A Case Based Approach to the Treatment of Severe Sepsis
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Our Patient

• 32 y/o M h/o TBI (remote) and resultant seizures
• Complains of 1 week of cough, worsening pleuritic chest pain
• Upon presentation to ED,
  – T = 102 ; R = 24 ; P = 110 ; BP = 124 / 76; SPO2 89% 2L
  – Decreased breath sounds on Right Base with crackles throughout left side
  – Chemistry unremarkable; Lactate 2.4
  – WBC 16.5; 75% segs; 10% bands
• Chest X-Ray Performed
What is your admit diagnosis?

- Pneumonia?
- Pleural effusion?
- Sepsis?
- Severe sepsis?
- Septic Shock?
The Challenge of Standardization in Severe Sepsis Therapies

Comorbidities

- Infection
- Immune Response
- Physiologic Derangement
- Organ Dysfunction
Original Systemic Inflammatory Response Syndrome Criteria

• Temperature greater than 38°C (100.4°F) or less than 36°C (96.8°F)
• Heart rate greater than 90 beats per minute
• Respiratory rate greater than 20 breaths per minute PaCO2 of less than 32mm Hg
• White blood cell count (>12,000/µL or < 4,000/µL or >10% immature [band] forms)

### SIRS-Manifestations of Infection

**Infection, documented or suspected, and some of the following:**

<table>
<thead>
<tr>
<th>General variables</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever (&gt;38.3°C)</td>
</tr>
<tr>
<td>Hypothermia (core temperature &lt; 36°C)</td>
</tr>
<tr>
<td>Heart rate &gt; 90/min⁻¹ or more than two SD above the normal value for age</td>
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<tr>
<td>Tachypnea</td>
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<tr>
<td>Altered mental status</td>
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<tr>
<td>Significant edema or positive fluid balance (&gt; 20 mL/kg over 24 hr)</td>
</tr>
<tr>
<td>Hyperglycemia (plasma glucose &gt; 140 mg/dL or 7.7 mmol/L) in the absence of diabetes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Inflammatory variables</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukocytosis (WBC count &gt; 12,000 µL⁻¹)</td>
</tr>
<tr>
<td>Leukopenia (WBC count &lt; 4000 µL⁻¹)</td>
</tr>
<tr>
<td>Normal WBC count with greater than 10% immature forms</td>
</tr>
<tr>
<td>Plasma C-reactive protein more than two SD above the normal value</td>
</tr>
<tr>
<td>Plasma procalcitonin more than two SD above the normal value</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Hemodynamic variables</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial hypotension (SBP &lt; 90 mm Hg, MAP &lt; 70 mm Hg, or an SBP decrease &gt; 40 mm Hg in adults or less than two SD below normal for age)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Organ dysfunction variables</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial hypoxemia (Pao₂/Fio₂ &lt; 300)</td>
</tr>
<tr>
<td>Acute oliguria (urine output &lt; 0.5 mL/kg/hr for at least 2 hrs despite adequate fluid resuscitation)</td>
</tr>
<tr>
<td>Creatinine increase &gt; 0.5 mg/dL or 44.2 µmol/L</td>
</tr>
<tr>
<td>Coagulation abnormalities (INR &gt; 1.5 or aPTT &gt; 60 s)</td>
</tr>
<tr>
<td>Ileus (absent bowel sounds)</td>
</tr>
<tr>
<td>Thrombocytopenia (platelet count &lt; 100,000 µL⁻¹)</td>
</tr>
<tr>
<td>Hyperbilirubinemia (plasma total bilirubin &gt; 4 mg/dL or 70 µmol/L)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tissue perfusion variables</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperlactatemia (&gt; 1 mmol/L)</td>
</tr>
<tr>
<td>Decreased capillary refill or mottling</td>
</tr>
</tbody>
</table>

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2012 Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock
Definition of Sepsis

• Sepsis: Probable or confirmed infection plus manifestations of infection.

