Overview

- Significance of the Problem
- Defining the continuum
- Early Recognition & Resuscitation
- Multidisciplinary approach to management
- Outcome studies
Severe Sepsis: A Significant Healthcare Challenge

- Hospitalizations have doubled 2000-2008**
- Most costly reason for hospitalization in 2009**
  - 15.4 billion in aggregate hospital cost
- 1 out of 23 patients in hospital had septicemia**
- Major cause of morbidity and mortality worldwide
  - Leading cause of death in noncoronary ICU (US)¹
  - 10th leading cause of death overall (US)²*
- In the US, more than 700 patients die of severe sepsis daily

* Based on data for septicemia
†Reflects hospital-wide cases of severe sepsis as defined by infection in the presence of organ dysfunction
** AHRQ Healthcare cost & Utilization Project October 2011

Maternal Sepsis: Incidence

- Septic shock: 0.002-0.01% of all deliveries
- 0.3-0.6% of all septic patients are pregnant
- Increased over the last decade
  - Older maternal age at delivery
    - Obesity, diabetes, CHTN, placental abruption and placenta accreta
    - Assistive reproductive technology and multi-fetal gestation
  - Obesity
    - HTN, DM, Cesarean, cardiopulmonary complications

Slides courtesy of Jeanne S. Sheffield, M.D.
Maternal Fetal Medicine
University of Texas Southwestern/2013
Burton and Sibai 2012
# High Reliable Sepsis Care

- Recognizes trouble before it starts
- Follows standard operating procedures (SOP) for managing sepsis.
- Does not take little things for granted.
- Understands the consequences:
  - Immediate
  - Long term
- Holds everyone accountable
  - takes personal responsibility for outcomes.

## Sepsis Impact on Mortality in Hospitals

Table 1. Inpatients With Sepsis Diagnoses in the Kaiser Permanente Northern California Cohort and the Healthcare Cost and Utilization Project Nationwide Inpatient Sample

<table>
<thead>
<tr>
<th></th>
<th>Kaiser Permanente Northern California (2010-2012) (n = 21,945)</th>
<th>Nationwide Inpatient Sample (2010) (n = 1,651,914)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Explicit (n)</td>
<td>Explict POA (n)</td>
</tr>
<tr>
<td>Hospitalizations</td>
<td>55,000 (11.4)</td>
<td>50,520 (10.5)</td>
</tr>
<tr>
<td>Hospital mortality</td>
<td>627 (1.4)</td>
<td>573 (1.0)</td>
</tr>
<tr>
<td>% (POA) of all hospital deaths among patients with sepsis</td>
<td>4.3 (45.0)</td>
<td>36.9</td>
</tr>
</tbody>
</table>

1 out of 2-3 Deaths r/t Sepsis, Most POA

In KPNC 2012 subset, patient meeting criteria for EGDT comprised 32.6 percent of sepsis deaths & patients with sepsis, normal BP & lactate < 4 comprised 55.9% of sepsis deaths.

Liu Y et al. JAMA 2014 May 18th, online.
How Does Severe Sepsis Compare to Your Current Care Priorities?

<table>
<thead>
<tr>
<th>Quality Projects</th>
<th>US Incidence</th>
<th># of Deaths</th>
<th>Mortality Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMI(^1)</td>
<td>895,000</td>
<td>171,000</td>
<td>19%</td>
</tr>
<tr>
<td>Stroke(^1)</td>
<td>700,000</td>
<td>157,800</td>
<td>23%</td>
</tr>
<tr>
<td>Pneumonia(^2)</td>
<td>1,300,000</td>
<td>61,800</td>
<td>4.8%</td>
</tr>
<tr>
<td>Severe Sepsis(^3)</td>
<td>751,000</td>
<td>215,000</td>
<td>29%</td>
</tr>
</tbody>
</table>

Why do you think that severe sepsis has not received the same focus as these other common disease states?


