Severe Sepsis & Septic Shock
Sepsis: the 1st 6 hours
Identification &
Initial Management

Chris Fee, MD
UCSF Division of Emergency Medicine
2007 Topics in Emergency Medicine

Objectives
- Gain respect for severe sepsis/septic shock
- Utilize lactate to identify high risk patients & monitor resuscitation
- Understand & implement the 6 hour sepsis bundle

What would you do?
Case #1
- 66 yo man presents with anterior CP

What would you do?
Case #2
- 19 yo woman with abdominal pain after a motor vehicle collision
  
  HR 120, BP 80/50
  
  After 1.5 L NS IV
  
  HR 90, BP 126/76

What would you do?
Case #3
- 66 yo woman with R weakness & aphasia

What would you do?
Case #4
- 58 yo man with cough, fever, SOB
  
  T 38.3 °C
  HR 106
  BP 110/62
  RR 22
  O2 sat 98% on 4L/min
  Lactate 4.4 mmol/L
Cases: Common Themes

- **1. Acute anterior wall STEMI**
  - Door to lytics (30 mins)/balloon time (90 mins)
  - Mortality: 10%
- **2. Isolated blunt abdominal trauma**
  - “Golden Hour of Trauma”
  - Mortality: 8%
- **3. Acute ischemic L MCA CVA**
  - 3 Hour window for lytics
  - Mortality: 10%
- **4. Severe sepsis due to community acquired pneumonia**
  - Mortality: 30%

Now what would you do?
Case #4 (same but different)

- **58 yo man with cough, fever, SOB**
  - T 38.3 °C
  - HR 126
  - BP 60/46
  - RR 22
  - O2 sat 98% on 4L/min

Outline

- Surviving Sepsis Campaign
  - Definitions & Epidemiology
  - Evidence-Based Recommendations
  - Implementation strategies
- Controversies
- Future Directions

Surviving Sepsis Campaign

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Organ Dysfunction

- Cardiovascular
  - SBP < 90 mmHg
  - MAP < 65
  - SBP decrease > 40 mmHg from baseline
- Renal
  - Creatinine > 2
  - UOP < 0.5ml/kg/hr for > 2 hrs
- Heme
  - Platelets < 100,000
- Metabolic
  - Lactate > 2.0 once CVP > 8-12 mmHg
- Respiratory
  - Bilateral pulmonary infiltrates with
    - a new (or increased) O2 requirement to maintain
  - SpO2 > 90%
  - PaO2/FIO2 < 300
- Hepatic
  - INR > 1.5
  - aPTT > 60 secs
  - Total bili > 2 mg/dL

SIRS

- Systemic Inflammatory Response Syndrome (SIRS) (≥ 2)
  - T > 38 °C or < 36 °C
  - HR > 90
  - RR > 20 or PaCO2 < 32mmHg
  - WBC > 12, < 4, or > 10% bands

Sepsis

- Infection
- Severe Sepsis
- Septic Shock

SIRS + ≥ 1 organ dysfunction or lactate ≥ 4mmol/L

Sepsis + hypotension (after 20mL/kg IV)

Sepsis + < 2 organ dysfunction or lactate < 4mmol/L

Pancreatitis

Trauma

Burns

Other

***At least 7 different definitions***


Pathogenesis

Systemic Inflammation or Inflammatory Response

Organism

Septic Shock

Death

Severe Sepsis

Multiple Organ Dysfunction & Refractory Hypotension

Global Tissue Hypoxia & Organ Dysfunction


Pathogenesis

Systemic Inflammation or Inflammatory Response

Organism

Septic Shock

Death

Severe Sepsis

Multiple Organ Dysfunction & Refractory Hypotension

Global Tissue Hypoxia & Organ Dysfunction


How many patients with severe sepsis/septic shock are seen in your workplace each year?

