Managing shock: fluids, inotropes and vasopressors

Allan Wardhaugh
Definition of Shock

Inadequate oxygen delivery to tissues to meet demand because of circulatory failure.
Shock - causes

- **Not enough fluid**
  - Sepsis
  - Haemorrhage
  - Dehydration
  - Maldistribution – ‘third spacing’ – many causes

- **Pump failure**
  - Sepsis
  - Cardiomyopathy/ myocarditis
  - Arrythmia

- **Very low circuit resistance**
  - AVM
  - Sepsis

- **Inadequate oxygen carrying capacity**
  - Anaemia
  - CO poisoning
Delivering oxygen to tissues

- Oxygen into lungs
  - airway management
- Oxygen into blood (in transportable form)
  - ventilation strategies, maintain Hb concentration
- Blood to tissues
  - Maintain cardiac output and adequate perfusion pressure
Oxygen delivery equation

\[ \text{O}_2 \text{ delivery} = (1.38 \times \text{Hb} \times \text{O}_2 \text{ sats}) + (\text{pO}_2 \times 0.023) \times \text{CO} \]

Adults = 1000ml/min (600ml/min/m\(^2\))

Neonate = 665 – 1000ml/min/m\(^2\)
Oxygen delivery (DO2) = CI x 1.38.Hb x SaO2 x 10

Oxygen consumption (VO2) = CI x CaO2 – CvO2×10

(neglecting the dissolved oxygen) = CI x 1.38.Hb x (SaO2–SvO2)

Oxygen extraction (O2ER) = VO2/DO2 = (CaO2-CvO2)/CaO2

(neglecting the dissolved oxygen) = (SaO2–SvO2)/SaO2
Economics of oxygen

<table>
<thead>
<tr>
<th></th>
<th><strong>DO₂</strong></th>
<th><strong>VO₂</strong></th>
<th>Extraction ratio (max 0.5)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Neonate</strong></td>
<td>1000</td>
<td>270</td>
<td>0.27</td>
</tr>
<tr>
<td><strong>5 yr old</strong></td>
<td>780</td>
<td>221</td>
<td>0.28</td>
</tr>
<tr>
<td><strong>Adult</strong></td>
<td>850</td>
<td>200</td>
<td>0.23</td>
</tr>
</tbody>
</table>

Oxygen consumption is not normally supply dependent
In disease

Figure 1: Relationship between oxygen consumption (VO$_2$) and oxygen delivery (DO$_2$) when DO$_2$ is acutely reduced by tamponade or hemorrhage in anesthetized animals (data pooled from several studies). Note that blood lactate levels increase as soon as DO$_2$ falls below a critically low value (DO$_2$crit).

Fig. 2 Schematic representation of the four types of acute circulatory failure. Importantly, several types of shock may coexist.
Regional supply dependency

![Graph showing VO2M vs DO2M for two groups with statistical significance](image)

- * p<0.05 vs BASE (DO2)
- + p<0.05 vs BASE (VO2)

**Fig. 4** Regional oxygen consumption (VO2)/oxygen delivery (DO2) relationship in the splanchnic circulation in patients with severe sepsis. Group I: patients with gradient between mixed venous and hepatic venous oxygen saturation lower than or equal to 10%. Group II: patients with gradient between mixed venous and hepatic venous oxygen saturation higher than 10%. Data are presented as means ± SEM. (adapted from [39] with permission). VO2M and DO2M refer to mesenteric VO2 and DO2, respectively.
Markers of VO$_2$ supply dependency

- Tachycardia
- Re-distribution of circulation
  - Skin perfusion (capillary refill time)
  - Oliguria
- Blood Lactate
- Venous sats
- Regional pCO$_2$
Lactate

- By product of glycolysis
  - Pyruvate converted to lactate if no O₂ available
- Metabolized by liver (50%), renal cortex (20%), skeletal muscle, heart, brain
- pH, base deficit will not detect hyperlactataemia in compensated acidosis – needs to be specifically measured
Lactate measurements - caveats

- Arterial best – venous and capillary unreliable

- Lung important source – may not always reflect inadequate oxygenation
  - High lung lactate production in ALI/ARDS

- WBC
  - Only 10% ATP production is mitochondrial
  - In sepsis, extra ATP generated by glycolysis – lactate produced by inflammation in absence of tissue hypoxia
Lactate measurements - caveats

- **Delayed clearance – liver failure**
  - Patients with chronic liver failure have normal lactate
  - High lactate with liver dysfunction still implies recent increased production

- **Renal failure**
Lactate clinical use

- Warning of tissue hypoxia or severe inflammatory state
- Admission lactate correlates variably with mortality
  - >4.5mmol/L PPV mortality 100% (CICU, US 1995)
  - >6mmol/L PPV mortality 32% (CICU Guy’s 1997)
- Decreasing lactate in first 24 hours associated with survival
Mixed venous saturations

Arterial $O_2$ Transport = $CO \times \text{CaO}_2 \times 10$
= $5 \times 20.1 \times 10$
= 1005 ml $O_2$/min

Venous $O_2$ Transport = $CO \times \text{CvO}_2 \times 10$
= $5 \times 15.5 \times 10$
= 775 ml $O_2$/min

Oxygen extraction = $VO_2/DO_2 = (\text{CaO}_2-\text{CvO}_2)/\text{CaO}_2$

Oxygen extraction = $(\text{SaO}_2-\text{SvO}_2)/\text{SaO}_2$

$\text{SvO}_2$ = Right atrial sats
$\text{ScvO}_2$ = SVC sats
Mixed venous sats

\[ \text{VO}_2 = \text{Arterial Oxygen Transport} - \text{Venous, Oxygen Transport} \]
\[ = (\text{CO} \times \text{CaO}_2 \times 10) - (\text{CO} \times \text{CvO}_2 \times 10) \]
\[ = \text{CO} \times (\text{CaO}_2 - \text{CvO}_2) \times 10 \]
\[ = \text{CO} \times (\text{Hb} \times \text{SaO}_2 \times 13.8) - \text{CO} \times (\text{Hb} \times \text{SvO}_2 \times 13.8) \]
\[ = \text{CO} \times \text{Hb} \times 13.8 \times (\text{SaO}_2 - \text{SvO}_2) \]

\[ \text{SvO}_2 = \text{Oxygen Delivered} - \text{Oxygen Consumed} \]
\[ = (\text{SaO}_2, \text{Hb}, \text{CO}) - (\text{VO}_2) \]
Mixed venous saturations

- When SvO2 falls, implies that the patient has become ‘supply dependent’ – either not enough delivery, or too much demand

- SvO2 normal >70%

- SvO2 <70% requires action to improve DO₂
Tissue Capnometry (regional VO$_2$/DO$_2$)

- Circulatory failure causes increased tissue pCO$_2$
- Gastric tonometry (mucosal pH measurement)
- Sublingual capnometry – easy, non-invasive
In practice

- Lactate
- $SvO_2$
- Clinical assessment of tissue perfusion
- Urine output
Summary so far

- Shock occurs when $DO_2$ fails to meet $VO_2$
- Simple clinical and lab indicators can identify that shock is occurring

