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CE Review and Update on Inotropes and Vasopressors

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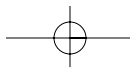
Patients presenting with shock have inadequate perfusion of tissues and lack adequate oxygen delivery to vital organs. Shock must be treated immediately to prevent multisystem organ failure and death. The components of blood pressure are cardiac output and systemic vascular resistance (SVR). Therefore, patients presenting with shock will have either an inadequate cardiac index (CI) or a low SVR due to arterial vasodilation (or rarely both). The classification of shock originates from the etiology of the physiologic state. Shock is classified as hypovolemic, cardiogenic, extracardiac obstructive, or distributive. Hypovolemic shock results from decreased preload secondary to dehydration or hemorrhage. Cardiogenic shock results from heart failure due to various causes (myopathy, cardiac valve disorders, or arrhythmias). Extracardiac obstruction can be secondary to tension pneumothorax or pulmonary emboli. Distributive shock can be due to sepsis, anaphylaxis, or neurogenic. Hypovolemic, cardiogenic, and extracardiac obstructive shock result from poor CI, and these patients will usually have an elevated SVR as a mechanism for compensation. Distributive shock results from excessive vasodilation and low SVR, and these patients will most commonly have a normal or elevated CI.

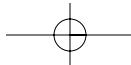
Pharmacologic agents that increase blood pressure by causing arteriole vasoconstriction are called vasopressors, and agents that increase cardiac contractility and therefore CI are considered inotropes. The purpose of this article is to review the common vasopressors and inotropes, which are used in the intensive care unit (ICU) to treat shock or congestive heart failure (CHF) or support patients in the postoperative setting. These include the catecholamines (dobutamine [Dobutrex], isoproterenol [Isuprel], dopamine, epinephrine, norepinephrine [Levophed], and phenylephrine [Neosynephrine]), phosphodiesterase inhibitors (PDIs) (milrinone [Primacor] and inamrinone [Inacor, formerly called amrinone]), and vasopressin (Pitressin) and its analog terlipressin.

Pharmacology **Catecholamines**

The catecholamines or sympathomimetic agents all act on receptors of the sympathetic (or adrenergic) nervous system. Stimulation of the beta₁- (β_1) receptor in the heart results in positive inotropic (increase in contractility and CI), chronotropic (increase in heart rate), and dromotropic (increase in conduction of impulse) effects. Stimulation of beta₂- (β_2) receptors results in smooth muscle relaxation including arterioles, which can result in vasodilation and a decrease in SVR. Stimulation of alpha- (α) receptors results in

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vasoconstriction and an increase in SVR and blood pressure, but can cause a reduction in CI due to the increase in afterload. The actions and hemodynamic effects of the various catecholamines are summarized in Table 1.

Phosphodiesterase Inhibitors

Unlike the catecholamines, milrinone and inamrinone are PDIs that do not affect the adrenergic receptors. The inhibition of phosphodiesterase leads to the inhibition of the breakdown of cyclic adenosine monophosphate. This results in increase in myocardial contractility (increase CI) and venous and arterial dilation (decrease preload and SVR). The resulting vasodilation may lead to a slight increase in heart rate.

Vasopressin

Barrett et al recently provided a comprehensive review of the mechanisms of action of vasopressin.¹ There are 3 vasopressin receptors (V_1 , V_2 , V_3). Activation of V_1 receptors results in vasoconstriction of systemic, splanchnic,

renal, and coronary arteries via activation of voltage-gated calcium channels resulting in an increase in intracellular calcium. V_2 receptors cause the antidiuretic effect of vasopressin, and the V_3 receptors are located in the anterior pituitary gland and cause secretion of adrenocorticotropic hormone. Vasopressin may cause vasodilation in some vascular beds (cerebral, pulmonary, coronary, and renal) through an increase in nitric oxide. Unlike catecholamines, this variable effect on the vasculature results in reduced pulmonary pressures and could have theoretic benefits for coronary and renal blood flow. As well, unlike those of catecholamines, the actions of vasopressin may be preserved during hypoxia and acidosis.

