Sepsis and Septic Shock

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Clinical Case

• 55 yr old woman with nausea, vomiting, diarrhea for 3 days and progressive dyspnea for 2 days.
• PMH: diabetes, schizophrenia, hypertension
• Initial exam: PB 152/76, HR 120, RR 28, O2% 98%. Moderate respiratory distress.

Does She Have Shock?

A. Yes
B. No
C. Maybe

Labs

- pH 6.81
- PO2 168
- PCO2 42
- HCO3 5.2
- O2% 97%
- WBC 31,000
- Hgb 11.3
- Glucose 131
- BUN 72
- Creatinine 14.7
- Calcium 8.6
- Lactate 17
Hospital Course

- Intubated for respiratory distress and acidosis
- Became progressively more hypotensive
- Started on levarterenol drip, empiric antibiotics, IV fluids, CVVHD
- Lactate rose to 42 over the next 15 hours
- Blood cultures = *Salmonella enteritidis*

What is shock?

- Syndrome of impaired tissue oxygenation and perfusion
- Mechanisms:
  - Absolute/relative decrease in oxygen delivery
  - Ineffective tissue perfusion
  - Ineffective utilization of delivered oxygen

The Major Classes of Shock

- Cardiogenic
- Extracardiac Obstructive
- Oligemic
- Distributive
Clinical Features

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Cardiogenic vs. Septic Shock

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<tr>
<th></th>
<th>Cardiogenic</th>
<th>Septic</th>
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<tbody>
<tr>
<td>Pulse Pressure</td>
<td>Decreased</td>
<td>Increased</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>Slightly low</td>
<td>Very low</td>
</tr>
<tr>
<td>Extremities</td>
<td>Cool &amp; pale</td>
<td>Warm &amp; pink</td>
</tr>
<tr>
<td>Capillary refill</td>
<td>Slow</td>
<td>Rapid</td>
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Approach To All Patients

• A - airway
• B - breathing
• C - circulation
• D - disposition (ICU)
• E - electrical cardioversion
• F - fluids

Hemodynamic Monitoring

• Heart rhythm
• Arterial blood pressure
• Intravascular volume assessment:
  ✓ Central venous pressure
    • Usually
  ✓ Pulmonary capillary wedge pressure
    • Rarely
Patients with early shock can have normal blood pressure.

Indices of Inadequate Perfusion:

- Systemic:
  - Increased lactate
  - Mixed venous oxygen saturation < 70%

- Regional:
  - Liver enzymes
  - Urine output < 0.5 ml/kg/hr
  - Sensorium
  - Clotting factors

* Indicators of inadequate perfusion trump blood pressure!

Clinical Features:

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<tr>
<th>Condition</th>
<th>Pre-Shock</th>
<th>Early Shock</th>
<th>Late Shock</th>
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<tbody>
<tr>
<td>Blood Pressure</td>
<td>Normal</td>
<td>Low</td>
<td>Very Low</td>
</tr>
<tr>
<td>SVR</td>
<td>Low</td>
<td>Very Low</td>
<td>Low to Normal</td>
</tr>
<tr>
<td>Cardiac Output</td>
<td>High</td>
<td>High</td>
<td>Low</td>
</tr>
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Cardiogenic
- PCWP: High
- CO: Low
- SVR: High

Extra-cardiac obstructive
- PCWP: (Low)
- CO: Low
- SVR: High

Oligemia
- PCWP: Low
- CO: Low
- SVR: High

Sepsis
- PCWP: Variable
- CO: Variable
- SVR: Low

Toxic Shock
- PCWP: (Low)
- CO: (High)
- SVR: Low

Anaphylaxis
- PCWP: Low
- CO: High
- SVR: Low
Mechanism Of Shock In Sepsis

- LPS
- LBP
- CD 14 Receptor
- TOLL-like receptors
- Monocyte/Macrophage
- TNFα
- IL-1β
- IL-8
- Mediator Cascade
- Shock

Common Effects Of Sepsis

<table>
<thead>
<tr>
<th>Organ</th>
<th>Effect</th>
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<tbody>
<tr>
<td>Kidney</td>
<td>Acute tubular necrosis</td>
</tr>
<tr>
<td>Lungs</td>
<td>Acute respiratory distress</td>
</tr>
<tr>
<td>Heart</td>
<td>Myocardial depression</td>
</tr>
<tr>
<td>Liver</td>
<td>Cholestasis or liver failure</td>
</tr>
<tr>
<td>GI</td>
<td>Stress erosions</td>
</tr>
<tr>
<td>Brain</td>
<td>Stupor</td>
</tr>
<tr>
<td>Blood</td>
<td>Neutrophil vacuolization</td>
</tr>
<tr>
<td>Metabolic</td>
<td>Hypocalcemia, hypo/hyperglycemia</td>
</tr>
</tbody>
</table>

Treatment goals in managing septic shock

- Restore tissue perfusion and oxygenation
- Treat specific etiology
- Monitor
- Treat organ-specific failure
- Prevent complications

Septic shock commonly results in multiple organ system failure
The ultimate goal of septic shock management is to improve tissue oxygen delivery!

