Inoropes and Vasopressors.
What is the right choice for my patient?

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Peds Intensivist
Case Scenario.

- 2 yr old boy, previously healthy presented with 2 days of fever, vomited once, 1 day of diarrhea (7 times loose), decreased oral intake.
- Exam: lethargic, febrile (39.2°C)
  - HR = 178, RR = 60, BP = 60/30
  - Cold extremities, cap refill = 4-5 sec

Your approach?? Fluid and Fast
Diagnosis?

- What type?
- Cause?
  - Hypovolemia
    Vomitting, diarrhea, poor intake
  - Sepsis
    Fever
  - Cardiogenic (myocarditis)
    Enteric viruses (coxsackie)
Cardiogenic: Caution with Fluid!

- Hx
- Liver
- Jugular vein
- Heart sounds
- Lung crackles
- CXray
- Echo?!
Case.

- BP = 80/40, perfusion improved
- 1 hr later BP 65/35
- Treated with:
  - Fluids
  - Dopamine 5 mic/kg/min........up to 20
  - Dobutamine added 5.......up to 20
  - Epinephrine 0.1.........up to 2
  - Norepinephrine 0.05.......up to 2
MCQ

A. Dopamine then Norepinephrine
B. Dopamine then Epinephrine
C. Dopamine then Dobutamine
D. Epinephrine then Norepi
E. Norepinephrine and Dobutamine
F. Epinephrine alone
G. Others
H. All of the above
BP or Oxygen Delivery?

Oxygen delivery = $\text{DO}_2 = \text{CO} \times \text{CaO}_2$

Cardiac Output = $\text{CO} = \text{HR} \times \text{SV}$

$\text{SV} \sim \text{Preload, Afterload and Contractility}$

$\text{CaO}_2 = \text{Hb} \times \text{SaO}_2 \times 1.34 + (0.003 \times \text{PaO}_2)$
Hemodynamic Response to Hemorrhage

% of Control

100

Vasc Resistance

Blood Pressure

Cardiac Output

% Plasma Loss

25%

50%
Management-General

- Goal: increase oxygen delivery and decrease oxygen demand
  - Oxygen
  - Fluid
  - PRBCs?
  - Temperature control, sedation
  - Antibiotics
  - Correct metabolic abnormalities
  - Inotropes and Vasopressors

\[
\text{DO}_2 = \text{CO} \times \text{CaO}_2
\]
\[
\text{CaO}_2 = \text{Hb} \times \text{SaO}_2 \times 1.34
\]
Cardiac Index (L/min/m²)

- **NORMAL**
- **HEART FAILURE**
- **Inotropes or Vasodilators**

**Diuresis**

Pulmonary Capillary Wedge Pressure (mm Hg)
- **Optimal Filling Pressure**
- **Pulmonary Edema**

RA, RV, PA, PCW
Clinical monitoring tools for cardiac output

- Level of consciousness, activity, or agitation
- State of hydration
- Peripheral edema
- Respiratory pattern
- Peripheral perfusion/capillary refill time
- Toe-to-core temperature gap
- Heart rate and rhythm
- Pulse characteristics
- Urine output
- Hepatomegaly
- Jugular venous pressure
- Pulmonary and cardiac auscultation
**Initial hemodynamics**

<table>
<thead>
<tr>
<th>BP</th>
<th>MAP</th>
<th>CVP</th>
<th>perf</th>
<th>CI</th>
</tr>
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<tbody>
<tr>
<td>75/55</td>
<td>62</td>
<td>5</td>
<td>57</td>
<td>3.2</td>
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**Therapy**

- Reduction in stroke volume
- Inappropriate volume load
- Vasopressor-induced increase in afterload

**Result**

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<td>67</td>
<td>15</td>
<td>52</td>
<td>2.8</td>
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**Stroke volume**

Preload (diastolic ventricular fiber stretch)

**Contractility**

Afterload (wall stress)
High CVP (RVEDP)

- Decreased right (single) ventricle compliance
- Tricuspid valve disease
- Intravascular volume overload
- Cardiac tamponade
- Pulmonary hypertension
- Ventricular Septal Defect
- Constrictive pericarditis
- Tachyarrhythmia
Dynamic Preload

