Advances in the Management of Shock: Fluid Resuscitation and Hypovolemic Shock

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Disclosures

• No financial disclosures
At the conclusion of the activity participants should be able to:

- Discuss the risks and benefits of different solutions (crystalloids, colloids, and blood) for fluid resuscitation
- Discuss an evidence-based approach to guide the intensity of volume administration in surgical and critically ill patients
- Recognize common complications associated with inadequate and excessive fluid administration
Advances in Fluid Resuscitation

- Timing of resuscitation
- Aggressiveness of resuscitation
- Monitoring of intravascular volume status and prediction of response to fluid administration
- Choice of fluids
  - Balanced vs. unbalanced crystalloids
  - Crystalloids vs. colloids
    - Hydroxyethyl starches
  - Hypertonic saline
• When do I drink?
• What do I drink?
• How much do I drink?
History of Intravenous Fluid Administration

- Malignant cholera. Documents communicated by the Central Board of Health, London, relative to the treatment of cholera by the copious injection of aqueous and saline fluids into the veins.
History of Intravenous Fluid Administration

- “in that disease there is a very great deficiency both of the water and saline matter of the blood”
- “I dissolved from two to three drachms of muriate of soda and two scruples of the subcarbonate of soda in six pints of water”
- “the cadaverous expression gradually gives place to appearances of returning animation...the sunken turned-up eye...becomes gradually fuller, till it sparkles with the brilliancy of health...and the poor patient, who but a few minutes before was oppressed with sickness, vomiting, and burning thirst, is suddenly relieved from every distressing symptom”
- “In this case 330 ounces [10 L] were so used in twelve hours...and in forty-eight hours she smoked her pipe free from distemper”
- “I have never yet seen one bad symptom attributable to it”
- “Although in every case, even the most desperate, the cholera symptoms were removed, some of my cases failed”
Timing Of Resuscitation

• Benefits of early resuscitation
  – Maintain vital organ perfusion
  – Prevent multiple organ system failure

• Hazards of early resuscitation
  – Increased bleeding
  – Increased coagulopathy
Early vs. Delayed Resuscitation

  - 598 patients with hypotension due to penetrating torso injury
  - Alternate day design of early vs. delayed resuscitation
  - Early resuscitation increased mortality (38% vs. 30%), hospital length of stay, and organ failure
Hypotensive Resuscitation

- HypoResus Trial (NCT01411852): ROC
  - 191 trauma patients with pre-hospital SBP ≤ 90
  - Randomized to:
    - Standard: 2 L NS and whenever SBP < 110
    - Controlled: 250 ml NS only when SBP < 70
    - Treatment continued for 2 hours after hospital arrival or until hemorrhage controlled

<table>
<thead>
<tr>
<th></th>
<th>Standard</th>
<th>Controlled</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crystalloid</td>
<td>2.04 L</td>
<td>1.04 L</td>
</tr>
<tr>
<td>Mortality</td>
<td>15%</td>
<td>5%</td>
</tr>
</tbody>
</table>

OR 0.39 (0.12 – 1.25)
Hypotensive Resuscitation

• Morrison, J Trauma 2011; 70:652
  – RCT of intraoperative hypotension (MAP 50 vs. 65) for trauma requiring emergency surgery

<table>
<thead>
<tr>
<th></th>
<th>MAP = 50</th>
<th>MAP = 65</th>
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<tbody>
<tr>
<td>PRBC</td>
<td>1335</td>
<td>2244</td>
</tr>
<tr>
<td>FFP</td>
<td>198</td>
<td>528</td>
</tr>
<tr>
<td>Platelets</td>
<td>61</td>
<td>114</td>
</tr>
<tr>
<td>EBL</td>
<td>1964</td>
<td>3008</td>
</tr>
</tbody>
</table>
Hypotensive Resuscitation

- Trend towards decreased mortality

Hazard ratio = 1.10
Trauma Resuscitation

- Damage control management
- Avoid triad of hypothermia, acidosis, and coagulopathy
- Hemostatic resuscitation
  - 1:1:1 PRBC:FFP:platelets
- Tranexamic acid