- Next – how to treat?
Treating shock – treat causes

- **Not enough fluid**
  - Sepsis – *antibiotics, give fluid*
  - Haemorrhage – *stop bleeding, give blood*
  - Dehydration - *fluid*
  - Maldistribution – ‘third spacing’ – *many causes - fluid*

- **Pump failure**
  - Sepsis - *inotropes*
  - Cardiomyopathy/ myocarditis - *inotropes*
  - Arrhythmia – *drugs, electricity*

- **Very low circuit resistance**
  - AVM - *embolise*
  - Sepsis - *vasopressors*

- **Inadequate oxygen carrying capacity**
  - Anaemia – *give blood*
  - CO poisoning etc. – *specific treatments*
Treating shock

- Volume resuscitation (septic shock)
- Pump failure - inotropes
- Circuit resistance - vasopressors
Treating shock - Volume resuscitation in sepsis

- How much fluid?
- Which fluid?
Volume – how much fluid

- Blood volume 65ml/kg adult, 80-90ml/kg infant
- 40ml/kg corrects volume in most cases if ongoing losses have stopped
- Ongoing losses hidden in
  - Intra-abdominal/ intra-thoracic haemorrhage
  - IVH in neonates
  - Sepsis
  - Gut obstruction
Aggressive volume resuscitation associated with improved survival in septic children

- Only study to show a beneficial intervention in paediatric septic shock – observational study
- Recruited all paediatric sepsis patients to ER in Washington DC Childrens Hospital – PA catheter in situ by 6 hours
- 34 patients – mean age 13.5 months

Divided into 3 groups (post hoc) by volume received in first hour

- Group 1 <20ml/kg
- Group 2 20 – 40ml/kg
- Group 3 >40ml/kg

Carcillo - Mortality

Totals in each group

14 11 9

<20ml/kg 20 - 40ml/kg >40ml/kg
Carcillo - ARDS

![Bar chart showing percentage distribution of fluid volumes per kg]

- <20ml/kg: 40%
- 20-40ml/kg: 15%
- >40ml/kg: 0%
Carcillo - Hypovolaemia at 6 hours

- <20 ml/kg: 50%
- 20 - 40 ml/kg: 20%
- >40 ml/kg: 0%
Goal directed treatment in sepsis – evidence of benefit in children

- 100 consecutive paediatric septic shock (3 different hospitals) patients with PA catheter by 6 hours
  - Aggressive volume resuscitation
  - Goals targeted – CI, SVR
  - Overall 80% 28 day survival.
  - Outcomes improved compared to historical controls

Ceneviva G et al – survival less likely in low cardiac output group
Pittsburgh study

- 9 year retrospective cohort of 91 children with septic shock
- Audited against ACCM septic shock management guidelines

Pittsburgh - outcomes

- Non-survivors had received more inotropes but not more fluid
- ACCM guidelines followed in only 30% cases
- Where guidelines followed, mortality 8%
- Where guidelines not followed, mortality 38%
Volume – epidemiological evidence

Mortality for sepsis reduced historically in units practising aggressive fluid resuscitation

---

R Booy, P Habibi, S Nadel, C de Munter, J Britto, A Morrison, M Levin, the Meningococcal Research Group
Reduction in case fatality rate from meningococcal disease associated with improved healthcare delivery.
Arch Dis Child 2001;85:5 386-390 doi:10.1136/adc.85.5.386
**Mortality in meningococcal disease: please report the figures accurately**

S M Tibby, I A Murdoch, A Durward
Department of Paediatric Intensive Care, Guy’s Hospital, St Thomas Street, London SE1 9RT, UK;

**Table 1** Mortality data for severe meningococcal patients retrieved to Guy’s Hospital January 1998 to November 2001

<table>
<thead>
<tr>
<th>Event</th>
<th>1998</th>
<th>1999</th>
<th>2000</th>
<th>2001</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths prior to team arrival</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Time to death from PICU team arrival</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than 6 hours</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>6 to 12 hours</td>
<td></td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>12 to 24 hours</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Greater than 24 hours</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total PICU deaths</td>
<td>5</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Total survivors</td>
<td>40</td>
<td>45</td>
<td>56</td>
<td>31</td>
</tr>
</tbody>
</table>
Fluid Resuscitation of Hypovolemic Shock: Acute Medicine’s Great Triumph for Children

Decreasing US Infant deaths/100,000 from hypovolemic shock

Shock:
Gastroenteritis
Abdo obstruction
Septicaemia
Volume

- 20ml/kg boluses over 5 minutes
- Stop if perfusion improved or signs of fluid overload (hepatomegaly)
- 60ml/kg in first hour common
- May need up to 200ml/kg in first hour

Mortality after Fluid Bolus in African Children with Severe Infection

Kathryn Maitland, M.B., B.S., Ph.D., Sarah Kiguli, M.B., Ch.B., M.Med.,
Peter Olupot-Olupot, M.B., Ch.B., Samuel O. Akech, M.B., Ch.B.,
Richard Nyeko, M.B., Ch.B., M.Med., George Mtove, M.D., Hugh Reyburn, M.B., B.S.,
Trudie Lang, Ph.D., Bernadette Brent, M.B., B.S., Jennifer A. Evans, M.B., B.S.,
James K. Tibenderana, M.B., Ch.B., Ph.D., Jane Crawley, M.B., B.S., M.D.,
and Diana M. Gibb, M.B., Ch.B., M.D., for the FEAST Trial Group*
FEAST

- Uganda, Kenya, Tanzania
- Children 60 days – 12 years severe febrile illness complicated by
  - impaired consciousness and/or respiratory distress
    - PLUS
  - impaired perfusion, (one or more of the following):
    - a capillary refill time of 3 or more seconds, lowerlimb
    - temperature gradient,
    - weak radial-pulse volume, or severe tachycardia (>180 beats per minute in children younger than 12 months of age, >160 beats per minute in children 1 to 5 years of age, or >140 beats per minute in children older than 5 years of age)

- Exclusion criteria
  - severe malnutrition,
  - gastroenteritis,
  - noninfectious causes of shock (e.g., trauma, surgery, or burns)
  - conditions for which volume expansion is contraindicated.
FEAST

- **Stratum A (normotensive) \( n=3141 \)**
  - No bolus
  - 20 – 40ml/kg 4.5% albumin
  - 20 – 40ml/kg 0.9% saline

- **Stratum B (hypotensive) \( n=29 \)**
  - 40ml/kg 4.5% albumin
  - 40ml/kg 0.9% saline
FEAST

A Mortality at 48 Hours

- Albumin bolus
- Saline bolus
- No bolus

Cumulative Probability of Death

Hours since Randomization
B  Mortality at 4 Weeks

Cumulative Probability of Death vs. Days since Randomization

- Albumin bolus
- Saline bolus
- No bolus
FEAST - conclusion

Fluid boluses significantly increased 48-hour mortality in critically ill children with impaired perfusion in resource-limited settings in Africa.
FEAST - questions

- Did lack of ability to escalate treatment increase mortality?
- Did patients present at a more advanced stage and with more co-morbidity than in developing world?
  - 15% presented in a coma,
  - 32% had jaundice
  - 57% had malaria
  - 32% had hemoglobin <5 g/dL
  - only 23% had a hemoglobin level >10 g/dL.
How much volume?

