Surviving Sepsis

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Disclosures

• No conflicts of interest
Sepsis

- Principles of management of septic shock in the operating room
- "Surviving Sepsis" guidelines
Add-on Case for Your OR

- “Please call the front desk”
- Butt case
- Add-on from Hell
The Case from Hell

- 76 year old man for exploratory laparotomy.
- 100kg
- Acute peritonitis
- ARDS and septic shock
- On intermittent positive pressure ventilation
- On vasopressors
- ? paracolic abscess on CT scan
The Patient is on Some Drips
What is Sepsis?
Sepsis

- Life-threatening organ dysfunction caused by a dysregulated host response to infection
- Increased Sequential [Sepsis-related] Organ Failure Assessment (SOFA) score of 2+
- In-hospital mortality greater than 10%.
<table>
<thead>
<tr>
<th>Organ System, Measurement</th>
<th>SOFA Score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Respiration</strong> PaO₂/FiO₂, mmHg</td>
<td>0</td>
</tr>
<tr>
<td>Normal</td>
<td>&lt;400</td>
</tr>
<tr>
<td><strong>Coagulation Platelets x10³/mm³</strong></td>
<td>Normal</td>
</tr>
<tr>
<td><strong>Liver Bilirubin, mg/dL (μmol/l)</strong></td>
<td>Normal</td>
</tr>
<tr>
<td><strong>Cardiovascular Hypotension</strong></td>
<td>Normal</td>
</tr>
<tr>
<td><strong>Central Nervous System Glasgow Coma Score</strong></td>
<td>Normal</td>
</tr>
<tr>
<td><strong>Renal Creatinine, mg/dL (μmol/l) or Urine output</strong></td>
<td>Normal</td>
</tr>
</tbody>
</table>
Septic Shock

- Subset of sepsis with profound circulatory, cellular, and metabolic abnormalities
- Associated with a greater risk of mortality than with sepsis alone
- Vasopressor to MAP > 65 mm Hg
- Lactate level > 2 mmol/L in the absence of hypovolemia
- Hospital mortality rates > 40%
Rapid Identification

- Out-of-hospital, emergency department, or general hospital ward settings, adult patients with suspected infection

- quickSOFA (qSOFA)
  - Respiratory rate >22/min
  - Altered mentation
  - Systolic <100 mm Hg

- Score >= 2 indicates poor outcomes
The Case from Hell

- 76 year old man for exploratory laparotomy.
- 100kg
- Acute peritonitis
- ARDS and septic shock
- On intermittent positive pressure ventilation
- On vasopressors
- ? paracolic abscess on CT scan
Why Are We Doing This Case?

• He is too sick for the OR.
• Can’t they stabilize him before we take him?
Why?

- Recommend anatomic diagnosis of infection requiring emergent source control be identified
- Or excluded as rapidly as possible in patients with sepsis or septic shock
- Source control as soon as medically and logistically practical (Best Practice Statement)
What to Do?

• How should we manage the hemodynamic compromise?
• What fluids should we give?
• What is the best way to oxygenate this patient?
• Is there anything else we should give?
• What is the evidence for these maneuvers?
Can’t We Just Set Some Goals?

• Numbers to aim for to make management easier
Shoemaker’s Goals of Therapy
1980s
Supranormal Values

• Blood volume increased by 500ml
• Cardiac Index > 4.5 l/min/m²
• Oxygen delivery > 600 ml/min/m²
• Oxygen consumption > 170 ml/min/m²
Goal Directed Therapy of Sepsis


Early Goal-Directed Therapy

- 263 patients
- 130 randomized to early goal-directed therapy
- 133 randomized to standard therapy
- First 6 hours, prior to ICU admission
## Results

