
Pharmacotherapy of Shock

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Definition

- Shock refers to conditions manifested by **hemodynamic alterations** e.g., hypotension, tachycardia, low cardiac output and oliguria caused by
 - intravascular volume deficit (**hypovolemic shock**)
 - myocardial pump failure (**cardiogenic shock**) or
 - peripheral vasodilation (**septic, anaphylactic or neurogenic shock**)
- The underlying problem in these situations is
 - **inadequate tissue perfusion** resulting from circulatory failure.

Pathophysiology

- Shock results in
 - failure of the circulatory system to deliver sufficient oxygen to body tissues despite normal or reduced Oxygen consumption
- General pathophysiologic mechanisms of different forms of shock are
 - **similar** except for initiating events

Cont...

- Hypovolemic shock is characterized by
 - acute intravascular volume deficiency due to external losses or internal redistribution of extracellular water.
 - This type of shock can be precipitated by hemorrhage, burns, trauma, surgery, intestinal obstruction, and dehydration from considerable insensible fluid loss, overaggressive loop-diuretic administration and severe vomiting or diarrhea.
 - Relative hypovolemia leading to hypovolemic shock occurs during significant vasodilation, which accompanies anaphylaxis, sepsis and neurogenic shock.

Cont...

- Regardless of the etiology, fall in blood pressure (BP) is compensated by
 - an increase in sympathetic outflow
 - activation of the renin-angiotensin system and other humoral factors that stimulate peripheral vasoconstriction.
- Compensatory vasoconstriction
 - redistributes blood away from the skin, skeletal muscles, kidneys, and GI tract toward vital organs (e.g., heart, brain) in an attempt to maintain oxygenation, nutrition and organ function.

Cont...

- Severe metabolic lactic acidosis
 - often develops secondary to tissue ischemia and causes localized vasodilation, which further exacerbates the impaired cardiovascular state

Clinical Presentations

- Shock presents with a diversity of signs and symptoms.
- Patients with hypovolemic shock may present with
 - Thirst, Anxiousness, Weakness, light-headedness and dizziness.
- Patients may also report scanty urine output and dark-yellow-colored urine.
- Hypotension, tachycardia, tachypnea, confusion, and oliguria are common symptoms.

Cont...

- Myocardial and cerebral ischemia, pulmonary edema (cardiogenic shock) and multisystem organ failure often follow.
- **Significant hypotension** (SBP < 90 mm Hg) with **reflex sinus tachycardia** (>120 beats/min) and increased respiratory rate (>30 breaths/min) are
 - often observed in hypovolemic patients.

Cont...

- Clinically, the patient presents with extremities cool to the touch and a “thready” pulse.
- The patient may be cyanotic due to hypoxemia.
- Sweating results in a moist, clammy feel.
- Digits will have severely slowed capillary refill.
- Mental status changes associated with volume depletion may range from subtle fluctuations in mood to agitation to unconsciousness.

Cont...

- Respiratory alkalosis secondary to hyperventilation is usually observed secondary to CNS stimulation of ventilatory centers as a result of trauma, sepsis, or shock.
- Lung auscultation may reveal crackles (pulmonary edema) or absence of breath sounds (pneumothorax, hemothorax).
- Chest roentgenogram can confirm early suspicions or disclose an undetected abnormality such as pneumonia (pulmonary infiltrates).
- Continued insult to the lungs may result in adult respiratory distress syndrome

Cont...

- Kidneys are exquisitely sensitive to changes in perfusion pressures.
- Moderate alterations can lead to significant changes in glomerular filtration rate.
- Oliguria, progressing to anuria, occurs because of vasoconstriction of afferent arterioles.
- Redistribution of blood flow away from the GI tract may cause stress gastritis, gut ischemia, and, in some cases, infarction, resulting in GI bleeding

Cont...

- Progressive liver damage (shock liver) manifests as
 - elevated serum hepatic transaminases and unconjugated bilirubin.
 - Impaired synthesis of clotting factors may increase prothrombin time (PT), international normalized ratio, and activated partial thromboplastin time (aPTT).

Diagnosis And Monitoring

- The following are key components in establishing the diagnosis as well as in assessing general mechanisms responsible for shock
 - Information from noninvasive and invasive monitoring and evaluation of past medical history
 - clinical presentation and
 - laboratory findings
- Regardless of the etiology, consistent findings include
 - hypotension (SBP less than 90 mm Hg)
 - depressed cardiac index (CI less than 2.2 L/min/m²)
 - tachycardia (heart rate greater than 100 beats/min) and
 - low urine output (less than 20 mL/hour)

Cont...

- Noninvasive assessment of BP using the sphygmomanometer and stethoscope may be inaccurate in the shock state.
- A pulmonary artery (Swan-Ganz) catheter can be used to determine
 - central venous pressure (CVP)
 - pulmonary artery pressure
 - CO and
 - pulmonary artery occlusive pressure (PAOP),
 - an approximate measure of the left ventricular end-diastolic volume and a major determinant of left ventricular preload

Cont...

- CO (2.5 to 3 L/min) and mixed venous oxygen saturation (70% to 75%) may be very low in a patient with extensive myocardial damage.
- Respiratory alkalosis is associated with low partial pressure of O₂ (25 to 35 mm Hg) and alkaline pH, but normal bicarbonate.
- The first two values are measured by arterial blood gas, which also yields partial pressure of carbon dioxide and arterial oxygen saturation.