CRASH-2 Investigators, Lancet 2011; 377:1096
Advances in Fluid Resuscitation

• Timing of resuscitation
• Aggressiveness of resuscitation
• Monitoring of intravascular volume status and prediction of response to fluid administration

• Choice of fluids
  – Balanced vs. unbalanced crystalloids
  – Crystalloids vs. colloids
    • Hydroxyethyl starches
  – Hypertonic saline
Volume Strategies

• Aggressive fluid administration
  – Maintain organ perfusion
• Fluid restriction (salt water drowning)
  – Edema decreases gut function and wound healing
  – Increased incidence of abdominal compartment syndrome
  – Improved outcome in ARDS
Benefits of Fluid Restriction

- Nisanevich, Anesthesiology 2005; 103;25
  - Randomized 156 patients undergoing intraabdominal surgery to restricted (4 ml/kg/h LR) vs. liberal fluids (10 ml/kg bolus and then 12 ml/kg/h LR); additional fluid if urine output < 0.5 ml/kg/h
    - Intraop fluids: 1408 ml vs. 3878 ml
    - Complications: 31% vs. 17%
  - Decreased time to passing flatus, bowel movement, and LOS
Fluid Resuscitation in Sepsis

• Maitland, NEJM 2011; 364:2483
  – African study of febrile children (n = 3,141) with impaired perfusion
  – Cohort A randomized to 20-40 ml bolus of 5% albumin vs. saline vs. no bolus
    • Mortality: 12.2%, 12.0%, 8.7% (P = 0.003)
  – Cohort B (severe hypotension; SBP < 70 if age > 5) randomized to albumin vs. saline bolus
    • Mortality 69% vs. 56% (NS)
Adverse Effects of Fluid Restriction

- Futier, Arch Surg 2010; 145:1193
  - Randomized 70 patients undergoing major abdominal surgery to restricted (6 ml/kg/h LR) vs. liberal fluids (12 ml/kg/h LR)
  - Colloid boluses if respiratory variation in peak aortic flow velocity > 13%
  - Fluid administration: 3380 vs. 5588 ml
  - Restricted group had more episodes of hypovolemia, lower ScvO₂, and increased incidence of anastomotic leak/abscess and postoperative sepsis
Early Goal-Directed Therapy

  - 263 patients with severe sepsis and septic shock
  - Randomized to standard therapy or early goal-directed therapy (EGDT)
  - Standard therapy
    - Crystalloid boluses for CVP 8-12
    - Vasopressors/vasodilators for MAP 65-90
    - Urine output $\geq 0.5 \text{ ml/kg/h}$
  - EGDT
    - Catheter for measurement of central venous oxygen saturation (ScvO2)
EGDT Protocol

• If ScvO2 < 70%
  – RBC transfusion to hematocrit > 30%
  – Dobutamine up to 20 μg/kg/min
  – Sedation and mechanical ventilation

• EGDT continued for at least 6 h before admission to the ICU
EGDT Results

• EGDT group had increased fluid administration (5.0 vs. 3.5 L), RBC transfusion, and inotropes in first 6 hours
• Standard therapy group had increased fluid administration over hours 7-72
• Fluid administration was similar in both groups over first 72 hours
EGDT MORTALITY RESULTS

ÆRivers, N Engl J Med 2001; 345:1368
Perioperative Fluid Management

- Corcoran, Anesth Analg 2012; 114:640
  - Meta-analysis of 23 RCTs of GDT and 12 RCTs of restrictive vs. liberal fluid therapy
  - Both liberal and GDT groups received more fluid
  - GDT had decreased pneumonia, renal complications, and hospital LOS
  - Liberal group had increased pneumonia, pulmonary edema, and hospital LOS
Fluid Therapy and ALI

• ARDSnet, NEJM 2006;354:2213
  – 1000 patients with ALI
  – Randomized to CVP vs. PAC
  – Randomized to fluid restriction vs. liberal fluid strategy
Fluid Management Decisions