• Severe Sepsis: sepsis plus organ dysfunction or hypoperfusion

• Sepsis with Hypotension: sepsis with SBP <90mmHg or MAP > 70 mmHg, or decrease in SBP >40 mmHg.

• Septic Shock: sepsis induced hypotension that persists despite adequate fluid resuscitation

Approach to Sepsis

ADCVANDIMAL- (before EHRs)
• Admit/Diagnosis/Condition
• Vitals (monitoring)
• Activity/Nursing  ⚠️ Airway/Breathing
• Diet  ⚠️ Not a time for snacks
• Intravenous fluids
• Medications
• Labs/Diagnostics
Protocolized Therapy in Sepsis

• EGDT-Rivers et al. 2001
  – original 2001 trial that changed practice patterns towards treatment of severe sepsis
• ARISE-Australian
  – Two arm trial: EGDT versus usual care
• ProCESS-American
  – Three arm trial that examine EGDT, EGDT “lite” and usual care
• ProMISE-United Kingdom,
  – Ongoing trial
**Early Goal Directed Therapy-Rivers et. al. 2001 NEJM.**

- **Supplemental oxygen ± endotracheal intubation and mechanical ventilation**
- **Central venous and arterial catheterization**
- **Sedation, paralysis (if intubated), or both**
  - CVP
    - < 8 mm Hg
      - Crystalloid
    - 8–12 mm Hg
      - Colloid
    - ≥65 mm Hg
  - MAP
    - < 65 mm Hg
      - Vasoactive agents
    - ≥90 mm Hg
  - ScvO₂
    - < 70%
      - Transfusion of red cells until hematocrit ≥30%
    - ≥70%
      - Inotropic agents
- **Goals achieved**
  - No
  - Yes
- **Hospital admission**
# 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></td>
<td>no. (%)</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 (49.2)</td>
<td>40 (33.3)</td>
<td>0.58 (0.39–0.87)</td>
<td>0.01</td>
</tr>
<tr>
<td>60-Day mortality†</td>
<td>70 (56.9)</td>
<td>50 (44.3)</td>
<td>0.67 (0.46–0.96)</td>
<td>0.03</td>
</tr>
<tr>
<td>Causes of in-hospital death‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sudden cardiovascular collapse</td>
<td>25/119 (21.0)</td>
<td>12/117 (10.3)</td>
<td>—</td>
<td>0.02</td>
</tr>
<tr>
<td>Multiorgan failure</td>
<td>26/119 (21.8)</td>
<td>19/117 (16.2)</td>
<td>—</td>
<td>0.27</td>
</tr>
</tbody>
</table>
ARISE-October 16, 2014, NEJM