- Up to 60 ml/kg in first hour – maybe up to 200ml/kg
- Monitor hepatomegaly or CVP and stop when liver big or CVP >10mmHg
- If BP decreases when CVP increases stop giving volume
Which fluid?
A Comparison of Albumin and Saline for Fluid Resuscitation in the Intensive Care Unit

The SAFE Study Investigators*

7000 critically ill adults
Figure 1. Kaplan–Meier Estimates of the Probability of Survival.
P=0.96 for the comparison between patients assigned to receive albumin and those assigned to receive saline.
<table>
<thead>
<tr>
<th>Variable</th>
<th>Albumin Group</th>
<th>Saline Group</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Patients</td>
<td>Value</td>
<td>No. of Patients</td>
</tr>
<tr>
<td><strong>Study fluid (ml)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 1</td>
<td>3410</td>
<td>1183.9±973.6</td>
<td>3418</td>
</tr>
<tr>
<td>Day 2</td>
<td>3059</td>
<td>602.7±892.7</td>
<td>3068</td>
</tr>
<tr>
<td>Day 3</td>
<td>2210</td>
<td>268.0±554.5</td>
<td>2202</td>
</tr>
<tr>
<td>Day 4</td>
<td>1686</td>
<td>192.3±427.0</td>
<td>1664</td>
</tr>
<tr>
<td><strong>Net positive fluid balance (ml)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 1</td>
<td>3363</td>
<td>1543.6±1619.7</td>
<td>3382</td>
</tr>
<tr>
<td>Day 2</td>
<td>3044</td>
<td>1015.3±1826.9</td>
<td>3052</td>
</tr>
<tr>
<td>Day 3</td>
<td>2190</td>
<td>422.1±1633.3</td>
<td>2182</td>
</tr>
<tr>
<td>Day 4</td>
<td>1671</td>
<td>137.2±1491.0</td>
<td>1649</td>
</tr>
<tr>
<td>Patients</td>
<td>Albumin Group</td>
<td>Saline Group</td>
<td>Relative Risk (95% CI)</td>
</tr>
<tr>
<td>------------------</td>
<td>---------------</td>
<td>--------------</td>
<td>------------------------</td>
</tr>
<tr>
<td>Overall</td>
<td>726/3473</td>
<td>729/3460</td>
<td>0.99 (0.91–1.09)</td>
</tr>
<tr>
<td>Trauma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>81/596</td>
<td>59/590</td>
<td>1.36 (0.99–1.86)</td>
</tr>
<tr>
<td>No</td>
<td>641/2831</td>
<td>666/2830</td>
<td>0.96 (0.88–1.06)</td>
</tr>
<tr>
<td>Severe sepsis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>185/603</td>
<td>217/615</td>
<td>0.87 (0.74–1.02)</td>
</tr>
<tr>
<td>No</td>
<td>518/2734</td>
<td>492/2720</td>
<td>1.05 (0.94–1.17)</td>
</tr>
<tr>
<td>ARDS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>24/61</td>
<td>28/66</td>
<td>0.93 (0.61–1.41)</td>
</tr>
<tr>
<td>No</td>
<td>697/3365</td>
<td>697/3354</td>
<td>1.00 (0.91–1.09)</td>
</tr>
</tbody>
</table>

**Figure 2.** Relative Risk of Death from Any Cause among All the Patients and among the Patients in the Six Predefined Subgroups.
Which crystalloid?

- Normal saline
- Hartmann’s solution
# Crystalloid electrolyte composition

<table>
<thead>
<tr>
<th></th>
<th>Na</th>
<th>K</th>
<th>Cl</th>
<th>Other</th>
<th>Tonicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.9% saline</td>
<td>150</td>
<td>0</td>
<td>150</td>
<td></td>
<td>308</td>
</tr>
<tr>
<td>0.45% saline/ 5% dextrose</td>
<td>75</td>
<td>0</td>
<td>75</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.18% saline/ 4% dextrose</td>
<td>30</td>
<td>0</td>
<td>30</td>
<td></td>
<td>286</td>
</tr>
<tr>
<td>Dextrose 5%</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
<td>252</td>
</tr>
<tr>
<td>Hartmann’s</td>
<td>131</td>
<td>5</td>
<td>111</td>
<td>Lactate 27</td>
<td>280</td>
</tr>
</tbody>
</table>
Hyperchloreaemia – causes persistent base deficit

- 81 cases meningococcal sepsis
- Base excess -9mmol/l at presentation
  - Mainly unmeasured anions
- Base deficit persisted at 48 hours
  - Hyperchloreaemia by 8 – 12 hours
- Each 1mmol/kg Chloride causes 0.4mmol/L base deficit
- Don’t treat the base deficit

Hyperchloraemic acidosis – harmful or benign?
Treating shock – Pump failure
Inotropes

- **Advantages**
  - Improve pump function
  - Increase SVR improving perfusion pressure
  - Increase diastolic BP improving coronary artery perfusion
  - Readily titratable against response

- **Disadvantages**
  - May increase afterload if they vasoconstrict
  - Increase myocardial oxygen demand
  - Arrhythmia
  - Extravasation danger – should go centrally
Available inotropes

- Natural catecholamines
  - Adrenaline
  - Dopamine
- Synthetic catecholamines
  - Dobutamine
- Phosphodiesterase inhibitors
  - Milrinone, enoximone
Which inotropes when?
Choice of inotrope

- Personal preference
- No RCT to rely on
- Prejudices common – remember these are often based on ‘level 4’ evidence.
- Watch the bottom line
- ‘Warm’ shock with good CO and low SVR less common in children
- ‘Cold’ shock with low CO and high SVR more common – some use vasodilators
Catecholamine synthesis

tyrosine hydroxylase

DOPA decarboxylase
dopamine-β-hydroxylase
phenylethanolamine-N-methyltransferase
Receptor function

- β receptors down-regulated by exposure to prolonged catecholamine exposure, ischaemia, CPB, SIRS
- ‘Uncoupled’ from G-protein by pH <7.0, hypocalcaemia, cytokines
<table>
<thead>
<tr>
<th>Receptor</th>
<th>Actions</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\alpha_1$</td>
<td>Vasoconstriction</td>
</tr>
<tr>
<td>$\alpha_2$</td>
<td>Vasodilation, -ve chronotrope</td>
</tr>
<tr>
<td>$\beta_1$</td>
<td>+ve inotrope &amp; chronotrope</td>
</tr>
<tr>
<td>$\beta_2$</td>
<td>Splanchnic/ Muscle Vasodilation, bronchodilation</td>
</tr>
<tr>
<td>DA$_1$</td>
<td>Vasodilation</td>
</tr>
<tr>
<td>DA$_2$</td>
<td>Inhibits PLN &amp; $\beta$-endorphin secretion</td>
</tr>
</tbody>
</table>
Dopamine