Fluctuation in SV induced by changes in preload during Positive Pressure Ventilation (with large variability in pulse pressure or SBP give volume or decrease Vt)
Cardiovascular Medications
What is the right choice in children?
Glossary of terms

- **Inotropes**: agents that improve myocardial contractility and enhance stroke volume
- **Chronotropic**: Increase heart rate
- **Lusotropic**: improve relaxation during diastole and decrease EDP in the ventricles
- **Pressors**: agents that increase systemic vascular resistance and increase blood pressure
Receptors Physiology

- **Alpha adrenergic:**
  - located in vascular walls, induces significant vasoconstriction.

- **Beta adrenergic:**
  - Beta-1 adrenergic receptors are most common in the heart, and mediate increases in inotropy and chronotropy.
  - Stimulation of beta-2 adrenergic receptors in blood vessels induces vasodilation.

- **Dopaminergic:**
  - In the renal, splanchnic (mesenteric), coronary, and cerebral vascular beds; stimulation of these receptors leads to vasodilation.
  - A second subtype of dopamine receptors causes vasoconstriction by inducing norepinephrine release.
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+++ : Very strong effect; ++ : Moderate effect; + : Weak effect; 0 : No effect.
Hypovolemic shock

- Volume
- Volume
- Volume
- Inotropes/ vasopressors could be considered
  (CVP might help)
Distributive Shock
(Anaphylaxis, Spinal, Drugs, Sepsis?)

- Volume expander
- Epinephrine (alpha effect)
- ?Beta 😊
Cardiogenic Shock

- **Normal BP or SVR**
  - Dobutamine
  - Dopamine
  - Milrinone

- **Low BP or SVR**
  - Epinephrine
  - Dopamine
Septic Shock
(Hypovolemic, Distributive, Cardiogenic)

**Stroke index high**
- Normal BP
  - None or dopamine
- Decreased BP
  - Norepinephrine
- Increased BP
  - None

**Stroke index low**
- Normal BP
  - Dobutamine or Dopa
- Decreased BP
  - Dopamine or Epi
  - Dobutamine & Norepi
- Increased BP
  - Dobutamine & Nitroprusside
Septic Shock
(Hypovolemic, Distributive, Cardiogenic)

- Hypotension
  - Good Heart: Norepinephrine
  - Bad Heart: Dopamine, Epinephrine, Dobutamine & Norepinephrine

- Bad Heart
  - Normal BP: Dobutamine
  - Increased BP: Dobutamine & Nitro? Milrinone
Recognize decreased mental status and perfusion. Begin high flow O₂. Establish IV/IO access.

**Initial resuscitation:** Push boluses of 20 cc/kg isotonic saline or colloid up to & over 60 cc/kg until perfusion improves or unless rales or hepatomegaly develop. Correct hypoglycemia & hypocalcemia. Begin antibiotics.

**shock not reversed?**

**Fluid refractory shock:** Begin inotrope IV/IO. Use atropine/ketamine IV/IO/IM to obtain central access & airway if needed. 
*Reverse cold shock* by titrating central dopamine or, if resistant, titrate central epinephrine. 
*Reverse warm shock* by titrating central norepinephrine.

**shock not reversed?**

**Catecholamine resistant shock:** Begin hydrocortisone if at risk for absolute adrenal insufficiency.

If 2nd PIV start inotrope.

dose range: dopamine up to 10 mcg/kg/min, epinephrine 0.05 to 0.3 mcg/kg/min.
Catecholamine resistant shock: Begin hydrocortisone if at risk for absolute adrenal insufficiency

Monitor CVP in PICU, attain normal MAP-CVP & ScvO\textsubscript{2} > 70%

- Cold shock with normal blood pressure:
  1. Titrate fluid & epinephrine, ScvO\textsubscript{2} > 70%, Hgb > 10 g/dL
  2. If ScvO\textsubscript{2} still < 70%
     Add vasodilator with volume loading (nitrosovasodilators, milrinone, imirnone, & others)
     Consider levosimendan