Terlipressin is a vasopressin analogue with increased selectivity for V_1 receptors. The pressor V_1 to antidiuretic V_2 ratio is 1 for vasopressin as compared with 2.2 for terlipressin.²

Pharmacokinetics

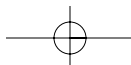
The half-life of catecholamines is only 1 or 2 minutes, and steady state (or maximum

Table 1: Clinical Effects of Sympathomimetic Amines

Agent	Adrenergic Receptor				
	Effects	Effect on HR	Effect on CI	Effect on SVR	Effect on MAP
Isoproterenol	β_1, β_2	Increase	Increase	Decrease	Variable
Dobutamine	β_1, β_2^a	Increase	Increase	Decrease	Variable
Dopamine	0.5–2 mcg/kg/min dopamergic	None	None	None but vasodilation of renal and mesenteric arteries	None or decrease
	2–5 mcg/kg/min β_1	Increase	Increase	None	None or slight increase
	>10 mcg/kg/min α	None	None or decrease	Increase	Increase
Epinephrine	≤ 0.2 mcg/kg/min β_1, β_2	Increase	Increase	Decrease	Variable
	>0.2 mcg/kg/min α	None	None or decrease	Increase	Increase
Norepinephrine	Some β_1 but more α	Variable	None or decrease	Increase	Increase
Phenylephrine	α	Decrease	None or decrease	Increase	Increase

Abbreviations: CI, cardiac index; HR, heart rate; MAP, mean arterial pressure; SVR, systemic vascular resistance.

^aOne enantiomer of dobutamine affects α -receptors, but β -receptor effects predominate.



concentrations) is achieved within 10 minutes after starting a continuous infusion. The short half-life is advantageous from the standpoint of being able to titrate these agents rapidly on the basis of effects and side effects. Their pharmacokinetics are not altered by renal or hepatic impairment. Phenylephrine has a half-life of 2 to 3 hours.

Milrinone's half-life in patients with normal renal function is approximately 2 hours and is increased in patients with reduced renal function. Inamrinone has a half-life of 4 to 8 hours in patients with normal renal function.

Vasopressin has an elimination half-life of less than 15 minutes. Terlipressin is a pro-drug (not yet approved for use in the United States) that is converted to vasopressin over a period of 4 to 6 hours. The elimination half-life of terlipressin is 50 minutes, and physiologic concentrations are maintained for 6 hours after the intravenous injection.²

Adverse Reactions

Cardiovascular Effects

Determinates of myocardial oxygen consumption include heart rate, ventricular wall tension, and contractility. β -Agonists and PDIs can increase heart rate and contractility thereby increasing myocardial oxygen demand. α -Agonists and vasopressin by increasing vascular resistance and systolic blood pressure can increase myocardial oxygen consumption by increasing ventricular wall tension. Vasoconstrictors (α -agonists and vasopressin) can also cause vasoconstriction of coronary vessels and decreased myocardial oxygen supply. Increases in myocardial oxygen consumption and/or decreases in myocardial oxygen supply can induce myocardial ischemia and worsen myocardial infarction especially in patients with known coronary artery disease. Therefore, patients receiving any of these agents should be monitored for signs of myocardial ischemia. In addition, PDIs may cause a reflex tachycardia that can induce myocardial ischemia.

Sympathomimetic amines that stimulate the β -receptors such as dobutamine and isoproterenol can directly cause tachyarrhythmias (atrial and ventricular) by increasing myocardial oxygen consumption. Pure alpha agents such as phenylephrine will cause a reflex bradycardia secondary to an increase in blood pressure. Agents with mixed α - and β -receptor

activity (eg, norepinephrine) can have variable effects on heart rate. As mentioned previously, PDIs can also cause tachycardias.