Surviving Sepsis Campaign Implementation Results

29,470 patients
2005-2013
Surviving Sepsis Campaign
Results (28,150 patients)
218 Hospitals

<table>
<thead>
<tr>
<th>Entry Point</th>
<th>Subjects</th>
<th>Mortality (hosp)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ED</td>
<td>55.8%</td>
<td>26.0</td>
</tr>
<tr>
<td>ICU</td>
<td>32.2%</td>
<td>40.3</td>
</tr>
<tr>
<td>Ward</td>
<td>11.9%</td>
<td>44.2</td>
</tr>
</tbody>
</table>

Mortality over 7 year period
36.7% to 27.5%  ARR: 7%  RRR: 25%  p= 0.005
ICU & Hos LOS 4% for every 10% ↑ in compliance

Levy, M et al. Intensive Care Medicine;2014;40;1623

Surviving Sepsis Campaign
2005-2012-Resuscation Bundle

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Low compliance</th>
<th>High Compliance (all elements-29.2%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital Mortality</td>
<td>38.6</td>
<td>29%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hospital mortality if origin is ED,%</td>
<td>30.9</td>
<td>26.0</td>
<td>0.001</td>
</tr>
<tr>
<td>Hospital mortality if origin is Ward,%</td>
<td>45.3</td>
<td>36.7</td>
<td>0.001</td>
</tr>
<tr>
<td>Hospital mortality if origin is ICU,%</td>
<td>49.8</td>
<td>44.2</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Levy, M et al. Intensive Care Medicine;2014;40;1623
## Surviving Sepsis Campaign

<table>
<thead>
<tr>
<th>Bundle Element</th>
<th>Mortality Odds Ratio</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactate &lt;2</td>
<td>0.80</td>
<td>0.73-0.89</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lactate 2 to &lt;3</td>
<td>0.67</td>
<td>0.59-0.76</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lactate &gt; 3</td>
<td>0.69</td>
<td>0.63-0.75</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Blood Cultures</td>
<td>0.82</td>
<td>0.77-0.87</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>0.85</td>
<td>0.81-0.90</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fluid Administration</td>
<td>0.86</td>
<td>0.73-1.01</td>
<td>&lt;0.07</td>
</tr>
<tr>
<td>CVP</td>
<td>0.84</td>
<td>0.78-0.91</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ScvO2</td>
<td>0.83</td>
<td>0.76-0.90</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Levy, M et al. Intensive Care Medicine 2014;40;1623

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## Implementation of Early Screening Tools and Triggers
Except on few occasions, the patient appears to die from the body's response to infection rather than from it."

Sir William Osler – 1904
The Evolution of Modern Medicine

Finding the Patients
Redefining what a ‘septic shock’ patient looks like

<table>
<thead>
<tr>
<th>Before</th>
<th>NOW</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supine in bed</td>
<td>Sitting up in bed</td>
</tr>
<tr>
<td>Ventilator</td>
<td>Nasal cannula</td>
</tr>
<tr>
<td>Fluids wide open</td>
<td>IV boluses</td>
</tr>
<tr>
<td>Increasing vasopressors</td>
<td>Weaning vasopressors</td>
</tr>
<tr>
<td>Minimally responsive</td>
<td>Awake</td>
</tr>
</tbody>
</table>

"Don’t look sick enough to be in ICU or to have a central line”

Must correct this misperception
Severe Sepsis: Defining a Disease Continuum

Infection
SIRS
Sepsis
Severe Sepsis

Adult Criteria
A clinical response arising from a nonspecific insult, including ≥ 2 of the following:
- Temperature: > 38°C or < 36°C
- Heart Rate: > 90 beats/min
- Respiration: > 20/min
- WBC count: > 12,000/mm³, or < 4,000/mm³, or > 10% immature neutrophils
- Glucose: > 120
- Acute Mental Status Change

SIRS
with a presumed or confirmed infectious process

Sepsis
with ≥ 1 sign of organ dysfunction, hypoperfusion or hypotension.

Examples:
- Cardiovascular (refractory hypotension)
- Renal
- Respiratory
- Hepatic
- Hematologic
- CNS
- Unexplained metabolic acidosis

Shock

Signs & Symptoms of Sepsis

- Chills
- Alteration in LOC
- Tachypnea
- Unexplained metabolic acidosis
- ↑ Heart rate
- Altered blood pressure
- Platelets
- Bands
- Skin perfusion
- ↓ Urine output (ped’s > 1 ml/kg/hr)
- Skin mottling
- Poor capillary refill
- Hyperglycemia
- Purpura/patchecia


Severe Sepsis: Defining a Disease Continuum

Infection  SIRS  Sepsis  Severe Sepsis

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- **Glucose**: > 120
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**SIRS with a presumed or confirmed infectious process**

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**Examples**:
- Cardiovascular (refractory hypotension)
- Renal
- Respiratory
- Hepatic
- Hematologic
- CNS
- Unexplained metabolic acidosis