Cont...

- Circulating arterial oxygen saturation can also be measured by an oximeter,
 - which is a noninvasive method that is fairly accurate and useful at the patient's bedside.
- Renal function can be grossly assessed by hourly measurements of urine output,
 - but estimation of creatinine clearance based on isolated serum creatinine values in critically ill patients may yield erroneous results.
- Decreased renal perfusion and aldosterone release result in sodium retention and, thus, low urinary sodium (<30 mEq/L).

Cont...

- In normal individuals, oxygen consumption (VO_2) is dependent on oxygen delivery (DO_2) up to a certain critical level (VO_2 flow dependency).
- At this point, tissue O_2 requirements have apparently been satisfied and further increases in DO_2 will not alter VO_2 (flow independency).
- However, studies in critically ill patients show a continuous, pathologic dependence relationship of VO_2 on DO_2

Cont...

- These indexed parameters are calculated as:
 - $DO_2 = CI \times (CaO_2)$ and
 - $VO_2 = CI \times (CaO_2 - CVO_2)$,
where
 - CI = cardiac index,
 - CaO_2 = arterial oxygen content and
 - CVO_2 = mixed venous oxygen content
- Currently available data do not support the concept that patient outcome or survival is altered by treatment measures directed to achieve supra-normal levels of DO_2 and VO_2

Cont...

- The $\text{VO}_2:\text{DO}_2$ ratio (oxygen extraction ratio) can be used to assess adequacy of perfusion and metabolic response.
- Patients who are able to increase VO_2 when DO_2 is increased are more likely to survive.
- However, low VO_2 and O_2 extraction ratio values are indicative of poor O_2 utilization and lead to greater mortality.

Cont...

- Blood lactate concentrations may be used as another measure of tissue oxygenation and may show better correlation with outcome than O₂ transport parameters in some patients.
- Gastric tonometry measures gut luminal PCO₂ at equilibrium by placing a saline-filled gas-permeable balloon in the gastric lumen.
- Increases in mucosal PCO₂ and calculated decreases in gastric intramucosal pH (pHi) are associated with mucosal hypoperfusion and perhaps increased mortality.

Cont...

- However, the following factors may confound pHi determinations
 - the presence of respiratory acid–base disorders
 - systemic bicarbonate administration
 - arterial blood gas measurement errors
 - enteral feeding products and
 - blood or stool in the gut
- Many clinicians believe that the change in gastric mucosal PCO₂ may be more accurate than pHi.

Parameter	Normal Value ^a
Blood pressure (systolic/diastolic)	100–130/70–85 mm Hg
Mean arterial pressure	80–100 mm Hg
Pulmonary artery pressure	25/10 mm Hg
Mean pulmonary artery pressure	12–15 mm Hg
Central venous pressure	8–12 mm Hg
Pulmonary artery occlusive pressure	12–15 mm Hg
Heart rate	60–80 beats/min
Cardiac output	4–7 L/min
Cardiac index	2.8–3.6 L/min/m ²
Stroke volume index	30–50 mL/m ²
Systemic vascular resistance index	1,300–2,100 dyne • sec/m ² • cm ⁵
Pulmonary vascular resistance index	45–225 dyne • sec/m ² • cm ⁵
Arterial oxygen saturation	97% (range 95–100%)
Mixed venous oxygen saturation	70–75%
Arterial oxygen content	20.1 vol% (range 19–21%)
Venous oxygen content	15.5 vol% (range 11.5–16.5%)
Oxygen content difference	5 vol% (range, 4–6%)
Oxygen consumption index	131 mL/min/m ² (range, 100–180)
Oxygen delivery index	578 mL/min/m ² (range, 370–730)
Oxygen extraction ratio	25% (range, 22–30%)
Intramucosal pH	7.40 (range, 7.35–7.45)
Index	Parameter indexed to body surface area

^aNormal values may not be the same as values needed to optimize management of a critically ill patient.

Desired Outcome

- The initial goal is to support O₂ delivery through the circulatory system by assuring
 - effective intravascular plasma volume
 - optimal O₂-carrying capacity and
 - adequate BP while definitive diagnostic and therapeutic strategies are being determined.
- The ultimate goals are
 - to prevent further progression of the disease with subsequent organ damage and, if possible
 - to reverse organ dysfunction that has already occurred.

Treatment

General Principles

- Supplemental O₂
 - should be initiated at the earliest signs of shock, beginning with 4 to 6 L/min via nasal cannula or 6 to 10 L/min by face mask.
- Adequate fluid resuscitation
 - to maintain circulating blood volume is essential in managing all forms of shock.
 - If fluid challenge does not achieve desired end points, pharmacologic support is necessary with **inotropic** and **vasoactive drugs**.

