VASOACTIVE AGENTS IN SEPSIS

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Definition of Shock and Septic Shock
Common Presentation of Pediatric Sepsis
International Guidelines
Common Vasoactive Drugs
Literature Review
Conclusion
The Third International Consensus Definitions for Sepsis and Septic Shock (2016)

Sepsis
- life-threatening organ dysfunction caused by a dysregulated host response to infection.
- organ dysfunction represented by an increase in the Sequential [Sepsis-related] Organ Failure Assessment (SOFA) score of 2 points or more
- in-hospital mortality > 10%.

Septic shock
- a subset of sepsis in which particularly profound circulatory, cellular, and metabolic abnormalities are associated with greater risk of mortality than with sepsis alone
- vasopressor requirement to maintain a mean arterial pressure of 65 mm Hg or greater and serum lactate level > 2 mmol/L in the absence of hypovolemia.
- The combination is associated with hospital mortality rates > 40%.

JAMA. 2016 February
Sepsis in Children

- neonates and young children more commonly present with “cold shock”
- a state of elevated SVR and low cardiac output with cold extremities and delayed capillary refill.
- reflects the inability of infants and young children to increase heart rate and cardiac stroke volume to the same extent as adults.
- vasoconstriction resulting in “cold shock”
  - response to a decrease in cardiac output with hypotension manifesting as a relatively late finding in young children
Role Of Vasoactive Agents In Sepsis

◦ Fluid resuscitation alone is frequently insufficient to restore a minimal organ perfusion pressure in septic shock.

◦ Fluid-refractory septic shock is defined as persistent shock despite at least 40–60 ml/kg of fluid resuscitation in the first hour.

➢ inotropic or vasopressor therapy should be initiated, ideally within the first 60 minutes of resuscitation.
Common Vasoactive Drugs

- Commonly used vasoactive agents in pediatric septic include
  - Dopamine
  - Epinephrine
  - Norepinephrine
  - Dobutamine
  - Phosphodiesterase inhibitors.
  - Vasopressin and analogue

- Different agents have varying effects on heart rate, myocardial contractility, and vascular tone, and should be selectively used based on the pathophysiologic parameters that require manipulation.
Dopamine

- stimulates dopamine (D₁ and D₂), α and β receptors.

- **Low** infusion rates (1–5 mcg/kg/min)
  - dopamine receptor agonism
  - augment renal sodium excretion
  - improves splanchnic perfusion.

- **Intermediate** dosing (5–10 mcg/kg/min)
  - β-receptor agonism
  - chronotropic and inotropic effects.
  - increase in systolic blood pressure, minimal change in diastolic pressure, and a subsequent increase in pulse pressure.
  - Systemic vascular resistance is unchanged secondary to the balance of dopamine’s ability to reduce regional arteriolar resistance in the mesentery and kidneys, with only a minor increase in other vasculature.

- **Higher** doses (10–20 mcg/kg/min)
  - predominant α effect
  - increased vascular resistance
Dobutamine

- acts on beta-1, beta-2, and alpha-1 adrenergic receptors.
- relative strong additive inotropic effect but weak chronotropic effect
- Alpha-1 agonist activity in the vasculature causes vasoconstriction, which balances the beta-2 vasodilatory effect, permitting relatively unchanged blood pressure
- increases myocardial contractility, with accompanying reflex reduction in sympathetic tone leads to a decrease in total peripheral resistance
- shown to cause a dose-dependent decrease in plasma norepinephrine.
- Overall, this leads to an increase in cardiac output by selective augmentation of stroke volume with a decrease in systemic vascular resistance.
- Doses of 5–20 mcg/kg/min are employed for inotropic support.
Epinephrine

- useful in treating shock associated with myocardial dysfunction and hypotension.
- activates $a_1$, $\beta_1$, and $\beta_2$ receptors.

