Fluid and Vasoactive Agents in Septic Shock
Fluid resuscitation

Improving tissue perfusion
- Early resuscitation phase
  - Avoid underload
  - Aggressive fluid management

Increasing tissue edema
- Late resuscitation phase
  - Avoid overload
  - Conservative fluid management

- 75 pediatric pts with septic shock
- Mortality: < 20 ml/kg fluid vs > 40 ml/kg fluid in the first hour (73% vs 33%, P<.05)
- Early fluid resuscitation was ass. with a 3-fold reduction in the odds of death (OD, 0.33; 95% CI, 0.13-0.85)
Increased Fluid Adm. in the First Three Hours of Sepsis Resuscitation Is Ass. With Reduced Mortality. Chest 2014

- Increased fluid adm. in the **first 3 hrs** of sepsis resuscitation is ass. with reduced mortality

<table>
<thead>
<tr>
<th>Variable</th>
<th>Nonsurvivors (n = 142)</th>
<th>Survivors (n = 452)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluid received in hours 0-3, mL</td>
<td>1,600 (600 to 3,010)</td>
<td>2,085 (940 to 4,080)</td>
<td>.007*</td>
</tr>
<tr>
<td>Fluid received in hours 3.1-6, mL</td>
<td>880 (360 to 1,680)</td>
<td>660 (290 to 1,485)</td>
<td>.09</td>
</tr>
<tr>
<td>Total fluid received in 6 h, mL</td>
<td>2,875 (1,390 to 47,20)</td>
<td>3,150 (1,630 to 5,665)</td>
<td>.10</td>
</tr>
<tr>
<td>Net positive fluid balance hours 0-3, mL</td>
<td>1,480 (550 to 2,815)</td>
<td>1,790 (705 to 3,665)</td>
<td>.051</td>
</tr>
<tr>
<td>Net positive fluid balance hours 3.1-6, mL</td>
<td>665 (250 to 1,595)</td>
<td>465 (100 to 1,170)</td>
<td>.0032*</td>
</tr>
</tbody>
</table>

**Multivariate Regression**

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion of fluid in first 3 h</td>
<td>0.34 (0.15-0.75)</td>
<td>.0076</td>
</tr>
<tr>
<td>Total fluid in 6 h</td>
<td>1.00 (1.00-1.00)</td>
<td>.0138</td>
</tr>
<tr>
<td>Age</td>
<td>1.02 (1.01-1.04)</td>
<td>.0050</td>
</tr>
<tr>
<td>Weight</td>
<td>1.00 (0.99-1.01)</td>
<td>.7008</td>
</tr>
<tr>
<td>Admission APACHE III score</td>
<td>1.00 (0.98-1.01)</td>
<td>.4670</td>
</tr>
<tr>
<td>SOFA score on day 1</td>
<td>1.20 (1.14-1.27)</td>
<td>&lt;.0001*</td>
</tr>
</tbody>
</table>
Fluid resuscitation in septic shock: A positive fluid balance and elevated CVP are associated with increased mortality. **CCM 2011**

- Retrosp. review of 778 pts enrolled VASST study
- Higher positive fluid balance and/or higher CVP at **12 hrs** was ass. with increased mortality

### Adjusted Survival Curves

**Fluid Balance Quartiles 12 hours**

<table>
<thead>
<tr>
<th>Fluid Balance Group</th>
<th>Adjusted Hazard Ratio versus Quartile 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 hrs</td>
<td></td>
</tr>
<tr>
<td>Quartile 1</td>
<td>0.569 (0.405–0.799)</td>
</tr>
<tr>
<td>Quartile 2</td>
<td>0.581 (0.414–0.816)</td>
</tr>
<tr>
<td>Quartile 3</td>
<td>0.762 (0.562–1.033)</td>
</tr>
</tbody>
</table>

**CVP Groups 12 hours**

<table>
<thead>
<tr>
<th>CVP Group</th>
<th>Adjusted Hazard Ratio versus CVP &gt;12 mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 hrs</td>
<td></td>
</tr>
<tr>
<td>CVP &lt;8 mm Hg</td>
<td>0.606 (0.363–0.913)</td>
</tr>
<tr>
<td>CVP 8–12 mm Hg</td>
<td>0.762 (0.562–0.943)</td>
</tr>
</tbody>
</table>
Fluid overload in pts with severe sepsis and septic shock treated with EGDT. *SHOCK 2015*