Treatment

Fluid Resuscitation For Hypovolemic Shock

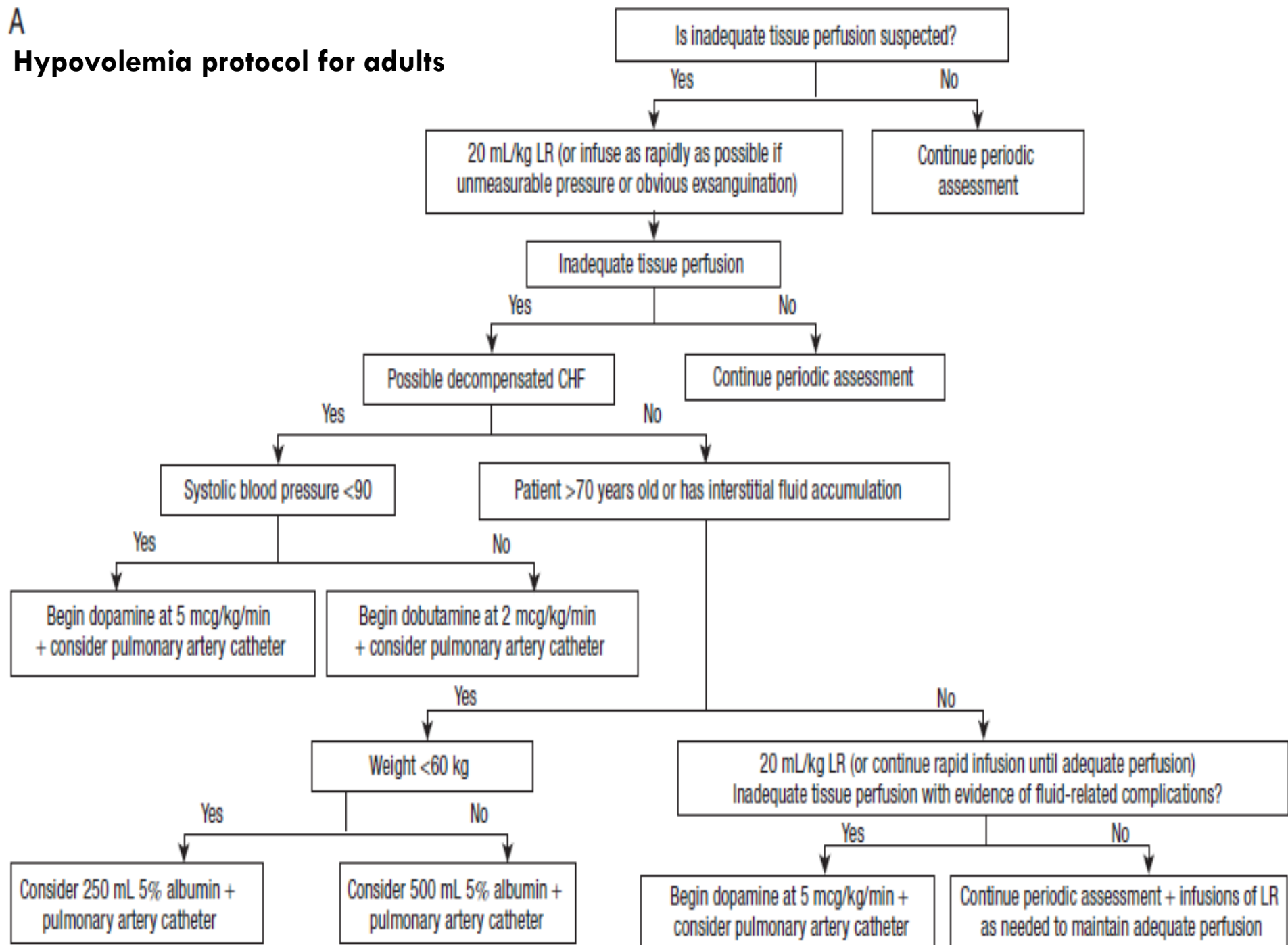
- Initial fluid resuscitation consists of
 - isotonic crystalloid (0.9% sodium chloride or lactated Ringer's solution)
 - colloid (5% Plasmanate or albumin, 6% hetastarch) or
 - whole blood
- Choice of solution is based on
 - O₂-carrying capacity (e.g., hemoglobin, hematocrit)
 - cause of hypovolemic shock
 - accompanying disease states
 - degree of fluid loss and
 - required speed of fluid delivery

Cont...

- Most clinicians agree that **crystalloids** should be the initial therapy of circulatory insufficiency.
- Crystalloids are preferred over colloids as initial therapy for burn patients because they are less likely to cause interstitial fluid accumulation.
- If volume resuscitation is suboptimal following several liters of crystalloid, colloids should be considered.
- Some patients may require blood products to assure maintenance of O₂-carrying capacity, as well as clotting factors and platelets for blood hemostasis.