**Low doses** (0.05–0.1 mcg/kg/min)

- $\beta_1$ receptors
  - increase in **heart rate** and **inotropy**.
  - Myocardial oxygen utilization may increase out of proportion to the increase in force of contraction.
- $\beta_2$ receptors
  - promotes **relaxation of resistance arterioles**
  - promoting a decrease in systemic vascular resistance and diastolic blood pressure.
Epinephrine

- **Moderate doses** (0.1–1 mcg/kg/min)
  - activation of $\alpha_1$ receptors
  - increase in systemic vascular resistance.
  - often balanced by the improved cardiac output and relaxation of the arteriolar beds.

- **High-dose infusions** (1–2 mcg/kg/min)
  - significant vasoconstriction
  - possible compromise of blood flow to individual organs
  - most predominant vascular effects are seen in the smaller arterioles, although veins and large arteries also have a response.

- Epinephrine infusion leads to **improved blood pressure and cardiac output**
  - Blood flow to abdominal viscera may decrease as flow is diverted to heart, brain, and skeletal muscle.
Norepinephrine

- a potent $\alpha_1$ and $\beta_1$ agonist but little $\beta_2$ activity
- *elevations of systemic vascular resistance* because the $\alpha_1$ effects are not opposed by $\beta_2$ stimulation.
- Reflex vagal activity reduces the heart rate, blunting the expected chronotropic effect of $\beta_1$ stimulation.
- Stroke volume increases, but cardiac output changes minimally.
- Glomerular filtration is maintained, unless the decrease in renal blood flow is very substantial.
- Mesenteric vessels are also constricted, decreasing splanchnic and hepatic blood flow.
- Coronary blood flow increases because of direct coronary dilation and increase in blood pressure.
Vasopressin

- results in significant vasconstriction, mediated by V₁ receptors.
- evaluated in refractory hypotension in septic shock (warm shock).

In septic shock, vasopressin hypersensitivity is observed with significant increase in BP, mediated via:
- direct V₁R mediated vasoconstriction
- absolute or relative AVP deficiency allow V₁R to remain available and block mechanisms inducing their down regulation
- potentiating vasopressor efficacy of catecholamines through blockage of ATP sensitive K⁺ channels
- increased ACTH and cortisol release
Vasopressin

- induced *selective pulmonary, coronary, cerebral vasodilatation*

- *improved urine output and creatinine clearance*

- more beneficial in *preserving vital organ functions* in sepsis as compared to catecholamines

- should be used with cardiac output (CO) and central venous oxygen saturation (ScvO2) monitoring, as they can reduce CO due to potent vasoconstriction.
Terlipressin

- **longer-acting** analogue of Vasopressin

- Slowly cleaved to lysine-vasopressin by endo- and exopeptidases in liver and kidney over 4-6 hrs

- **intermittent bolus use** feasible rather than continuous infusion.

- Unlike vasopressin, does not appear to increase fibrinolytic activity.
Milrinone

- phosphodiesterase inhibitor

- combined inotropic and vasodilating effects ("inodilator"), both increasing cardiac contractility and reducing afterload

- lusitropic effects.

- less myocardial oxygen compared with adrenergic inotropic drugs such as dobutamine

- also a pulmonary vasodilator.
Levosimendan

- calcium-sensitizer **inotropic** agent with **vasodilatory** properties
- exerting beneficial effects particularly in cardiac surgery, a setting where it recently showed a survival benefit when compared with dobutamine
- absence of increase in myocardial oxygen consumption likely brings to a myocardial protective effect.
- Experimental studies in septic animal models showed that Levosimendan
  - improves myocardial function
  - attenuates intestinal dysfunction
  - improves microvascular oxygenation
  - protects against endotoxemic acute renal failure
  - exerts immunomodulatory effects.
Choice of Vasoactive Drugs

◦ selection of the appropriate vasoactive agent should be driven by clinical features of a patient’s presentation with
  ➢ low cardiac output and high systemic vascular resistance (“cold shock”)
  ➢ high cardiac output and low systemic vascular resistance (“warm shock”).