- ARDSnet, NEJM 2006;354:2564
  - First priority was management of hypotension
  - Fluid management then dependent upon two factors
    - Adequate urine output ($\geq 0.5 \text{ ml/kg/h}$)
    - Presence of ineffective circulation
      - PAC group: $CI < 2.5 \text{ L/min/m}^2$
      - CVP group: Cold, mottled extremities with slow capillary refill (> 2 seconds)
<table>
<thead>
<tr>
<th>Measured intravascular pressure (mm Hg)</th>
<th>MAP &lt; 60 mm Hg or a need for any vasopressor (except dopamine ≤5 µg/kg/min); consider correctable causes of shock first</th>
<th>MAP ≥60 mm Hg without vasopressors (except dopamine ≤5 µg/kg/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Average urinary output &lt;0.5 ml/kg/hr</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Average urinary output ≥0.5 ml/kg/hr</td>
</tr>
<tr>
<td>Conservative strategy</td>
<td>Liberal strategy</td>
<td>Effective Circulation</td>
</tr>
<tr>
<td>CVP</td>
<td>PAOP&lt;sup&gt;g&lt;/sup&gt;</td>
<td>Ineffective Circulation</td>
</tr>
<tr>
<td>Conservative strategy</td>
<td>Liberal strategy</td>
<td>Effective Circulation</td>
</tr>
<tr>
<td>Range 1</td>
<td></td>
<td>Cardiac index &lt; 2.5 liters/min/m² or cold, mottled skin with capillary-refilling time &gt; 2 sec</td>
</tr>
<tr>
<td>&gt;13</td>
<td>&gt;18</td>
<td>1. Vasopressor&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>&gt;18</td>
<td>2. Fluid bolus&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>&gt;18</td>
<td>3. KVO IV</td>
</tr>
<tr>
<td>Range 2</td>
<td></td>
<td>Dobutamine&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>9–13</td>
<td>15–18</td>
<td>4. KVO IV</td>
</tr>
<tr>
<td></td>
<td>13–18</td>
<td>Dobutamine&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Range 3</td>
<td></td>
<td>Furosemide&lt;sup&gt;b,1,2,4&lt;/sup&gt;</td>
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<tr>
<td>4–8</td>
<td>10–14</td>
<td>5. Fluid bolus&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>8–12</td>
<td>6. Fluid bolus&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Range 4</td>
<td></td>
<td>7. KVO IV</td>
</tr>
<tr>
<td>&lt;4</td>
<td>&lt;10</td>
<td>Dobutamine&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>&lt;8</td>
<td>8. KVO IV</td>
</tr>
<tr>
<td></td>
<td>&lt;14</td>
<td>Furosemide&lt;sup&gt;b,1,2,4&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> KVO IV
<sup>b</sup> Furosemide
<sup>c</sup> Fluid bolus
<sup>d</sup> Vasopressor
<sup>e</sup> Range 1
<sup>f</sup> Range 2
<sup>g</sup> Range 3
<sup>h</sup> Range 4
# Target CVP Range

<table>
<thead>
<tr>
<th></th>
<th>Effective circulation with UOP ≥ 0.5 ml/kg/h</th>
<th>Effective circulation with UOP &lt; 0.5 ml/kg/h</th>
<th>Ineffective circulation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Liberal</strong></td>
<td>10-14</td>
<td>14-15</td>
<td>15-18</td>
</tr>
<tr>
<td><strong>Conservative</strong></td>
<td>&lt;4</td>
<td>8-9</td>
<td>9-13</td>
</tr>
</tbody>
</table>
Daily Fluid Balance

![Bar chart showing daily fluid balance with two categories: Liberal and Conservative. The x-axis represents days 1 to 7, and the y-axis represents fluid balance from -500 to 3000. The Liberal category has higher fluid balance compared to the Conservative category.](image-url)
Case Example

- MAP 65 mm Hg
- Urine output 15 ml/h
- Warm extremities with good capillary refill
- CVP 10 mm Hg
- Should we give fluid, furosemide, or dobutamine to optimize urine output?
# Target CVP Range

<table>
<thead>
<tr>
<th>Conservative</th>
<th>Effective circulation with UOP ≥ 0.5 ml/kg/h</th>
<th>Effective circulation with UOP &lt; 0.5 ml/kg/h</th>
<th>Ineffective circulation</th>
</tr>
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<tbody>
<tr>
<td>&lt;4</td>
<td>8-9</td>
<td>9-13</td>
<td></td>
</tr>
</tbody>
</table>