**Shock**

SSC Guidelines: Screening

- We recommend routine screening of potentially infected seriously ill patients for severe sepsis to increase the early identification of sepsis and allow implementation of early sepsis therapy (1C)
- Potential new screening process
- Performance improvement efforts in severe sepsis should be used to improve patient outcomes (UG)


Sepsis Screen: The Diseases Chest Pain Signal

Pts qualify for Severe Sepsis with:
1. Real or suspected infection
2. 2 SIRS criteria
3. One organ dysfunction

Labor & Delivery Screen
Early Recognition: The Screening Process

- **TIME IS TISSUE!!**
  - Similar to polytrauma, AMI, or stroke, the speed and appropriateness of therapy administered in the initial hours after severe sepsis develops are likely to influence outcomes.\(^1\)

- To screen effectively, it must be part of the nurses’ daily routines—i.e., part of admission and shift assessment
- Must define a process for what to do with the results of the screen

If you don’t screen you will miss patients that may have benefited from the interventions.

Make it Process Dependent

• Weave into fabric of current practice
• Assess every shift and more frequently if needed
• Identify strategies for initiation of therapy response once patient is identified

Severe Sepsis Algorithm

Screened Positive for Severe Sepsis

For lactic acid less than 2.0
Initiate General Care Severe Sepsis Bundle on back and complete interventions

SEPSIS INDUCED HYPOPERFUSION?
(Clinical picture of severe sepsis plus one or both of the following criteria)
1. Hypotension AFTER initial fluid bolus (30 mL/kg)
OR
2. Require vasopressor
OR
3. Initial lactic acid greater than or equal to 4 mEq/L with any BP

YES
Activate CODE SEPSIS
Initiate transfer to ICU

Meanwhile, continue resuscitation of 250-1000 mL boluses if hypotensive after the initial bolus – per physician order

NO
For lactic acid 2.0-3.0 or initial hypotension that responded to the 30 mL/kg fluid bolus, initiate transfer to ICU

Initiate Intermediate Care Severe Sepsis Bundle on back and complete interventions.
Screening: Barriers/Strategies

- **Barriers**
  - Time for nurses to do it (perception vs. reality)
  - Screening is not sensitive only for severe sepsis
  - Positive screen is not a diagnosis of severe sepsis
- **Strategies**
  - Must assign responsibility and enforce accountability
  - Perform audits to measure compliance and identify problems
  - Round on unit and ask nurses how it is going and discuss issues

Screening

- **Lesson Learned:** Bedside nurse must do screening
- **Education/Simulation/Education**
  - Every 6 months
  - Build into orientation
  - Must be part of their documentation structure
  - Practice-Practice-Practice

The END RESULT—anytime patient has 2 or more SIRS—will think that this patient might have sepsis and can screen at that time
FULLY COMPUTERIZE…. 

AUTOMATED SEPSIS AWARENESS

Clinical Scenario 1: Early identification and intervention

• 88 year old, 51.6kg, white, female presented to ED at 1345 from ECF
• History: CAD, COPD, dementia, Alzheimer disease, depression, SVT
• Chief Complaint: rib pain, chest congestion and SOB
• Awake, alert and oriented, slight combative (history of combative behavior)
Clinical Scenario 2: 
Early identification and intervention

- 51 year old with past medical history of hepatitis C, ETOH abuse with cirrhosis, asthma/COPD; 111kg (weight)
- She presents the emergency department for 5 days worsening generalized malaise, difficulty breathing, body aches diffusely and right-sided pleuritic chest pain. Reported fever of 103 yesterday
- VS in triage: 1630: 82/54, HR 155, RR 22, T: 97.4
- Does she screen positive for severe sepsis?

Yes: HR 155, RR 22; suspected infection: body aches, pleuritic pain; Organ dysfunction: low BP

Clinical Scenario III

- On 3/20/07 at 10pm a 65 year old, 78 kg female with history of asthma and CAD admitted from ER to floor with SOB and rib pain. R/O pneumonia
- Hx: dementia, IDDM, PVD, arthritis and depression
- Admission VS include: BP- 88/60, HR-135, T-102, RR-30. pulse ox is 90% on 3 liters nasal cannula

Does she screen positive for severe sepsis?
Clinical Scenario IV

- 51 year female from ED-CDU to floor
- Presented to ED with abd pain-suspect diverticulitis; CT scan-possible perforation
- Surgery consulted when lactate obtained and it was 4.8
- Admission VS: Temp 97.9, HR-126, RR-28, antibiotics started this am
  