◦ Often children have dynamic shifts from one hemodynamic state to another, so constant clinical monitoring and changes in agent may be necessary.
Current International Pediatric Guidelines
ACCM algorithm for Pediatric Septic Shock (2007)

Figure 1. Algorithm for time sensitive, goal-directed stepwise management of hemodynamic support
Recognize decreased mental status and perfusion. Begin high flow $O_2$. 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

Monitor CVP in PICU, attain normal MAP-CVP & $ScvO_2 > 70\%$
Monitor CVP in PICU, attain normal MAP-CVP & ScvO2 > 70%

Cold shock with normal blood pressure:
1. Titrate fluid & epinephrine, ScvO2 > 70%, Hgb > 10g/dL
2. If ScvO2 still < 70%
   Add vasodilator with volume loading (nitrovasodilators, milrinone, imrinone, & others)
   Consider levsimendan

Cold shock with low blood pressure:
1. Titrate fluid & epinephrine, ScvO2 > 70%, Hgb > 10 g/dL
2. If still hypotensive consider norepinephrine
3. If ScvO2 still < 70% consider dobutamine, milrinone, enoximone or levsimendan

Warm shock with low blood pressure:
1. Titrate fluid & norepinephrine, ScvO2 > 70%, Hgb > 10 g/dL
2. If still hypotensive consider vasopressin, terlipressin or angiotensin
3. If ScvO2 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/m²

shock not reversed?

Refractory shock: ECMO
Literature Review
Dopamine Versus Epinephrine as First-Line Vasoactive Drugs in Pediatric Septic Shock.

- Double-blind, prospective, randomized controlled trial
- February 1, 2009, to July 31, 2013.
- PICU, Hospital Universitário da Universidade de São Paulo, Brazil
- **120 children** enrolled (63, dopamine; 57, epinephrine)
- aged 1 month to 15 years
- primary outcome: **28-day mortality**
- secondary outcomes:
  - rate of healthcare-associated infection,
  - the need for other vasoactive drugs,
  - multiple organ dysfunction score.

Ventura et al, Crit Care Med. 2015
Dopamine Versus Epinephrine as First-Line Vasoactive Drugs in Pediatric Septic Shock.

- Patients were randomly assigned to receive either
  - dopamine (5-10 μg/kg/min)
  - epinephrine (0.1-0.3 μg/kg/min)
- Total 17 deaths (14.2%)
- 13 (20.6%) in the dopamine group and four (7%) in the epinephrine group (p=0.033).
- Dopamine was associated with death (odds ratio, 6.5; 95% CI, 1.1-37.8; p=0.037) and healthcare-associated infection (odds ratio, 67.7; 95% CI, 5.0-910.8; p=0.001).
- Use of epinephrine was associated with a survival odds ratio of 6.49

CONCLUSIONS:
- Dopamine was associated with an increased risk of death and healthcare-associated infection.
- Early administration of epinephrine was associated with increased survival

Ventura et al, Crit Care Med. 2015
Figure 3. Kaplan-Meyer survival function according to group.
Dopamine Versus Norepinephrine In The Treatment Of Septic Shock: A Meta-analysis

- All studies on the outcome of patients with septic shock treated with dopamine compared to norepinephrine.
- Observational and randomized trials were analyzed separately.
- Five observational (1,360 patients) and six randomized (1,408 patients) trials, totaling 2,768 patients (1,474 received norepinephrine and 1,294 received dopamine).

**Observational studies**
- After exclusion of a trial which was responsible for the heterogeneity, dopamine administration was associated with an increased risk of death (relative risk, 1.23; confidence interval, 1.05–1.43; \( p < .01 \)).