A

Hypovolemia protocol for adults



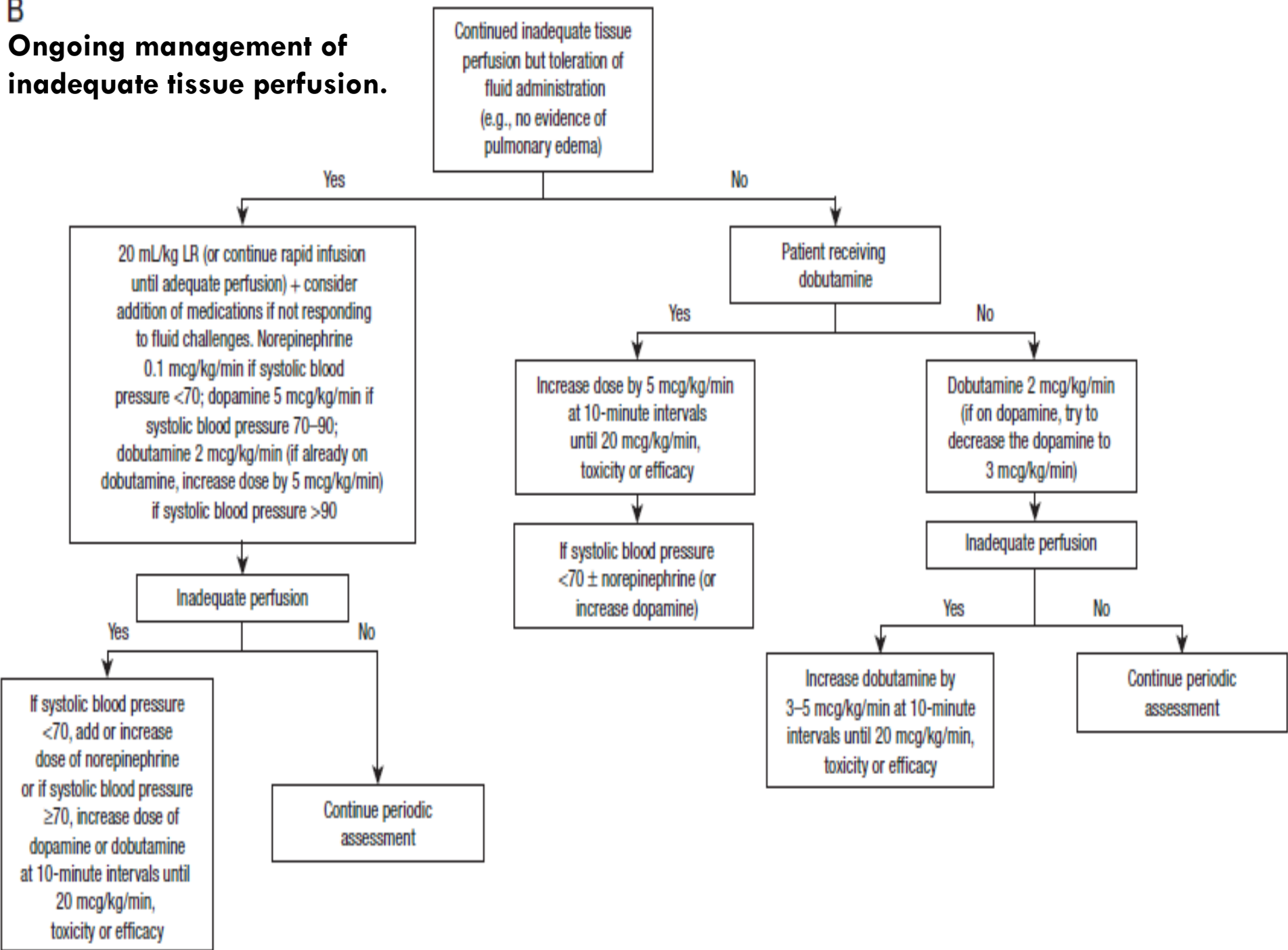
Cont...

- Hypovolemia protocol for adults
 - This protocol is not intended to replace or delay therapies such as surgical intervention or blood products for restoring oxygen-carrying capacity or hemostasis.
 - If available, some measurements may be used in addition to those listed in the algorithm, such as mean arterial pressure or pulmonary artery catheter recordings.
 - The latter may be used to assist in medication choices (e.g., agents with primary pressor effects may be desirable in patients with normal cardiac outputs, whereas dopamine or dobutamine may be indicated in patients with suboptimal cardiac outputs).

Cont...

- Lower maximal doses of the medications in this algorithm should be considered when pulmonary artery catheterization is not available.
- Colloids that may be substituted for albumin are hetastarch 6% and dextran 40.

B
Ongoing management of inadequate tissue perfusion.



Crystalloids

- Crystalloids consist of electrolytes (e.g., Na^+ , Cl^- , K^+) in water solutions, with or without dextrose.
- Lactated Ringer's solution may be preferred because it is unlikely to cause the hyperchloremic metabolic acidosis seen with infusion of large amounts of normal saline.
- Crystalloids are administered at a rate of 500 to 2,000 mL/hour, depending on the severity of the deficit, degree of ongoing fluid loss, and tolerance to infusion volume.
- Usually 2 to 4 L of crystalloid normalizes intravascular volume.

Cont...

- **Advantages** of crystalloids include
 - rapidity and ease of administration
 - compatibility with most drugs
 - absence of serum sickness and
 - low cost.
- The primary **disadvantage** is
 - the large volume necessary to replace or augment intravascular volume.
 - Approximately 4 L of normal saline must be infused to replace 1 L of blood loss.
 - In addition, dilution of colloid oncotic pressure leading to pulmonary edema is more likely to follow crystalloid than colloid resuscitation.

Colloids

- **Colloids** are
 - larger molecular weight solutions (more than 30,000 daltons) that have been recommended for use in conjunction with or as replacements for crystalloid solutions.
 - Albumin is a monodisperse colloid because all of its molecules are of the same molecular weight, whereas
 - hetastarch and dextran solutions are polydisperse compounds with molecules of varying molecular weights.