### Table 3. Kaplan–Meier Estimates of Mortality and Causes of In-Hospital Death.*

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>STANDARD THERapy (N = 133)</th>
<th>EARLY GOAL-DIRECTED THERAPY (N = 130)</th>
<th>RELATIVE RISK (95% CI)</th>
<th>P VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>no. (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In-hospital mortality†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>59 (46.5)</td>
<td>38 (30.5)</td>
<td>0.58 (0.38–0.87)</td>
<td>0.009</td>
</tr>
<tr>
<td>Patients with severe sepsis</td>
<td>19 (30.0)</td>
<td>9 (14.9)</td>
<td>0.46 (0.21–1.03)</td>
<td>0.06</td>
</tr>
<tr>
<td>Patients with septic shock</td>
<td>40 (56.8)</td>
<td>29 (42.3)</td>
<td>0.60 (0.36–0.98)</td>
<td>0.04</td>
</tr>
<tr>
<td>Patients with sepsis syndrome</td>
<td>44 (45.4)</td>
<td>35 (35.1)</td>
<td>0.66 (0.42–1.04)</td>
<td>0.07</td>
</tr>
<tr>
<td>28-Day mortality†</td>
<td>61 (40.3)</td>
<td>40 (22.2)</td>
<td>0.58 (0.39–0.87)</td>
<td>0.01</td>
</tr>
<tr>
<td>60-Day mortality†</td>
<td>70 (50.9)</td>
<td>50 (44.3)</td>
<td>0.67 (0.46–0.96)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Causes of in-hospital death‡

<table>
<thead>
<tr>
<th>Cause</th>
<th>Standard Therapy</th>
<th>Early Goal-Directed Therapy</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sudden cardiovascular collapse</td>
<td>25/119 (21.0)</td>
<td>12/117 (10.3)</td>
<td>0.02</td>
</tr>
<tr>
<td>Multiorgan failure</td>
<td>26/119 (21.8)</td>
<td>19/117 (16.2)</td>
<td>0.27</td>
</tr>
</tbody>
</table>

*CI denotes confidence interval. Dashes indicate that the relative risk is not applicable.
†Percentages were calculated by the Kaplan–Meier product-limit method.
‡The denominators indicate the numbers of patients in each group who completed the initial six-hour study period.
Results

• During the 1st 6 hours
  • EGDT group received more
    – intravenous fluid (5.0 vs. 3.5 L, $p < 0.001$)
    – red cell transfusions ($p < 0.001$)
    – inotropic therapy ($p < 0.001$)

• During the subsequent 66 hrs
  • Control group
    – More red cell transfusions ($p < 0.001$)
    – More vasopressors ($p = 0.03$)
    – More mechanical ventilation ($p < 0.001$)
    – More pulmonary artery catheterization ($p = 0.04$)
A systematic review and meta-analysis of early goal-directed therapy for septic shock: the ARISE, ProCESS and ProMISE Investigators

Surviving Sepsis Campaign Guidelines
Critical Care Medicine 2004-2016

• International effort to increase awareness and improve outcome in severe sepsis
• 55 Critical Care and ID experts from 25 international organizations
• Consensus conference
• Graded review of the literature
• Graded recommendations
TABLE 3. Comparison of 2016 Grading Terminology with Previous Alphanumeric Descriptors

<table>
<thead>
<tr>
<th>Strength</th>
<th>2016 Descriptor</th>
<th>2012 Descriptor</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Strong</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Weak</td>
<td>2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Quality</th>
<th>2016 Descriptor</th>
<th>2012 Descriptor</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>High</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>Low</td>
<td>C</td>
</tr>
<tr>
<td></td>
<td>Very Low</td>
<td>D</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ungraded strong recommendation</th>
<th>Best Practice Statement</th>
<th>Ungraded</th>
</tr>
</thead>
</table>
Initial Resuscitation

- At least 30 mL/kg of IV crystalloid fluid be given within the first 3 hours  
  - (strong recommendation, low quality of evidence)
- Additional fluids be guided by frequent reassessment of hemodynamic status  
  - (BPS)
- Assess cardiac function if the type of shock is not clear  
  - (BPS)
- Use dynamic over static variables to predict fluid responsiveness  
  - (weak recommendation, low quality of evidence)
Dynamic Variables to Predict Fluid Responsiveness

• Static variables
  – CVP, left or right heart pressures or volumes

• Dynamic variables
  – Passive leg raises
  – Fluid challenges against:
    • Stroke volume measurements
    • Variations in systolic pressure, pulse pressure, or stroke volume to changes in intrathoracic pressure induced by mechanical ventilation
Initial Resuscitation

• Target MAP of 65 mm Hg if using vasopressors
  – (strong recommendation, moderate quality of evidence).