  Screen patient for severe sepsis

Screening for Severe Sepsis Milestones and Checklist

- Develop screening process for ED, rapid response team and ICU (eventually housewide)
- Ensure screening process has clear “next steps” defined for nursing staff
- Develop audit process to evaluate compliance and effectiveness
Homeostasis Is Unbalanced in Severe Sepsis


Inflammation, Coagulation and Impaired Fibrinolysis In Severe Sepsis

Reprinted with permission from the National Initiative in Sepsis Education (NISE).
MICROCIRCULATION: SUBLINGUAL BLOOD FLOW

Healthy Volunteer
- BP: 120/80 mm Hg
- SaO₂: 98%

Septic Shock Patient
- Resuscitated with fluids and dopamine
  - HR: 82 BPM
  - BP: 90/35 mmHg
  - SaO₂: 98%
  - CVP: 25 mmHg

Pathophysiologic Characteristics in Severe Sepsis

- Maldistribution of blood flow
- Imbalance of oxygen supply & demand
- Metabolic alterations & activation of the stress response
Maldistribution of Blood Flow

- Mechanical obstruction
  - Micro-emboli
  - Increased blood viscosity
  - Compression
- Systemic & local mediator & ion influence
  - Constriction vs. dilation
- Loss of regulatory activities/endothelial cell injury
  - Reactive hyperemia
  - Anticoagulation

Imbalance of Oxygen Supply & Demand
OXYGEN SUPPLY/DEMAND DYNAMICS

ScvO2 impacted by:
- O2 supply
- O2 transport
  - Volume
  - Hgb
  - Cardiac performance
- O2 demand

Occult Tissue Hypoxia

- Tissue hypoxia is often occult, reaches an advanced and lethal stage before its presence is known and resuscitation is attempted.
- Vital signs are inadequate for detecting global tissue hypoxia and not adequate as a resuscitation end point.
- Up to 50% of patients resuscitated from shock may have continued global tissue hypoxia (elevated lactate and decreased ScvO2) despite normalized vital signs and central venous pressure.

Inadequacy of Arterial Pressure

- Adequate pressure does not always mean adequate flow to tissues.
- Systemic hypoperfusion usually precedes hypotension, especially in patients with sepsis.

O₂ Supply Debt
Metabolic Alterations & The Stress Response

Initiation of the Stress Response

Sympathetic Nervous System Activation

Hypothalamus Activation

• SNS Activation
  – Gut hypothesis
  – ↑ BMR
  – Inhibition of insulin secretion
  – Inhibition of glucose uptake by the tissues

• Hypothalamus Activation
  – Adrenal cortex stimulation
  – Changes in carbohydrate, protein & fat metabolism resulting in ↑ glucose concentration
Cornerstones of Multidisciplinary Management of Severe Sepsis/Septic Shock

- Prevention
- Screening and Early Identification
- Early Intervention: Source control, Blood cultures and broad spectrum antibiotics
- 3 hour Bundle: Initial resuscitation
- 6 hour Bundle: Septic Shock

Grade System

A (high) RCTs
B (moderate) Downgraded RCTs or upgraded observational studies
C (low) Well-done observational studies with control RCTs
D (very low) Downgraded controlled studies or expert opinion based on other evidence

**TABLE 4. Factors Determining Strong vs. Weak Recommendation**

<table>
<thead>
<tr>
<th>What Should be Considered</th>
<th>Recommended Process</th>
</tr>
</thead>
<tbody>
<tr>
<td>High or moderate evidence (Is there high or moderate quality evidence?)</td>
<td>The higher the quality of evidence, the more likely a strong recommendation.</td>
</tr>
<tr>
<td>Certainty about the balance of benefits vs. harms and burdens (Is there certainty?)</td>
<td>The larger the difference between the desirable and undesirable consequences and the certainty around that difference, the more likely a strong recommendation. The smaller the net benefit and the lower the certainty for that benefit, the more likely a weak recommendation.</td>
</tr>
<tr>
<td>Certainty in or similar values (Is there certainty or similarity?)</td>
<td>The more certainty or similarity in values and preferences, the more likely a strong recommendation.</td>
</tr>
<tr>
<td>Resource implications (Are resources worth expected benefits?)</td>
<td>The lower the cost of an intervention compared to the alternative and other costs related to the decision–is fewer resources consumed—the more likely a strong recommendation.</td>
</tr>
</tbody>
</table>
Sepsis Definition and Early Recognition Variables Might Change in 2016