Cont...

- The theoretical **advantage** of colloids is
 - their prolonged intravascular retention time compared to crystalloid solutions.
 - Isotonic crystalloid solutions have substantial interstitial distribution within minutes of IV administration, but colloids remain in the intravascular space for hours or days, depending on factors such as capillary permeability.
 - However, even with intact capillary permeability, the colloid molecules eventually leak through capillary membranes.

Cont...

- **Albumin**

- 5% and 25% concentrations are available.
- It takes approximately three to four times as much lactated Ringer's or normal saline solution to yield the same volume expansion as 5% albumin solution.
- However, albumin is much more costly than crystalloid solutions.
- The 5% albumin solution is relatively iso-oncotic, whereas 25% albumin is hyperoncotic and tends to pull fluid into the compartment containing the albumin molecules.

Cont...

- In general, 5% albumin is used for hypovolemic states.
- The 25% solution should not be used for acute circulatory insufficiency unless diluted with other fluids or unless it is being used in patients with excess total body water but intravascular depletion, as a means of pulling fluid into the intravascular space.

Cont...

- **Hetastarch**

- 6% has comparable plasma expansion to 5% albumin solution but is usually less expensive, which accounts for much of its use.
- should be avoided in situations in which short-term impairments in hemostasis could have adverse consequences cardiopulmonary bypass surgery intracranial hemorrhage,
 - because it may aggravate bleeding due to mechanisms such as decreased factor VIII activity.
- may cause elevations in serum amylase concentrations but does not cause pancreatitis.

Cont...

- **Dextran**

- Dextran-40, dextran-70, and dextran-75 are available for use as plasma expanders (the number indicates the average molecular weight $\times 1,000$).
- These solutions are not used as often as albumin or hetastarch for plasma expansion, possibly due to concerns related to
 - aggravation of bleeding (i.e., anticoagulant actions related to inhibiting stasis of microcirculation) and
 - anaphylaxis, which is more likely to occur with the higher molecular weight solutions.

Cont...

- Colloids (especially albumin) are expensive solutions,
 - and a large study involving almost 7,000 critically ill patients found no significant difference in 28-day mortality between patients resuscitated with either normal saline or 4% albumin.
 - For these reasons, **crystalloids** should be considered **first-line** therapy in patients with hypovolemic shock.

Cont...

- **Adverse effects of colloids**
 - are generally extensions of their pharmacologic activity
 - e.g., fluid overload, dilutional coagulopathy
 - Albumin and dextran may be associated with **anaphylactoid reactions** or anaphylaxis.
 - **Bleeding** may occur in certain patients receiving hetastarch and dextran.

Blood Products

Whole blood

- Whole blood could be used for large volume blood loss, but most institutions use component therapy, with crystalloids or colloids used for plasma expansion.

Cont...

- **Packed RBC**

- Packed red blood cells contain hemoglobin that increases the O₂ –carrying capacity of blood, thereby increasing O₂ delivery to tissues.
- This is a function not performed by crystalloids or colloids.
- Packed red cells are usually indicated in patients with continued deterioration after volume replacement or obvious exsanguination.
- The product needs to be warmed before administration, especially when used in children

Cont...

- **Fresh frozen plasma (FFP)**
 - Fresh frozen plasma replaces clotting factors.
 - Although it is often over-used, the product is indicated if there is
 - ongoing hemorrhage in patients with a PT or aPTT greater than 1.5 times normal
 - severe hepatic disease or
 - other bleeding disorders.

Cont...

- **Platelets**

- used for bleeding due to severe thrombocytopenia (platelet counts less than $10,000/\text{mm}^3$) or in patients with rapidly dropping platelet counts, as seen in massive bleeding

- **Cryoprecipitate and factor VIII**

- Care generally not indicated in acute hemorrhage but may be used once specific deficiencies have been identified.

Cont...

- **Risks** associated with infusion of blood products include
 - transfusion-related reactions
 - virus transmission (rare)
 - hypocalcemia resulting from added citrate
 - elevations in serum potassium and phosphorus concentrations from use of stored blood that has hemolyzed
 - increased blood viscosity from supra-normal hematocrit elevations and
 - hypothermia from failure to appropriately warm solutions before administration.

Treatment

Pharmacologic Therapy For Shock

- Inotropic agents and vasopressors are generally not indicated in the initial treatment of hypovolemic shock (assuming that fluid therapy is adequate)
 - as the body's normal response is to increase CO and constrict blood vessels to maintain BP.
- However, once the cause of circulatory insufficiency has been stopped or treated and fluids have been optimized,
 - medications may be needed in patients who continue to have signs and symptoms of inadequate tissue perfusion

Cont...

- Pressor agents such as norepinephrine and high-dose dopamine should be avoided if possible
 - because they may increase BP at the expense of peripheral tissue ischemia.
- In patients with unstable BP despite massive fluid replacement and increasing interstitial fluid accumulation,
 - inotropic agents such as dobutamine are preferred if BP is adequate (SBP 90 mm Hg or greater) because they should not aggravate the existing vasoconstriction.

Cont...