- Precursor of noradrenaline.
- Useful in moderate fluid refractory hypotension
- Mediates part of its action by stimulating presynaptic sympathetic nerves in heart
<table>
<thead>
<tr>
<th></th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>α₁</td>
<td>Vasoconstriction</td>
</tr>
<tr>
<td>α₂</td>
<td>Vasodilation</td>
</tr>
<tr>
<td></td>
<td>-ve chronotrope</td>
</tr>
<tr>
<td>β₁</td>
<td>+ve inotrope &amp; chronotrope</td>
</tr>
<tr>
<td>β₂</td>
<td>Splanchnic/Muscle</td>
</tr>
<tr>
<td></td>
<td>Vasodilation, bronchodilation</td>
</tr>
<tr>
<td>DA₁</td>
<td>Vasodilation</td>
</tr>
<tr>
<td>DA₂</td>
<td>Inhibits PLN &amp; β-endorphin secretion</td>
</tr>
<tr>
<td>Dopamine 5 – 15 mcg/kg/min</td>
<td></td>
</tr>
<tr>
<td>---------------------------</td>
<td></td>
</tr>
<tr>
<td>$\alpha_1$</td>
<td>Vasoconstriction</td>
</tr>
<tr>
<td>$\alpha_2$</td>
<td>Vasodilation</td>
</tr>
<tr>
<td></td>
<td>-ve chronotrope</td>
</tr>
<tr>
<td>$\beta_1$</td>
<td>+ve inotrope &amp; chronotrope</td>
</tr>
<tr>
<td>$\beta_2$</td>
<td>Splanchnic/ Muscle</td>
</tr>
<tr>
<td></td>
<td>Vasodilation, bronchodilation</td>
</tr>
<tr>
<td>DA$_1$</td>
<td>Vasodilation</td>
</tr>
<tr>
<td>DA$_2$</td>
<td>Inhibits PLN &amp; $\beta$-endorphin secretion</td>
</tr>
</tbody>
</table>
Dopamine 15 – 25 mcg/kg/min

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\alpha_1$</td>
<td>Vasoconstriction</td>
</tr>
<tr>
<td>$\alpha_2$</td>
<td>Vasodilation, -ve chronotrope</td>
</tr>
<tr>
<td>$\beta_1$</td>
<td>+ve inotrope &amp; chronotrope</td>
</tr>
<tr>
<td>$\beta_2$</td>
<td>Splanchnic/Muscle Vasodilation, bronchodilation</td>
</tr>
<tr>
<td>DA$_1$</td>
<td>Vasodilation</td>
</tr>
<tr>
<td>DA$_2$</td>
<td>Inhibits PLN &amp; $\beta$-endorphin secretion</td>
</tr>
<tr>
<td>Dopamine &gt; 25 mcg/kg/min</td>
<td></td>
</tr>
<tr>
<td>--------------------------</td>
<td></td>
</tr>
<tr>
<td><strong>α</strong>₁</td>
<td>Vasoconstriction</td>
</tr>
<tr>
<td>α₂</td>
<td>Vasodilation</td>
</tr>
<tr>
<td>β₁</td>
<td>-ve chronotrope</td>
</tr>
<tr>
<td>β₂</td>
<td>+ve inotrope &amp; chronotrope</td>
</tr>
<tr>
<td>DA₁</td>
<td>Splanchnic/ Muscle Vasodilation, bronchodilation</td>
</tr>
<tr>
<td>DA₂</td>
<td>Vasodilation</td>
</tr>
<tr>
<td></td>
<td>Inhibits PLN &amp; β-endorphin secretion</td>
</tr>
</tbody>
</table>
Adrenaline

- Desert island inotrope
- More effective than other catecholamines in decreased endogenous catecholamine synthesis or down-regulated $\beta_1$ receptors
- Increases myocardial oxygen demand
- Increases pulmonary vascular resistance
- Stimulates NaK pump in muscle - hypokalaemia
<table>
<thead>
<tr>
<th>Adrenaline</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>α₁</td>
<td>Vasoconstriction</td>
</tr>
<tr>
<td>α₂</td>
<td>Vasodilation</td>
</tr>
<tr>
<td></td>
<td>-ve chronotrope</td>
</tr>
<tr>
<td>β₁</td>
<td>+ve inotrope &amp;</td>
</tr>
<tr>
<td></td>
<td>chronotrope</td>
</tr>
<tr>
<td>β₂</td>
<td>Splanchnic/ Muscle</td>
</tr>
<tr>
<td></td>
<td>Vasodilation,</td>
</tr>
<tr>
<td></td>
<td>bronchodilation</td>
</tr>
<tr>
<td>DA₁</td>
<td>Vasodilation</td>
</tr>
<tr>
<td>DA₂</td>
<td>Inhibits PLN &amp; β-endorphin secretion</td>
</tr>
<tr>
<td>Receptor</td>
<td>Effect</td>
</tr>
<tr>
<td>----------</td>
<td>--------</td>
</tr>
<tr>
<td>$\alpha_1$</td>
<td>Vasoconstriction</td>
</tr>
<tr>
<td>$\alpha_2$</td>
<td>Vasodilation, -ve chronotrope</td>
</tr>
<tr>
<td>$\beta_1$</td>
<td>+ve inotrope &amp; chronotrope</td>
</tr>
<tr>
<td>$\beta_2$</td>
<td>Splanchnic/Muscle Vasodilation, bronchodilation</td>
</tr>
<tr>
<td>DA$_1$</td>
<td>Vasodilation</td>
</tr>
<tr>
<td>DA$_2$</td>
<td>Inhibits PLN &amp; $\beta$-endorphin secretion</td>
</tr>
<tr>
<td>Receptor</td>
<td>Effect</td>
</tr>
<tr>
<td>----------</td>
<td>--------</td>
</tr>
<tr>
<td>$\alpha_1$</td>
<td>Vasoconstriction</td>
</tr>
<tr>
<td>$\alpha_2$</td>
<td>Vasodilation, -ve chronotrope</td>
</tr>
<tr>
<td>$\beta_1$</td>
<td>+ve inotrope &amp; chronotrope</td>
</tr>
<tr>
<td>$\beta_2$</td>
<td>Splanchnic/ Muscle Vasodilation, bronchodilation</td>
</tr>
<tr>
<td>DA$_1$</td>
<td>Vasodilation</td>
</tr>
<tr>
<td>DA$_2$</td>
<td>Inhibits PLN &amp; $\beta$-endorphin secretion</td>
</tr>
</tbody>
</table>
Adrenaline $> 1\text{mcg/kg/min}$

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\alpha_1$</td>
<td>Vasoconstriction</td>
</tr>
<tr>
<td>$\alpha_2$</td>
<td>Vasodilation</td>
</tr>
<tr>
<td>$\beta_1$</td>
<td>-ve chronotrope</td>
</tr>
<tr>
<td>$\beta_2$</td>
<td>+ve inotrope &amp; chronotrope</td>
</tr>
<tr>
<td>$\text{DA}_1$</td>
<td>Splanchnic/Muscle</td>
</tr>
<tr>
<td>$\text{DA}_2$</td>
<td>Vasodilation, bronchodilation</td>
</tr>
<tr>
<td></td>
<td>Inhibits PLN &amp; $\beta$-endorphin secretion</td>
</tr>
</tbody>
</table>
Dobutamine

