Amjad Bani Hani
Asst. Prof of Cardiac Surgery and Intensive Care

SIRS, SEPSIS, AND MODS
In 1992, the American College of Chest Physicians (ACCP) and the Society of Critical Care Medicine (SCCM) introduced definitions
Definitions

- Infection
- Systemic Inflammatory Response Syndrome (SIRS)
- Sepsis
- Severe Sepsis
- Septic Shock
Definitions (ACCP/SCCM):

- **Infection**: A microbial phenomenon characterized by an inflammatory response to the presence of microorganisms or the invasion of normally sterile host tissue by those organisms.
Infection: Part of a bigger picture

- Infection:
  - Presence of organisms in a closed space or location where not normally found

‘SIRS’
SIRS

- self-defense mechanism.
- Inflammation is the body's response to nonspecific insults that arise from chemical, traumatic, or infectious stimuli.
- The inflammatory cascade is a complex process that involves humoral and cellular responses, complement, and cytokine cascades.
SIRS: Systemic Inflammatory Response Syndrome

- SIRS: A clinical response arising from a nonspecific insult manifested by ≥2 of the following:
  - Temperature ≥38°C or ≤36°C
  - HR ≥90 beats/min
  - Respirations ≥20/min, Paco2 ≥ 32
  - WBC count ≥12,000/mL or ≤4,000/mL or >10% immature neutrophils

‘Sepsis’
Sepsis is the systemic response to infection.

SIRS in the presence of proven or suspected infection.
Sepsis: More Than Just Inflammation

- Sepsis:
  - SIRS criteria
  - Known or suspected infection

‘Severe Sepsis’
‘Severe Sepsis’

- Sepsis associated with
- Organ-dysfunction
  - Hypotension
  - Hypoperfusion
Severe Sepsis: Acute Organ Dysfunction

- Severe Sepsis = Sepsis with signs of **acute** organ dysfunction in any of the following systems:
  - Cardiovascular (septic shock)
  - Renal
  - Respiratory
  - Hepatic
  - Hemostasis
  - CNS
  - Unexplained metabolic acidosis

‘Septic Shock’
‘Septic Shock’

- Sepsis with hypotension despite adequate fluid resuscitation

- Include all patients on vasopressors or inotropic support
Sepsis: A Complex Disease

The **Multiple Organ Dysfunction Syndrome (MODS)**

- The development of potentially **reversible** physiologic derangement involving two or more organ systems not involved in the disorder that resulted in ICU admission.
The Multiple Organ Failure Syndrome (MOFS)

- The development of potentially irreversible physiologic derangement involving two or more organ systems not involved in the disorder that resulted in ICU admission
Jargon 2002: PIRO

Predisposition

Insult

Response

Organ Dysfunction

Infection

Inflammation

Physiologic

Biochemical

Specific Organ

Severity

Severe Sepsis
Predisposition

- Pre-existing disease
  - Cardiac, Pulmonary, Renal
  - HIV
- Age (extremes of age)
- Gender (males)
- Genetics
  - TNF polymorphisms (TNF promoter high secretor genotype)
Response

- Physiology
  - Heart rate
  - Respiration
  - Fever
  - Blood pressure
  - Cardiac output
  - WBC
  - Hyperglycemia

- Markers of Inflammation
  - TNF
  - IL-1
  - IL-6
  - Procalcitonin
  - PAF
IDENTIFYING ACUTE ORGAN DYSFUNCTION AS A MARKER OF SEVERE SEPSIS

- Altered Consciousness
- Reduced GCS
- Tachycardia
- Systolic BP ≤90, or MAP ≤70 despite fluids
- Vasopressors
- Tachypnea
- \( \text{PaO}_2/\text{FiO}_2 \leq 250 \)
- Mechanical Ventilation
- PEEP >7.5
- Liver Enzymes
- >2x ULN
- Low pH with high lactate (eg, pH, 7.3 & lactate>ULN)
- Urine Output <0.5 mL/kg/hr despite fluids
- ↑ Creatinine >50% from baseline
- Acute dialysis
- Platelets <100,000/mm³
- ↑ PT/aPTT
- ↑ D-dimer

Organ Dysfunction

- Lungs ➢ Adult Respiratory Distress Syndrome
- Kidneys ➢ Acute Tubular Necrosis
- CVS ➢ Shock
- CNS ➢ Metabolic encephalopathy
- PNS ➢ Critical Illness Polyneuropathy
- Coagulation ➢ Disseminated Intravascular Coagulopathy
- GI ➢ Gastroparesis and ileus
- Liver ➢ Cholestasis
- Endocrine ➢ Adrenal insufficiency
- Skeletal Muscle ➢ Rhabdomyolysis

✓ Specific therapy exists
Magnitude of the Problem
- Severe sepsis takes more lives than breast, colon/rectal, pancreatic, and prostate cancer combined.