- Cold shock with low blood pressure:
  1. Titrate fluid & epinephrine, ScvO\textsubscript{2} > 70%, Hgb > 10 g/dL
  2. If still hypotensive consider norepinephrine
  3. If ScvO\textsubscript{2} still < 70% consider dobutamine, milrinone, enoximine or levosimendan

- Warm shock with low blood pressure:
  1. Titrate fluid & norepinephrine, ScvO\textsubscript{2} > 70%
  2. If still hypotensive consider vasopressin, terlipressin or angiotensin
  3. If ScvO\textsubscript{2} still < 70% consider low dose epinephrine

shock not reversed?

Persistent catecholamine resistant shock: Rule out and correct pericardial effusion, pneumothorax, & intra-abdominal pressure >12 mm/Hg.

Consider pulmonary artery, PICCO, or FATD catheter, &/or doppler ultrasound to guide fluid, inotrope, vasopressor, vasodilator and hormonal therapies.

Goal C.I. > 3.3 & < 6.0 L/min/m\textsuperscript{2}

shock not reversed?

Refractory shock: ECMO
Additional considerations

- Mechanical ventilation and oxygen therapy (to conserve CO)
- Analgesia, anxiolysis and sedation
- Electrolyte homeostasis esp Ca and Mg
- Nutrition - avoid hypoglycemia
- Anemia is unjustified
- Last but not the least:
  Maintain appropriate intravascular volume
You think It is too much?
Case Scenario

- 17 yr-old female, 60 kg
- Fever for 2 days
- Rash for 1 day (maculopapular), injected mucous membranes.
- Sick looking in ER
- IV Cefuroxime
- Less responsive, hypotensive
- ????????
More Information

☐ ? Allergy to pencillines
☐ HR 150 (temp 39.9°C), RR 40, BP 75/30
☐ Warm extremities, pounding peripheral pulses, Cap refill 1 sec.
☐ Few drops of concentrated urine by cath

What Type of Shock?
What is your initial management?
Shock

- Hypovolemia: Fluid, fluid, and fluid
- Anaphylaxis (Distributive): Fluid & Epi
- Septic (Distributive vs Mixed): Fluid &???
- Cardiogenic: ± Fluid & ???
PRINCIPLE 1

One drug, many receptors

- A given drug often has multiple effects because of actions upon more than one receptor.

- As an example, Dobutamine increases cardiac output by beta-1 adrenergic receptor activation; however, it also acts upon beta-2 adrenergic receptors and thus induces vasodilation and can cause hypotension.
Dose-response curve

Many agents have dose-response curves, such that the primary adrenergic receptor subtype activated by the drug is dose-dependent.

As an example, Dopamine stimulates beta-1 adrenergic receptors at doses of 2 to 10 mcg/kg per minute, and alpha adrenergic receptors when doses exceed 10 mcg/kg per minute.
Direct versus reflex actions

A given agent can affect MAP both by direct actions on adrenergic receptors and by reflex actions triggered by the pharmacologic response.

Norepinephrine-induced beta-1 adrenergic stimulation alone normally would cause tachycardia. The elevated MAP from norepinephrine's alpha-adrenergic receptor-induced vasoconstriction results in a reflex decrease in HR. The net result a stable or slightly reduced HR.
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Dopamine (mcg/kg/min)

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Ultrasonic dilution methods
Vasopressors in Adults

- Vasopressors are a powerful class of drugs that induce vasoconstriction and elevate mean arterial pressure

- Alpha-1 = vasoconstriction
- Beta-1 = inotropy plus chronotropy
- Beta-2 = vasodilation
Vasopressors in Adults

- Vasopressors are indicated for a mean arterial pressure < 60 mmHg, or a decrease of systolic blood pressure that exceeds 30 mmHg from baseline, when either condition results in end-organ dysfunction due to hypoperfusion
Vasopressors in Adults