EGDT

- CVP
- MAP
- ScVo2
- Hgb/HCT

Usual

- ?
- ?
ProCESS Trial-May 1, 2014, NEJM

**EGDT**
- CVP
- MAP
- ScVo2/CVC
- Hgb>10

**Standard**
- Clinical Assessment
- Systolic Pressure & Shock Index (HR/SysBP)
- Hypoperfusion assessment
- Hgb>7.5

**Usual**
- ?
- ?
- ?
- ?
<table>
<thead>
<tr>
<th></th>
<th>Usual Care</th>
<th>EGDT</th>
<th>Std Protocol</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rivers</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>60D Mortality</td>
<td>56.90%</td>
<td>44.30%</td>
<td>n/a</td>
</tr>
<tr>
<td>Lactic Acid</td>
<td>6.9±4.5</td>
<td>7.7±4.7</td>
<td>n/a</td>
</tr>
<tr>
<td>PreRand IVF</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>0-6 IVF mls</td>
<td>3499±2438</td>
<td>4981±2984</td>
<td>n/a</td>
</tr>
<tr>
<td>0-72 IVF mls</td>
<td>13358±7729</td>
<td>13443±6390</td>
<td>n/a</td>
</tr>
<tr>
<td>Time to Rand min</td>
<td>90</td>
<td>78</td>
<td>n/a</td>
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<tr>
<td><strong>Process</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>60D Mortality</td>
<td>18.90%</td>
<td>21%</td>
<td>18.20%</td>
</tr>
<tr>
<td>Lactic Acid</td>
<td>4.9±3.1</td>
<td>4.8±3.1</td>
<td>5±3.6</td>
</tr>
<tr>
<td>PreRand IVF</td>
<td>2083±1405</td>
<td>2254±1472</td>
<td>2226±1363</td>
</tr>
<tr>
<td>0-6 IVF mls</td>
<td>2279±1881</td>
<td>2805±1957</td>
<td>3285±1743</td>
</tr>
<tr>
<td>0-72 IVF mls</td>
<td>6633±4560</td>
<td>7253±4605</td>
<td>8193±4989</td>
</tr>
<tr>
<td>Time to Rand min</td>
<td>181</td>
<td>197</td>
<td>185</td>
</tr>
<tr>
<td><strong>ARISE</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>90D Mortality</td>
<td>18.80%</td>
<td>18.60%</td>
<td>n/a</td>
</tr>
<tr>
<td>Lactic Acid</td>
<td>6.6±2.8</td>
<td>6.7±3.3</td>
<td>n/a</td>
</tr>
<tr>
<td>PreRand IVF</td>
<td>2591±1331</td>
<td>2515±1244</td>
<td>n/a</td>
</tr>
<tr>
<td>0-6 IVF mls</td>
<td>1713±1401</td>
<td>1964±1415</td>
<td>n/a</td>
</tr>
<tr>
<td>6-72 IVF mls*</td>
<td>4382±3136</td>
<td>4274±3071</td>
<td>n/a</td>
</tr>
<tr>
<td>Time to Rand min</td>
<td>168</td>
<td>162</td>
<td>n/a</td>
</tr>
</tbody>
</table>
What Now?

• Where do I admit?
• Place a central venous line?
• Place an arterial line?
• How do I achieve source control?
• Which variables are important, and what are the optimal targets?
Antibiotics

• Give them early, get it right!
  – Initially inappropriate therapy results in profoundly detrimental outcomes
    • CID 2000; 31 (supp 4): 131
    • Chest 2009; 136: 1237
  – Guidelines suggest within the hour of presentation for those with septic shock

• An initially broad approach followed by rapid and responsible de-escalation is warranted
Hospital Course

- Shortly after CXR, respiratory status deteriorated
- Required Intubation
- RSI with Etomidate + Succinylcholine
  - Developed hypotension
  - (L) IJ Triple lumen placed
Orders: Respiratory Care

• Once intubated, the patient was initiated on the “Vent Bundle”
• Plans were made to transport to CT scanner
• Pulmonary & Critical Care was consulted from the ED for admission to the ICU
Mechanical Ventilation

• The lung-protective ventilatory strategy should be used in most patients

• Earlier is better!! – Don’t delay th getting right Vt
  – AJRCCM 2015; 191: 177
  – NEJM 2000; 342: 1301
Mechanical Ventilation

• Ventilator bundles can help streamline initiation
  – Initial settings
  – Protocolized titration of PEEP / FiO2
  – VTE Prophylaxis
  – Oral Care
  – Elevate Head of Bed
  – Stress Ulcer Prophylaxis
Mechanical Ventilation

• Remember, the goal is to PROTECT THE LUNG!
Lung-Protective Ventilation
Our Patient
IV Fluids

• Volume resuscitation is crucial for the effective treatment of sepsis

• Which IV fluid?
  – Crystalloid
  – Colloid
  – Blood

• How much of it?
Crystalloid

- Three common fluids:
  - Normal Saline
  - Lactated Ringers
  - Bicarbonate Preparations

- None of the above is ideal

- Some data suggest that more balanced fluids (Lactated Ringers) provide benefit over NaCl
  - JAMA 2012; 308: 1566