Because of the increase in afterload, α -agonists can decrease CI and induce heart failure. Agents with mixed α - and β -effects such as dopamine and epinephrine will generally increase CI in lower doses, but may decrease CI in higher doses. Therefore, when titrating vasopressors to blood pressure, CI and signs of heart failure should be monitored.

Whereas vasoconstrictors generally increase blood pressure, inotropes and vasodilators (such as the PDIs, dobutamine, and isoproterenol) may actually decrease blood pressure and induce hypotension.

Central Nervous System

Sympathomimetic amines can cause central nervous system stimulation, tremors, restlessness, and even confusion and psychosis. These effects are dose related and abate rapidly upon discontinuation.

Metabolic Effects

Sympathomimetic amines can increase serum glucose levels through glycolysis and gluconeogenesis. Therefore, blood glucose levels should be monitored.

β_2 -Agonists such as isoproterenol and dobutamine can decrease serum potassium levels, which may also induce arrhythmias. Therefore, serum potassium levels should also be monitored.

Skin Necrosis

All vasoconstrictors can cause severe tissue necrosis if they extravasate. Therefore, vasopressors should be given via central line when possible. For α -agonists such as norepinephrine, phenylephrine, and dopamine, tissue necrosis from extravasation may be prevented by injecting the α -blocker phentolamine subcutaneously into the area of infiltrate. Because the earlier this treatment is given, the more likely it is to be effective, at our institution we have a protocol so that nurses may administer the phentolamine immediately upon detection of extravasation (ie, they do not need to obtain a physician order). Vasoconstrictors can also induce skin lesions and other signs of peripheral ischemia due to the decrease in blood flow especially in patients with peripheral vascular disease.

Renal and Splanchnic Blood Flow

Excessive vasoconstriction may decrease blood flow to vital organs including kidneys and the gastrointestinal tract. However, open label trials in septic shock patients suggest that when carefully titrated to a mean arterial pressure (MAP) of 60–65 mm Hg, the vasopressors norepinephrine and phenylephrine will actually increase urine output and do not appear to have a detrimental effect on renal function.^{3–5}

Because of potential adverse effects of vasopressors on renal blood flow, in the past many clinicians utilized low-dose dopamine in patients with critical illness in an attempt to decrease the incidence of renal failure or prevent renal failure when patients were on other vasopressors. However, a large-scale randomized, placebo-controlled multicenter trial, the ANZICS trial, in 328 patients with critical illness found that low-dose or “renal dose” dopamine did not decrease the incidence of renal failure or rule out the need for renal replacement therapy.⁶ Two meta-analysis have also been conducted and both conclude that renal dose dopamine does not rule out the need for renal replacement therapy and does not improve mortality.^{7,8} Holmes et al published a review of some of the other adverse effects that renal dose dopamine may have on ICU patients including the following: dopamine-induced diuresis may worsen renal function in patients who already have an inadequate volume status; suppression of thyroid-stimulating hormone, growth hormone, prolactin, and luteinizing hormone; and immunosuppression.⁹ Clearly based on the ANZICS trial and the meta-analysis showing no clinical benefit, renal dose dopamine should no longer be utilized.

Studies utilizing gastric tonometry have demonstrated that vasopressors such as epinephrine and norepinephrine can decrease splanchnic blood flow and increase regional lactic acidosis.^{10–12} Theoretically, these effects may have several adverse consequences including inducing gastrointestinal tract ischemia or necrosis and increasing the translocation of bacteria and their associated endotoxin from the gastrointestinal tract into the blood stream. Small trials have also suggested that dobutamine at a standard dose of 5 mcg/kg/min may reverse this effect due to either vasodilation from β effects or from an increase in oxygen delivery because of the increase in CI.^{11,13} However, these are

relatively small studies that have not shown clinical benefit in terms of morbidity or mortality, and not all studies have shown consistent effectiveness. Therefore, the routine use of dobutamine for this effect cannot be recommended at this time.