De Backer et al; Crit Care Med 2012
Figure 2. Forest plot of risk ratio (RR) of death (28 days or nearest estimate) in observational trials. The p value for aggregate RR of dopamine (dopa) compared to norepinephrine (norepi) in observational studies was .72. Relative weights of the different trials in the analysis: Martin et al (11) 20%; Hall et al (24) 18%; Sakr et al (3) 21%; Povoа et al (13) 21%; and Boulain et al (12) 19%. There was significant heterogeneity among the trials (p < .001, $I^2 = 79.3$; confidence interval, 50.9%–91.3%); the trial by Povoа et al (13) was identified to be responsible for the heterogeneity (see text for details). CI, confidence interval.
Dopamine Versus Norepinephrine In The Treatment Of Septic Shock: A Meta-analysis

Randomized trials
- dopamine was associated with an increased risk of death (relative risk, 1.12; confidence interval, 1.01–1.20; p <0 .035).
- 2 trials reported arrhythmias
- Arrhythmias were more frequent with dopamine than with norepinephrine (relative risk, 2.34; confidence interval, 1.46–3.77; p < .001).

Conclusions: Dopamine is associated with greater mortality and a higher incidence of arrhythmic events compared to norepinephrine.

De Backer et al; Crit Care Med 2012
Figure 3. Forest plot of risk ratio (RR) of death (28 days or nearest estimate) in interventional trials. The $p$ value for aggregate RR of dopamine ($dopa$) compared to norepinephrine ($norepi$) in interventional studies was .035. Relative weights of the different trials in the analysis: Martin et al (27) 2%; Marik et al (30) 1%; Ruokonen et al (29) 1%; Mathur et al (25) 4%; De Backer et al (15) 81%; and Patel et al (16) 10%. No heterogeneity was observed ($p = .77; I^2 = 0$; confidence interval, 0%–25%).
Vasopressin Vs Norepinephrine Infusion In Patients With Septic Shock.

- multicenter, randomized, double-blind trial
- 778 patients (396 vasopressin; 382 norepinephrine),
- patients with 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.
- primary end point: 28-day mortality rate

Vasopressin Vs Norepinephrine Infusion In Patients With Septic Shock.

- 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
- 90-day mortality (43.9% and 49.6%, respectively; P=0.11).
- no significant differences in the overall rates of serious adverse events (10.3% and 10.5%, respectively; P=1.00).

CONCLUSIONS:

- Low-dose vasopressin did not reduce mortality rates as compared with norepinephrine among patients with septic shock who were treated with catecholamine vasopressors.
Vasopressin In Pediatric Vasodilatory Shock:

- **Objective:** Evaluate the efficacy and safety of vasopressin as an **adjunctive agent** in **pediatric vasodilatory shock**.

- **Multicenter, double-blind trial**

  - Children with vasodilatory shock were randomized to receive low-dose vasopressin (0.0005-0.002 U/kg/min) or placebo in addition to open-label vasoactive agents.

  - Vasoactive infusions were titrated to clinical endpoints of adequate perfusion.

  - **Primary outcome:** Time to vasoactive-free hemodynamic stability.

  - **Secondary outcomes** included mortality, organ-failure-free days, length of critical care unit stay, and adverse events.

  

  Canadian Critical Care Trials Group; Am J Respi Crit Care Med 2009
Vasopressin In Pediatric Vasodilatory Shock:

- 65 children were randomized to receive the study drug (33 vasopressin, 32 placebo)
- No significant difference in the primary outcome between the vasopressin and placebo groups (49.7 vs. 47.1 hours; P = 0.85).
- 10 deaths (30%) in the vasopressin group and five (15.6%) in the placebo group (relative risk, 1.94; 95% confidence interval, 0.75-5.05; P = 0.24).
- No significant differences with respect to
  - organ failure-free days (22 vs. 25.5 days; P = 0.11)
  - ventilator-free days (16.5 vs. 23 days; P = 0.15)
  - length of stay (8 vs. 8.5 days; P = 0.93),
  - adverse event rate ratios (12.0%; 95% confidence interval, -2.6 to 26.7; P = 0.15).