- Retrosp. cohort study (N=405)
- Severe sepsis and septic shock treated with adequate EGDT
- Clinical evidence of fluid overload (pitting edema, crackles, anasarca, or pulm. vascular congestion or edema on CXR)
  - Increased use of medical interventions and hospital mortality

<table>
<thead>
<tr>
<th>Multivariate analyses</th>
<th>Clinical evidence of fluid overload day 1 (n = 272)</th>
<th>Clinical evidence of persistent fluid overload (n = 182)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thoracentesis(^1)</td>
<td>3.40 (1.37–10.3)</td>
<td>3.83 (1.74–9.15)</td>
</tr>
<tr>
<td>Ultrafiltration(^2)</td>
<td>—</td>
<td>1.90 (0.90–4.19)</td>
</tr>
<tr>
<td>Diuretics(^3)</td>
<td>—</td>
<td>1.65 (1.00–2.72)</td>
</tr>
<tr>
<td>30-d ICU readmission, OR (95% CI)(^1)</td>
<td>—</td>
<td>1.61 (0.94–2.79)</td>
</tr>
<tr>
<td>Hospital mortality, OR (95% CI)(^1)</td>
<td>2.27 (1.31–4.09)</td>
<td>1.92 (1.16–3.22)</td>
</tr>
</tbody>
</table>
Fluid overload

- Tissue edema
  Starling equation: \( J_V = K_f ([P_c - P_i] - \sigma (\pi_i - \pi_c)) \)

- Damaged glycocalyx and endothelial tight junction
- Protein-rich plasma translocated into interstitial space
Tissue edema

- Fluid resuscitation
- Organ ischemia
- Reduced capillary blood flow
- Venous hypertension
- Leaky capillary
- Tissue edema
- Visceral swelling

Diagram showing the relationship between tissue edema and other conditions such as cerebral edema, myoccardial edema, pulmonary edema, hepatic congestion, and gut edema.
Fluid responsiveness

- Reliable prediction of FR (responder vs nonresponder)
- Use of fluids in responders whose end-organ perfusion parameters have not been met.
- Greater emphasis put on the use of VAA in nonresponders.
- There is no gold standard for determining FR.
- CVP is a poor measure of volume status & does not reliably predict FR & easily lead to excess fluid overload. (‘stopping rule’, not a target)
- Use of dynamic measures of FR over static measures such as CVP or ScvO2.
**Fluid responsiveness**

- Respiratory variations in pulse pr. (PPV), stroke volume (SVV), aortic flow velocity, SVC/IVC diameter, pulse oxymeter pleth signal in PPV pts: > app. 10-15% (ROC ~0.7-0.8)
- Passive leg raising (PLR) maneuver (ROC ~0.9)
- Fluid challenge (small volume)
• Respiratory variation in aortic blood flow velocity was the only variable to be shown to predict FR in children

• Static measures (HR, SBP, CVP, end diastolic volume) & dynamic measures based on ABP were not predictive.

• Passive leg raising ($\Delta CI_{\text{PLR}}$, change in CI) appeared to be a good predictor of FR
Fluid responsiveness & tissue edema

- Natriuretic peptide: damage endothelial glycocalyx
Fluid resuscitation

Initial fluid bolus (up to 60 ml/kg)

Initial inotrope (low dose dopamine)

Goal achieved

Maintenance tx

Yes

Fluid challenge

No

Fluid rechallenge

Yes

No
Choice of resuscitation fluids

- **Colloids**
  - Albumin (iso-oncotic 4-5%, hyperoncotic 20-25%)
  - Synthetic: hydroxyethyl starch (HES), gelatin, dextran

- **Crystalloids**
  - Normal saline
  - Balanced crystalloid: Ringer’s lactate, Hartmann’s sol., Plasma-Lyte
Colloids

- **Albumin**
  - Greater incr. in intravascular volume expansion (1:1.4)
  - Antioxidant and anti-inflammatory properties
  - May reduce vascular endothelial leukocyte adhesion

- **Synthetic colloids**
  - Greater incr. in intravascular volume expansion
  - No benefit over crystalloids
  - Accumulation in skin, liver, and kidney (HES)
    - Pruritus, hyperbilirubinemia, coagulopathy, and AKI
  - Potential mortality hazard ass. with HES
A Comparison of Albumin and Saline for Fluid Resuscitation in the Intensive Care Unit (SAFE trial). NEJM 2004