- When pressure cannot be maintained with inotropes, or when inotropes with vasodilatory properties cannot be used due to concerns about inadequate BP,
 - pressors may be required as a last resort.

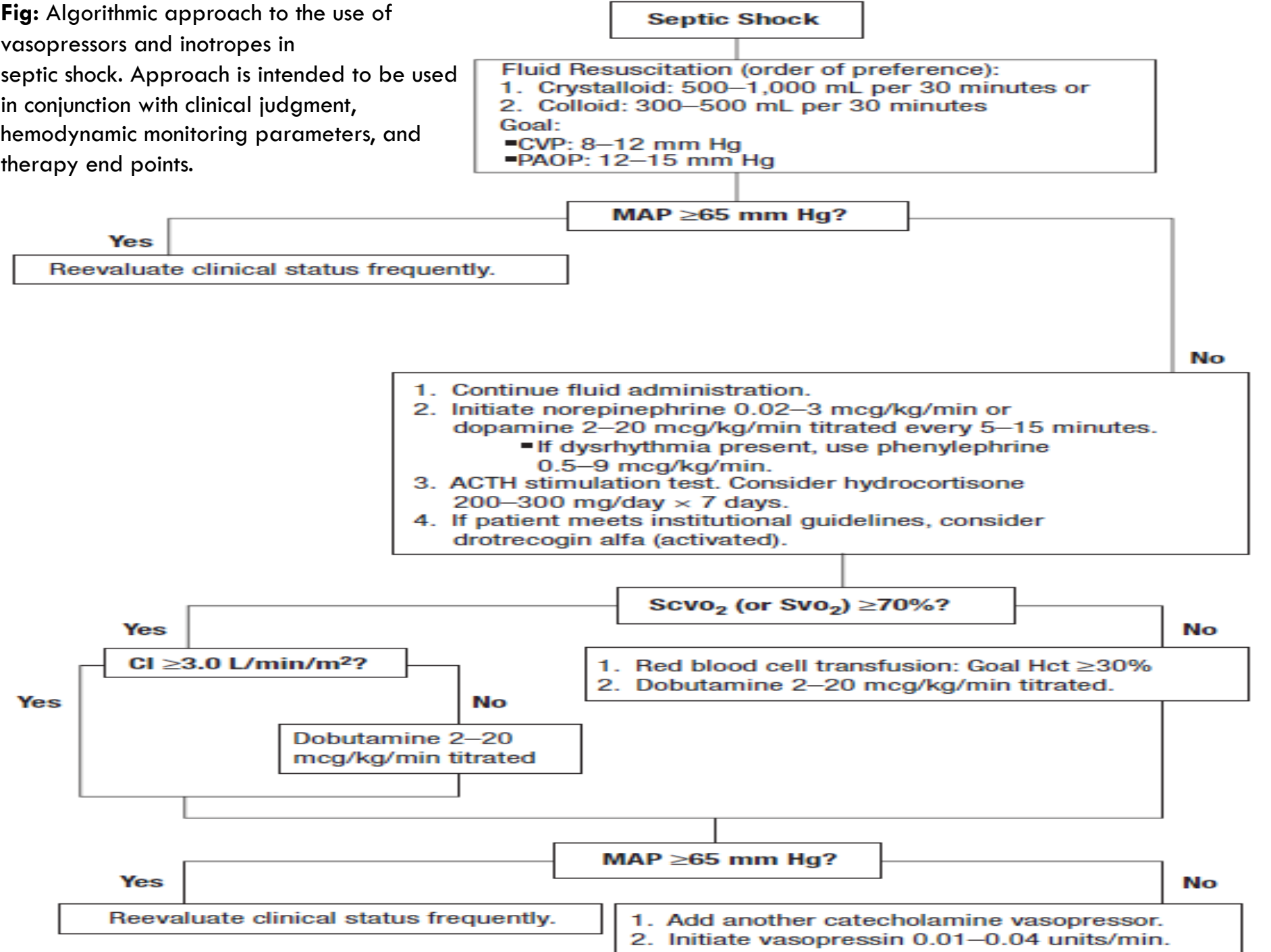
Cont...

- The choice of vasopressor or inotropic agent in septic shock should be made according to the needs of the patient.
 - The traditional approach is to start with dopamine, then norepinephrine; dobutamine is added for low CO states, and occasionally epinephrine and phenylephrine are used when necessary.
 - However, recent observations of improved outcomes with norepinephrine and decreased regional perfusion with dopamine are calling into question the use of dopamine as a first-line agent

Cont...

- In general, these drugs act rapidly with short durations of action and are given as continuous infusions.
- Potent vasoconstrictors such as norepinephrine and phenylephrine should be given through central veins due to the possibility of extravasation and tissue damage with peripheral administration.
- Careful monitoring and calculation of infusion rates are advised because dosing adjustments are made frequently and varying admixture concentrations are used in volume-restricted patients.

Fig: Algorithmic approach to the use of vasopressors and inotropes in septic shock. Approach is intended to be used in conjunction with clinical judgment, hemodynamic monitoring parameters, and therapy end points.