- The use of Bicarbonate as a Chloride-sparing agent?
Colloid

- Two major options:
  - Albumin
  - Semisynthetic colloid
- Semisynthetic colloid (Hetastarch)
  - Multiple trials showing adverse outcomes
  - Avoid use
- Albumin
  - No major advantages over saline, but no clear harm
  - May be useful in certain populations
- NEJM 2013; 369: 1243
Blood

• Traditionally, the goal has been to achieve “normal” hemoglobin concentration (~ 10 mg / dL)
• Red blood cells carry oxygen, so increasing the red cell mass should increase oxygen-carrying capacity
• Unfortunately, transfused cells may not carry oxygen as well as native cells, and there are risks with transfusion
• Should the goal be 10 mg/dL or lower?
Transfusions

- Several trials have evaluated the target in various populations
- TRICC – the “stable critically ill” (NEJM 1999; 340: 409)
  - Hb concentration 7-9 safe vs 10-12
  - Results in fewer transfusions
  - No statistically significant difference in all-comers
  - Appears to be most beneficial in younger and lesser severity of illness
Transfusions

• Many other studies have evaluated a more conservative threshold in multiple populations
  – High-Risk Patients after Hip Surgery (NEJM 2011; 365: 2453)
  – Acute upper GI Bleed (NEJM 2013; 368: 11)
  – Septic Shock (NEJM 2014; 371: 1381)
• All of these were prospective, randomized, controlled trials
• All found a restrictive strategy to be safe, in many cases with improved outcomes
**Transfusions**

- **Acute MI / Active Coronary Artery Disease**
  - Only population with data to support a more liberal threshold
  - No primary, prospective data; however, subgroups and retrospective data support this

- Large, retrospective analysis of Medicare patients suggests liberal strategy (NEJM 2001; 345: 1230)
How much fluid?

• Enough . . .
• Pick a goal and hit it
  – CVP
  – Lactate clearance
  – Mean Arterial Pressure
  – Urine output
• But not too much!
Figure 2. Kaplan–Meier Estimates of the Probability of Survival and of Survival without the Need for Assisted Ventilation during the First 60 Days after Randomization.
Hemodynamic Support

We’ve given enough fluid . . . Now what?
• What is the appropriate target?
• What is the appropriate monitor?
• What is the appropriate agent?
• Is there concurrent bradycardia?
• Is there concurrent depressed LV function?
Vasopressors

• Numerous trials have compared various vasopressors
  – Norepi vs Phenylephrine
    • Crit Care. 2008;12(6):R143)
  – Norepi vs Vasopressin
    • Crit Care Med. 2009 Mar;37(3):811-8
    • Intensive Care Med. 2006 Nov;32(11):1782-9
    • Crit Care. 2006;10(2):R40
    • NEJM. 2008;358:877
  – Norepi vs Epi
    • Intensive Care Med. 2008 Dec;34(12):2226-34
• No differences in mortality, length of stay in ICU or hospital
Arterial Lines

- Recommended in the guidelines but . . .
  - Ungraded evidence
  - No randomized trials
- Many question the necessity
- Potential harm (digital ischemia due to thrombosis of radial artery, etc)
- Consider on case-by-case basis
  - Frequent ABG’s
  - Inability to obtain cuff pressure
- As with all lines, remove ASAP!
Figure 2. Mean Arterial Pressure during the 5-Day Study Period.

Mean arterial pressures were significantly lower in the low-target group than in the high-target group during the 5 protocol-specified days (P=0.02 by repeated-measures regression analysis), although the values exceeded the target values of 80 to 85 mm Hg in the high-target group and 65 to 70 mm Hg in the low-target group. The I bars represent 95% confidence intervals.
Orders: Circulation

- **Choice of Vasoactive Agent (1)**
  - First line: norepinephrine (1B)
  - Second line: epinephrine (2B)
  - Can replace norepinephrine

- **Dopamine is associated with higher incidence of arrhythmias (2)**
  - Subgroup analysis: increased death rate in cardiogenic shock

Orders: Circulation

Vasopressor Therapy (cont)

- **Vasopressin**
  - 0.03 units/minute add on therapy
  - Not a stand alone pressor