Infection-Sepsis-Septic Shock

The New Definitions

- **Infection**: Invasion of a sterile host by a microorganism without organ dysfunction
- **Sepsis**: presence of infection (suspected or confirmed) with Sepsis-induced tissue hypoperfusion or organ dysfunction
- **Septic Shock**: Sepsis with hypotension that persists despite adequate fluid resuscitation

Presented Seoul Korea WFSICCM 2015
CORE MEASURE

• Sepsis management will be a core measure that is reported to CMS starting October 1st, 2015
• Compliance is All or None—so all measure on the 3 and 6 hour bundles need to be met in the appropriate timeframe to be compliant

Included & Excluded Populations

Included Populations:
• Discharges age 18 and over with an ICD-10-CM Principal or Other Diagnosis Code of Sepsis, Severe Sepsis, or Septic Shock

Excluded Populations:
• Directive for Comfort Care within 3 hours of presentation of severe sepsis
• Directive for Comfort Care within 6 hours of presentation of septic shock
• Administrative contraindication to care
• Length of Stay >120 days
• Transfer in from another acute care facility
• Patients with severe sepsis who expire within 3 hours of presentation
• Patients with septic shock who expire within 6 hours of presentation
SEP-1

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 earliest chart annotation consistent with all elements severe sepsis or septic shock ascertained through chart review.

Fluid bolus is given rapidly, IV wide open, pressure bag if necessary; goal is 500ml every 15-30 minutes.

SEP-1

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 hypotension after initial fluid administration (MAP < 65 mm Hg) or if initial lactate was ≥4 mmol/L, re-assess volume status and tissue perfusion and document findings according to table 1.

7. Re-measure lactate if initial lactate elevated.
### TABLE 1
**DOCUMENT REASSESSMENT OF VOLUME STATUS AND TISSUE PERFUSION WITH:**

**Either**
- Repeat focused exam (after initial fluid resuscitation) by licensed independent practitioner including vital signs, cardiopulmonary, capillary refill, pulse and skin findings.

**Or two of the following:**
- Measure CVP
- Measure ScvO2
- Bedside cardiovascular ultrasound
- Dynamic assessment of fluid responsiveness with passive leg raise or fluid challenge

---

### No Management Bundle/Care of the Severe Sepsis/Septic Shock Patient

- Source control (1C) As rapid as possible <12hrs drain
- Continue to recommend the use of lung protective strategies for pts with ALI/ARDS (no change)
- Recommend—No steroids if can get MAP > 65 with fluids and vasopressors; if unable, then administer 200mg/day (2C)
- Start insulin gtt if get (2) consecutive BG > 180; target glucose < 180
- Also added nutritional recommendations to guidelines

Serum Lactate is associated with mortality in severe sepsis independent of organ failure and shock

Objective:
- Test whether the association between initial serum lactate level and mortality in patients presenting to the ED with severe sepsis is independent of organ dysfunction and shock

Design:
- Retrospective, single center cohort study
- Academic teaching hospital

Patients:
- 830 adults admitted with severe sepsis in the ED
- Stratified lactate into 3 groups: low (<2), intermediate (2-3.9) and high (> or equal to 4)
Serum Lactate is associated with mortality in severe sepsis independent of organ failure and shock

Results:
- Intermediate and high serum lactate significantly associated with mortality regardless of the presence of shock or other organ dysfunction
- A single serum lactate seems to risk-stratify patients independent of organ dysfunction or hemodynamic instability

SSC Guidelines

Resuscitation-Lactate Clearance

Should be protocolized, quantitative resuscitation of patients with sepsis induced hypoperfusion (defined as hypotension persisting after initial fluid challenge or blood lactate >4mmol/L)

In patients with elevated lactate levels as a marker of tissue hypoperfusion, we suggest targeting resuscitation to normalize lactate as rapidly as possible (2C)
SSC Guidelines: Antibiotics

- We recommend that intravenous antibiotic therapy be started as early as possible and within the first hour of recognition of septic shock (1B) and severe sepsis without septic shock (1C)

Remark: Although the weight of evidence supports prompt administration of antibiotics following the recognition of severe sepsis or septic shock, the feasibility with which clinicians may achieve this ideal state has not been scientifically validated


Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock

*2,154 septic shock patients

*Effective antimicrobial administration within the 1st hour of documented hypotension was associated with increased survival in patients with septic shock.