Canadian Critical Care Trials Group; Am J Respi Crit Care Med 2009
### TABLE 3. OUTCOMES

<table>
<thead>
<tr>
<th>Variable</th>
<th>Vasopressin</th>
<th>Placebo</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Time to hemodynamic stability in hours, median (IQR)†</strong></td>
<td>49.7 (29.8–218.5)*</td>
<td>47.1 (25.6–87.1)</td>
<td>0.85</td>
</tr>
<tr>
<td><strong>Secondary outcomes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30-d mortality, n (%)</td>
<td>10 (30.3)</td>
<td>5 (15.6)</td>
<td>0.24</td>
</tr>
<tr>
<td>Vasoactive-free days‡</td>
<td>25.2 (0.0–28.3)</td>
<td>27.5 (23.1–28.9)</td>
<td>0.13</td>
</tr>
<tr>
<td>Organ failure-free days†</td>
<td>22.0 (0.0–26.5)</td>
<td>25.5 (18.0–27.8)</td>
<td>0.11</td>
</tr>
<tr>
<td>Ventilator-free days‡</td>
<td>16.5 (0.0–24.0)</td>
<td>23.0 (13.0–25.5)</td>
<td>0.15</td>
</tr>
<tr>
<td>Highest number of organ failures</td>
<td>3.0 (3.0–6.0)</td>
<td>3.0 (3.0–4.0)</td>
<td>0.66</td>
</tr>
<tr>
<td>Highest PELOD score after randomization</td>
<td>22.0 (13.5–71.0)</td>
<td>13.0 (11.3–22.8)</td>
<td>0.03</td>
</tr>
<tr>
<td>Change in PELOD score‡</td>
<td>1.0 (0.0–43.5)</td>
<td>0.0 (0.0–8.8)</td>
<td>0.14</td>
</tr>
<tr>
<td>Length of PCCU stay, d</td>
<td>8.0 (4.3–15.0)</td>
<td>8.5 (5.3–16.8)</td>
<td>0.93</td>
</tr>
<tr>
<td>4 h AVP levels, pg/ml</td>
<td>99.2 (64.4–149.9)</td>
<td>2.9 (1.0–6.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Change in vasoactive score (from baseline to highest score)**</td>
<td>0.0 (−0.4–12.1)</td>
<td>0.0 (0.0–7.0)</td>
<td>0.93</td>
</tr>
<tr>
<td>Mean arterial blood pressure 1 hour post-study drug</td>
<td>73.5 (62.5–88.8)</td>
<td>74.0 (60.0–80.0)</td>
<td>0.18</td>
</tr>
<tr>
<td>Change from baseline in mean arterial blood pressure 1 hour post-study drug</td>
<td>14.3 (16.6)</td>
<td>5.1 (11.5)</td>
<td>0.02</td>
</tr>
<tr>
<td>Urine output at 24 hours, ml/kg/h</td>
<td>1.7 (0.7–3.5)</td>
<td>1.5 (0.7–3.7)</td>
<td>0.65</td>
</tr>
<tr>
<td>Change in biochemical variables during study intervention</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum lactate, mmol/L</td>
<td>0.2 (0.1–1.3)</td>
<td>0.2 (0.0–1.3)</td>
<td>0.57</td>
</tr>
<tr>
<td>Creatinine, μmol/L, mean (SD)</td>
<td>19.1 (45.4)</td>
<td>10.4 (25.0)</td>
<td>0.35</td>
</tr>
<tr>
<td>Bilirubin, μmol/L, mean (SD)</td>
<td>19.8 (15.9)</td>
<td>29.3 (54.2)</td>
<td>0.58</td>
</tr>
<tr>
<td>Platelet count, mean (SD)</td>
<td>−50.6 (66.5)</td>
<td>−47.64 (49.7)</td>
<td>0.84</td>
</tr>
<tr>
<td>INR, mean (SD)</td>
<td>0.5 (2.1)</td>
<td>0.2 (0.6)</td>
<td>0.38</td>
</tr>
</tbody>
</table>
CONCLUSIONS:

◦ Low-dose vasopressin did not demonstrate any beneficial effects.

◦ Although not statistically significant, there was a concerning trend toward increased mortality.

◦ 10 deaths (30%) in the vasopressin group versus only five (15.6%) in the placebo group (relative risk, 1.94; 95% confidence interval, 0.75–5.05; p=0.24).66
Terlipressin as a rescue therapy for catecholamine-resistant septic shock in children.