- Large-scale, prospective, blinded, RCT (N=6997)
- No difference in 28-day mortality

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- Post-hoc analysis: signif. reduction in adjusted OR of death in severe sepsis (OR 0.71; 95% CI, 0.52–0.97; P=0.03) ICM 2011
Multicenter, open-label trial, 1818 pts with severe sepsis
Albumin with crystalloid (serum alb ≥ 30 g/l) vs crystalloid alone
Higher MAP & lower net positive fluid balance over the first 7d
No signific. difference in 28-day or 90-day mortality rates
Subgroup analysis on pts with septic shock (N=1121): signific. lower 90-day mortality (43.6 vs 49.9%) (p=0.03)
Albumin in Severe Sepsis or Septic Shock

- Meta-analysis of large-scale, randomized trials

- Potential beneficial effect of albumin compared to saline in pts with severe sepsis or septic shock.
- RASP & PRECISE trial (ongoing)
Hydroxyethyl Starch or Saline for Fluid Resuscitation in Intensive Care (CHEST trial). NEJM 2012

• HES (130/0.4, Voluven) vs Saline in ICU pts (N=7000)
• No significant difference in 90 day-mortality
• More need of RRT (7.0% vs 5.8%, RR 1.21; 95% CI 1.00 to 1.45; P=0.04) and adverse events (pruritus, skin rash)
• Post hoc analysis: higher Cr, smaller U/O
Hydroxyethyl Starch 130/0.42 versus Ringer’s Acetate in Severe Sepsis (6S trial). NEJM 2012

- HES vs Ringer's Acetate in Severe Sepsis/Septic Shock (N=798)
- 90 day-mortality: 51% vs 43% (RR, 1.17; 95% CI, 1.01 to 1.36; P=0.03)
- Use of RRT: 22% vs 16% (RR, 1.35; 95% CI, 1.01 to 1.80; P=0.04)
Fluid Resuscitation with HES in Pts with Sepsis is ass. with an Increased Incidence of AKI and Use of RRT. JCC 2014

- Increase in AKI incidence, need of RRT, RBC transfusion, and 90-day mortality in patients with sepsis.
Crystalloids

- **Normal saline**
  - Supraphysiologic conc. of chloride
  - **Hyperchloremic metabolic acidosis** d/t a reduction in a SID
  - Signif. reduction in renal a. flow and renal cortical perfusion
  - Immune dysfunction

- **Balanced crystalloids**
  - Organic anions (lactate, acetate, gluconate) instead of chloride
  - Large vol. of mildly hypotonic solution (Ringer’s lactate) reduce extracellular tonicity
Ass. Btw Chloride-Liberal vs Chloride-Restrictive IV Fluid Adm. Strategy & AKI in Critically Ill Adults. *JAMA 2012*

- Prospective, open-label, sequential period study (N=1533)
- Chloride-liberal (free use of Cl\(^-\)-rich fluid) vs chloride-restrictive (restricted any use of Cl\(^-\)-rich fluid) period
- Signif. decreased AKI incidence & use of RRT in chloride-restrictive
Association Btw Choice of IV Crystalloid and In-Hospital Mortality Among Critically Ill Adults With Sepsis CCM 2014

- Propensity-matched cohort study (N=6,730)
- Balanced fluids was ass. with a low risk of in-hospital mortality
Classification of vasoactive agents

- Vasoconstrictor
- Inoconstrictor
- Vasodilator
- Inodilator

Reassess (± fluid)

- Inappropriately low Vascular Tone/VR
- Impaired Cardiac Contractility
- Overzealous Arteriolar Constriction

<table>
<thead>
<tr>
<th>Agent</th>
<th>Alpha-1</th>
<th>Beta-1</th>
<th>Beta-2</th>
<th>Dopamine</th>
<th>Vasopressin-1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dobutamine</td>
<td>+</td>
<td>++++</td>
<td>+++</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Dopamine</td>
<td>+++</td>
<td>++++</td>
<td>++</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>++++</td>
<td>++++</td>
<td>+++</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Milrinone</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>++++</td>
<td>++++</td>
<td>++</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Phenylephrine</td>
<td>+++</td>
<td>++++</td>
<td>++++</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Vasopressin</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

0 = no significant receptor affinity; through ++++ = minimal to maximal receptor affinity.