*Each hour of delay over the next 6 hours was associated with an average decrease in survival of 7.6% (range 3.6-9.9%)

CCM 2006 Vol. 34 No.6
### Mortality by Time to Antibiotics
#### Severe Sepsis: SSC Database

<table>
<thead>
<tr>
<th>Time to Abx HOURS</th>
<th>OR</th>
<th>CI</th>
<th>CI</th>
<th>P Value</th>
<th>Prob of Death</th>
<th>CI</th>
<th>CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.0</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>13.7</td>
<td>13.3</td>
<td>15.3</td>
</tr>
<tr>
<td>1</td>
<td>1.10</td>
<td>1.05</td>
<td>1.15</td>
<td>&lt;0.001</td>
<td>14.9</td>
<td>13.7</td>
<td>16.1</td>
</tr>
<tr>
<td>2</td>
<td>1.21</td>
<td>1.10</td>
<td>1.32</td>
<td>&lt;0.001</td>
<td>16.1</td>
<td>15.1</td>
<td>17.2</td>
</tr>
<tr>
<td>3</td>
<td>1.33</td>
<td>1.15</td>
<td>1.52</td>
<td>&lt;0.001</td>
<td>17.4</td>
<td>16.2</td>
<td>18.7</td>
</tr>
<tr>
<td>4</td>
<td>1.46</td>
<td>1.22</td>
<td>1.75</td>
<td>&lt;0.001</td>
<td>18.8</td>
<td>17.1</td>
<td>20.6</td>
</tr>
<tr>
<td>5</td>
<td>1.60</td>
<td>1.20</td>
<td>2.01</td>
<td>&lt;0.001</td>
<td>20.3</td>
<td>18.0</td>
<td>22.8</td>
</tr>
<tr>
<td>6</td>
<td>1.76</td>
<td>1.34</td>
<td>2.31</td>
<td>&lt;0.001</td>
<td>21.9</td>
<td>18.8</td>
<td>25.3</td>
</tr>
</tbody>
</table>

**5% Increase in Mortality for Every Hour Delayed**

### Mortality by Time to Antibiotics
#### Septic Shock: SSC Database

<table>
<thead>
<tr>
<th>Time to Abx HOURS</th>
<th>OR</th>
<th>CI</th>
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<th>P Value</th>
<th>Prob of Death</th>
<th>CI</th>
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</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>22.2</td>
<td>20.7</td>
<td>23.8</td>
</tr>
<tr>
<td>1</td>
<td>1.03</td>
<td>1.00</td>
<td>1.06</td>
<td>&lt;.046</td>
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**5% Increase in Mortality for Every Hour Delayed**
Antibiotic Types

• Recommend that initial empiric anti-infective therapy include one or more drugs that have activity against all likely pathogens (bacterial &/or fungal or viral) and that penetrate in adequate concentrations into tissue that is the presume source. (1B)

Mortality as a Function of Adequacy of Empiric Antimicrobial Therapy

Initiation of Inappropriate Antimicrobial Therapy Results in a Fivefold Reduction of Survival in Human Septic Shock

- Objective: Determine the impact of the initiation of inappropriate antimicrobial therapy on survival to hospital discharge of patients with septic shock
- Retrospective review of 5,715 patients from 22 different hospitals in Canada, US and Saudi Arabia
- Data collected from 1996-2005

Kumar A. et al. Chest, 2009; 136; 1237-1248

Antimicrobial Therapy Result in a 5-Fold Reduction of Survival in Human Septic Shock

- 5,715 patients in septic shock in three countries
- 55% of cases were from community acquired infection
- Decrease in survival with inappropriate initial antibiotics was fivefold

Kumar A. et al. Chest, 2009; 136; 1237-1248
Early Goal Directed Therapy

Methodology: 263 severe sepsis patients

- Early Goal-Directed Therapy (EGDT)
  - Continuous ScvO2 monitoring & tx with fluids, blood, inotropes &/or vasoactives to maintain:
    - ScvO2 >70%, SaO2 > 93%, Hct ≥ 30%, CI/VO2
    - CVP ≥ 8-12
    - MAP ≥ 65
    - UO ≥ .5ml/kg/hr

- Standard Therapy
  - CVP ≥ 8-12
  - MAP ≥ 65
  - UO ≥ .5ml/kg/hr

Early Goal-Directed Therapy Results

28-day Mortality

- 49.2% EGDT
- 33.3% Standard Therapy

*Key difference was in sudden CV collapse, not MODS


Evidence of Early Goal Directed Therapy

- First 6 hours of EGDT:
  - 1500cc more fluid
  - 64% received blood products vs. 18.5%
  - 13.7% received inotropes vs. 0.8%
  - No difference in vasopressor use or mechanical ventilation

The effect of a quantitative resuscitation strategy on mortality in patients with sepsis: A meta-analysis

Alan E. Jones, MD; Michael D. Brown, MD, MSc; Stephen Trzeciak, MD, MPH; Nathan I. Shapiro, MD, MPH; John S. Garrett, MD; Alan C. Heffner, MD; Jeffrey A. Kline, MD; on behalf of the EMOCKNET investigators

- This meta-analysis evaluates the treatment effect of using a quantitative resuscitation strategy in the treatment of patients with sepsis.