• Guide resuscitation to normalize lactate, if elevated, as a marker of tissue hypoperfusion
  – (weak recommendation, low quality of evidence)
Fluid Therapy - Colloid or Crystalloid?

- **Crystalloid 1st**
  - (strong recommendation, moderate quality of evidence)

- **Balanced crystalloids or saline acceptable**
  - (weak recommendation, low quality of evidence)

- **Albumin may be added if large amounts of crystalloid required**
  - (weak recommendation, low quality of evidence)

- **No hetastarch**
  - (strong recommendation, high quality of evidence)
Safe Study

- Saline vs Albumin Fluid Evaluation
- ANZICS – 16 academic tertiary hospitals
- 3497 patients resuscitated with albumin
- 3500 patients resuscitated with saline

SAFE Results

726 deaths in the albumin group      729 deaths in the saline group

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.
SAFE Results

• No significant differences
  – Days spent in the ICU (6.5 albumin and 6.2 saline group)
  – Days spent in the hospital (15.3 and 15.6)
  – Days of mechanical ventilation (4.5 and 4.3)
  – Days of renal-replacement therapy (0.5 and 0.4)
SAFE Results

<table>
<thead>
<tr>
<th>Patients</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>0.99 (0.91–1.09)</td>
</tr>
<tr>
<td>Trauma</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1.36 (0.99–1.86)</td>
</tr>
<tr>
<td>No</td>
<td>0.96 (0.88–1.06)</td>
</tr>
<tr>
<td>Severe sepsis</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.87 (0.74–1.02)</td>
</tr>
<tr>
<td>No</td>
<td>1.05 (0.94–1.17)</td>
</tr>
<tr>
<td>ARDS</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.93 (0.61–1.41)</td>
</tr>
<tr>
<td>No</td>
<td>1.00 (0.91–1.09)</td>
</tr>
</tbody>
</table>

TBI mortality: Albumin 24.5% vs Saline 15.1%, p=0.009
Severe sepsis: Albumin 30.7% vs Saline 35.3%, p=0.09
Hetastarch
Forest plot of all cause mortality in relation to risk of bias in trials

Nicolai Haase et al. BMJ 2013;346:bmj.f839

Sponsored by industry, had potential academic bias, or lack of blinding.

11% increased risk of mortality.
And higher risk of RRT (RR, 1.36; 95% CI, 1.08–1.72; (high-quality evidence)
Back to our Patient

- Fully fluid resuscitated
- Still hypotensive
- What vasopressors should we choose?
Vasopressors

• Norepinephrine is the first-choice vasopressor (strong recommendation, moderate quality of evidence).

• Add either vasopressin (up to 0.03 U/min) (weak recommendation, moderate quality of evidence) to norepinephrine to raise MAP

• Or add epinephrine (weak recommendation, low quality of evidence) to norepinephrine to raise MAP

• Or add vasopressin (up to 0.03 U/min) (weak recommendation, moderate quality of evidence) to decrease norepinephrine dosage
VASST

• Vasopressin in Septic Shock Trial
• 1º hypothesis - Low dose vasopressin – (0.03 units/min) will decrease 28 day mortality from 60% to 50% in septic shock compared to norepinephrine alone
• 2º stratification
  – Severe septic shock norepinephrine dose > 15 mcg/min
  – Less severe septic shock = norepinephrine 5-14 mcg/min
• Resulted in 50% in each group

VASST

• Inclusion
  – Severe septic shock
  – SIRS criteria 2/4
  – Infection
  – 1 organ dysfunction

• Exclusion
  – Septic shock > 24h
  – Unstable heart
  – Received any vasopressin

• Method
  – Blinded infusion of vasopressin 0.01units/min or norepinephrine 5mcg/min
  – Titrated to MAP 65-75 mmHg
  – If vasopressin reached 0.03units/min or norepi 15mcg/min then other pressors were added
VASST

- 28 day mortality
  - Norepi Vasopressin p value
  - Total 39.3% 35.4% 0.26
  - More severe sepsis 42.5% 44% 0.84
  - Less severe sepsis 35.7% 26.5% 0.04

- Bottom line; mortality decreased with low dose vasopressin only in patients with less severe sepsis
Dopamine?