**Effective circulation**

UOP < 0.5 ml/kg/h

Furosemide, not volume
Advances in Fluid Resuscitation

• Timing of resuscitation
• Aggressiveness of resuscitation
• Monitoring of intravascular volume status and prediction of response to fluid administration
• Choice of fluids
  – Balanced vs. unbalanced crystalloids
  – Crystalloids vs. colloids
    • Hydroxyethyl starches
  – Hypertonic saline
Evaluation of Intravascular Volume (I)

• General signs of dehydration
  – Diminished skin turgor
  – Thirst
  – Mucous membrane moisture
  – Elevated hematocrit
Evaluation of Intravascular Volume (II)

• Circulatory signs
  – Peripheral vasoconstriction
  – Heart rate and blood pressure
  – Orthostatic vital signs
    • In healthy volunteers, removal of 20-30% blood volume has no hemodynamic effects but decreases tissue perfusion
    • 20 mm Hg BP decrease implies fluid deficit of 6-8% BW
    • Failure of heart rate to increase suggests autonomic dysfunction
Evaluation of Intravascular Volume (III)

• Decreased renal perfusion
  – Oliguria
  – Concentrated urine
  – Low urine sodium (FENa)
  – High urine osmolarity
  – Increased BUN/creatinine ratio
• But hormonal changes (increased ADH/aldosterone; decreased ANP) produce similar effects
Evaluation of Intravascular Volume (IV)

• Hemodynamic monitoring
  – Decreased CVP or PAOP
  • Only useful at the extremes
Utility of CVP and PAOP

• Marik, Chest 2008; 134:172
• “Does central venous pressure predict fluid responsiveness? A systematic review of the literature and the tale of seven mares”
Hemodynamic Monitoring

• Marik, Chest 2008; 134:172
  – Systematic review of 24 studies of CVP and fluid responsiveness
  – Essentially no relationship between CVP and blood volume, CVP and response to fluid administration, or change in CVP and change in blood volume or blood pressure

• Similar data in other studies with PAOP
RAP Before Volume Expansion In Responders and Nonresponders

Right atrial pressure (mmHg)

- Responders
- Non-responders

Calvin²: 5 5
Schneider³: 7 11
Reuse⁴: 9 8
Wagner⁸: 7 10
Michard¹²: 9 9

* p < 0.05

Evaluation of Intravascular Volume (IV)

• Hemodynamic monitoring
  – Decreased CVP or PAOP
    • Only useful at the extremes
  – Decreased cardiac output
  – Decreased LVEDV (TEE)
  – Esophageal Doppler (corrected flow time)
Esophageal Doppler
Esophageal Doppler

- Stroke distance
- Flow time
- Mean acceleration
Normovolemia

Hypovolemia

LV Failure
Esophageal Doppler

- Wakeling, Br J Anaesth 2005; 95:634
  - Randomized patients undergoing major bowel surgery to esophageal Doppler or CVP
  - Decreased LOS, complications, time to return of gut function in Doppler group
Evaluation of Intravascular Volume (V)

- Dynamic evaluations
  - Orthostatic vital signs
  - Trendelenberg position
  - Passive leg raising
  - Fluid challenge
  - Respiratory variation
Fluid Challenge

– Rapid infusion until CVP/PAOP exceeds safety value or hemodynamic abnormality is reversed
Volume Status and Positive Pressure Ventilation

**INSPIRATION**
- Increased intra-thoracic pressure
- Decreased venous return

**EXPIRATION**
- Decreased intra-thoracic pressure
- Increased venous return
TTE and IVC Diameter

<12 vs. >20 mm
>18% vs. <12%
Respiratory Variation

- Start of positive pressure inspiration
  - Blood squeezed from pulmonary capillaries into left heart
  - Increased ejection from left ventricle to extra-thoracic tissues (decreased afterload)
  - Net effect is increased stroke volume/SBP/PP
- Maintained positive pressure
  - Decreased venous return decrease SV/SBP/PP
- Release of positive pressure
  - Blood pools in pulmonary capillaries
  - Decreased ejection from left ventricle to extra-thoracic tissues (loss of decreased afterload)
  - Net effect is further decrease in stroke volume/SBP/PP
Respiratory Variation

- **SPV (Systolic pressure variation)**
  - Difference between minimal and maximal values of systolic BP during mechanical breath