**Determinants:**
- Blood pressure
- Cardiac output
- Oxygen content

**Interventions:**
- Fluids
- Vasoactive drugs
- Blood transfusion
- Supplemental oxygen

Early resuscitation is key:
- Goal-directed protocols
  - Central venous catheter
  - Hydration to CVP (or PCWP) = 8-12
  - Vasopressors if MAP < 65
- Target SvO2 > 70%
- Early involvement of intensivists
- Early transfer to an ICU facility

Hemodynamic Treatment Of Septic Shock

- IV fluids
- IV fluids
- IV fluids
- Vasopressors

Fluid Selection

<table>
<thead>
<tr>
<th>Distribution</th>
<th>% Intravascular</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.9% NaCl</td>
<td>Extracellular space 20%</td>
</tr>
<tr>
<td>Lactated Ringer’s</td>
<td>Extracellular space 20%</td>
</tr>
<tr>
<td>D5W</td>
<td>Total body water space 8%</td>
</tr>
<tr>
<td>RBCs*</td>
<td>Intravascular space 100%</td>
</tr>
</tbody>
</table>

* Use 2:3 plasma:PRBC transfusion ratio

IV Catheter Flow Rates (ml/min)

What Else Can You Do?

- Definitely:
  - Vasopressors
  - Activated protein C
  - Intensivists
  - Closed ICUs

- Maybe:
  - Low dose steroids
  - Glycemic control
  - Vasopressin
  - Avoid etomidate

Treat the underlying infection:

- Antibiotics – broad spectrum; give early
- Remove potentially infected devices
- Drain pus
- Debride/remove dead tissue

What Vasopressor Do You Most Commonly Use In Septic Shock?

A. Dopamine
B. Levarterenol (Levophed)
C. Phenylephrine (Neosynephrine)
D. Dobutamine
E. Epinephrine
Kaplan-Meier Curves for 28-Day Survival in the Intention-to-Treat Population

Forest Plot for Predefined Subgroup Analysis According to Type of Shock

Vasopressors In Septic Shock

What about dobutamine?

- Dobutamine is a **vasodilating** inotrope
- Main role is in patients with combined septic plus cardiogenic shock
  - Should be combined with an alpha adrenergic agent
  - However, use of dobutamine to “drive” up already high cardiac output is not effective
**Effect Of Activated Protein C In Sepsis**

- Randomized, double blinded, controlled
- 1,690 patients
- Serious bleeding:
  - 2% control
  - 3.5% protein C

![Graph showing survival rates for Protein C vs Placebo](Bernard, N. Engl. J. Med. 2001; 344:699-709)

**Indications For Drotrecogin (activated protein C)**

- Known or suspected infection AND
- SIRS (3 of 4):
  - Fever or hypothermia
  - Tachycardia
  - Tachypnea
  - Leukocytosis or leukopenia
- APACHE II ≥ 25 OR
- At least 2 acute organ failures:
  - Cardiovascular
  - Renal
  - Respiratory
  - Hematologic (platelets)
  - Metabolic acidosis

**Drotrecogin Contraindications**

- Absolute:
  - Active bleeding
  - Recent surgery/trauma
  - Recent GI bleeding
  - CVA, head trauma, brain surgery in past 2 months
  - Brain tumor/aneurysm
  - Recent epidural

- Relative:
  - Platelets < 30,000
  - INR > 3
  - Anticoagulation
  - Cirrhosis
  - Bleeding disorder
  - Pregnancy

**Drotrecogin Dosing:**

- 24 mg/kg/hr x 4 days
  - Maximum dose = 3,200 mg/hr
- Turn infusion off 2 hours before procedures
- No adjustment necessary for renal failure
- Average cost /patient = $$$$$
### Intensivists Improve Outcomes

**Effect of a surgical intensivist:**
- 3-fold mortality reduction
- Decreased sepsis
- Decreased renal failure
- Decreased reintubation

**Effect of a medical intensivist:**

![Graph showing outcomes](image)

Pronovost, et al. JAMA 1999; 281:1310

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### Closed ICUs Improve Outcomes

Rhode Island Hospital SICU

![Graph showing outcomes](image)


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### When Do You Use Corticosteroids In Septic Shock?

A. Always
B. Never
C. Only if a random cortisol is low
D. Only if an ACTH stim test is abnormal
Corticosteroid Insufficiency In Septic Shock

- 25-75% of patients with septic shock are corticosteroid insufficient
- Definition: cortisol level < 10 mcg/dL or increase < 9 mcg/dL after ACTH stimulation test
- Corticosteroid replacement may improve outcomes in adrenal insufficiency
- Beware of patients receiving etomidate!!

Surviving Sepsis Guideline 2008

- Consider steroids when patients do not respond to fluids and vasopressors
- ACTH stimulation test is not recommended
- Hydrocortisone preferred:
  - Dose should be < 300 mg/day

Do Steroids Work In Septic Shock?

- YES: 300 septic patients (JAMA 2002)
- YES: Meta-analysis of 20 studies (JAMA 2009)

How Do You Use Glycemic Control In Your Patients With Septic Shock?