JCPT 2015
Comparison of Dopamine and Norepinephrine in the Treatment of Shock (SOAP II). NEJM 2010

- Multicenter, randomized, blinded trial in pts with shock (N=1,679)
- DOP (~20 μg/kg/min) vs NE (~0.19 μg/kg/min) as 1st-line vasopressor
- 28-day mortality rate:
  - 52.5% (DOP) vs 48.5% (NE) (OR 1.17 [0.97-1.42], p=0.07)
- More arrhythmic events in DOP (24.1% vs 12.4%, P<0.001)
- Signif. increase in mortality rate in pts with cardiogenic shock

(Septic shock, N=1044)
Dopamine versus norepinephrine in the treatment of septic shock: A meta-analysis. CCM 2012

- Dopamine was ass. with
  - Increased risk of death (RR, 1.12; CI, 1.01–1.20; p = .035)
  - More frequent arrhythmias (RR, 2.34; CI, 1.46–3.77; p = .001)

- Prospective, double-blinded, RCT (N=280)
- No diff. in to achieve MAP goal, vasopressor-free days & mortality (overall or in severe sepsis subgroup).
- Epinephrine was ass. with signif. but transient tachycardia & lactic acidosis (first 24 h), and increased insulin requirement.

- Multicenter, randomized, double-blinded in septic shock (N=330)
- No diff. in hemodynamic efficacy, mortality & serious adverse events.
- Epi. was ass. with transient lower pH (~day 4) & higher lactate (day 1)

<table>
<thead>
<tr>
<th></th>
<th>Epinephrine (n=161)</th>
<th>Norepinephrine plus dobutamine (n=169)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>At day 7</td>
<td>40 (25%)</td>
<td>34 (20%)</td>
<td>0.30</td>
</tr>
<tr>
<td>At day 14</td>
<td>56 (35%)</td>
<td>44 (26%)</td>
<td>0.08</td>
</tr>
<tr>
<td>At day 28</td>
<td>64 (40%)</td>
<td>58 (34%)</td>
<td>0.31</td>
</tr>
<tr>
<td>At discharge from intensive care</td>
<td>75 (47%)</td>
<td>75 (44%)</td>
<td>0.69</td>
</tr>
<tr>
<td>At discharge from hospital</td>
<td>84 (52%)</td>
<td>82 (49%)</td>
<td>0.51</td>
</tr>
<tr>
<td>At day 90</td>
<td>84 (52%)</td>
<td>85 (50%)</td>
<td>0.73</td>
</tr>
</tbody>
</table>

Data are number of deaths (%).
Vasopressin versus Norepinephrine Infusion in Patients with Septic Shock (VASST). NEJM 2008

- Multicenter, randomized, double-blinded trial (N=778)
- Pts receiving at least 5 μg/min of NE
- Low dose VP (0.01-0.03 U/min) vs NE (5-15 μg/min)
- No diff. in 28-day mortality (35.4% vs 39.3%, P=0.26), 90-day mortality (43.9% vs 49.6%, P=0.11) & serious adv. events
- Rapid decrease in total NE dose while maintaining MAP
Vasopressin for treatment of vasodilatory shock: an ESICM systemic review and meta-analysis. ICM 2012

- Overall, use of VP or terlipressin did not produce any survival benefit in pts with vasodilatory shock.
- Negative correlation btw VP dose and NE dose (P=0.03): Sparing effects of VP on NE requirement.

### Adults

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Events</th>
<th>Total Events</th>
<th>Control Events</th>
<th>Total Events</th>
<th>Weight</th>
<th>Risk Ratio M–H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albanese 2005</td>
<td>5</td>
<td>10</td>
<td>4</td>
<td>10</td>
<td>2.1%</td>
<td>1.25 [0.47, 3.33]</td>
</tr>
<tr>
<td>Dunser 2003</td>
<td>17</td>
<td>24</td>
<td>17</td>
<td>24</td>
<td>15.0%</td>
<td>1.00 [0.70, 1.44]</td>
</tr>
<tr>
<td>Lauzier 2006</td>
<td>3</td>
<td>13</td>
<td>3</td>
<td>10</td>
<td>1.0%</td>
<td>0.77 [0.20, 3.03]</td>
</tr>
<tr>
<td>Morelli 2008</td>
<td>26</td>
<td>39</td>
<td>14</td>
<td>20</td>
<td>15.0%</td>
<td>0.95 [0.66, 1.37]</td>
</tr>
<tr>
<td>Morelli 2009</td>
<td>15</td>
<td>30</td>
<td>10</td>
<td>15</td>
<td>7.7%</td>
<td>0.75 [0.45, 1.24]</td>
</tr>
<tr>
<td>Russell 2008</td>
<td>140</td>
<td>396</td>
<td>150</td>
<td>382</td>
<td>59.2%</td>
<td>0.90 [0.75, 1.08]</td>
</tr>
</tbody>
</table>