- **Delta Down**
  - Difference between the minimal value of systolic BP during mechanical breath and its value during apnea

- **PPV (Pulse pressure variation)**
  - Difference between the maximal and minimal values of the pulse pressure during one mechanical breath related to the average between these values

- **Pulse plethysmogram variation**
Baseline
(“apnea”)

mmHg
150
75
PAP
CVP
0-

PAP
CVP
0-

E1
Insp
Insp
Insp

Magder, AJRCCM 2004; 169:151
# Predictors of Fluid Response

<table>
<thead>
<tr>
<th></th>
<th>CVP</th>
<th>PPV</th>
<th>SPV</th>
<th>dDOWN</th>
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<tbody>
<tr>
<td>Responder</td>
<td>9</td>
<td>18</td>
<td>12</td>
<td>9</td>
</tr>
<tr>
<td>Non-responder</td>
<td>10</td>
<td>4</td>
<td>6</td>
<td>3</td>
</tr>
</tbody>
</table>

Preisman, Br J Anaesth 2005; 95:746
Stroke Volume Variation

• Often PPV plus pulse contour analysis (continuous cardiac output)
  – Pulsion PiCCO
  • Intrathoracic blood volume
  – Flotrac/Vigileo
Normal Dynamic Variable Values

- SPV < 10 mm Hg
- PPV < 13%
- SVV < 15%
- Requires positive pressure ventilation with TV > 8 ml/kg, no spontaneous ventilation, sinus rhythm, normal right heart function, closed chest
Advances in Fluid Resuscitation

- Timing of resuscitation
- Aggressiveness of resuscitation
- Monitoring of intravascular volume status and prediction of response to fluid administration
- Choice of fluids
Choice of Resuscitation Fluid

- Crystalloid-crystalloid controversy
- Crystalloid-colloid controversy
- Colloid-colloid controversy
- Hypertonic saline

![Coca-Cola vs Pepsi](image)
Choice of Resuscitation Fluid

• Are all crystalloids equal?
  – Balanced vs. unbalanced solutions

• Are all colloids equal?
  – Albumin
  – Synthetic colloids
    • Hydroxyethyl starches: molecular weight, molar substitution ratio

• Are colloids superior to crystalloids?
  – Efficacy as plasma volume expanders for short-term resuscitation
  – Adverse effects: renal dysfunction, coagulopathy, tissue storage
  – Morbidity and mortality

• Role of blood transfusion (hemoglobin 7 g/dL)

• Individual patient factors
  – Is sepsis different from other critically ill patients?
## Recent Systematic Reviews

<table>
<thead>
<tr>
<th>Study</th>
<th>Comparison</th>
<th>Sepsis</th>
<th>Trials</th>
<th>Patients</th>
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<tbody>
<tr>
<td>Dart, 2010</td>
<td>HES vs. other fluids</td>
<td>No</td>
<td>34</td>
<td>2,607</td>
</tr>
<tr>
<td>Alderson, 2011</td>
<td>Albumin vs. crystalloid</td>
<td>No</td>
<td>38</td>
<td>10,842</td>
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<tr>
<td>Delaney, 2011</td>
<td>Albumin</td>
<td>Yes</td>
<td>17</td>
<td>1,977</td>
</tr>
<tr>
<td>Perel, 2012</td>
<td>Colloids vs. crystalloids</td>
<td>No</td>
<td>74</td>
<td>9,920</td>
</tr>
<tr>
<td>Bunn, 2012</td>
<td>Colloids vs. colloids</td>
<td>No</td>
<td>86</td>
<td>5,484</td>
</tr>
<tr>
<td>Mutter, 2013</td>
<td>HES and renal function</td>
<td>No</td>
<td>42</td>
<td>11,399</td>
</tr>
</tbody>
</table>

Over 30 trials in the past decade
Saline and Metabolic Acidosis

- Saline has Na 154, Cl 154
- Produces hyperchloremic metabolic acidosis
  - Dilution of serum bicarbonate
  - Strong ion difference = 0
Saline and Metabolic Acidosis