- A. Target glucose 80-110
- B. Target glucose 110-140
- C. Target glucose 140-180
- D. Only treat if glucose > 200
Insulin in Critically Ill

Target glucose: 80-110 mg/dl


Tight glycemic control: 2010 meta-analysis

- 7 randomized-controlled studies reviewed
- 11,425 patients
- Tight glycemic control did NOT:
  - Reduce 28-day mortality
  - Reduce requirement for renal replacement therapy
- Tight glycemic control was associated with significantly increased hypoglycemia

Chest 2010; 137: 544-51

The AACE/ADA recommendations for Hospitalized Patients*

- A target of 140-180 mg/dl is preferable for MOST patients.
- A target of 110-140 mg/dl may be appropriate in SELECTED patients (patients treated in sites with extensive experience and appropriate support):
  - perhaps CABG surgical patients
  - sites with low rates of hypoglycemia
  - patients on TPN etc).
- A target > 180 mg/dl or < 110 mg/dl is NOT recommended.

*Diabetes Care, Volume 33, supplement 1: January 2010

Vasopressin In Septic Shock

- Vasopressin levels are low in septic shock
- Vasopressin replacement may:
  - Improve blood pressure
  - Diminish need for other vasopressors
- Do not use in pediatric septic shock!! (Am J Respir Crit Care Med 2009; 180:632-9)
- Dose = 0.04 units/min
Effect of Vasopressin On 28-Day Mortality

N = 778

Management of oliguria in septic shock:

- Volume challenge
- Loop diuretic for fluid management
- Monitor and maintain fluid balance
- Dose-adjust medications
- Avoid nephrotoxic drugs & dye
- Renal replacement therapy

What about renal failure?

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<th>ATN</th>
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<tr>
<td>BUN/creatinine ratio</td>
<td>&gt;20</td>
<td>10-20</td>
</tr>
<tr>
<td>Urine specific gravity</td>
<td>&gt;1.020</td>
<td>&gt;1.010</td>
</tr>
<tr>
<td>Urine osmolality (mOsm/L)</td>
<td>&gt;500</td>
<td>&lt;350</td>
</tr>
<tr>
<td>Urine sodium (mmol/L)</td>
<td>&lt;20</td>
<td>&gt;40</td>
</tr>
<tr>
<td>Fractional excretion of Na (%)</td>
<td>&lt;1</td>
<td>&gt;2</td>
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Not all distributive shock is septic shock
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### Toxic Shock Syndrome: Clinical Features

- Abrupt onset: fever, myalgias, headache
- Multiple organ failure
- Severe metabolic abnormalities
- Blood cultures usually negative
- Palmar skin exfoliation

### Toxic Shock Syndrome

- TSST-1 produced by Staph aureus, group A Strep, & group G Strep
- Common sites of infection:
  - Vagina (menstrual-associated)
  - Surgical wounds
  - Foreign bodies
  - Mucous membrane injury

### Toxic Shock Syndrome: Treatment

- IV fluids: often need 10-20 liters in first day
- Remove foreign bodies
- Anti-staphylococcal antibiotics
- IV immunoglobulin - possibly effective
### Vasopressors For Toxic Shock Syndrome

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<th>Contractility</th>
<th>Vasoconstriction</th>
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<td>Dopamine</td>
<td>2+</td>
<td>2+</td>
<td>0</td>
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<tr>
<td>2-10 mcg/kg/min</td>
<td>2+</td>
<td>2+</td>
<td>0</td>
</tr>
<tr>
<td>&gt;10 mcg/kg/min</td>
<td>1+</td>
<td>2+</td>
<td>3+</td>
</tr>
<tr>
<td>Dobutamine</td>
<td>2+</td>
<td>4+</td>
<td>1-</td>
</tr>
<tr>
<td>Levarterneol</td>
<td>2-</td>
<td>2-</td>
<td>4+</td>
</tr>
<tr>
<td>Phenylephrine</td>
<td>2-</td>
<td>0</td>
<td>4+</td>
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<tr>
<td>Epinephrine</td>
<td>4+</td>
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### Anaphylactic Shock

- Offending agent can be difficult to identify
- Serum tryptase level useful when diagnosis uncertain

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### Anaphylactic Shock: Initial Therapy

- Maintain airway
- Stop absorption!
- Epinephrine is the vasopressor of choice
  - 1:1,000 concentration (0.5 - 1.0 ml SQ)
  - 1:10,000 concentration (5 - 10 ml IV)
- Inhaled albuterol
**Anaphylactic Shock: Secondary Treatment**

- Antihistamines
- Corticosteroids
- 18 - 24 hour observation

**Relative Effects of Different Vasopressors**

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**Summary: Keys To Sepsis Survival**

- Early recognition
- Early stratification
- Early resuscitation
- Early use of:
  - Central venous catheters
  - Intensive care units
  - Critical care specialists

**Clinical Case Outcome**

- Blood pressure improved over 48 hours
- Extubated hospital day #9
- Remained on dialysis
- Transferred to skilled nursing facility on hospital day #21