- Synthetic mixture of two stereo-isomers.
- One isomer has $\beta$ effects, the other $\alpha_1$.
- Often used in myocarditis/cardiovascular disease.
- Used in neonates – low stores of presynaptic noradrenaline, so less responsive to dopamine?
- Safer than other catecholamines to use peripherally.
<table>
<thead>
<tr>
<th>Receptor</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>α₁</td>
<td>Vasoconstriction</td>
</tr>
<tr>
<td>α₂</td>
<td>Vasodilation, -ve chronotrope</td>
</tr>
<tr>
<td>β₁</td>
<td>+ve inotrope &amp; chronotrope</td>
</tr>
<tr>
<td>β₂</td>
<td>Splanchnic/ Muscle, Vasodilation, bronchodilation</td>
</tr>
<tr>
<td>DA₁</td>
<td>Vasodilation</td>
</tr>
<tr>
<td>DA₂</td>
<td>Inhibits PLN &amp; β-endorphin secretion</td>
</tr>
<tr>
<td>Receptor</td>
<td>Effect</td>
</tr>
<tr>
<td>----------</td>
<td>--------</td>
</tr>
<tr>
<td>$\alpha_1$</td>
<td>Vasoconstriction</td>
</tr>
<tr>
<td>$\alpha_2$</td>
<td>Vasodilation, -ve chronotrope</td>
</tr>
<tr>
<td>$\beta_1$</td>
<td>+ve inotrope &amp; chronotrope</td>
</tr>
<tr>
<td>$\beta_2$</td>
<td>Splanchnic/Muscle Vasodilation, bronchodilation</td>
</tr>
<tr>
<td>$DA_1$</td>
<td>Vasodilation</td>
</tr>
<tr>
<td>$DA_2$</td>
<td>Inhibits PLN &amp; $\beta$-endorphin secretion</td>
</tr>
<tr>
<td>Dobutamine &gt;20mcg/kg/min</td>
<td>α₁</td>
</tr>
<tr>
<td>-------------------------</td>
<td>----</td>
</tr>
<tr>
<td></td>
<td>α₂</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>β₁</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>β₂</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>DA₁</td>
</tr>
<tr>
<td></td>
<td>DA₂</td>
</tr>
</tbody>
</table>
Phosphodiesterase inhibitors

- Enoximone and milrinone – bipyridine PDE3 inhibitors.
- PDE3 specific to myocardium.
- Increases myocardial contractility, enhances vascular smooth muscle relaxation - lusiotropic.
- Decreases preload and afterload, reduce LVEDP and RVEDP improves diastolic dysfunction.
- Heart rate and myocardial oxygen consumption relatively unchanged.
- They are not generally first line agents, but are useful in situations with β receptor down-regulation.
- Commonly used post cardio-pulmonary bypass
- Milrinone – shorter half-life, more pro-arrhythmogenic. Accumulates in renal impairment.
Milrinone

- Half-life 30-60 mins
- Accumulates renal failure
- Noradrenaline may be used to counter excessive vasodilatation
Treating shock – Circuit resistance failure
Physiology – fluid filled circuit and Ohm’s Law

\[ I = \frac{V}{R} \]

Flow = Pressure Difference/ Resistance

Perfusion pressure = Cardiac output × Resistance
Flow needs to be adequate for Perfusion pressure
Low SVR in shock

- Bounding pulse
- ‘Flash’ capillary refill
- Wide pulse pressure
- Low diastolic pressure
Myocardial perfusion

Pulsatile nature of left coronary artery blood flow. Flow is lower during phases of isovolumetric contraction (a) and ejection (b) than during diastole (c).
Noradrenaline

- Used for ‘warm’ shock
- 2nd line in children
<table>
<thead>
<tr>
<th></th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\alpha_1$</td>
<td>Vasoconstriction</td>
</tr>
<tr>
<td>$\alpha_2$</td>
<td>Vasodilation, -ve chronotrope</td>
</tr>
<tr>
<td>$\beta_1$</td>
<td>+ve inotrope &amp; chronotrope</td>
</tr>
<tr>
<td>$\beta_2$</td>
<td>Splanchnic/ Muscle Vasodilation, bronchodilation</td>
</tr>
<tr>
<td>DA$_1$</td>
<td>Vasodilation</td>
</tr>
<tr>
<td>DA$_2$</td>
<td>Inhibits PLN &amp; $\beta$-endorphin secretion</td>
</tr>
</tbody>
</table>

Noradrenaline
Noradrenaline
<0.5mcg/kg/min

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\alpha_1$</td>
<td>Vasoconstriction</td>
</tr>
</tbody>
</table>
| $\alpha_2$ | Vasodilation
-ve chronotrope |
<p>| $\beta_1$  | +ve inotrope &amp; chronotrope                  |
| $\beta_2$  | Splanchnic/ Muscle Vasodilation, bronchodilation |
| DA$_1$    | Vasodilation                                |
| DA$_2$    | Inhibits PLN &amp; $\beta$-endorphin secretion  |</p>
<table>
<thead>
<tr>
<th>Noradrenaline 0.5-4mcg/kg/min</th>
<th>α₁</th>
<th>Vasoconstriction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>α₂</td>
<td>Vasodilation</td>
</tr>
<tr>
<td></td>
<td>β₁</td>
<td>+ve inotrope &amp;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>chronotrope</td>
</tr>
<tr>
<td></td>
<td>β₂</td>
<td>Splanchnic/ Muscle</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vasodilation,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>bronchodilation</td>
</tr>
<tr>
<td>DA₁</td>
<td></td>
<td>Vasodilation</td>
</tr>
<tr>
<td>DA₂</td>
<td></td>
<td>Inhibits PLN &amp; β-endorphin secretion</td>
</tr>
</tbody>
</table>
Vasopressin

- Initially high endogenous vasopressin in septic shock and haemorrhagic shock
- Secretion normally stimulated by hypovolaemia and hypotension
- Prolonged hypotension or septic shock levels decrease
<table>
<thead>
<tr>
<th>Proposed Mechanism</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depletion of neurohypophyseal stores due to excessive stimulation/baroreceptor firing</td>
<td>Hypoxia, acidosis, and hypotension are powerful stimuli of vasopressin release (Table 2)</td>
</tr>
<tr>
<td></td>
<td>Only 10 to 20% of the total neurohypophyseal pool of vasopressin can be readily released\textsuperscript{17}</td>
</tr>
<tr>
<td>Decreased stimulation of vasopressin release due to:</td>
<td>The autonomic nervous system is impaired in sepsis\textsuperscript{56,57}</td>
</tr>
<tr>
<td>Impaired autonomic reflexes</td>
<td>Atrial stretch receptors tonically inhibit vasopressin\textsuperscript{16}</td>
</tr>
<tr>
<td>Tonic inhibition by atrial stretch receptor (volume loading, mechanical ventilation)</td>
<td></td>
</tr>
<tr>
<td>Inhibition of vasopressin release due to:</td>
<td>NO inhibits vasopressin release\textsuperscript{37}</td>
</tr>
<tr>
<td>NO release in sepsis</td>
<td>High levels of norepinephrine inhibit vasopressin release\textsuperscript{38}</td>
</tr>
<tr>
<td>High circulating norepinephrine levels</td>
<td></td>
</tr>
</tbody>
</table>
Sepsis or Tissue Hypoxia with Lactic Acidosis

- ↑ Nitric oxide synthase
- ↓ ATP, ↑ H⁺, ↑ lactate in vascular smooth muscle
- ↑ Vasopressin secretion