Total (95% CI): 512 / 461 = 100.0% | Risk Ratio = 0.91 [0.79, 1.05]

### Children

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Events</th>
<th>Total Events</th>
<th>Control Events</th>
<th>Total Events</th>
<th>Weight</th>
<th>Risk Ratio M–H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Choong 2009</td>
<td>10</td>
<td>35</td>
<td>5</td>
<td>34</td>
<td>34.0%</td>
<td>1.94 [0.74, 5.10]</td>
</tr>
<tr>
<td>Yildizdas 2008</td>
<td>20</td>
<td>30</td>
<td>20</td>
<td>28</td>
<td>66.0%</td>
<td>0.93 [0.66, 1.32]</td>
</tr>
</tbody>
</table>

Total (95% CI): 65 / 62 = 100.0% | Risk Ratio = 1.20 [0.56, 2.54]
Inodilators (dobutamine vs milrinone)

- Can improve CO, regional blood flows, & microcirculatory perfusion.
- Dobutamine produces greater myocardial contractility, while milrinone produces greater vasodilation and reduction in cardiac filling pressure.
- Dobutamine is recommended in pts with severe renal failure when milrinone could accumulate.
- Milrinone reduces PVR more than dobutamine and is preferable in pts with significant RV dysfunction.
- Dobutamine causes more tachycardia, arrhythmias, & myocardial ischemia than milrinone, while milrinone is more likely to cause hypotension.
- Data on outcome is still lacking.
Inodilators (levosimendan)

- Increase cardiac myocyte calcium responsiveness (inotropy) & open ATP-dependent potassium channels (vasodilation).
- No increase in myocardial oxygen consumption.
- Preserving diastolic relaxation (lusitropy).
- Immunomodulatory and anti-inflammatory properties.
- Useful in pts with renal impairment.
- LeoPARD trial (on going)
- In pediatric pts (after cardiac surgery), beneficial effect in vent. function, ScvO$_2$, lactate, and CI.
Levosimendan reduces mortality in patients with severe sepsis and septic shock. *JCC 2015*

- Compared to dobutamine
  - Signif. reduced mortality (47% vs 61%, RR = 0.79 [0.63-0.98], P=.03)
  - Lower blood lactate, higher CI & total fluid infused
Fluid and vasoactive agents

1. Fluid responsiveness
   - Fluid challenge
     - Yes: Initial fluid resuscitation
     - No: Fluid responsiveness
       - Yes: Initial inotrope
       - No: Goal achieved
         - Yes: Maintenance Tx
         - No: Fluid responsiveness

2. Goal achieved
   - Yes: Maintenance Tx
   - No: Initial inotrope

3. Initial inotrope
   - Yes: Norepinephrine, Vasopressin
   - No: Epinephrine, Dobu, Milr, LEVO

4. Hypotension
   - Yes: Hypoperfusion
     - Yes: Epinephrine, Dobu, Milr, LEVO
     - No: Hypoperfusion

5. Hypoperfusion
   - Yes: Hypotension
   - No: Fluid responsiveness

6. Maintenance Tx
   - Yes: Initial fluid resuscitation
   - No: Goal achieved

The flowchart outlines the decision-making process for fluid and vasoactive agents, starting with the evaluation of fluid responsiveness and progressing through various stages until maintenance therapy is determined.
Conclusions

- Early aggressive fluid resuscitation and then more conservative fluid management with early use of vasoactive agents may be beneficial in septic shock.
- Further fluid challenge after initial fluid resuscitation should be based on a reliable prediction of fluid responsiveness.
- Consider balanced crystalloid if a large volume of resuscitation is needed or metabolic acidosis is pre-existing.
- Albumine may be beneficial in severe septic shock.
- There is a lack of evidence on the choice of vasoactive agents in pediatric septic shock.
- Norepinephrine is preferred as first line VAA in adult septic shock (vasoplegic shock). Adding vasopressin in cases of persistent hypotension, and levosimendan in cases of poor perfusion may be effective.