• Scheingraber, Anesthesiology 1999; 90:1265
  – Gynecologic surgery
  – Normal saline vs. LR at 30 ml/kg/h
  – Normal saline produced hyperchloremic metabolic acidosis at 2 hours (pH 7.28, base excess −6.7)
  – No changes in LR group
Saline and AKI

- Chloride may promote acute kidney injury
  - Tubular chloride reabsorption and chloride delivery to the macula densa activates tubuloglomerular feedback to produce renal arteriolar vasoconstriction and decreased GFR
Chloride Excess in Critical Care

- Yunos, JAMA 2012; 308:1566
  - Open label sequential period study (2008 vs. 2009) in Australian ICU
  - Initial: 0.9% NaCl, 4% gelatin, 4% albumin
  - Change: Hartmann solution, Plasma-Lyte 148, chloride-poor 20% albumin
  - Chloride administration decreased from 694 to 496 mmol/patient
  - AKI decreased from 14% to 8% (OR 0.52)
  - RRT decreased from 10% to 6% (OR 0.52)
  - But no change in mortality or LOS
# Effects Of Fluids

<table>
<thead>
<tr>
<th>Fluid compartment</th>
<th>0.9% NaCl</th>
<th>5% Albumin</th>
<th>25% Albumin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intravascular</td>
<td>![Arrow]↑</td>
<td>![Arrow]↑</td>
<td>![Arrow]↑</td>
</tr>
<tr>
<td>Interstitial</td>
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<td>![Arrow]→</td>
<td>![Arrow]↓</td>
</tr>
<tr>
<td>Intracellular</td>
<td>![Arrow]→</td>
<td>![Arrow]→</td>
<td>![Arrow]↓</td>
</tr>
</tbody>
</table>
Colloids More Effective as Volume Expanders

• Trof, Intensive Care Med 2010; 36:697
  – 48 patients with hypovolemia
  – Randomized to NS, 4% gelatin, 6% HES, or 5% albumin
  – Protocolized therapy with 200 ml boluses at most every 10 minutes over 90 minutes
  – Cardiac index increased 2% with NS and 12% with colloid
Volume Expansion with Colloids in Sepsis

- Capillary leak in sepsis
  - SAFE study (albumin) 1:1.3-1.4
  - VISEP (HES) 1:1.4-1.6
  - Upadhyay (gelatin) 1: 1.0
Crystalloid vs. Colloid

- Schierhout, BMJ 1998; 316:961
  - Meta-analysis of 19 randomized trials of crystalloid vs. colloid with fluid resuscitation protocols
  - 1,315 patients
  - Colloid solutions increased mortality from 20% to 24%
SAFE Study

- Finfer, NEJM 2004; 350:2247
- Saline vs. albumin fluid evaluation
- Australia and New Zealand Intensive Care Society Clinical Trials Group
- 6,997 critically ill patients requiring volume resuscitation
- Randomized to resuscitation with 4% albumin vs. saline
SAFE Results

• Mortality
  – Albumin 726/3473 (20.9%)
  – Saline 729/3460 (21.1%)
  – Kaplan-Meier survival curves identical

• Days on mechanical ventilation, need for renal replacement therapy, and organ failure data equivalent

• Baseline albumin did not influence lack of benefit

• Subgroup of trauma patients with TBI had excess of 21 deaths with albumin (59/241 or 25% vs. 38/251 or 15%; p < 0.01)

Colloids vs. Crystalloids

- Perel, Cochrane Database Syst Rev 2013: CD00056
  - Albumin: 24 trials, 9,920 patients
    - RR 1.01 (0.93 – 1.10)
  - Hydroxyethyl starch: 25 trials, 9,147 patients
    - RR 1.10 (1.02 – 1.19)
  - Gelatin: 11 trials, 506 patients
    - RR 0.91 (0.49 – 1.72)
  - Dextran: 9 trials, 834 patients
    - RR 1.24 (0.94 – 1.65)
Albumin and Sepsis

• Delaney, Crit Care Med 2011; 39:386
  – Meta-analysis of 17 studies, 1977 patients
  – OR for mortality 0.82 (0.67 – 1.0; p = 0.047)
Colloid Vs. Colloid Controversy

- Molecular weight (average and distribution)
  - Albumin 69,000
  - Hydroxyethyl starch 450,000
  - Dextrans 10,000 - 90,000