• Dopamine as an alternative agent to norepinephrine only in patients with low risk of tachyarrhythmias, who are bradycardic (weak recommendation, low quality of evidence).

• No low-dose dopamine for renal protection (strong recommendation, high quality of evidence).
Inotropes

• Dobutamine in patients with persistent hypoperfusion despite adequate fluid loading and the use of vasopressor agents
  – (weak recommendation, low quality of evidence)

• Dobutamine titrated to an end point reflecting perfusion

• Reduced or discontinued if worsening hypotension or arrhythmias
Back to the OR

- Oxygen saturation is falling
- Volume control ventilation
- Vt 600ml (pt. weighs 100kg)
- Rate 14
- Plateau pressure 35cm H2O
- FiO2 = 1
- PEEP 5cm H2O
- ABG pH 7.32, pO2 50, pCO2 48, SO2 83%
Mechanical Ventilation of Sepsis-Induced Acute Lung Injury

- Lung protective ventilation
  - (strong recommendation, high quality of evidence)
  - “Low” tidal volume - 6 mL/kg
  - End-inspiratory plateau pressures <30 cm H2 O

- Based on ARDSNet trial NEJM 2000; 342: 1301–1308
ARDSNet – Low Tidal Volumes

- 861 pts with acute lung injury
- Volume assist control mode
- Low tidal volume 6 ml/kg
  - Predicted body weight
  - Plateau pressure 30 cmH2O or less
- High tidal volume 12 ml/kg
  - Plateau pressure 50 cmH2O or less
ARDSNet

Mortality 31.0 % (Low Vt) vs 39.8 % (High Vt)  P=0.007
ARDSNet Criticisms

- 12ml/kg is too much
  - Nobody uses it
- U shaped dose response curve?
Back to the OR

- Oxygen saturation is falling
- Volume control ventilation
- VT 600ml (pt. weighs 100kg)
- Rate 14
- Plateau pressure 35cm H2O
- FiO2 = 1
- PEEP 5cm H2O
- ABG pH 7.32, pO2 50, pCO2 48, SO2 83%

Ht is 5’4”; PBW is 60kg
Mechanical Ventilation of Sepsis-Induced Acute Lung Injury

- Higher PEEP vs lower PEEP (weak recommendation, moderate quality of evidence)
- Recruitment maneuvers in severe ARDS (weak recommendation, moderate quality of evidence)
- Pronation in ARDS and a Pao2/Fio2 ratio < 150 (strong recommendation, moderate quality of evidence)
Methods to “Ideal” PEEP

- Titrate PEEP according to bedside measurements of thoraco-pulmonary compliance
Methods to “Ideal” PEEP

• Titrate PEEP upward on a tidal volume of 6 mL/kg PBW until the plateau airway pressure is 28-30 cm H2O

• Use a PEEP/Fio2 titration table that titrates PEEP based on the combination of Fio2 and PEEP required to maintain adequate oxygenation

<table>
<thead>
<tr>
<th>Fraction of Inspired Oxygen (Fio2)</th>
<th>PEEP ranges, cm H2O</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.3</td>
<td>5</td>
</tr>
<tr>
<td>0.4</td>
<td>5-8</td>
</tr>
<tr>
<td>0.5</td>
<td>8-10</td>
</tr>
<tr>
<td>0.6</td>
<td>10</td>
</tr>
<tr>
<td>0.7</td>
<td>10-14</td>
</tr>
<tr>
<td>0.8</td>
<td>14</td>
</tr>
<tr>
<td>0.9</td>
<td>14-18</td>
</tr>
<tr>
<td>1.0</td>
<td>18-24</td>
</tr>
</tbody>
</table>
Pronation

- Significant improvement in oxygenation
Pronation

- Proseva Group, N Engl J Med 2013; 368:2159-2168
- PaO$_2$:FiO$_2$ ratio of <150 mm Hg
- Proned for 16 hours per day
ICU Strategies for Acute Lung Injury