↓ Nitric oxide
↓ Open K⁺
↓ Cytoplasmic Ca²⁺
↓ cGMP
↓ Phosphorylated myosin
↓ Plasma vasopressin
↓ Vasopressin stores

Vasodilatation
Vasopressin

- Injection in humans with normal BP – no effect unless very high doses used
- Injection of physiological doses in hypovolaemia – vasoconstriction
- Enhances sensitivity to catecholamines
- Coronary, Pulmonary and cerebral vasodilator at physiological doses.
- Clinical studies – 0.01 – 0.04U/min improve BP and responsiveness to catecholamines in septic and vasodilatory shock
- Higher doses cause pulmonary, coronary and renal vasoconstriction
- RCT in adults shows improved CI, BP and fewer arrhythmias if used with norad compared with norad alone
Vasopressin vs Noradrenaline

- 396 patients on norad 5mcg/min
- Randomised to either vasopressin or norad 5 – 15mcg/kg/min

**Table 4. Rates and Risks of Death from Any Cause According to the Severity of Shock.**

<table>
<thead>
<tr>
<th>Stratum</th>
<th>Norepinephrine Group</th>
<th>Vasopressin Group</th>
<th>P Value</th>
<th>Absolute Risk Reduction (95% CI)</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no./total no. (%)</td>
<td></td>
<td></td>
<td>%</td>
<td></td>
</tr>
<tr>
<td>More severe septic shock</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>28-day mortality</td>
<td>85/200 (42.5)</td>
<td>88/200 (44.0)</td>
<td>0.76</td>
<td>-1.5 (-11.2 to 8.2)</td>
<td>1.04 (0.83 to 1.3)</td>
</tr>
<tr>
<td>90-day mortality</td>
<td>105/199 (52.8)</td>
<td>103/199 (51.8)</td>
<td>0.84</td>
<td>1.0 (-8.8 to 10.8)</td>
<td>0.98 (0.81 to 1.18)</td>
</tr>
<tr>
<td>Less severe septic shock</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>28-day mortality</td>
<td>65/182 (35.7)</td>
<td>52/196 (26.5)</td>
<td>0.05</td>
<td>9.2 (-0.1 to 18.5)</td>
<td>0.74 (0.55 to 1.01)</td>
</tr>
<tr>
<td>90-day mortality</td>
<td>83/180 (46.1)</td>
<td>69/193 (35.8)</td>
<td>0.04</td>
<td>10.4 (0.4 to 20.3)</td>
<td>0.78 (0.61 to 0.99)</td>
</tr>
</tbody>
</table>

Goal targeted treatment
Prof WC Shoemaker

- Low CI, VO₂ associated with death
  - Adult surgical patients, ‘severely ill’
  - 67 survivors, 31 non-survivors compared

- Oxygen consumption may be ‘supply dependent’ in states of shock
Physiologic patterns in Surviving and Nonsurviving Shock Patients (1973)

- Observational study 98 post-operative adult patients with shock
  - 67 survived, 31 died
- VO$_2$ and DO$_2$ significantly lower in non-survivors compared to survivors
- DO$_2$ higher than ‘normal’ in survivors
- “..values of normal, unstressed persons are not necessarily the therapeutic goals for the post-operative shock patient.”
Fig. 1 Pathophysiological changes in the VO₂/DO₂ relationship. *Solid black line* Normal relationship; *dotted lines* abnormal relationships 1 increased VO₂ needs; 2 impaired EO₂; 3 other mechanisms (see text). *Gray curves* Corresponding EO₂/DO₂ relationships.
Supply dependency

- Aim to achieve $\text{DO}_2$ above critical point
- In critically ill patients this means supraphysiological values
  - $\text{CO} > 4.5\text{L/min/m}^2$
  - $\text{DO}_2 > 600\text{ml/min/m}^2$
  - $\text{VO}_2 > 170\text{ml/min/m}^2$
Shoemaker – Prospective studies
Clinical trial of survivors cardiorespiratory patterns as therapeutic goals in critically ill postoperative patients. (1982)

- 100 consecutive critically ill postoperative patients
- Detailed physiological objectives
  - Control group physiological norms
  - Treatment group median values of survivors in earlier studies
  - E.g. CI 2.8 – 3.5 control, 4.5 in treatment
- Mortality
  - Control 48%
  - Treatment 13%
Prospective trial of supranormal values of survivors as therapeutic goals in high-risk surgical patients (1987)

○ Series 1 (n= 276) – pre and post-op randomised to control and protocol
  ● Control mortality 34%
  ● Protocol mortality 19%

○ Series 2 (n= 133) – pre-op randomised to CVP-control, PA catheter control and PA catheter protocol (supra-physiological goals)
  ● CVP control mortality 23%
  ● PA control mortality 33%
  ● PA protocol mortality 4%
Goal directed treatment works....
….oh no it doesn’t
Barts trial 1994

- 100 patients, randomised
- Controls
- Treatment – goals achieved using dobutamine
  - CI above 4.5 L/min/m²
  - DO₂ above 600 ml/min/m²
  - VO₂ above 170 ml per minute per square meter
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Control Group (N = 50)</th>
<th>Treatment Group (N = 50)</th>
<th>Not Randomized (N = 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days in unit — median (range)</td>
<td>10 (1–64)</td>
<td>10 (1–48)</td>
<td>10 (1–29)</td>
</tr>
<tr>
<td>Ventilation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of days — median (range)</td>
<td>8 (0–54)</td>
<td>8 (0–41)</td>
<td>2 (0–26)</td>
</tr>
<tr>
<td>No. of patients</td>
<td>44</td>
<td>46</td>
<td>7</td>
</tr>
<tr>
<td>Days in hospital — median (range)</td>
<td>23.5 (1–244)</td>
<td>19 (1–187)</td>
<td>20 (11–102)</td>
</tr>
<tr>
<td>Mortality — %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In intensive care unit</td>
<td>30</td>
<td>50*</td>
<td>—</td>
</tr>
<tr>
<td>In hospital</td>
<td>34</td>
<td>54*</td>
<td>—</td>
</tr>
<tr>
<td>Predicted risk of death — median % (range)</td>
<td>34 (3–91)</td>
<td>34 (3–85)</td>
<td>6 (3–32)</td>
</tr>
<tr>
<td>Cause of death — no. of patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intractable hypotension</td>
<td>4</td>
<td>4</td>
<td>—</td>
</tr>
<tr>
<td>Cardiac event</td>
<td>2</td>
<td>4</td>
<td>—</td>
</tr>
<tr>
<td>Multiple organ failure</td>
<td>9</td>
<td>17</td>
<td>—</td>
</tr>
</tbody>
</table>

*P = 0.04 for the comparison between the control and treatment groups.
In-Hospital Survival of Patients in the Treatment and Control Groups

762 adult patients
- Randomised to
  - Supranormal CI
  - Target normal $S_vO_2$
  - Control (normal CI)
Gattinoni

Diagram showing survival probability over days after randomization for three groups: control group (157 events), cardiac-index group (156 events), and oxygen-saturation group (164 events).
Why does it not work?