- One of every three patients who develop severe sepsis will die within a month.

Source: Society of Critical Care
Comparison With Other Major Diseases

Incidence of Severe Sepsis

<table>
<thead>
<tr>
<th>Disease</th>
<th>Incidence</th>
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<tr>
<td>AIDS*</td>
<td>1303-1310</td>
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<tr>
<td>Colon Cancer§</td>
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<tr>
<td>Breast Cancer§</td>
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</tr>
<tr>
<td>CHF+</td>
<td></td>
</tr>
<tr>
<td>Severe Sepsis‡</td>
<td>300</td>
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Mortality of Severe Sepsis

<table>
<thead>
<tr>
<th>Disease</th>
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<tr>
<td>AIDS*</td>
<td>250,000</td>
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<tr>
<td>Breast Cancer§</td>
<td>200,000</td>
</tr>
<tr>
<td>AMI+</td>
<td>150,000</td>
</tr>
<tr>
<td>Severe Sepsis‡</td>
<td>100,000</td>
</tr>
</tbody>
</table>

Sepsis, Mortality Rates

- Overall = 30% - 50%

- By syndrome definition:
  - SIRS = 4-7%
  - Sepsis = 16%
  - Severe sepsis = 20%
  - Septic shock = 46%
Severe Sepsis is deadly

- Sands, et al: 34%
- Zeni, et al: 50%
- Angus, et al: 28%

Mortality
Severe Sepsis is Common
Severe Sepsis is increasing in incidence
Epidemiology of Sepsis
The International Cohort Study

Percent of cases within each category

<table>
<thead>
<tr>
<th>Infection</th>
<th>Sepsis</th>
<th>Severe Sepsis</th>
<th>Septic Shock</th>
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<tbody>
<tr>
<td>18</td>
<td>28</td>
<td>24</td>
<td>30</td>
</tr>
</tbody>
</table>

35% mortality

8353 patients with LOS > 24h
4277 infections (2696 on admission)

Alberti, Int Care Med 2002
## Sources of Sepsis
### The International Cohort Study

<table>
<thead>
<tr>
<th>Source</th>
<th>Severe Sepsis</th>
<th>Septic Shock</th>
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<tbody>
<tr>
<td>Respiratory</td>
<td>66</td>
<td>53</td>
</tr>
<tr>
<td>Abdomen</td>
<td>9</td>
<td>20</td>
</tr>
<tr>
<td>Bacteremia</td>
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<td>16</td>
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<tr>
<td>Urinary</td>
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<td>11</td>
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<tr>
<td>Multiple</td>
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</table>
Microbiology of Sepsis
The International Cohort Study

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<th></th>
<th>Severe Sepsis</th>
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<tr>
<td>Gram-positive</td>
<td>44</td>
<td>40</td>
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<tr>
<td>Gram-negative</td>
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<td>47</td>
</tr>
<tr>
<td>Fungal</td>
<td>9</td>
<td>13</td>
</tr>
<tr>
<td>Polymicrobial</td>
<td>-</td>
<td>-</td>
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</tbody>
</table>
Etiology

- Infectouse
- Non-Infectouse
• Bacterial sepsis
• Burn wound infections
• Candidiasis
• Cellulitis
• Cholecystitis
• Community-acquired pneumonia[3]
• Diabetic foot infection
• Erysipelas
• Infective endocarditis
• Influenza

• Intraabdominal infections - Eg, diverticulitis, appendicitis
• Gas gangrene
• Meningitis
• Nosocomial pneumonia
• Pseudomembranous colitis
• Pyelonephritis
• Septic arthritis
• Toxic Schock Syndrom
• Urinary tract infections (male and female)
Noninfectious

- Acute mesenteric ischemia
- Adrenal insufficiency
- Autoimmune disorders
- Burns
- Chemical aspiration
- Cirrhosis
- Cutaneous vasculitis
- Dehydration
- Drug reaction
- Electrical injuries
- Erythema multiforme
- Hemorrhagic shock