- Half-life
- COP
- Side effects
- Cost
Hydroxyethyl Starch Solutions

- Branched polysaccharide polymer derived from amylopectin
- Hydroxyethyl ether groups attached to glucose units
- Molecular weight and molar substitution ratio can be varied
- Hespan has 450,000 MW and 0.7 ratio
- Potential advantages of medium MW starches (200,000/0.5) and tetrastarches (130,000/0.4)
Medium Weight Starches

• Pentastarch (HES 200/0.5), Voluven (HES 130/0.4), acetyl starch (HES 200/0.5)
• No adverse effects on coagulation (HES 450/0.7 limited to 20 mL/kg/day)
• Decreased inflammation
Pentastarch

- Brunkhorst, NEJM 208; 358:125
  - RCT of intensive insulin therapy x pentastarch (HES 200/0.5)/LR for sepsis
  - Pentastarch had increased renal failure (35% vs. 23%) and trend towards increased mortality at 90 days (41% vs. 34%)
  - Effects were dose-dependent
Controversy Over Colloids

- Reinhart, Anesth Analg 2011; 112:507
  - Boldt responsible for 85 publications on volume therapy, many involving colloid solutions
  - Retractions due to lack of IRB approval and definitive fraud
  - Impact on clinical practice unresolved
Renal Effects of Colloids

• Bayer, Crit Care Med 2011; 39:1335
  – Patients with severe sepsis treated with Voluven (2005), 4% gelatin (2006), or saline (2008)
  – Acute kidney injury decreased from 70% with Voluven and 68% with gelatin to 47% with saline
  – Crystalloid volumes only twice colloid volumes over time
HES and Kidney Injury

• Dart, Cochrane Database Syst Rev 2010; CD007594
  – 34 studies, 2,607 patients
  – Kidney failure RR = 1.50 (1.20- 1.87)
  – RRT RR = 1.38 (0.89 – 2.16)
  – Increased risk in septic patients
    • Renal failure 1.55 (1.22 – 1.96)
    • RRT 1.59 (1.2 – 2.1)
  – Inadequate data to analyze different HES products
Colloids in ICU (CHEST Trial)

- Myburgh, NEJM 2012; 367:1901
  - 6,651 ICU patients randomized to Voluven (HES 130/0.4) or saline for all fluid resuscitation
  - Less study fluid (526 vs. 616 ml) and less non-study fluid (851 vs. 1115 ml) in the HES group during first 4 days
  - Identical HR, MAP, and lactate levels
  - Mortality 18% vs. 17%
  - RRT in 7% vs. 6%
  - Adverse events in 5.3% vs. 2.8% (P < 0.001)
Colloids in Severe Sepsis (6S Study)

- Perner, NEJM 2012; 367:72
  - 798 patients with severe sepsis randomized to HES 130/0.42 or Ringer’s acetate
  - Mortality 51% vs. 43% (RR 1.17; P = 0.03)
  - RRT in 22% vs. 16% (RR 1.35; P = 0.04)
  - Severe bleeding in 10% vs. 6% (RR 1.52; P = 0.09)
CRISTAL Study

- Annane, JAMA 2013; 310:1809
  - 2,857 ICU patients randomized to colloid vs. crystalloid resuscitation from hypovolemic shock
  - 28 day mortality 25% vs. 27% (RR 0.96, P = 0.26)
  - 90 day mortality 31% vs. 34% (RR 0.92, P = 0.03)
  - More days alive off mechanical ventilation
  - More days alive off vasopressor therapy
Choice of Fluid in Septic Shock