Receptor Pharmacology of Selected Inotropic and Vasopressor Agents Used in Septic Shock^a

Agent	α_1	α_2	β_1	β_2	D
Dobutamine (0.5–4 mg/mL D ₅ W or NS)					
2–10 mcg/kg/min	+	0	++++	++	0
>10–20 mcg/kg/min	++	0	++++	+++	0
Dopamine (0.8–3.2 mg/mL D ₅ W or NS)					
1–3 mcg/kg/min	0	0	+	0	++++
3–10 mcg/kg/min	0/+	0	++++	++	++++
>10–20 mcg/kg/min	+++	0	++++	+	0
Epinephrine (0.008–0.016 mg/mL D ₅ W or NS)					
0.01–0.05 mcg/kg/min	++	++	++++	+++	0
>0.05–3 mcg/kg/min	++++	++++	+++	+	0
Norepinephrine (0.016–0.064 mg/mL D ₅ W)					
0.02–3 mcg/kg/min	+++	+++	+++	+ / ++	0
Phenylephrine (0.1–0.4 mg/mL D ₅ W or NS)					
0.5–9 mcg/kg/min	+++	+	+	0	0

^aActivity ranges from no activity (0) to maximal (+++++) activity.

D, dopamine; D₅W, dextrose 5% in water; NS, normal saline.

Cont...

- **Dopamine**

- is often the initial vasopressor used in septic shock because it increases BP by increasing myocardial contractility and vasoconstriction.
- Although dopamine has been reported to have dose-related receptor activity at dopamine, $\beta 1$, and $\alpha 1$ receptors, this dose–response relationship has not been confirmed in critically ill patients.

Cont...

- In patients with septic shock, there is overlap of hemodynamic effects with doses as low as 3 mcg/kg/min.
- Doses of 5 to 10 mcg/kg/min are initiated to improve MAP.
- In septic shock, these doses increase CI by improving ventricular contractility, heart rate, MAP, and systemic vascular resistance (SVR).
- The clinical utility of dopamine in septic shock is limited because large doses are frequently necessary to maintain CO and MAP.

Cont...

- At doses above 20 mcg/kg/min, there is limited further improvement in cardiac performance and regional hemodynamics.
- The use of dopamine is also hampered frequently by tachycardia and tachydysrhythmias.
- Other adverse effects limiting its use in septic shock include increases in PAOP, pulmonary shunting, and decreases in PaO₂

Cont...

- Dopamine should be used with caution in patients with elevated preload, as it may worsen pulmonary edema. Low doses of dopamine (1 to 3 mcg/kg/min) once were advocated for use in patients with septic shock receiving vasopressors with or without oliguria.
- The goal of therapy is to minimize or reverse renal vasoconstriction caused by other pressors, to prevent oliguric renal failure, or to convert it to nonoliguric renal failure.

Cont...

- Based on recent clinical trial results, low-dose dopamine for treatment or prevention of acute renal failure cannot be justified and should be eliminated from routine clinical use.

Cont...

- **Norepinephrine**

- is a combined α - and β -agonist, but it primarily produces vasoconstriction, thereby increasing SVR.
- It generally produces either no change or a slight decrease in CO.
- Norepinephrine is initiated after vasopressor doses of dopamine (4 to 20 mcg/kg/min), alone or in combination with dobutamine (5 mcg/kg/min), fail to achieve the desired goals.

Cont...

- Doses of dopamine and dobutamine are kept constant or stopped; in some instances, dopamine is kept at low doses for purported renal protection.
- Norepinephrine, 0.01 to 2 mcg/kg/min, reliably and predictably improves hemodynamic parameters to normal or supra-normal values in most patients with septic shock.
- Recent data suggest that norepinephrine should potentially be repositioned as the vasopressor of choice in septic shock.

Cont...

- **Dobutamine**

- is primarily a selective β_1 -agonist with mild β_2 and vascular α_1 activity, resulting in strong positive inotropic activity without concomitant vasoconstriction.
- Dobutamine produces a larger increase in CO and is less arrhythmogenic than dopamine.
- Clinically, β_2 -induced vasodilation and the increased myocardial contractility with subsequent reflex reduction in sympathetic tone lead to a decrease in SVR.

Cont...

- Even though dobutamine is optimally used for low CO states with high filling pressures or in cardiogenic shock, vasopressors may be needed to counteract arterial vasodilation.
- The addition of dobutamine (held constant at 5 mcg/kg/min) to epinephrine regimens can improve gastric mucosal perfusion as measured by improvements in pHi, arterial lactate concentrations, and PCO₂ gap.
- Dobutamine should be started with doses ranging from 2.5 to 5 mcg/kg/min.

Cont...

- Doses above 5 mcg/kg/min provide limited beneficial effects on O₂ transport values and hemodynamics and may increase adverse cardiac effects.
- Infusion rates should be guided by clinical endpoints and mixed venous oxygen saturation/central venous oxygen saturation.
- Decreases in partial pressure of O₂, as well as myocardial adverse effects such as tachycardia, ischemic changes on ECG, tachydysrhythmias, and hypotension, are seen.

Cont...

- **Phenylephrine**

- is a pure α_1 -agonist and is thought to increase BP through vasoconstriction.

- It may also increase contractility and CO.

Phenylephrine may be beneficial in septic shock because of its selective α -agonism, vascular effects, rapid onset, and short duration.

Cont...

