 min</td>
<td>10-20 min</td>
<td>1-3 min</td>
<td>hepatic</td>
<td>Hypotension, reflex tachycardia if volume depleted</td>
<td></td>
</tr>
<tr>
<td>Nitroprusside</td>
<td>1 min</td>
<td>1-2 hr</td>
<td>3-5 min</td>
<td>hepatic</td>
<td>Hypotension, cyanide/thiocyanate toxicity</td>
<td></td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>1 min</td>
<td>15-30 min</td>
<td>5 min</td>
<td>hepatic</td>
<td>Dysrhythmias, tissue necrosis, ischemia</td>
<td></td>
</tr>
<tr>
<td>Phenylephrine</td>
<td>1 min</td>
<td>15-30 min</td>
<td>15-30 min</td>
<td>hepatic</td>
<td>Extravasation causes tissue necrosis</td>
<td></td>
</tr>
<tr>
<td>Vasopressin (septic shock)</td>
<td>5-15 min</td>
<td>30-60 min</td>
<td>10-20 min</td>
<td>hepatic</td>
<td>Dysrhythmias, tissue necrosis, ischemia</td>
<td></td>
</tr>
</tbody>
</table>