- Hematologic malignancy
- Intestinal perforation
- Medication side effect - Eg, from theophylline
- Myocardial infarction
- Pancreatitis
- Seizure
- Substance abuse - Stimulants such as cocaine and amphetamines
- Surgical procedures
- Toxic epidermal necrolysis
- Transfusion reactions
- Upper gastrointestinal bleeding
- Vasculitis
Pathogenesis of SIRS/MODS

- Preoperative Illness
- Trauma or Operation
- Tissue Injury
  - optimal oxygen delivery and support
  - Inadequate Resuscitation
    - Excessive Inflammatory Response
    - SIRS/MODS
  - Recovery
Initiation of Inflammatory Response

From Wheeler & Bernard, NEJM 1999
Mediators of Septic Response
Pro-inflammatory Mediators

- Bacterial Endotoxin
- TNF-α
- Interleukin-1
- Interleukin-6
- Interleukin-8
- Platelet Activating Factor (PAF)
- Interferon-Gamma
- Prostaglandins
- Leukotrienes
- Nitric Oxide
Anti-inflammatory Mediators

- Interleukin-10
- PGE2
- Protein C
- Interleukin-4
- Interleukin-12
- Lipoxins
- GM-CSF
- TGF
- IL-1RA
Pathophysiology of Sepsis

In simple terms sepsis can be viewed as an imbalance of inflammation, coagulation, and fibrinolysis.

In normal patients homeostasis is maintained when these are balanced.
Pathophysiology of Sepsis

During a normal response to bacteria in the blood, the immune system releases inflammatory mediators to promote recovery of the tissue. These mediators are known as:

- Tumor Necrosis Factor (TNF)
- Interleukins (IL)
- Cytokines
- Prostaglandins
- Platelet Activating Factor

Source: New England Journal of Medicine, 2003
Pathophysiology of Sepsis

Once the bacteria or antigen is isolated, the pro-inflammatory mediators attract neutrophils or WBCs which attack the antigen and try to engulf it.

Graphics: Delores Zittel, 2006
Pathophysiology of Sepsis

To prevent the response from damaging normal tissue, anti-inflammatory mediators are released including transforming growth factors and interleukins (IL-4). This balance of inflammatory and anti-inflammatory mediators restricts the inflammation response to the local site of infection.

Source: Critical Care Nurse Supplement, 2004
The Compensatory Anti-inflammatory Response syndrome (CARS) in Critically ill patients

Nicholas S. Ward, MD<sup>a</sup><sup>,*</sup>, Brian Casserly, MD<sup>a</sup>, and Alfred Ayala, PhD<sup>b</sup>

<sup>a</sup>Division of Pulmonary, Critical Care, and Sleep Medicine, The Warren Alpert Medical School of Brown University, 593 Eddy Street, APC 707, Providence, RI 02912, USA

<sup>b</sup>Division of Surgical Research, Department of Surgery, The Warren Alpert Medical School of Brown University, Providence, RI 02912, USA
Cellular/molecular elements

Lymphocyte dysfunction (ie, reduced proliferative and/or type 1 helper T-cell [Th1] cytokine production in response-defined antigens or specific T-cell stimuli)

Lymphocyte Apoptosis

Down-regulation of monocyte HLA receptors Monocyte deactivation (ie, reduced Th1/ proinflammatory cytokine production in response stimuli)

IL-10 production

Transforming growth factor-beta production Prostaglandin E2 production
Molecular Mediators in Pathophys

- Parallel to SIRS is CARS
  - Compensatory Anti-inflammatory Response System
    - Attempts to down regulate the SIRS response
    - IL-4, IL-10, transforming growth factor beta, CSF, soluble receptors to TNF, antagonists to TNF-alpha and IL-1
    - If CARS reaction is severe it will manifest as anergy and infection susceptibility
Fig. 2. Trauma-induced injury actives innate immune responses to produce pro- and antiinflammatory cytokines. Imbalance between the systemic inflammatory response syndrome and the compensatory antiinflammatory response (immunosupression) increases morbidity of trauma patients. In the first hours, the magnitude of the systemic inflammatory response syndrome is correlated with early multiple organ failure and infections. In the following days, immunosupression contributes to the increased incidence of nosocomial infections and late sepsis. CARS = compensatory anti-inflammatory response; MOF = multiple organ failure; SIRS = systemic inflammatory response syndrome.
Pathophysiology of Sepsis

When the body is unable to maintain the appropriate balance, the immune response is no longer local but becomes systemic. Inflammation and altered clotting quickly spread through the body.