A. <5
B. 6-10
C. 11-15
D. 16-20
E. >20

Incidence of Severe Sepsis

AIDS*

Cases/100,000

250

200

150

100

50

0

Cancer

Acute MI†

Severe Sepsis‡

Deaths/Year

Mortality of Severe Sepsis

AIDS*

Breast CA§

Acute MI†

Severe Sepsis‡

Deaths/Year

Probability of Death

Septic Shock (n=1134)

Severe Sepsis (n=927)

Sepsis (n=1063)

Infection no SIRS (n=584)

Severe Sepsis-Associated Mortality

![Bar Chart]


Newer Diagnostic Criteria for Sepsis

Infection (documented or suspected) and SOME of the following:

- General variables
  - Temp > 38.3 or < 36°C
  - HR > 90
  - Tachypnea
  - Altered mental status
  - Significant edema or positive fluid balance (>20 mL/kg/24 hrs)
  - Glucose > 120 (no DM)
- Inflammatory variables
  - WBC > 12 or < 4 or > 10% bands
  - CRP > 2 SD above normal
  - Procalcitonin > 2 SD above normal
- Hemodynamic variables
  - SBP < 90, MAP < 70 or SBP decrease > 40
  - S<sub>V</sub>O<sub>2</sub> < 70%
  - CVP index > 3.5 L/min/m²
- Organ Dysfunction variables
  - PaO<sub>2</sub>/FiO<sub>2</sub> < 300
  - Acute oliguria
  - Creatinine increase > 0.5
  - INR > 1.5 or aPTT > 60s
  - Ileus
  - Platelets < 100,000
- Total bilirubin > 4
- Tissue perfusion variables
  - Lactate elevation
  - Decreased cap refill or mottling


Identification (2 Step Process)

- Step 1. Is the patient septic?
  - ≥2 SIRS criteria + suspected infection
- Step 2. Does the patient have severe sepsis/septic shock?
  - Any one of the following:
    1. Persistent hypotension (after 20 mL/kg IVF)
    2. 1 or more organ system dysfunction
    3. Lactate > 4 mmol/L

Why???

Do You Currently Order Lactate Levels on Patients with Suspected Sepsis?

A. Yes
B. No, it's not going to change my management
C. No, the lab turnaround makes it essentially useless to me
D. No, it's not available where I work
E. No, other reason

Lactate

![Bar Chart]

**Lactate**

“Cryptic Shock”

- Tissue hypoperfusion without hypotension

- On the brink of cardiovascular collapse
  - ↓ Myocardial contractility & compliance
  - If not treated aggressively, leads to multiple organ failure & mortality

**Lactate Resuscitation**

- Lactate clearance inversely related to mortality (measured at 6 hrs from initiation)

- Best available marker for need of ongoing resuscitation


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**So You Can Identify Severe Sepsis/Septic Shock, Now What?**

<table>
<thead>
<tr>
<th>Step 3</th>
<th>Grade of Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Source control</td>
<td>E</td>
</tr>
<tr>
<td>Early cultures &amp; antibiotics</td>
<td>D&amp;E</td>
</tr>
<tr>
<td>Early goal-directed therapy</td>
<td>B</td>
</tr>
<tr>
<td>Protective ventilation strategies</td>
<td>B</td>
</tr>
<tr>
<td>Activated protein C</td>
<td>B</td>
</tr>
<tr>
<td>Intensive insulin therapy</td>
<td>D</td>
</tr>
<tr>
<td>Low dose steroids</td>
<td>C/E</td>
</tr>
<tr>
<td>Narrowing antibiotic spectrum once sensitivities are available</td>
<td>ICU</td>
</tr>
</tbody>
</table>

**Early Goal-Directed Therapy**

Physical exam, vitals, urine output, CVP, mental status are UNRELIABLE indicators of perfusion

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**Early Goal-Directed Therapy**

- Inadequate O₂ delivery = key to progression
  - Surrogate measure of cardiac output & oxygen extraction at the tissue level
    - Mixed venous (SvO₂) and central venous (ScvO₂) O₂ saturation
  - Manipulate preload, afterload, contractility
    - Goal: balance O₂ demand & delivery

Early Goal-Directed Therapy

1. SIRS + suspected infection
2. SBP < 90 (after 20 mL/kg IVF) or lactate ≥ 4 or multiorgan dysfunction

Supplemental O2 ± endotracheal intubation & mechanical ventilation

Vasoactive agents <65 mm Hg; >90 mm Hg
Norepinephrine: pressor of choice

ScvO2
Transfusion of red cells until hematocrit > 30%
<70%
≥ 70%

Inotropic agents
Dobutamine

In-hospital mortality 16%
* 46.5% controls vs 30.5% in EGDT group
* Relative risk of death = 0.58

Does Your ED/Practice Currently Utilize an EGDT Protocol?