Hematologic

Inamrinone can induce thrombocytopenia. Because the clinical effects of milrinone are similar to those of inamrinone without the adverse hematologic and hepatic effects, the clinical utility of inamrinone is limited.

Sympathomimetic amines can cause an increase in white blood cell counts (stress response).

Precautions, Contraindications, and Interactions

Although a complete list of all precautions, contraindications, and interactions would be very lengthy, the following are some of the most important pearls that clinicians should keep in mind.

- Hypovolemic and septic shock patients should always be given volume resuscitation prior to vasopressors or inotropes. If preload is inadequate, vasopressors will cause further reductions in cardiac output, and inotropes will worsen tachyarrhythmias and induce ischemia.
- The PDIs and sympathomimetic amines with β effects that increase CI should be used with caution in patients with severe aortic or pulmonary valve stenosis until the stenosis or obstruction is surgically relieved. If valvular pathology remains, severe myocardial ischemia may occur. These agents may also aggravate outflow tract obstruction in idiopathic hypertrophic subaortic stenosis. This may result in a decrease in CI as a higher quantity of blood is trapped in the ventricle.
- As discussed previously, sympathomimetic amines and PDIs can cause arrhythmias, and all of these agents can cause myocardial ischemia. Therefore, cardiac monitoring is imperative in the clinical use of these pharmacologic agents. Electrolytes (especially potassium and magnesium) should be monitored and replaced, if needed, to reduce the likelihood of arrhythmias.

Halogenated anesthetics may sensitize the myocardium to arrhythmias from sympathomimetic

amines. Monoamine oxidase inhibitors such as the antidepressants phenelzine and tranylcypromine, the anti-Parkinson agent selegiline, and the antimicrobial agent linezolid increase the pressor response to sympathomimetic amines. It is recommended to avoid these combinations if possible. If sympathomimetic amines are needed in patients on MAO inhibitors, start at one tenth the usual dose.

Clinical Uses

Hemodynamic Goals in Septic Shock and Acute Respiratory Distress Syndrome

Two main hemodynamic goals are as follows: (1) provide an adequate perfusion pressure that will ensure blood flow to vital organs and (2) provide an adequate level of oxygen delivery. The American College of Critical Care Medicine (ACCM) has published guidelines for hemodynamic support of adult patients with septic shock.¹⁴ In terms of perfusion pressure, the general guideline (mostly from animal models) is that a MAP of 60 to 65 mm Hg is generally needed to perfuse organs. One clinical trial demonstrated that achieving a higher MAP of 75 or 85 mm Hg did not have any benefit in terms of blood flow, urine output, or splanchnic perfusion.¹⁵ Therefore, a MAP of 60 to 65 mm Hg appears to be a reasonable goal.

In terms of optimizing oxygen delivery, the goals are less clear. Studies have suggested that patients with critical illness (both surgical and septic shock patients) have better outcomes in terms of morbidity and mortality if they have higher than normal levels of oxygen delivery and consumption (defined as CI > 4.5 L/min, oxygen delivery [DO₂] of > 600 mL/min/m², and oxygen consumption [VO₂] > 170 mL/min/m²).^{16,17} However, multicenter prospective evaluations of treating patients to these “hyperdynamic” levels of oxygen delivery and consumption have not shown a consistent benefit, and one trial showed a detrimental effect on mortality when utilizing high doses of dobutamine to achieve these goals.¹⁸ Part of the issue may be the timing of interventions to achieve optimal goals.