Source: Critical Care Nurse Supplement, 2004
Pathophysiology of Sepsis

- The release of the inflammatory mediators starts the Coagulation Cascade leading to the development of a clot.

- To maintain this clot, inhibitors are released to suppress fibrinolysis or breakdown. This is necessary to have time for the body to destroy the bacteria before the clot is gone.

Source: Critical Care Nurse Supplement, 2004
Homeostasis Is Unbalanced in Severe Sepsis

Activation of Coagulation

The enhanced clotting continues making tiny clots or “microthrombi” in the vascular system which impairs blood flow and organ perfusion.
Fibrinolysis, or the breakdown of clots, is the body’s response to the increased clotting and inflammation.

In sepsis this breakdown is inhibited or slowed through

- Plasminogen Activator Inhibitor-1 (PAI-1)
- Thrombin Activatable Fibrinolysis Inhibitor (TAFI)
Activation of Fibrinolysis

The increase levels of these two inhibitors, Plasminogen Activator Inhibitor-1 (PAI-1) and Thrombin Activatable Fibrinolysis Inhibitor (TAFI), suppress fibrinolysis even more creating a state of “coagulopathy”.
SEVERE SEPSIS PATHOPHYSIOLOGY

Microvascular dysfunction
↑ Inflammation
↑ Coagulation
↓ Fibrinolysis

→ Hypoperfusion/hypoxia → Organ dysfunction
  Microvascular thrombosis
  Endothelial dysfunction
  Global tissue hypoxia
  Direct tissue damage
Making Matters Worse
The Role of Endothelium in Sepsis

Normal endothelium has anticoagulant abilities and plays a role in the body’s homeostasis abilities including:

- Vasomotor tone
- Movement of cells and nutrients
- Maintaining blood fluidity

When activated, endothelium also plays a role in the inflammatory, coagulation, and fibrinolytic components of sepsis.
Making Matters Worse

- In sepsis the endothelium becomes damaged which makes the “inflammatory process” worse by releasing more cytokines (TNF-a and IL-1) causing neutrophils to stick to its’ lining.

- The “activation” of the capillary endothelium leads to increased permeability causing fluid to “leak” out of the capillaries and into the extracellular spaces.

Source: http://www.xigris.com/Learning_Modules/course_01/module_02/index.htm
Question: Why do Septic Patients Die?

• Answer: Organ Failure
Organ Failure and Mortality

• Knaus, et al. (1986):
  • Direct correlation between number of organ systems failed and mortality.
  • Mortality Data:

<table>
<thead>
<tr>
<th>#OSF</th>
<th>D1</th>
<th>D2</th>
<th>D3</th>
<th>D4</th>
<th>D5</th>
<th>D6</th>
<th>D7</th>
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</thead>
<tbody>
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<td>1</td>
<td>22%</td>
<td>31%</td>
<td>34%</td>
<td>35%</td>
<td>40%</td>
<td>42%</td>
<td>41%</td>
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<tr>
<td>2</td>
<td>52%</td>
<td>67%</td>
<td>66%</td>
<td>62%</td>
<td>56%</td>
<td>64%</td>
<td>68%</td>
</tr>
<tr>
<td>3</td>
<td>80%</td>
<td>95%</td>
<td>93%</td>
<td>96%</td>
<td>100%</td>
<td>100%</td>
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SEVERE SEPSIS-ASSOCIATED MORTALITY INCREASES WITH THE NUMBER OF ORGAN DYSFUNCTIONS

Severe Sepsis: The Final Common Pathway

*Endothelial Dysfunction and Microvascular Thrombosis*

- Hypoperfusion/Ischemia
- Acute Organ Dysfunction (Severe Sepsis)
- Death
Sepsis Pathogenesis

Unbalanced Immune Reaction
- Tissue Factor
  - Procoagulant State
    - Microvascular Thrombosis

Mediators of Inflammation
- Vasodilation
- Capillary Leak
Evolution of Sepsis care

**Established Core Rx:**
- Source Control
- Antibiotics
- Resuscitation
- Supportive Care

**Established Core Rx:**
- Source Control
- More Antibiotics
- Faster Resuscitation
- Better Supportive Care

In general the process of care has improved

**Mortality**

- No Steroids
  - Endotoxin Antagonists
  - LPS/LPS receptor antagonist
  - anti-TNF
  - NSAIDs
  - Nitric Oxide Synthase Inhibitors
  - Tissue Factor Pathway Inhibitors
  - anti-TLR4

- Xigris
- Tight Glycemic Control

- Steroids
- Loose Glycemic Control

- Interleukin Antagonists
Guidelines for sepsis

How do you Quickly deliver complex care?