- **Neosynephrine not recommended except for:**
  - Patients with severe arrhythmias (tachycardia)
  - Cardiac output is known to be high
  - Salvage therapy

Ionotropic therapy

- **Dobutamine**
  - May be useful with concurrent myocardial dysfunction (1B)
  - Echocardiogram may be useful to guide therapy

Steroids

- One of the most controversial topics in the management of sepsis
- Multiple studies have evaluated their utility
  - No definite benefit
  - No definite harm
- If you choose to give, don’t stim; just do it!
  - NEJM 2008; 358: 111 (hydrocortisone 50 mg IV Q 6 hrs)
  - Rapidly wean (over a period of days)
Pain, Agitation and Delirium

• Need objective scale for drug administration
  – Targeted sedation
  – Avoid deliriogenic drugs (benzos)
• Short acting agents
• On mech ventilation pts: Daily....
  – SAT
  – SBT
• CCM 2013; 41: 263
Our Patient

• After 3 L of IV fluid (Lactated Ringers), remained hemodynamically stable
• Cardiothoracic surgery consulted
  – Not stable for OR due to gas exchange
  – Right-sided chest tube placed with drainage of 2 L foul-smelling pus
• Developed ~70 mL air leak (~ 15% of Vt)
• Repeat Chest X-Ray
Damage Control Then Source Control

- **Drain Pus/Abscesses**
  - Thoughtful approach to imaging
- **Relieve obstruction**
  - GI tract
  - GU Tract
- **Remove foreign bodies/hardware**
  - Challenging at times
  - Devastating if delayed without cause
- **Remove devitalized tissue**
  - Investigate skin/soft tissue symptoms thoroughly
- **Immunosuppression alters presentation**

Random statements from the front line.
Source Control: By the Guidelines

1. Find the source and get definitive control within 12 hours (grade 1C)
2. Exception peripancreatic necrosis: (grade 2B)
   - definitive intervention best delayed until demarcation nonviable tissues has occurred
3. Get control in the severely ill with least physiologically insulting method (UG)
   - percutaneous drainage rather than surgery
4. Remove possible vascular access sources AFTER establishing additional access (UG)

Additional Considerations

• Etomidate for rapid sequence intubation:
  – Reversible adrenal insufficiency by dose-dependent inhibition of 11β-hydroxylase
  – Ketamine: suitable alternative
  – Consider relative/actual adrenal insufficiency when used

Jabre et al. Lancet 2009; 374: 293–300
• **Glucose control:**
  – Standardized insulin regimen dosing when 2 consecutive blood glucose levels are >180 mg/dL. (1A).
  – Monitor Frequently until stable -q1-2 Hours, (1C).
  – Point-of-care testing of capillary may not accurately estimate arterial blood or plasma glucose values (UG).

Additional Considerations

• **Sodium Bicarbonate therapy:**
  - NOT recommended for hemodynamics or reducing vasopressor requirements in patients with hypoperfusion-induced lactic acidemia with pH ≥7.15 (2B).
  - Useful with hyperkalemia
  - Offers a lower chloride alternative with fluid resuscitation

Additional Considerations

• Renal replacement therapy
  – Continuous renal replacement therapies and intermittent hemodialysis are equivalent in patients with severe sepsis and acute renal failure (2B).
  – Use continuous therapies to facilitate management of fluid balance in hemodynamically unstable septic patients (2D).

Biomarkers for Diagnosis: Not Yet

Garnacho-Montero et al. Critical Care 2014, 18:R116
Just Say No

- Routine PA catheter use
- Routine blood transfusion to 10 mg/dL
- Routine colloid administration OR Use of Hetastarch at all
- Tight Glucose Control
- No cosyntropin Stim Tests
Our Patient

• Bronchoscopy performed
  – No endobronchial lesion
  – Unable to occlude air leak
• Desaturated during bronchoscopy; unable to tolerate single-lung ventilation
• Remains in ICU
  – Continue supportive care
  – To OR for lobectomy should condition allow