Rivers et al conducted a prospective randomized trial assessing early goal directed (EGD) therapy in the treatment of severe sepsis and septic shock.¹⁹ In this particular trial, to provide early therapy in the emergency department, therapy was directed by the use of a central

venous catheter. Patients were included in the study if they had septic shock (sepsis with systolic blood pressure \leq 90 mm Hg) or severe sepsis (sepsis with lactic acid \geq 4 mmol/L). They were randomized to standard care (treatment at the discretion of the clinician with critical care consultation and admitted for inpatient care as soon as possible) or EGD, which included treatment in the emergency department with colloids or crystalloids to achieve a CVP of 8 to 12 mm Hg, vasopressors to achieve a MAP \geq 65 mm Hg, and transfusion of red cells or dobutamine to achieve a central venous oxygen saturation (ScvO₂) of 70% or greater. The target was to achieve hemodynamic goals in the EGD patients within 6 hours. They demonstrated a dramatic significant reduction in mortality in the EGD group (30.5% EGD vs 46.5% standard therapy group, $P = .009$). Based on the results of this trial, the Surviving Sepsis Campaign guidelines include EGD therapy as a part of their recommendations.²⁰ The Surviving Sepsis Campaign guidelines are a compilation of evidence-based recommendations for the treatment of sepsis and septic shock. Implementation of the Surviving Sepsis Campaign guidelines has been shown in clinical trials to reduce both morbidity and mortality.^{21,22}

Vasopressors for Septic Shock

In septic shock, Acute Respiratory Distress Syndrome, and other forms of noncardiogenic shock, hypotension is secondary to intravascular volume depletion and excessive vasodilation. Initial resuscitation should always include volume resuscitation with colloids or crystalloids. After adequate fluid resuscitation has been achieved, if the blood pressure is still inadequate for effective perfusion (<60–65 mm Hg), agents that cause vasoconstriction are used. The ACCM practice parameters for hemodynamic support of sepsis summarize the literature evaluating vasopressors in septic shock.¹⁴ Dopamine has been used for many years for this purpose. Studies have documented that both norepinephrine and phenylephrine are effective for septic shock when dopamine fails.^{3–5} There are very few randomized comparisons of these vasopressors in septic shock. One small comparison showed that dopamine in doses of 10 to 25 mcg/kg/min was successful in establishing an adequate arterial pressure in only 31% of patients whereas norepinephrine in doses of 1.5 \pm 1.2 mcg/kg/min was

significantly more successful than dopamine.²³ The ACCM guidelines state that either dopamine or norepinephrine can be used for increasing MAP.¹⁴ Because it has no effects on β -receptors, phenylephrine is an alternative especially in the setting of tachyarrhythmias. Because of the documented effects of epinephrine on splanchnic perfusion, the ACCM guidelines recommend that epinephrine be reserved for refractory hypotension.

Although the ACCM guidelines state that either dopamine or norepinephrine can be used initially for septic shock, dopamine frequently fails to achieve an adequate perfusion pressure. Therefore, in the sepsis protocol in our institution we include only norepinephrine or phenylephrine as the initial vasopressor for increasing MAP.

A lack of adequate vasopressin levels has been proposed as part of the mechanism of hypotension in sepsis, and because it works by a different mechanism, vasopressin would be expected to elevate blood pressure levels in patients who do not achieve an adequate pressure with sympathomimetic amines. Obricsh et al provide a comprehensive review of studies that have documented that low-dose constant infusion of vasopressin will decrease the requirements of sympathomimetic amines in septic shock.²⁴ To limit adverse effects such as mesenteric, renal, skin, or cardiac ischemia, and decreased CI, the authors recommend limiting the dose to 0.03 units per minute. The ACCM guidelines also state that low-dose vasopressin may be effective in raising blood pressure in patients refractory to other vasodilators.

One area of controversy is whether it is more beneficial to initially use sympathomimetic amines and reserve vasopressin for refractory shock, or to use both initially. A large-scale randomized trial called the VASST (Vasopressin and Septic Shock Trial) is currently under way. This trial will look at mortality differences between these 2 strategies in an attempt to answer this question.