Mobilization and coordination of people and resources.
EARLY GOAL-DIRECTED THERAPY IN THE TREATMENT OF SEVERE SEPSIS AND SEPTIC SHOCK

EMANUEL RIVERS, M.D., M.P.H., BRYANT NGUYEN, M.D., SUZANNE HAVSTAD, M.A., JULIE RESSLER, B.S., ALEXANDRIA MUZZIN, B.S., BERNHARD KNOBLICH, M.D., EDWARD PETERSON, PH.D., AND MICHAEL TOMLANOVICH, M.D., FOR THE EARLY GOAL-DIRECTED THERAPY COLLABORATIVE GROUP*

## System-based Approaches to sepsis

### Early-Goal Directed Therapy

- INCLUSION = SEPSIS AND [BP < 90 after fluid OR Lactate > 4]

<table>
<thead>
<tr>
<th>Control</th>
<th>Intervention</th>
<th>EGDT</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVP 8-12</td>
<td>Fluids</td>
<td>CVP 8-12</td>
</tr>
<tr>
<td>MAP &gt; 65</td>
<td>Vasopressors</td>
<td>MAP &gt; 65</td>
</tr>
<tr>
<td>Transfusions Dobutamine</td>
<td></td>
<td>ScvO2 &gt; 70%</td>
</tr>
<tr>
<td>49% mortality</td>
<td></td>
<td>33% mortality</td>
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</tbody>
</table>

System-based Approaches to sepsis

The New England Journal of Medicine

EARLY GOAL-DIRECTED THERAPY IN THE TREATMENT OF SEVERE SEPSIS AND SEPTIC SHOCK

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Used to promote:
1. CVP > 8 as an initial target
2. Use of Svo2 monitoring and use of blood/dobutamine

System-based Approaches to sepsis

<table>
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</thead>
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<tr>
<td>49% mortality</td>
<td>33% mortality</td>
</tr>
</tbody>
</table>

Do whatever you normally do.  

Use a rigid protocol with multiple dedicated team members

They did not control for the system of care.

A Multidisciplinary Community Hospital Program for Early and Rapid Resuscitation of Shock in Nontrauma Patients

BEFORE (control)          AFTER (protocol)

Do what you normally do. We will be watching.

A Multidisciplinary Community Hospital Program for Early and Rapid Resuscitation of Shock in Nontrauma Patients

A Multidisciplinary Community Hospital Program for Early and Rapid Resuscitation of Shock in Nontrauma Patients

A Multidisciplinary Community Hospital Program for Early and Rapid Resuscitation of Shock in Nontrauma Patients

All physicians, nurses, and patient care technicians in the emergency department and intensive care units received formal order set clinical education. Additionally, all hospital floor clinical nurse specialists and advance practice nurses, along with the house staff physicians in these areas, were in-serviced on the order sets....These educational endeavors included training in sepsis pathophysiology, monitoring of central venous pressures, assessment of central venous blood oxygen saturation, and the pharmacotherapy of sepsis.

1. EDUCATION
2. ORDER SET with recommendations and goals for sepsis treatment.

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<tbody>
<tr>
<td>CVP &gt; 8, MAP &gt; 65, ScVO2 &gt; 70%, HCT &gt; 30</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>MAP &gt; 70, SaO2 &gt; 92, UOP &gt; 30ml/h, SvO2 &gt; 60, CI &gt; 2.5</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>ABX in 4 h, CVP &gt; 8, MAP &gt; 65, ScVO2 &gt; 70%, HCT &gt; 30, Check Lactate Steroids</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Appropriate ABX in 4 h, CVP &gt; 8, MAP &gt; 65, ScVO2 &gt; 70%</td>
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<tr>
<td>Early ABX, Blood Cultures, Appropriate ABX, CVP &gt; 8, MAP &gt; 65, ScVO2 &gt; 70%</td>
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<td>Specific Interventions</td>
<td>Fluids Blood, Pressors</td>
<td>ABX, Fluids Pressors</td>
<td>ABX, Fluids Blood Pressors</td>
<td>ABX, Fluids Pressors Steroid, Xigris, Other Supportive Care</td>
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<tr>
<td>System Interventions</td>
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</tr>
<tr>
<td>Absolute Change in Mortality</td>
<td>-16%</td>
<td>-12%</td>
<td>-19%</td>
<td>-16%</td>
<td>-7%</td>
</tr>
</tbody>
</table>
- Identify Sepsis as early as possible

- Broad Spectrum antibiotics ASAP and Identify source(s) of infection

- Identify severity: Vitals, mental status, UOP, LACTATE, other labs.