• No high-frequency oscillatory ventilation in ARDS (strong recommendation, moderate quality of evidence)
• No recommendation for noninvasive ventilation in ARDS
• NMBs for ≤ 48 hours in ARDS and a Pao2/Fio2 ratio < 150 mm Hg (weak recommendation, moderate quality of evidence)
ICU Strategies

• Conservative fluid strategy for ARDS without tissue hypoperfusion *(strong recommendation, moderate quality of evidence)*

• No ß-2 agonists unless bronchospasm *(strong recommendation, moderate quality of evidence)*

• No pulmonary artery catheter for ARDS *(strong recommendation, high quality of evidence)*

• Lower tidal volumes over higher tidal volumes without ARDS *(weak recommendation, low quality of evidence)*

• Head of the bed elevated between 30 and 45 degrees to limit aspiration and ventilator-associated pneumonia *(strong recommendation, low quality of evidence)*
ICU Strategies

• Spontaneous breathing trials in ventilated patients ready for weaning (strong recommendation, high quality of evidence)

• Weaning protocol in ventilated patients when tolerated (strong recommendation, moderate quality of evidence)
Steroids

• High dose corticosteroids are ineffective or harmful - Grade A (2012)

• 1980s: Dexamethasone Shok-Pak: ?1g

• Bone NEJM 317:653-658, 1987
  • Mortality 59% vs 29%
Steroids

- Against using IV hydrocortisone to treat septic shock patients if adequate fluid resuscitation and vasopressor therapy are able to restore hemodynamic stability

- If this is not achievable, we suggest IV hydrocortisone at a dose of 200 mg per day  
  – (weak recommendation, low quality of evidence).
Low Dose Steroids

All Patients

Annane D – Low Dose Steroids in Septic Shock – JAMA 2002
CORTICUS

- 500 patients
CORTICUS

- Hydrocortisone does not decrease mortality in septic shock
- Does not increase reversal of shock but shock reverses quicker
- No polyneuropathy increase
- More superinfection
- ACTH is test not useful
- Hydrocortisone should not be routinely used in septic shock
- There may be a role in those still hypotensive after 1 hour
Glucose Control

- Protocolize treatment
- Start insulin when two blood glucose levels are $> 180$ mg/dL.
- Target an upper blood glucose level $\leq 180$ mg/dL rather than $\leq 110$ mg/dL
  - (strong recommendation, high quality of evidence)
Tight Blood Glucose Control in ICU

- Prospective, randomized, controlled study
- 1548 patients
- Surgical intensive care unit – 60% cardiac surgery
- On mechanical ventilation
- Conventional management
  - Target BS 180 to 200
  - Insulin IVI started for BS > 215
- Or Insulin IVI
  - Target BS 80 to 110

Van Den Berghe G. NEJM 2001, 345; 1359-1367
Survival

ICU Mortality 8% vs 4.6% p<0.04
In-hospital mortality reduced by 34 percent

Van Den Berghe G. NEJM 2001, 345; 1359-1367
NICE-SUGAR Study

- 6104 patients randomized to tight (81-108) or loose (<180). ANZICS/Canada
Glucontrol

- ECCRN and ESICM sponsored, PRBCT, 21 ICUs across Europe
- At 1st interim analysis the study was stopped
  - increased hypoglycemia
  - increased mortality in tight Group
  - increased protocol violations

- Other studies showed severe hypoglycemia (<40) in 6-29% with tight control
Blood Products

- Red cells Hb< 7 g/dL in the absence of myocardial ischemia, severe hypoxemia, or acute hemorrhage (strong recommendation, high quality of evidence)

- Erythropoietin: Not recommended (strong recommendation, moderate quality of evidence)

- FFP: Not recommended to correct PT/PTT, unless there is bleeding or a planned invasive procedures. (weak recommendation, very low quality of evidence)

- Platelets
  - Prophylactic, in the absence of bleeding if < 10,000/mm3
  - Significant risk of bleeding if < 20,000/mm3
  - Active bleeding, surgery, or invasive procedures if < 50,000/mm3 (weak recommendation, very low quality of evidence)
Take Home Points

• Septic shock continues to have very high mortality

• Patients may present to us in a very unstable state but still require surgery to treat the underlying cause of their sepsis

• Surviving Sepsis Campaign Guidelines
  – Useful algorithm
  – Based on the best available evidence