- Patients recruited up to 48 hours after admission to ICU
- Time in hospital prior to admission to ICU likely to be significant
It may work after all – but only if used early
EARLY GOAL-DIRECTED THERAPY IN THE TREATMENT OF SEVERE SEPSIS AND SEPTIC SHOCK

Emanuel Rivers, M.D., M.P.H., Bryant Nguyen, M.D., Suzanne Havstad, M.A., Julie Ressler, B.S., Alexandria Muzzin, B.S., Bernhard Knoblich, M.D., Edward Peterson, Ph.D., and Michael Tomlanovich, M.D., for the Early Goal-Directed Therapy Collaborative Group*
Figure 1. Overview of Patient Enrollment and Hemodynamic Support.
Largest mortality benefit of any sepsis study
NNT 6 (3.6 – 23)
Benefit from individualised resuscitation to more detailed goals

do the basics very well vs. doing basics well

Search for cryptic shock - Venous desaturation
ACCM/PALS haemodynamic support guidelines for paediatric septic shock: an outcomes comparison with and without monitoring central venous oxygen saturation
A Comparison of ACCM-PALS Guidelines to Standard Care on Outcome from Pediatric Septic Shock
A Randomized Control Trial (C Oliveira et al 2008)

102 Septic Shock Patients

Goal normal perfusion

28 day Mortality
20/51
39.2%

Goal $O_2$ sat > 70%

28 day Mortality
6/51
11.8%

OR 0.2 95% CI 0.07-0.57
Intervention group

Severe Sepsis

Fluid responsive shock
  - Observe in PICU

Fluid refractory shock
  - Central venous line, ScvO₂ continuous monitoring, arterial line, arterial blood pressure monitoring

  - Titrate dopamine and volume to normal perfusion pressure for age, urine output > 1 ml/kg/h and CRF < 2

  - Add inotropes, volume, packed RBC to no differential between peripheral and central pulses and ScvO₂ > 70%

  - If ScvO₂ < 70%
    - Crystalloid bolus 10-20 ml/kg: if no signs of fluid overload (rales or hepatomegaly)
    - Inotrope: dobutamine (5-20 mcg/kg/min) milrinone (0.25-1.0 mcg/kg/min) epinephrine (0.05-0.3 mcg/kg/min)
    - RBC if haemoglobin < 10 g/dl

  - Titrate epinephrine for cold shock and norepinephrine for warm shock
  - Give hydrocortisone if at risk of adrenal insufficiency

Normal blood pressure
  - ScvO₂ < 70%
    - Vasodilator or type III PDE inhibitor and volume

Low blood pressure
  - ScvO₂ < 70%
    - Epinephrine and volume

Low blood pressure
  - ScvO₂ > 70%
    - Norepinephrine and volume
Mortality associated with CV O₂ sat < 70% was averted with intervention (C Oliveira et al)

<table>
<thead>
<tr>
<th>Mortality rate if</th>
<th>Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Control group</strong></td>
<td></td>
</tr>
<tr>
<td>CV O₂ sat &lt; 70%</td>
<td>68.8 %</td>
</tr>
<tr>
<td>CV O₂ sat &gt; 70%</td>
<td>21.7 %</td>
</tr>
<tr>
<td><strong>Intervention group</strong></td>
<td></td>
</tr>
<tr>
<td>CV O₂ sat &lt; 70%</td>
<td>13.3 %</td>
</tr>
</tbody>
</table>
2007 American College of Critical Care Medicine clinical practice parameters for hemodynamic support of pediatric and neonatal septic shock*

Joe Brierley; Karen Choong; Tim Cornell; Allan DeCaen; Andreas Deymann; Allan Doctor; Alan Davis; John Duff; Marc-Andre Dugas; Alan Duncan; Barry Evans; Jonathan Feldman; Kathryn Felmet; Gene Fisher; Lorry Frankel; Howard Jeffries; Bruce Greenwald; Juan Gutierrez; Kato Han; James Hanson; Jan Hazelzet; Lynn Hernan; Jane Kiff; Niranjan Kissoon; Alexander Kon; Jose Irazusta; John Lin; Angie Lorts; Michelle Mariscalco; Renuka Mehta; Simon Nadel; Trung Nguyen; Carol Nicholson; Mark Peters; Regina Okhuysen-Cawley; (Crit Care Med 2009; 37:000–000)
Stepwise management of hemodynamic support in infants and children

0 min
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?

5 min
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?

15 min
Catecholamine resistant shock: Begin hydrocortisone if at risk for absolute adrenal insufficiency

60 min
Monitor CVP in PICU, attain normal MAP-CVP & ScvO₂ > 70%

Cold shock with normal blood pressure:
1st goals: Titrate epinephrine, ScvO₂ > 70%, Hgb > 10 g/dL
2nd goals: add vasodilator* (nitrovasodilators, milrinone, iminon, & others) with volume loading, consider levosimendan

Cold shock with low blood pressure:
1st goals: Titrate epinephrine, ScvO₂ > 70%, Hgb > 10 g/dL
2nd goals: Add norepinephrine
- Add dobutamine if ScvO₂ < 70%
- Consider milrinone, enoximone or levosimendan
- shock not reversed?

Warm shock with low blood pressure:
1st goals: titrate norepinephrine, ScvO₂ > 70%
2nd goals: consider vasopressin, terlipressin or angiotensin
- Add dobutamine or low dose epinephrine if ScvO₂ < 70%

Persistent catecholamine resistant shock:
- Rule out and correct pericardial effusion, pneumothorax, & intra-abdominal pressure >12 mmHg.
- Use pulmonary artery catheter, PICCO monitor, FATD/FO doppler ultrasound to guide fluid, inotrope, vasopressor, vasodilator and hormonal therapies.
- Goal CI > 3.3 & < 6.0 L/min/m²
- shock not reversed?

Refractory shock: ECMO (110 mL/Kg/min) &/or CRRT (>35 mL/Kg/hr)
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?*
Don’t forget the basics - antibiotics

- Effects of time from
  - triage to antibiotic administration,
  - qualification for early goal-directed therapy to antibiotic administration,
  - triage to appropriate antibiotic administration
- 261 adults

- Median times
  - from triage to antibiotics was 119 mins (interquartile range, 76-192 mins)
  - from qualification to antibiotics was 42 mins (interquartile range, 0-93 mins).
- Time from triage or time from qualification for early goal-directed therapy to antibiotics – no effect on mortality.
- Time from triage to **appropriate** antibiotics, there was a significant association
  - at the <1 hr cut off for triage to antibiotics - mortality 19.5 vs. 33.2%;
  - At the <1 hour cut off time from qualification for early goal-directed therapy to antibiotics, - mortality 25.0 vs. 38.5%;

- Elapsed times from triage and qualification for early goal-directed therapy to administration of appropriate antimicrobials are primary determinants of mortality in patients with severe sepsis and septic shock treated with early goal-directed therapy.

Gaieski DF, Mikkelsen ME, Band RA, Pines JM, Massone R, Furia FF, Shofer FS, Goyal M. Impact of time to antibiotics on survival in patients with severe sepsis or septic shock in whom early goal-directed therapy was initiated in the emergency department. Crit Care Med 2010 38(4):1045-53.
Stepwise management of hemodynamic support in infants and children

0 min

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?