- Volume and physiologic resuscitation ASAP with GOALS.

- Tweak your system so these things happen FAST
- Train all providers
- Vital sign/Laboratory alerting systems
- Biomarkers
No randomized-controlled data

Time from EDGT qualification to ABX

Time from hypotension to appropriate ABX

Galeski DF, Mikkelsen ME, Band RA, et al. Impact of time to antibiotics on survival in patients with severe sepsis or septic shock in whom early goal-directed therapy was initiated in the emergency department*. Critical Care Medicine 2010;38(4):1045–53.

Source Control

- Don’t be satisfied with a diagnosis of sepsis and no source.

- If a source exists and is potentially removable, get the ball rolling.
Defining the severity of sepsis

- Importance of looking for organ failure is self-evident.

- Identification of “shock” dramatically alters the treatment and mortality.

- Blood Pressure, Response to Fluid, LACTATE
Early, quantitative resuscitation goals vs. standard care have resulted in improved mortality

The effect of a quantitative resuscitation strategy on mortality in patients with sepsis: A meta-analysis *.
Jones, Alan E. MD; Brown, Michael D. MD, MSc; Trzeciak, Stephen MD, MPH; Shapiro, Nathan I. MD, MPH; Garrett, John S. MD; Heffner, Alan C. MD; Kline, Jeffrey A. MD; on behalf of the Emergency Medicine Shock Research Network investigators
Surviving Sepsis targets of fluid resuscitation

What are they?

- SBP
- MAP
- CVP
- U/o
- Lactate
- ScvO₂
- Hct
Surviving Sepsis targets of fluid resuscitation

What are they?

- SBP > 90
- MAP > 65
- CVP 8 - 12
- U/o > 0.5 ml/kg/hr
- Lactate < 1
- ScvO₂ > 70
- Hct > 30
- Crystalloids are favored as the initial fluid
- Hydroxyethyl starches are likely harmful
- Albumin may have a role, particularly if a lot of fluid is given
Chronic Phase

- Monitor for and prevent recurrence of sepsis
  - VAP, CLABSI, UTI. Infection Control Practices.
- Lung Protective Ventilator Strategies
- Protocolized Sedation, Daily Awakenings
- Nutritional Support
- Early Mobilization
- Success with these measures is most likely with a multi-disciplinary approach.
- System-based strategies are effective for improving sepsis care
- Processes should aim to:
  - Identify patients early and identify the severity of sepsis
  - Quickly administer appropriate antibiotics and source control
  - Establish institutional goals for physiologic resuscitation
  - Multidisciplinary chronic phase of care to ensure compliance
How do we manage sepsis and septic shock?

1) Investigate and treat sepsis
   - Try and find and treat source
   - Early blood cultures
   - Start antibiotics asap ideally within 1 hour and after cultures taken

2) Assess extent of end organ hypoperfusion and improve oxygen delivery (early goal directed therapy)
Oxygen delivery

What does it mean?
Oxygen delivery

What does it mean?

Delivery (DO₂) = O₂ content x cardiac output

= ([Hb] x SpO₂ x 1.34) x (HR x SV)

Oxygen content = [Hb] x SpO₂ x 1.34

Cardiac output = HR x SV
Fluid Challenge

What is the difference between an infusion and a challenge?
Fluid Challenge

What is the difference between an infusion and a challenge?

250 to 500 ml colloid (or blood products)
500 to 1000ml Hartmann’s
[NOT 5% dextrose]
As fast as possible (with pressure bag)
You at the bedside
Fluid Challenge

Aim is to improve SV (and hence CO) by increasing preload

Frank-Starling mechanism
Markers of perfusion

What are they?
Markers of perfusion

What are they?

- Clinical signs
  - Warm skin, conscious level, u/o
- Haemodynamic variables
  - CVP
- Bloods
  - Serum Lactate
  - ScvO₂
CVP

What does it mean?
CVP

What does it mean?