- A **randomized, non blind study** in the pediatric intensive care unit of a university hospital.
- **58 children** with septic shock and **refractory hypotension** despite fluid loading and high doses of catecholamines.
- Randomly enrolled to terlipressin (TP, n=30) or control (n=28).
- TP was administered as intravenous bolus doses of 20 microg/kg every 6 h for a maximum of 96 h.
- Hemodynamic changes, PaO2/FIO2 rates, length of stay, and mortality rate in PICU were recorded prospectively.

Yildizdas et al; Intensive Care Med. 2008
Terlipressin As A Rescue Therapy For Catecholamine-resistant Septic Shock In Children

RESULTS:

- **Mean arterial pressure and PaO2/FIO2 significantly increased.**
- Heart rate significantly decreased 30 min after each TP treatment
- Mean stay in the PICU was
  - shorter in the TP group (13.4+/−7.9 vs. 20.2+/−9.7 days)
  - longer among non survivors of the TP group vs. control (10.4+/−6.9 vs. 6.2+/−3.4 days).
- **Mortality did not differ** from control (67.3% vs. 71.4%).
- Blood urea nitrogen, creatinine, AST, ALT, and urine output of patients in the TP group did not change after terlipressin.

Yildizdas et al; Intensive Care Med. 2008
Hemodynamic Effects Of I.V. Milrinone Lactate In Pediatric Patients With Septic Shock

- Prospective, double-blinded, randomized, placebo-controlled, descriptive, interventional study.
- 26-bed pediatric ICU at Children's Medical Center of Dallas and a 10-bed pediatric trauma ICU at Parkland Memorial Hospital.
- 12 patients (age range, 9 months to 15 years) with non hyperdynamic septic shock despite administration of catecholamines
  - cardiac index [CI] normal [3.5 to 5.5 L/min/m$^2$] or low [< or =3.5 L/min/m$^2$]
  - systemic vascular resistance index [SVRI] normal [800 to 1,600 dyne.s.cm$^5$/m$^2$] or high [> or =1,600 dyne.s.cm$^5$/m$^2$];
  - pulmonary capillary wedge pressure [PCWP] normal [8 to 12 mm Hg] or higher
  - with clinical signs of poor perfusion

Barton P; Chest. 1996
Hemodynamic Effects Of I.V. Milrinone Lactate In Pediatric Patients With Septic Shock

- Patients were randomized to receive either a loading dose of 50 mcg/kg i.v. of milrinone followed by a continuous i.v. infusion of 0.5 mcg/kg/min (Group A) or an equal volume loading dose and continuous infusion of placebo (Group B).
- After 2 h, group A received an equal-volume loading dose followed by a continuous infusion of placebo while the milrinone infusion continued,
- group B received a 50 mcg/kg loading dose of milrinone followed by a continuous infusion of 0.5 mcg/kg/min while the placebo infusion remained.
- Outcome variable were measured at baseline, 0.5, 1.0, 2.0, 2.5, 3.0, and 4.0 h.
- Echocardiographic measurements were taken at baseline, hour 2, and hour 4 in all subjects.
- No changes in other inotropic or mechanical ventilatory support were allowed during the study period.

Barton P et al; Chest. 1996
Hemodynamic Effects Of I.V. Milrinone Lactate In Pediatric Patients With Septic Shock

MAIN RESULTS:
- Milrinone significantly increased
  - Cardiac Index
  - stroke volume index (SVI)
  - right and left ventricular stroke work index
  - oxygen delivery (Do2) at 0.5, 1.0, and 2.0 h post loading dose (p < 0.05)
- while significantly decreasing
  - Systemic Vascular Resistance Index
  - Pulmonary vascular resistance index
  - Mean pulmonary arterial pressure at 0.5, 1.0, and 2.0 h postloading dose (p < 0.05).