- Using pooled data from nine studies that randomized a total of 1001 subjects, we found the magnitude of the decrease in mortality (OR 0.50 with the upper limit 95% CI 0.69) was profound when the resuscitation strategy was implemented early.
Abstracts and Publications

Rivers, 2001

Publications

Abstracts

Number Need To Treat

1 of every 6 Patients

4125 Before 3328 After

SSC Guidelines
Fluid Therapy

1. We recommend crystalloids be used in the initial fluid resuscitation of severe sepsis (1B)
2. We suggest the use of albumin in the fluid resuscitation of severe sepsis and septic shock when patients require substantial amounts of crystalloids. (2C)
3. We recommend against the use of hydroxyethyl starches (HES) for fluid resuscitation of severe sepsis and septic shock patients (1B)

Vasopressors

- Vasopressor therapy initially to target a mean arterial pressure (MAP) of 65 mm Hg (grade 1C).
- Norepinephrine as the first choice vasopressor (grade 1B).
- Epinephrine (added to and potentially substituted for norepinephrine) when an additional agent is needed to maintain adequate blood pressure (grade 2B).
- Vasopressin 0.03 units/minute can be added to norepinephrine (NE) with intent of either raising MAP or decreasing NE dosage (UG).
- Low dose vasopressin is not recommended as the single initial vasopressor for treatment of sepsis-induced hypotension and vasopressin doses higher than 0.03-0.04 units/minute should be reserved for salvage therapy (failure to achieve adequate MAP with other vasopressor agents) (UG).
- Dopamine as an alternative vasopressor agent to norepinephrine only in highly selected patients (eg, patients with low risk of tachyarrhythmias and absolute or relative bradycardia) (grade 2C).

Multicenter Study of Central Venous Oxygen Saturation (ScvO2) as a Predictor of Mortality in Patients With Sepsis

- Objective:
  - Primary: an abnormal (both low and high) ScvO2 is associated with increased mortality in emergency department (ED) patients with septic shock.
  - Secondary: determine whether the initial ScvO2 or the maximum ScvO2 achieved was associated with mortality.
  - 619 patients from 4 hospitals; prospectively collected data
**Multicenter Study of Central Venous Oxygen Saturation (ScvO2) as a Predictor of Mortality in Patients With Sepsis**

Pope; et al

---

**Maximum ScvO2 in 6 hours relates to mortality**

Considering the maximum ScvO2 achieved in the ED, the presence of both hypoxia and hyperoxia was associated with a higher mortality rate compared with that of the normoxia group.

---

**ProCESS Trial**

- RCT of septic shock patients to protocol based EGDT (439), protocol based standard (446) or usual care (456)
- 31 Academic Tertiary ER’s
- Average time to randomization from arrival to ED 3.3 hrs & from meeting entry criteria 60 minutes
- Significant difference in use of therapy
- No difference in 90 day or 1 year mortality

Authors state it was not a replication of the EGDT Trial.
Current Controversy: Results of ProCESS Trial

- Mortality in usual care arm 18% (larger population of UTI sepsis than pneumonia sepsis)
- 1351 pts in 31 centers over 5 yrs, roughly 8 patients per center
- All groups in the study received on average >2/L of fluid prior to randomization & 75% received antibiotics prior to randomization (Both part of the 3hr bundle)
- Protocol changed to include patients receiving only 1 liter of fluid/define as septic shock
- 70% of hospitals in the trial had some form of a sepsis protocol
- Average time to randomization from arrival to ED 3.3 hrs & from meeting entry criteria 60 minutes
- 60% of patients by 6 hrs has central line. Dobutamine use 50%
- Did no report whether protocol arms reach their goals

ARISE Trial

- 51 centers (Australia or New Zealand)
- Randomized in ED with early septic shock to receive either EGDT or usual care.
- 1600 enrolled patients, 796 were assigned to the EGDT group and 804 to the usual-care group.
- Results-90 day mortality