A. Yes
B. No, lack of specialized monitoring equipment
C. No, too many ED resources required
D. No, need for central venous cannulation
E. No, other reason(s)

Surviving Sepsis Campaign
- Definitions & Epidemiology
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- Future Directions

Concept of the “Bundle”
- Institute for Healthcare Improvement (www.ihi.org)
  - Bundle: group of interventions that, when implemented together, result in better outcomes than individually

Concept of the “Bundle”
The Acute MI Model

Acute management
- IV fluids, intubation (endotracheal), oxygen therapy, fluid resuscitation

Cardiac monitoring
- Echocardiography

Thrombolytics
- Streptokinase, urokinase, alteplase, tissue plasminogen activator (tPA)

Anticoagulants
- Heparin, low-molecular-weight heparin

Antiplated therapies
- ASA, glycoprotein (GP) IIb/IIIa inhibitors, adenosine diphosphatase (ADP) receptor blockers

Invasive procedures for diagnosis/monitoring
- Angiography, intracoronary ultrasound, vascular catheterization

Invasive procedures for tissue reperfusion and vessel revascularization
- Percutaneous transluminal coronary angioplasty (PTCA), stenting, coronary artery bypass grafting (CABG)

Secondary prevention strategies
- Angiotensin-converting enzyme (ACE) inhibitors, lipid-lowering agents (statins), additional antihypertensive agents

Which Antibiotics to Give?

Source | Antibiotic
-------|------------------------
Community-acquired pneumonia | 54% 3rd generation cephalosporin + azithromycin or fluoroquinolone
Health care-associated pneumonia | Carapenem +/- fluoroquinolone or Cefepime or piperacillin/tazobactam +/- fluoroquinolone
Abdomen | 26% Carapenem or ampicillin + metronidazole + gentamicin/tobramycin or fluoroquinolone
Urinary tract | 10% Piperacillin/tazobactam or ticarcillin/clavulanate or carbapenem or ampicillin + gentamicin or fluoroquinolone
Catheter | Vancomycin
Unknown | Carapenem + vancomycin or third- or fourth-generation cephalosporin, piperacillin/tazobactam, or ticarcillin/clavulanate + gentamicin

6 Hour (Resuscitation) Bundle
Steps 1-3 (ED Care)

- Prompt identification
  - Includes lactate measurement
- Early cultures & appropriate antibiotics
- EGDT
  - Includes measurement of CVP & S_o2

Severe sepsis (2001-2004): 2/3 present via ED
Average ED length of stay: 4.7 hours (20% spent >6 hours)
24 Hour (Management) Bundle
The 4th Step (ICU Care)...

- Source control
- Protective ventilation strategies
- Low dose steroids (???)
- Intensive insulin therapy (???)
- Activated protein C (???)
- Narrowing of antibiotic spectrum

Example Sepsis Bundles

- MUST (Multiple Urgent Sepsis Therapies)
  - www.mustprotocol.com
- STOP (Strategies to Timely Obviate the Progression of Sepsis in the ED)
  - www.llu.edu/llumc/emergency/patientcare
- UCSF
  - Included with syllabus

Strategies for Initiating EGDT

- ED-based
  - Henry Ford Hospital, MUST protocol
- Rapid response team-based
  - Good Samaritan Hospital (community)
- ICU-based
  - UCSF

If you do utilize EGDT, what model do you use?

A. ED-based
B. Rapid Response Team-based
C. ICU-based
D. Not sure
E. Don’t utilize EGDT where I work

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Controversies
Lactate & “Cryptic Shock”

• Subgroup in River’s EGDT study
  • 20% (EGDT) vs 60.9% (control) mortality

• MUST Protocol Implementation
  • 37/116 in protocol had “cryptic shock”


Donnino MW. Chest 2003;90S.

Controversies
When to Order a Lactate?

• “Blood culture = lactate”

• ≥2 SIRS criteria & suspected infection (i.e. septic)

Controversies
EGDT 1st 6 Hours – Was it the volume?

Fluids Red Cell Transfusion Dobutamine ScvO2 ≥ 70%

EGDT Control

P<0.001 0.5% 2.4% 13.7% 60%
P<0.001 0.8% 6.2% 13.7% 60%
P<0.001 3.5% 19.8% 5.8% 60%

Rivers E, et al. NEJM 2001;345:1368-77. (see accompanying Letters to the Editor. NEJM 2002;346:1025-1026.)