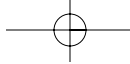
Inotropes in Septic Shock

Once an adequate perfusion pressure has been established in septic shock, the next goal to assess is whether or not oxygen delivery to tissues is adequate. As previously discussed, what defines an adequate level of delivery is controversial. Oxygen delivery is optimized by evaluating the components that determine

oxygen delivery: arterial oxygen saturation, hemoglobin, and CI. Inotropes can be used to increase oxygen delivery by increasing CI. However, because they may also cause vasodilation, they may need to be utilized in combination with vasoconstrictors to maintain blood pressure. Dobutamine is the inotrope that has been the most widely studied in septic shock. In the study of EGD by Rivers et al, dobutamine was used to increase oxygen delivery when it was inadequate as determined by a low central venous saturation. The ACCM guidelines recommend that dobutamine be used as the first choice for septic shock patients with low CI and/or low venous saturation and an adequate MAP following fluid resuscitation. Dobutamine may also be useful in patients with evidence of tissue hypoperfusion (such as low urine output or elevated lactic acid). However, strategies to routinely increase CI to “supranormal” values ($CI > 4.5 \text{ L/min/m}^2$) have not been shown to improve outcome.¹⁴ An important point that is stressed in published guidelines is that vasopressors and inotropes *should be titrated separately* to different goals. Vasopressors are titrated to maintain an adequate MAP while inotropes are titrated to the desired effect on oxygen delivery (eg, desired CI or central venous saturation $> 70\%$).

Inotropes for Cardiogenic Shock, CHF, Postoperative Support

The catecholamines with mixed α,β such as dopamine and epinephrine and the pure inotropes such as dobutamine and milrinone have been used for many years for the treatment of heart failure (following myocardial infarction or acute exacerbations of CHF) and for supporting CI after procedures such as coronary artery bypass grafting and valve replacement surgery. In the treatment of cardiogenic shock, agents with combined α,β are frequently initially used to increase both CI and MAP. When MAP is adequate, pure inotropes such as dobutamine and milrinone are frequently used for treating heart failure or for postoperative CI support. When pure inotropes are used, a combination of a vasopressor such as norepinephrine can be utilized, if necessary, to maintain MAP. However, vasopressors should be titrated carefully as the increase in afterload can decrease CI. Very few large-scale randomized trials compare inotropes in the setting of heart failure or



postprocedure support. The small trials that are published compare only hemodynamic effects and effects on heart rate, arrhythmias, and myocardial oxygen balance. The results of comparative trials between dobutamine and the PDIs inamirnone or milrinone can be summarized as follows^{25–30}:

- PDIs generally have a greater effect on decreasing PCWP and SVR than dobutamine, but have an equal effect on increasing the CI.
- Studies generally show that the PDIs have the same or less effect on increasing HR.
- PDIs have no effect on myocardial oxygen consumption, whereas dobutamine generally increases myocardial oxygen consumption. However, dobutamine also increases myocardial oxygen delivery, which counterbalances the effect on consumption.
- There have been no clinically significant differences demonstrated between the PDIs and dobutamine in terms of inducing myocardial ischemia.
- One theoretical advantage of PDIs is that they do not have the issue of tolerance (declining efficacy) over time as compared to dobutamine. Tolerance to dobutamine does occur in 48 to 72 hours. However, inotropic support should be a short-term treatment until more definitive therapy or mechanical support (eg, ventricular assist device) can be provided as long-term treatment with inotropes has been associated with increased mortality.
- A potential disadvantage is the long half-life of the PDIs as compared with that of dobutamine as adverse reactions such as tach-

yarrhythmias may take longer to dissipate with the PDIs after discontinuation.

- Several studies have shown that PDIs can have additive effects when combined with dobutamine.^{31–33} Therefore, PDIs and dobutamine may be used in combination when an adequate CI cannot be obtained with either agent alone.

Dosing and Administration

Reported doses of sympathomimetic amines vary greatly in various clinical trials. Doses of norepinephrine and phenylephrine for septic shock are generally higher than those reported in textbooks or product labeling. Table 2 summarizes the dosing used at our institution.