- Hypovolemia should be corrected prior to the institution of vasopressor therapy for maximum efficacy.
- Patients should be reevaluated frequently once vasopressor therapy has been initiated.
- Common issues that arise include:
  - tachyphylaxis, which may require dose titration, and
  - additional hemodynamic insults, which should be recognized and managed
Vasopressors in Adults

- Norepinephrine or Phenylephrine as the first-line agent for patients with hyperdynamic septic shock.
- Vasopressin may be of benefit if these agents are inadequate.
- Dopamine could be the first-line agent for patients with hypodynamic septic shock; however, patients should be closely monitored for lack of response and the need for a second agent.
- Epinephrine is the preferred agent for most patients with anaphylactic shock.
Vasopressors in Adults

- Dopamine is the preferred initial agent for cardiogenic shock.
- Once an adequate perfusion pressure has been obtained, Dobutamine may be added and the dopamine titrated off, as tolerated.
Complications of vasopressor therapy

- Hypoperfusion (particularly affecting the extremities, mesentery or kidneys)
- Dysrhythmias
- Myocardial ischemia
- Peripheral extravasation with skin necrosis
- Hyperglycemia
Vasopressin versus norepinephrine infusion in patients with septic shock


- BACKGROUND: Vasopressin is commonly used as an adjunct to catecholamines to support blood pressure in refractory septic shock, but its effect on mortality is unknown. We hypothesized that low-dose vasopressin as compared with norepinephrine would decrease mortality among patients with septic shock who were being treated with conventional (catecholamine) vasopressors.

- METHODS: In this multicenter, randomized, double-blind trial, we assigned patients who had septic shock and were receiving a minimum of 5 microg of norepinephrine per minute to receive either low-dose vasopressin (0.01 to 0.03 U per minute) or norepinephrine (5 to 15 microg per minute) in addition to open-label vasopressors. All vasopressor infusions were titrated and tapered according to protocols to maintain a target blood pressure. The primary end point was the mortality rate 28 days after the start of infusions.

- RESULTS: A total of 778 patients underwent randomization, were infused with the study drug (396 patients received vasopressin, and 382 norepinephrine), and were included in the analysis. There was no significant difference between the vasopressin and norepinephrine groups in the 28-day mortality rate (35.4% and 39.3%, respectively; P=0.26) or in 90-day mortality (43.9% and 49.6%, respectively; P=0.11). There were no significant differences in the overall rates of serious adverse events (10.3% and 10.5%, respectively; P=1.00). In the prospectively defined stratum of less severe septic shock, the mortality rate was lower in the vasopressin group than in the norepinephrine group at 28 days (26.5% vs. 35.7%, P=0.05); in the stratum of more severe septic shock, there was no significant difference in 28-day mortality (44.0% and 42.5%, respectively; P=0.76). A test for heterogeneity between these two study strata was not significant (P=0.10).

- CONCLUSIONS: Low-dose vasopressin did not reduce mortality rates as compared with norepinephrine among patients with septic shock who were treated with catecholamine vasopressors. (Current Controlled Trials number
Vasopressin versus Norepinephrine infusion in patients with septic shock


CONCLUSIONS:
Low-dose vasopressin did not reduce mortality rates as compared with norepinephrine among patients with septic shock who were treated with catecholamine vasopressors.
**Vasopressors for shock**


- **BACKGROUND:** Besides reversing the underlying cause, the first line treatment for the symptoms of shock is usually the administration of intravenous fluids. If this method is not successful, vasopressors such as dopamine, dobutamine, adrenaline, noradrenaline and vasopressin are recommended. It is unclear if there is a vasopressor of choice, either for the treatment of particular forms of shock or for the treatment of shock in general.

- **OBJECTIVES:** To assess the efficacy of vasopressors for circulatory shock in critically ill patients. Our main aim was to assess whether particular vasopressors reduce overall mortality. We also intended to identify whether the choice of vasopressor influences outcomes such as length-of-stay in the intensive care unit and health-related quality of life.

- **SEARCH STRATEGY:** We searched MEDLINE, the Cochrane Central Register of Controlled Trials, EMBASE, PASCAL BioMed, CINAHL, BIOSIS, and PsychINFO: all from inception to November 2003; for randomized controlled trials. We also asked experts in the field and searched meta-registries for ongoing trials.