Barton P et al; Chest. 1996
Hemodynamic Effects Of I.V. Milrinone Lactate In Pediatric Patients With Septic Shock

- No clinically or statistically significant changes in heart rate, systolic and diastolic BP, mean systemic arterial pressure, or PCWP

CONCLUSIONS:

- In a volume-resuscitated pediatric patient with septic shock, when administered in addition to catecholamines, milrinone will improve cardiovascular function.
- No adverse effects were observed

Barton P et al; Chest. 1996
Levosimendan reduces mortality in patients with severe sepsis and septic shock

- A meta-analysis of randomized trials
- 7 studies (246 patients)
- Levosimendan was associated with **significantly reduced mortality** compared with standard inotropic therapy
- (59/125 [47%] in the levosimendan group and 74/121 [61%] in the control group; risk ratio = 0.79 [0.63-0.98], numbers needed to treat = 7).
- **Blood lactate** was significantly reduced in the levosimendan group,
- **cardiac index and total fluid infused** were significantly higher in the levosimendan group.
- No difference in mean arterial pressure and norepinephrine usage was noted.

Zangrillo et al, J Crit Care. 2015
Fig. 2. Forest plot for the risk of mortality at longest follow-up available.
Levosimendan In Cold Shock

- Beneficial effects of levosimendan infusion in 2 infants (39 and 64 days old) with low cardiac output septic shock refractory to volume replacement and to the catecholamines dopamine and dobutamine.

- Levosimendan infusion (0.15 μg/kg/min) promptly
  - increased both patients' myocardial contractility
  - improved tissue perfusion,
  - reducing lactate levels
  - increasing urine output.

- Adverse effect was moderate hypotension in one infant, who reversed by adding norepinephrine to levosimendan.

- Potential beneficial effects of levosimendan infusion to restore hemodynamics in infants with low cardiac output septic shock resistant to catecholamines

Papoff et al, Paediatric Emergency care 2012
Recognize decreased mental status and perfusion. Begin high flow \( \text{O}_2 \). 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.

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

Monitor CVP in PICU, attain normal MAP-CVP & \( \text{SevO}_2 \) > 70%
Monitor CVP in PICU, attain normal MAP-CVP & ScvO2 > 70%

Cold shock with normal blood pressure:
1. Titrate fluid & epinephrine, ScvO2 > 70%, Hgb > 10 g/dL
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   Consider levosimendan

Cold shock with low blood pressure:
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3. If ScvO2 still < 70% consider dobutamine, milrinone, enoximone or levosimendan

Warm shock with low blood pressure:
1. Titrate fluid & norepinephrine, ScvO2 > 70%,
2. If still hypotensive consider vasopressin, terlipressin or angiotensin
3. If ScvO2 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/m2

shock not reversed?

Refractory shock: ECMO

Figure 1.
Algorithm for intensive care management of severe shock in pediatric intensive care.
Neonates and young children more commonly present with “cold shock”

Inotropic or vasopressor therapy should be initiated after 40–60 ml/kg of fluid resuscitation, ideally within the first 60 minutes of resuscitation.

Different vasoactive agents should be selectively used based on the pathophysiologic parameters that require manipulation.

Often children have dynamic shifts from one hemodynamic state to another, so constant clinical monitoring and changes in agent may be necessary.

Dopamine was associated with an increased risk of death and healthcare-associated infection in a recent paediatric study.

Early administration of epinephrine was associated with increased survival.
Dopamine is associated with greater mortality and a higher incidence of arrhythmic events compared to norepinephrine in adult trials.

Low-dose Vasopressin did not demonstrate any beneficial effects in pediatric vasodilatory shock but showing trend toward increased mortality.

Terlipressin significantly increased mean arterial pressure and PaO2/FIO2 but did not improve survival in children with Catecholamine-resistant Septic Shock.

In a volume-resuscitated pediatric patient with septic shock, when administered in addition to catecholamines, milrinone was shown to improve cardiovascular function.

Levosimendan was associated with significantly reduced mortality in patients with septic shock compared with standard inotropic therapy in a meta-analysis of randomized trials in adult.

Potential beneficial effects of levosimendan infusion to restore hemodynamics in infants with low cardiac output septic shock resistant to catecholamines.
Thank You