- Rochwerg, Ann Intern Med 2014; 161:347

<table>
<thead>
<tr>
<th>Study, Year (Reference)</th>
<th>Events/Total, n/N</th>
<th>Weight, %</th>
<th>Odds Ratio: M-H, Fixed (95% CI)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Colloids</td>
<td>Crystalloids</td>
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<tr>
<td>Haupt and Rackow, 1982 (38)</td>
<td>8/13</td>
<td>3/4</td>
<td>0.2</td>
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<tr>
<td>Finfer et al, 2004 (2)</td>
<td>185/603</td>
<td>217/615</td>
<td>20.4</td>
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<td>Brunhorst et al, 2008 (1)</td>
<td>107/261</td>
<td>93/274</td>
<td>7.3</td>
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<td>Li et al, 2008 (39)</td>
<td>14/30</td>
<td>20/30</td>
<td>1.5</td>
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<td>McIntyre et al, 2008 (41)</td>
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<td>7/19</td>
<td>0.6</td>
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<td>Dubin et al, 2010 (37)</td>
<td>3/12</td>
<td>7/13</td>
<td>0.7</td>
</tr>
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<td>Myburgh et al, 2012 (3)</td>
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<td>224/945</td>
<td>23.3</td>
</tr>
<tr>
<td>Lv et al, 2012 (40)</td>
<td>7/22</td>
<td>12/20</td>
<td>1.2</td>
</tr>
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<td>Guidet et al, 2012 (6)</td>
<td>40/99</td>
<td>32/95</td>
<td>2.7</td>
</tr>
<tr>
<td>Perner et al, 2012 (4)</td>
<td>202/398</td>
<td>173/400</td>
<td>11.6</td>
</tr>
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<td>Haase et al, 2013 (5)</td>
<td>44/117</td>
<td>50/124</td>
<td>4.2</td>
</tr>
<tr>
<td>Annane et al, 2013 (16)</td>
<td>252/774</td>
<td>286/779</td>
<td>26.4</td>
</tr>
<tr>
<td>Total</td>
<td>3326</td>
<td>3318</td>
<td>100.00</td>
</tr>
<tr>
<td>Total events</td>
<td>1119</td>
<td>1124</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: chi-square = 23.20; I² = 53% 
Test for overall effect: Z = 0.18 (P = 0.85)
Network Meta-Analysis

Figure Legend:
Network map for 6-node analysis.
BC = balanced crystalloid; H-HES = high-molecular-weight hydroxyethyl starch; L-HES = low-molecular-weight hydroxyethyl starch.
# Benefits of Balanced Crystalloids

<table>
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<tr>
<th>Comparison</th>
<th>Trials With Direct Comparisons, n</th>
<th>Direct Estimate (95% CI); Quality of Evidence</th>
<th>Indirect Estimate (95% CrI); Quality of Evidence</th>
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<tr>
<td>L-HES vs. saline</td>
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<td>1.07 (0.89-1.29); Moderate†</td>
<td>0.59 (0.25-1.35); Very low†§</td>
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<td>1.13 (0.71-1.80); Very low†§</td>
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<tr>
<td>Albumin vs. saline</td>
<td>2</td>
<td>0.81 (0.64-1.03); Moderate†</td>
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<td>0.83 (0.52-1.33); Low†§</td>
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<td>Balanced crystalloid vs. H-HES</td>
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Crl = credibility interval; H-HES = high-molecular-weight hydroxyethyl starch; L-HES = low-molecular-weight hydroxyethyl starch; NMA = network meta-analysis.

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# Benefits of Albumin

## Table 4. NMA Results of 6-Node Analysis, Including Confidence Assessments

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Benefits of Hypertonic Saline

- Increased intravascular volume expansion
- Decreased extravascular fluid
- Decreased cerebral edema
- Decreased ICP
Hypertonic Saline

• Bunn, Cochrane Database
  – 12 trials with data on mortality
    • Trauma  RR 0.84 (0.61 – 1.16)
    • Burns   RR 1.49 (0.56 – 3.95)
    • Surgery RR 0.62 (0.08 – 4.57)
Research Outcomes Consortium

- Pre-hospital resuscitation with 250 ml NS vs. 7.5% saline vs. 7.5% saline with dextran (n = 1,073)
- No difference in mortality
- Patients with shock who received hypertonic saline had earlier deaths

JAMA 2010; 304:1455
Ann Surg 2011; 253:431
My Fluid Choices

• Hypotensive hemostatic resuscitation in traumatic hemorrhagic shock
• Conservative intraoperative fluid administration using dynamic variables
• Initial resuscitation with a balanced crystalloid solution; consider iso-oncotic albumin if large volumes required, especially in sepsis
• Avoid hydroxyethyl starch solutions
• Transfusion to maintain hemoglobin > 7 g/dL
• Alter these conclusions as new data become available
THANK YOU!