- **SELECTION CRITERIA:** We included randomized controlled trials comparing various vasopressors, vasopressors with placebo or vasopressors with intravenous fluids for the treatment of any kind of circulatory failure (shock). Mortality was the main outcome.

- **DATA COLLECTION AND ANALYSIS:** Two reviewers abstracted data independently. Disagreement between two reviewers was discussed and resolved with a third reviewer. We used random effects models for combining quantitative data. **MAIN RESULTS:** We identified eight randomized controlled trials. Reporting of methodological details was for many items not satisfactory: only two studies reported allocation concealment, and two that the outcome assessor was blind to the intervention. Two studies compared norepinephrine plus dobutamine with epinephrine alone in patients with septic shock (52 patients, relative risk of death 0.98, 95% confidence interval 0.57 to 1.67). Three studies compared norepinephrine with dopamine in patients with septic shock (62 patients, relative risk 0.88, 0.57 to 1.36). Two studies compared vasopressin with placebo in patients with septic shock (58 patients, relative risk 1.04, 0.06 to 19.33). One study compared terlipressin with norepinephrine in patients with refractory hypotension after general anaesthesia but there were no deaths (20 patients).

- **REVIEWERS' CONCLUSIONS:** The current available evidence is not suited to inform clinical practice. We were unable to determine whether a particular vasopressor is superior to other agents in the treatment of states of shock.
CONCLUSIONS:
The current available evidence is not suited to inform clinical practice. We were unable to determine whether a particular vasopressor is superior to other agents in the treatment of states of shock.
Choice of agent in septic shock

The most appropriate vasopressor choice depends on whether the patient has:

- Hyperdynamic shock
- Hypodynamic shock
Hyperdynamic shock

- Patients with hyperdynamic septic shock (hypotension, low SVR, and high CI) tend to have warm extremities ("warm sepsis").

- Agents with prominent alpha vasoconstrictor effects (eg, norepinephrine and phenylephrine) are most effective in this setting, increasing MAP by increasing the SVR.

- The published experience with norepinephrine is more extensive than with phenylephrine.

- Supporting this approach, a double-blind trial randomly assigned 32 patients with hyperdynamic septic shock to receive norepinephrine (35 to 350 mcg/min) or dopamine (3 to 25 mcg/kg per minute). Patients who received norepinephrine were more likely to achieve an adequate hemodynamic response (93 versus 31 percent). Also, more than 90 percent of the dopamine failures responded to norepinephrine.

Hypodynamic shock

- Patients with hypodynamic septic shock (hypotension, low to modestly reduced SVR, and low CI) manifest hypoperfusion of the extremities ("cold sepsis").
- **Dopamine** may be preferable in patients with hypodynamic sepsis because it can increase the MAP with minimal increase of the SVR. As a result, myocardial oxygen consumption is minimized.
- Given the potential for dopamine to fail as a single agent, though, one must be prepared to rapidly add or substitute a second agent such as **norepinephrine**.
- Of concern, retrospective analysis of data collected from 462 patients with septic shock during a prospective cohort study found a higher ICU mortality among the patients who received dopamine (odds ratio 2.05, 95% CI 1.25-3.37). However, the study was severely limited by its retrospective design, which permitted most patients to receive multiple vasoactive agents and many to receive dopamine only in "renal" dosing. These observational data need to be confirmed by a controlled trials before a change of clinical practice is warranted.

- **Does dopamine administration in shock influence outcome? Results of the Sepsis Occurrence in Acutely Ill Patients (SOAP) Study.** Sakr Y et al. Crit Care Med. 2006 Mar
Hypodynamic shock

- **Epinephrine** is not routinely used as an initial, single agent in septic shock because it has been shown to impair splanchnic blood flow and tissue perfusion. Although the addition of **dobutamine** might blunt these effects, epinephrine remains a third-line agent.
"Renal dose" dopamine

- **Dopamine** selectively increases renal blood flow when administered to normal volunteers at 1 to 3 mcg/kg per minute.