5 min

With 2nd PIV start inotrope.
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.

With 2nd PIV start inotrope.

dose range: dopamine up to 10 mcg/kg/min, epinephrine 0.05 to 0.3 mcg/kg/min.
RCT in 300 adults with septic shock. 19 ICUs in France.
Randomised
- Hydrocortisone 50mg/kg IV qds and fludricortisone 50mcg PO daily
- or placebo for 7/7.
Short synacthen test at enrolment.
229 non-responders, 70 responders to synacthen test.
In non-responders,
- 63% mortality placebo,
- 53% mortality treatment – hazard ratio 0.67.
No difference in responders.
No difference in adverse events.
Conclusion that low dose hydrocortisone and fludrocortisone improve outcome in adult septic patients who have adrenal insufficiency.
Study has been criticised for employing incorrect statistical analysis. Does not establish case for blind treatment without doing a synacthen test.
NNT 17, but with confidence intervals around absolute risk reduction including zero.

RESOLVE study – steroid subgroup

<table>
<thead>
<tr>
<th>Table 2. Comparison of various outcome measures among children in the RESOLVE trial who received or did not receive adjunctive corticosteroid therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Received Adjunctive Corticosteroids (n = 193)</strong></td>
</tr>
<tr>
<td>Mean ± sd or %</td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>Mortality, %</td>
</tr>
<tr>
<td>MV, days</td>
</tr>
<tr>
<td>V-I Support, days</td>
</tr>
<tr>
<td>CTCOFR, days</td>
</tr>
<tr>
<td>δPOPC score</td>
</tr>
<tr>
<td>PICU LOS, days</td>
</tr>
<tr>
<td>Hospital LOS, days</td>
</tr>
</tbody>
</table>

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

**Cold shock with normal blood pressure:**
1° goals: Titrate epinephrine, ScvO₂ > 70%, Hgb > 10 g/dL
2° goals: add vasodilator* (nitrosovasodilators, milrinone, imrinoine, & others) with volume loading, consider levosimendan

**Cold shock with low blood pressure:**
1° goals: Titrate epinephrine, ScvO₂ > 70%, Hgb > 10 g/dL
2° goals: Add norepinephrine
   Add dobutamine if ScvO₂ < 70%
Consider milrinone, enoximone or levosimendan

**Warm shock with low blood pressure:**
1° goals: titrate norepinephrine, ScvO₂ > 70%,
2° goals: consider vasopressin, terlipressin or angiotensin
   Add dobutamine or low dose epinephrine if ScvO₂ < 70%

*shock not reversed?*

**Persistent catecholamine resistant shock:** Rule out and correct pericardial effusion, pneumothorax, & intra-abdominal pressure >12 mm/Hg.
Use pulmonary artery catheter, PICCO monitor, FATD &/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 (110 mL/Kg/min) &/or CRRT (> 35 mL/Kg/hr)
- Central O2 sats not easy to introduce in sepsis management protocols
- Lactate more easily measured

Jones AE, Shapiro NI, Trzeciak S et al. Lactate Clearance vs Central Venous Oxygen Saturation as Goals of Early Sepsis Therapy. *JAMA. 2010; 303*(8):739-746
Figure. Study Flow Diagram

452 Patients were assessed for eligibility

152 Excluded
   64 Met specific exclusion criteria
   88 Had other reasons
       36 Declined to participate
       51 Could not provide consent or contact next of kin
       1 Was already enrolled in another interventional study

300 Randomized

150 Randomized to lactate clearance group
   147 Received lactate clearance protocol
      3 Did not receive protocol
   1 Family withdrew care prior to protocol completion

150 Randomized to ScvO₂ group
   147 Received ScvO₂ protocol
      3 Did not receive protocol
      2 Unable to place central line
      1 Family withdrew care prior to protocol completion

150 Included in the primary analysis
150 Included in the primary analysis

ScvO₂ indicates central venous oxygen saturation.
Table 5. Hospital Mortality and Length of Stay

<table>
<thead>
<tr>
<th>Variable</th>
<th>Lactate Clearance Group (n = 150)</th>
<th>ScvO₂ Group (n = 150)</th>
<th>Proportion Difference (95% Confidence Interval)</th>
<th>P Value^b</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>In-hospital mortality, No. (%)^a</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intent to treat</td>
<td>25 (17)</td>
<td>34 (23)</td>
<td>6 (−3 to 15)</td>
<td></td>
</tr>
<tr>
<td>Per protocol</td>
<td>25 (17)</td>
<td>33 (22)</td>
<td>5 (−3 to 14)</td>
<td></td>
</tr>
<tr>
<td><strong>Length of stay, mean (SD), d</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICU</td>
<td>5.9 (8.46)</td>
<td>5.6 (7.39)</td>
<td>.75</td>
<td></td>
</tr>
<tr>
<td>Hospital</td>
<td>11.4 (10.89)</td>
<td>12.1 (11.68)</td>
<td>.60</td>
<td></td>
</tr>
<tr>
<td><strong>Hospital complications</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ventilator-free days, mean (SD)</td>
<td>9.3 (10.31)</td>
<td>9.9 (11.09)</td>
<td>.67</td>
<td></td>
</tr>
<tr>
<td>Multiple organ failure, No. (%)</td>
<td>37 (25)</td>
<td>33 (22)</td>
<td>.68</td>
<td></td>
</tr>
<tr>
<td>Care withdrawn, No. (%)</td>
<td>14 (9)</td>
<td>23 (15)</td>
<td>.15</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ICU, intensive care unit; ScvO₂, central venous oxygen saturation.
^aPrimary study end point.
^bContinuous data are compared using an unpaired t test; categorical variables, using the χ² test.
Personnel issues
The role of healthcare delivery in the outcome of meningococcal disease in children: case-control study of fatal and non-fatal cases


- Case control study of fatal vs. non-fatal meningococcal disease 1997-1999
- 145 cases; 355 controls
- Factors associated with death
  - Not under care of paediatrician
  - Failure of supervision by a consultant
  - Failure in administration of inotropes
Common errors (1)

- Failure to establish secure access
- Ventilation delayed until arrest
Common errors (1)

- Failure to establish secure access
- Ventilation delayed until arrest
- Intra-Osseous needle after 90 sec in shocked child

- Recognise severe disease
  - low WCC
  - coagulopathy
  - extensive rash
Common errors (2)

- Inadequate fluid admin
- Myocardial depressant drugs administered for induction of anaesthesia
Common errors (2)

- Inadequate fluid admin
- Myocardial depressant drugs administered for induction of anaesthesia
  - 20mls/kg and rpt
  - 200mls/kg not unusual
  - Fentanyl (+/- ketamine)
  - Pancuronium/Sux
  - not thiopentone
  - midazolam
  - propofol
Common errors (3)

KCl boluses

- Large ET leak
  - Nasal intubation
  - dobutamine used alone
Common errors (3)

KCl boluses
- Total Body K⁺ normal or high, anticipate acidosis
- Large ET leak
  - high pressure leak only
- Nasal intubation
  - Avoid in coagulopathy
- dobutamine used alone
  - AVOID dobutamine
    - If no CVL then
      - IO dopamine/adrenaline
Summary

- Volume
- Inotropes
- Aggressive early treatment