- Phenylephrine may be a useful alternative in patients
 - who cannot tolerate the tachycardia or tachydysrhythmias with use of dopamine or norepinephrine
 - with known underlying myocardial dysfunction and
 - refractory to dopamine or norepinephrine (because of β -receptor desensitization).
- It is generally initiated at dosages of 0.5 mcg/kg/min and may be titrated every 5 to 15 minutes to desired effects. Adverse effects such as tachydysrhythmias are infrequent when it is used as a single agent or with higher doses

Cont...

- **Epinephrine**

- has combined α - and β -agonist effects and has traditionally been reserved as the vasopressor of last resort because of reports of peripheral vasoconstriction, particularly in the splanchnic and renal beds.
- At the high infusion rates used in septic shock, α -adrenergic effects are predominantly seen, and SVR and MAP are increased.
- It is an acceptable single agent in septic shock due to its combined vasoconstrictor and inotropic effects.

Cont...

- Epinephrine may be particularly useful when used earlier in the course of septic shock in young patients and those without known cardiac abnormalities.
- Infusion rates of 0.04 to 1 mcg/kg/min alone increase hemodynamic and O₂ transport variables to supra-normal levels without adverse effects in patients without coronary heart disease.

Cont...

- Large doses (0.5 to 1 mcg/kg/min) may be required when epinephrine is added to other agents.
- Smaller doses (0.1 to 0.5 mcg/kg/min) are effective if dobutamine and dopamine infusions are kept constant.
- Although DO_2 increases mainly as a function of consistent increases in CI (and a more variable increase in SVR), VO_2 may not increase and the oxygen extraction ratio may fall.

Cont...

- Lactate concentrations may rise during the first few hours of epinephrine therapy but normalize over the ensuing 24 hours in survivors.
- Caution must be used before considering epinephrine for managing hypoperfusion in hypodynamic patients with coronary artery disease to avoid ischemia, chest pain, and myocardial infarction.

Cont...

- **Vasopressin**

- causes vasoconstrictive effects that, unlike adrenergic receptor agonists, are preserved during hypoxia and severe acidosis.
- It also causes vasodilation in the pulmonary, coronary, and selected renal vascular beds that may reduce pulmonary artery pressure and preserve cardiac and renal function.

Cont...

- However, based on available evidence, vasopressin is not recommended as a replacement for norepinephrine or dopamine in patients with septic shock but may be considered in patients who are refractory to catecholamine vasopressors despite adequate fluid resuscitation.
- If used, the dose should not exceed 0.01 to 0.04 units/min.

Cont...

- **Corticosteroids**

- were shown in a meta-analysis to improve hemodynamics and survival and reduce the duration of vasopressor support in septic shock.
- Corticosteroids can be initiated in septic shock when adrenal insufficiency is present or when weaning of vasopressor therapy proves futile.
- A daily dose equivalent to 200 to 300 mg hydrocortisone should be continued for 7 days.
- Adverse events are few because of the short duration of therapy

Evaluation Of Therapeutic Outcomes

- The initial monitoring of a patient with suspected volume depletion should include
 - vital signs
 - urine output
 - mental status and
 - physical examination.
- Placement of a CVP line provides a useful (although indirect and insensitive) estimate of the relationship between increased right atrial pressure and CO

Cont...

- Pulmonary artery catheterization
 - The indications for pulmonary artery catheterization are controversial.
 - Because there is a lack of a well-defined outcome of data associated with this procedure, its use is presently best reserved for complicated cases of shock not responding to conventional fluid and medication therapies.
 - Complications related to catheter insertion, maintenance, and removal include damage to vessels and organs during insertion, arrhythmias, infections, and thromboembolic damage.

Cont...

- Laboratory tests indicated for the ongoing monitoring of shock include
 - electrolytes
 - renal function tests (blood urea nitrogen, serum creatinine)
 - complete blood count to assess possible infection,
 - O₂-carrying capacity of the blood
 - ongoing bleeding; PT and aPTT to assess clotting ability
 - lactate concentration and base deficit to detect inadequate tissue perfusion.

Cont...

- Cardiovascular and respiratory parameters should be monitored continuously
 - Trends, rather than specific CVP or PAOP numbers, should be monitored because of inter-patient variability in response.
- Successful fluid resuscitation should increase
 - SBP (greater than 90 mm Hg)
 - CI (greater than 2.2 L/min/m²) and
 - urine output (0.5 to 1 mL/kg/hour) while decreasing SVR to the normal range.
 - MAP greater than 60 mm Hg should be achieved to ensure adequate cerebral and coronary perfusion pressure

Cont...

- Intravascular volume overload is characterized by
 - high filling pressures (CVP greater than 12 to 15 mm Hg)
 - PAOP greater than 20 to 24 mm Hg) and
 - decreased CO (less than 3.5 L/min).
- If volume overload occurs,
 - furosemide, 20 to 40 mg, should be administered by slow IV push to produce rapid diuresis of intravascular volume and “unload” the heart through venous dilation

Cont...

- Coagulation problems are
 - primarily associated with low levels of clotting factors in stored blood as well as dilution of endogenous clotting factors and platelets following administration of the blood.
 - As a result, a coagulation panel (PT, international normalized ratio, aPTT) should be checked in patients undergoing replacement of 50% to 100% of blood volume in 12 to 24 hours.