- Animal studies also suggest that low-dose dopamine in the setting of vasopressor-dependent sepsis helps preserve renal blood flow.

- However, a beneficial effect of low or "renal dose" dopamine is less proven in human patients with sepsis or other critical illness.

- Critically ill patients who do not have evidence of renal insufficiency or decreased urine output will develop a diuresis in response to dopamine at 2 to 3 mcg/kg per minute, with variable effects on creatinine clearance, but the benefit of this diuresis is questionable.

- One small study demonstrated that the addition of low dose dopamine to patients receiving other vasopressors increases splanchnic blood flow but does not alter other indices of mesenteric perfusion, such as gastric intramucosal pH (pHi).
At present, there are no data to support the routine use of low dose dopamine to prevent or treat acute renal failure or mesenteric ischemia.

In general, the most effective means of protecting the kidneys in the setting of septic shock appears to be the maintenance of MAP >60 mmHg while attempting to avoid excessive vasoconstriction (ie, the SVR should not exceed 1300 dynes x sec/cm²).
Supranormal cardiac index

- Elevation of the cardiac index with inotropic agents to supranormal values (ie, >4.5 L/minute per m²) potentially increases oxygen delivery to peripheral tissues.
- In theory, increased oxygen delivery may prevent tissue hypoxia and improve outcomes, and initial studies appeared to support this hypothesis.
- However, later larger trials showed that goal-oriented hemodynamic therapy to increase either cardiac index to >4.5 L/min per m² or oxygen delivery to >600 to 650 mL/min per m² with volume expansion or dobutamine resulted in either no improvement or worsened morbidity or mortality.
  - A randomized and controlled trial of the effect of treatment aimed at maximizing oxygen delivery in patients with severe sepsis or septic shock. Alia I et al. Chest 1999 Feb
- Therefore, the routine administration of vasopressors or inotropes to improve cardiac output or oxygen delivery to supranormal levels is not advocated.
Comparison of dopamine and norepinephrine in the treatment of shock.

De Backer D et al. Brussels, Belgium

BACKGROUND: Both dopamine and norepinephrine are recommended as first-line vasopressor agents in the treatment of shock. There is a continuing controversy about whether one agent is superior to the other. METHODS: In this multicenter, randomized trial, we assigned patients with shock to receive either dopamine or norepinephrine as first-line vasopressor therapy to restore and maintain blood pressure. When blood pressure could not be maintained with a dose of 20 microg per kilogram of body weight per minute for dopamine or a dose of 0.19 microg per kilogram per minute for norepinephrine, open-label norepinephrine, epinephrine, or vasopressin could be added. The primary outcome was the rate of death at 28 days after randomization; secondary end points included the number of days without need for organ support and the occurrence of adverse events. RESULTS: The trial included 1679 patients, of whom 858 were assigned to dopamine and 821 to norepinephrine. The baseline characteristics of the groups were similar. There was no significant between-group difference in the rate of death at 28 days (52.5% in the dopamine group and 48.5% in the norepinephrine group; odds ratio with dopamine, 1.17; 95% confidence interval, 0.97 to 1.42; P=0.10). However, there were more arrhythmic events among the patients treated with dopamine than among those treated with norepinephrine (207 events [24.1%] vs. 102 events [12.4%], P<0.001). A subgroup analysis showed that dopamine, as compared with norepinephrine, was associated with an increased rate of death at 28 days among the 280 patients with cardiogenic shock but not among the 1044 patients with septic shock or the 263 with hypovolemic shock (P=0.03 for cardiogenic shock, P=0.19 for septic shock, and P=0.84 for hypovolemic shock, in Kaplan-Meier analyses).

CONCLUSIONS: Although there was no significant difference in the rate of death between patients with shock who were treated with dopamine as the first-line vasopressor agent and those who were treated with norepinephrine, the use of dopamine was associated with a greater number of adverse events.
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**CONCLUSIONS:** Although there was no significant difference in the rate of death between patients with shock who were treated with dopamine as the first-line vasopressor agent and those who were treated with norepinephrine, the use of dopamine was associated with a greater number of adverse events.
Thank You