Controversies
Standardized Order Sets

• Cookbook or evidence-based medicine??

• Significantly reduced mortality & length of stay

Controversies
Single Center & Small n

- Review of all published EGDT data
  - 12 trials (1298 patients)
    - **Aggregate risk reduction of 20.3%**
  - Did not use formal methods for meta-analyses


Controversies
High Cost / Resource Utilization

- **23.4% reduction in hospital costs**

- Most cost effective if >16 patients/year

- True for all models (ED-, Rapid Response Team-, and ICU-based care)


Controversies
Proprietary Equipment

- PreSep catheter & Vigilance monitor (Edwards Lifesciences)

- Can use central line (in RA) & draw blood gases for serial ScvO2 levels instead

Controversies
Pharma Support of SSC Guidelines

- Lilly & Edwards funded Surviving Sepsis Campaign
  - ? overstated benefits of activated protein C
    - No mention of ADDRESS/RESOLVE trial data

- Guidelines from other unbiased sources are similar

Eichacker PO, Natanson C, Danner RL. NEJM 2006;355:1640-2.

Future Directions
Diagnostics

- More specific markers for bacterial sepsis
  - Procalcitonin???
  - Soluble Flt-1???

- Predicting who may progress from severe sepsis to septic shock
  - Heart rate variability

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Future Directions
Diagnostics

- Blood/urine/CSF cultures negative
- 3 days in ICU with broad-spectrum antibiotics
- *Clostridium difficile* colitis
- Rash
- $$$
- Influenza A positive nasal wash

Future Directions
Diagnostics

- Identification of bacteria causing severe sepsis/septic shock in patients using a **16S microarray**
  - 10ml blood
  - Compares rDNA in sample to microarray of rDNA from known bacteria (internal library)
  - In theory: obtain rapid speciation of any bacteria in the bloodstream

Future Directions
Refinements to EGDT?

- Statins
- Drugs designed against superantigen & mannose
- Inhibition of tissue factor
- Interferon gamma to boost macrophage function
- Apoptosis inhibition
Mortality Reductions: Sepsis vs. Acute Coronary Syndromes

<table>
<thead>
<tr>
<th>Trial Type</th>
<th>Cardiology Trials</th>
<th>Sepsis Trials</th>
<th>NS (to prevent 1 death)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGDT</td>
<td>16%</td>
<td>12%</td>
<td>0%</td>
</tr>
<tr>
<td>NHLBI ASCEND</td>
<td>8%</td>
<td>4%</td>
<td>0%</td>
</tr>
<tr>
<td>NHLBI would</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>ACC AHA</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>ACC AHA II</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>ACC AHA III</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
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</tbody>
</table>

Cardiology Trials
- APC, AlloPacchel II > 25
- EGDT
- Low dose steroids
- ARDSnet vent
- Tiglott glycemic control

Sepsis Trials
- GP IIb/IIIa inhibitors
- Streptokinase in MI
- APC, AlloPacchat II > 25
- EGDT
- Low dose steroids
- ARDSnet vent
- Tiglott glycemic control

NNT to prevent 1 death

Long Way To Go...

- 2004 survey of academic EDs in 18 states
  - 7% reported use of EGDT
- Barriers
  - 75%; lack of specialized monitoring equipment
  - 43%; too many ED resources required
  - 36%; need for central venous cannulation

Take Home Points

- Early identification paramount
  - SIRS criteria, lactate levels
- Concept of “cryptic shock”
  - “Blood culture = lactate”
- Establish sepsis bundles of care in your workplace
  - Physician champion, interdepartmental/ multidisciplinary collaboration

Thank You

- Any Questions?

UCSF Sepsis Bundle

Step 1: Recognize Sepsis

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UCSF Sepsis Bundle

Step 2: Assess for Severe Sepsis/Shock

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  - www.survivingsepsis.org

- Early Goal-Directed Therapy
  - www.ihi.org
  - www.mustprotocol.com
  - www.llu.edu//llumc/emergency/patientcare

- Treatment Bundles
  - www.ihi.org
  - www.mustprotocol.com
  - www.llu.edu//llumc/emergency/patientcare

- Review