Starling’s Law

Estimate of LVEDV (i.e. preload)

Not always a good correlation with volume-responsiveness

However if low strongly suggestive of hypovolaemia
Lactate

What does it mean?
Lactate

What does it mean?

- Increased production (anaerobic glycolysis)
  - Tissue hypoperfusion
  - Tissue dysoxia
- Reduced metabolism
  - Hepatic
  - Renal
- <1 is normal, 1-2 is a concern, >2 is bad, >4 is very bad
What does it mean?
What does it mean?

- Balance between oxygen delivery and consumption (VO$_2$)
- \( \text{ScvO}_2 = \text{SaO}_2 - \frac{\text{VO}_2}{\text{CO}} \)
- Target > 70%
ScvO2

What can I do if it’s low?
ScvO2

What can I do if it’s low?

Delivery = [Hb] \times \text{SpO}_2 \times 1.34 \times \text{HR} \times \text{SV}
What can I do if it’s low?

Delivery = [Hb] x SpO2 x 1.34 x HR x SV

Fluid optimise
Transfuse packet cells

Hct > 30%

Inotropes
Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock: 2012


Crit Care Med. 2013; 41:580-637

Intensive Care Medicine 2013; ..
Current Surviving Sepsis Campaign Guideline

Sponsors

- American Association of Critical-Care Nurses
- American College of Chest Physicians
- American College of Emergency Physicians
- Australian and New Zealand Intensive Care Society
- Asia Pacific Association of Critical Care Medicine
- American Thoracic Society
- Brazilian Society of Critical Care (AIMB)
- Canadian Critical Care Society
- Chinese Society of Critical Care Medicine
- Emirates Intensive Care Society
- European Respiratory Society
- European Society of Clinical Microbiology and Infectious Diseases
- European Society of Intensive Care Medicine
- European Society of Pediatric and Neonatal Intensive Care
- Infectious Diseases Society of America
- Indian Society of Critical Care Medicine
- International Pan Arab Critical Care Medicine Society
- Japanese Association for Acute Medicine
- Japanese Society of Intensive Care Medicine
- Pediatric Acute Lung Injury and Sepsis Investigators
- Society Academic Emergency Medicine
- Society of Critical Care Medicine
- Society of Hospital Medicine
- Surgical Infection Society
- World Federation of Critical Care Nurses
- World Federation of Pediatric Intensive and Critical Care Societies
- World Federation of Societies of Intensive and Critical Care Medicine

Participation and endorsement:

- German Sepsis Society
- Latin American Sepsis Institute
“Time Zero”

- Time Zero = time of presentation
  - ED, Medical Floors, ICU
- Both bundles time based
- Most important time based elements:
  - Antibiotic timing
  - Resuscitation timing (EGDT)
1. We recommend that intravenous antimicrobial therapy be started as early as possible and within the first hour of recognition of septic shock (1B) and severe sepsis without septic shock (grade1C).
## Hospital Mortality by Time to ABX

<table>
<thead>
<tr>
<th>Time to ABX(^1), hrs</th>
<th>OR(^2)</th>
<th>95% CI</th>
<th>p-value</th>
<th>Probability of mortality(^3)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 (ref)</td>
<td>1.00</td>
<td>---</td>
<td>---</td>
<td>18.7</td>
<td>17.5</td>
</tr>
<tr>
<td>1</td>
<td>1.05</td>
<td>1.02</td>
<td>1.07</td>
<td>&lt; 0.001</td>
<td>19.3</td>
</tr>
<tr>
<td>2</td>
<td>1.09</td>
<td>1.04</td>
<td>1.15</td>
<td>&lt; 0.001</td>
<td>20.0</td>
</tr>
<tr>
<td>3</td>
<td>1.14</td>
<td>1.06</td>
<td>1.23</td>
<td>&lt; 0.001</td>
<td>20.8</td>
</tr>
<tr>
<td>4</td>
<td>1.19</td>
<td>1.08</td>
<td>1.32</td>
<td>&lt; 0.001</td>
<td>21.5</td>
</tr>
<tr>
<td>5</td>
<td>1.25</td>
<td>1.11</td>
<td>1.41</td>
<td>&lt; 0.001</td>
<td>22.3</td>
</tr>
<tr>
<td>6</td>
<td>1.31</td>
<td>1.13</td>
<td>1.51</td>
<td>&lt; 0.001</td>
<td>23.1</td>
</tr>
</tbody>
</table>