Milrinone may be initiated with a bolus dose of 50 mcg/kg intravenously over 10 minutes followed by a continuous infusion of 0.5 mcg/kg/min for patients with creatinine clearance of more than 50 mL/min/m². The infusion can be adjusted from 0.375 to 0.75 mcg/kg/min. Adjustments for renal insufficiency are summarized in Table 3.

For septic shock, the Surviving Sepsis Guidelines recommend that vasopressin be given at a continuous infusion of 0.01 to 0.04 mcg/min.²⁰ It is *not titrated*, and this dose should not be exceeded to limit adverse reactions.

Conclusions

Although some areas in the treatment of critically ill patients with shock remain

Table 2: Continuous Infusion Dosing Recommendations for Sympathomimetic Amines

Dobutamine	Start at 2.5–5 mcg/kg/min and increase by the same every 10 min until the desired effect on CI or venous saturation or a maximum of 20 mcg/kg/min
Dopamine	Start at 2–5 mcg/kg/min and increase by the same every 10 min until the desired effect on CI or MAP has been reached or a maximum of 20 mcg/kg/min
Epinephrine	Start at 0.02–0.05 mcg/kg/min and increase by the same every 10 min up to a maximum of 0.2 mcg/kg/min if being used for cardiac output support in postoperative patients or CHF. No maximum if being utilized for MAP in septic shock
Norepinephrine	Start at 0.1 mcg/kg/min and increase by the same every 10 min until MAP \geq 65 mm Hg ^a
Phenylephrine	An initial bolus of 100 mcg over 1 min may be given in urgent situations, then start 30–40 mcg/min, and increase by the same every 10 min until MAP \geq 65 ^a

Abbreviations: CHF, congestive heart failure; CI, cardiac index; MAP, mean arterial pressure.

^aAlthough there is no maximum for norepinephrine or phenylephrine at our institution, we routinely notify the prescribing physician when \geq 0.6 mcg/kg/min of norepinephrine or \geq 180 mcg/min of phenylephrine is needed to reach desired MAP in septic shock.

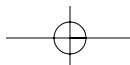


Table 3: Recommended Infusion Rate of Milrinone Based on Renal Function

CrCl, mL/min/1.73 m ²	Rate, mcg/kg/min
5	0.2
10	0.23
20	0.28
30	0.33
40	0.38
50	0.43
>50	0.5

Abbreviation: CrCl, creatinine clearance.

controversial such as the best vasopressor or combination of vasopressors to use, and what the optimal hemodynamic goals are, several conclusions can be drawn from the published literature:

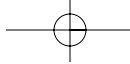
1. The traditional approach of awaiting ICU admission and inserting a pulmonary artery catheter without having a protocolized treatment does not improve morbidity or mortality of critically ill patients and patients with shock.
2. Early optimization begun in the emergency department does improve morbidity and mortality.
3. A standardized or protocolized treatment approach such as the Surviving Sepsis Guidelines will improve morbidity and mortality.

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Correction

For the article “Ethical Issues Related to Pandemic Flu Planning and Response,” which appeared in volume 18 issue 4 of *AACN Advanced Critical Care* on pages 356–360, a few corrections must be noted.

On page 356, the last full sentence on the page should read: “The virus is responsible for the deaths of millions of domestic fowl and migratory birds in Asia, Eastern Europe, the Middle East, and Africa, and as of mid-September, 329 humans had been infected, including 201 who died.”⁹”

On page 358, in the first full paragraph of the second column, references 25 and 26 should both be cited at the end of the sentence “It is a nonnegotiable standard that takes all nursing activities into account and supersedes specific policies or practices of institutions or others.”^{25,26}”

In reference 7, the URL has been changed to: <http://www3.niaid.nih.gov/healthscience/healthtopics/Flu/Research/ongoingResearch/Pandemic/TimelineHumanPandemics.htm>.

These errors have been corrected in the online version of the article, which is available at www.aacnadvancedcriticalcare.com.