\(^{1}\) Time to ABX is based on 15,948 observations that are greater than or equal to zero

\(^{2}\) Hospital mortality odds ratio referent group is 0 hours for the time to ABX and is adjusted by the number of baseline organ failures, infection type (community vs. nosocomial), and geographic region (Europe, North America, and South America)
We recommend that initial fluid challenge in patients with sepsis-induced tissue hypoperfusion with suspicion of hypovolemic be started with $\geq 1000$ mL of crystalloids (to achieve a minimum of $30\text{ml/kg}$ of crystalloids in the first 4 to 6 hours). (Grade 1B).
## Logistic Regression Model

<table>
<thead>
<tr>
<th>Compliance indicator</th>
<th>Hospital mortality odds ratio(^1)</th>
<th>95% CI</th>
<th>(p)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Serum lactate within 6 hours</td>
<td>0.71</td>
<td>0.67 – 0.75</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>2. Blood cultures before antibiotics</td>
<td>0.81</td>
<td>0.76 – 0.86</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>3. Broad spectrum antibiotics</td>
<td>0.83</td>
<td>0.79 – 0.88</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>4. Fluids and vasopressors</td>
<td>0.57</td>
<td>0.54 – 0.61</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>5. CVP ≥ 8 mm Hg within 6 hours</td>
<td>0.74</td>
<td>0.69 – 0.79</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>6. ScvO(_2) ≥ 70% within 6 hours</td>
<td>0.73</td>
<td>0.67 – 0.78</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>7. Resuscitation bundle</td>
<td>0.77</td>
<td>0.72 – 0.83</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>8. Low-dose steroids policy</td>
<td>0.82</td>
<td>0.77 – 0.88</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>9. Drotrecogin alfa policy</td>
<td>0.93</td>
<td>0.88 – 0.98</td>
<td>0.008</td>
</tr>
<tr>
<td>10. Glucose control maintained</td>
<td>0.70</td>
<td>0.69 – 0.74</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>11. IPP &lt; 30 cm H(_2)O</td>
<td>0.78</td>
<td>0.71 – 0.86</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>12. Management bundle</td>
<td>0.72</td>
<td>0.68 – 0.77</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>High resuscitation performance</td>
<td>0.79</td>
<td>0.75 – 0.83</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>High management performance</td>
<td>0.84</td>
<td>0.80 – 0.88</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>
SSC Bundle:

TO BE COMPLETED WITHIN 3 HOURS OF TIME OF PRESENTATION †:

1. Measure lactate level
2. Obtain blood cultures prior to administration of antibiotics
3. Administer broad spectrum antibiotics
4. Administer 30ml/kg crystalloid for hypotension or lactate ≥4mmol/L

† “time of presentation” is defined as the time of triage in the Emergency Department or, if presenting from another care venue, from the earliest chart annotation consistent with all elements severe sepsis or septic shock ascertained through chart review.
SSC Bundle:

TO BE COMPLETED WITHIN 6 HOURS OF TIME OF PRESENTATION:

5. Apply vasopressors (for hypotension that does not respond to initial fluid resuscitation to maintain a mean arterial pressure (MAP) ≥65mmHg)

6. In the event of persistent arterial hypotension despite volume resuscitation (septic shock) or initial lactate ≥4 mmol/L (36mg/dl):
   - Measure central venous pressure (CVP)*
   - Measure central venous oxygen saturation (ScvO₂)*

7. Remeasure lactate*

* Targets for quantitative resuscitation included in the guidelines are CVP of ≥8 mm Hg, ScvO₂ of ≥70% and lactate normalization.
The Importance of Early Detection

- Efforts to just treat recognized sepsis alone are incomplete.

- A critical aspect of mortality reduction in the Campaign has been pushing practitioners to identify sepsis early.

- It may well be that earlier recognition accounts for much of the signal in mortality reduction and partially explains sharply increasing incidence.

- Without recognition that the clock is ticking, there is simply no incentive to recognize a challenging diagnosis early.
6 Hour Resuscitation Bundle

- Early Identification
- Early Antibiotics and Cultures
- Early Goal Directed Therapy
Rhode Island Hospital EGDT Data

Time from Entering ED to Receiving Antibiotics
Reduced by 42%

Time from Entering ED to Catheter Insertion
Reduced by 60%

Time from Entering ED to Transfer to MICU
Reduced by 51%
THANK YOU