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<th></th>
<th>EGDT</th>
<th>Usual Care</th>
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<tr>
<td>Fluids</td>
<td>1964 ± 1415</td>
<td>1713 ± 1401</td>
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<tr>
<td>Vasopressor infusion</td>
<td>66.6%</td>
<td>57.8%</td>
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<tr>
<td>red-cell transfusions</td>
<td>13.6%</td>
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<td>Dobutamine</td>
<td>15.4% vs.</td>
<td>2.6%</td>
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<td>Mortality</td>
<td>18.6%</td>
<td>18.8%</td>
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Optimize Cardiac Performance

Fluid Bolus to define place on curve:

• Record SV
• Give 250-500 NS bolus over 15 minutes
• Record SV
• If see greater than a 10-15% increase in SV — pt is on steep portion of curve and will still respond to fluid (fluid responsive)

---

**Figure 1.** Frank-Starling curve. Increasing venous return to the left ventricle increases left ventricular end-diastolic pressure (LVEDP) and volume, thereby increasing ventricular preload. This results in an increase in stroke volume (SV). The "pumping" operating point is at a LVEDP of ~8 mmHg and a SV of ~70 ml/min.

**Figure 2.** Family of Frank-Starling curves. Changes in the fluid and isotropic shift the Frank-Starling curve up or down.

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**Clinical Investigations in Critical Care**

Changes in BP Induced by Passive Leg Raising Predict Response to Fluid Loading in Critically Ill Patients

Yaxier Monnet, MD; Morin Rienzo, MD; David Osmaa, MD; Nadia Anguel, MD; Christian Richard, MD; Michael R. Pinsky, MD, Dr lc; Jean-Louis Teboul, MD, PhD

Crit Care Med 2006 Vol. 34, No. 5

Passive leg raising predicts fluid responsiveness in the critically ill


**Diagnosis of central hypovolemia by using passive leg raising**

Julien Matzel
Norair Artopetian
Emmanuel Lorise
Christophe Tribouilloy
Ziad Massy
Michel Shina
PLR??

- 150 – 300 ml volume
- Effects < 30 sec. Not more than 4 minutes
- Self-volume challenge
  - Reversible

PLR Effects on Starling Curve

- If the increase in cardiac preload induced by PLR induces significant changes in SV (a to b), the patient will likely be fluid responsive

- If the same changes in cardiac preload during PLR do not significantly change SV (a’ to b’), the heart is likely preload dependent and should not be administered

Monnet 2007
Compliance with Measures & Outcomes

SSC: Change in Compliance Over Time

SSC: Change in Mortality Over Time

* p<0.01 compared to site quarter 1

Intermountain Health

Sepsis Bundle System
07-Oct-2010
Intermountain Health: SS and Shock

Miller, Dang, Nelson, et al.: Sepsis Bundle and Mortality
Am J Respir Crit Care Med. Vol 188, Iss. 5, pp. 77-82, Jul 1, 2013
Intermountain Health: Shock

Miller, Dong, Nelson, et al.: Sepsis Bundle and Mortality
Am J Respir Crit Care Med Vol 186, Iss. 1, pp 77-82, Jul 1 2012

Northern Kaiser Combine Sepsis Mortality Rate 13%
Septic Shock Mortality Rate: 19%-24%
Combine Sepsis Mortality Rate: 14%

The ImPreSS Study

- Global prospective observational study
  How compliance of the 3 & 6hr bundles from the SSC correlates with outcomes based on geographic areas –1794 patients in 62 countries

Results: After adjusting the crude mortality differences for ICU admission, severe sepsis/septic shock, location of dx, APACHE II score and country compliance of the bundles remained independently associated with improvements in hospital morality for both bundles
Which components of the bundle did you find gaps in performance?

Common Barriers/Issues

- CVP
- Lactate
- Antibiotics
- Fluid boluses
- Consistency in bundle application
**Fluid Status Assessment**

- Provider confidence/competency in placing central lines or doing ECHO with Passive leg raise
- Defined who will place central line when pt has lactate > 4mMol/L or still hypotensive after initial fluid bolus
  - ED or ICU?
  - What happens on off shifts and weekends?
- Adequate equipment in ED/ICU to insert and monitor CVP
  - Educate nurses in ED on hemodynamic monitoring and ScvO2
  - Is there sufficient nursing staff to handle the acuity and intensity of these patients in the ED?
- Cardiac Exam?

**Lactate measurement**

- Lab vs POC
- Venous vs arterial
- Turnaround time
**Antibiotics**

- Appropriate initial antibiotics
  - Guide for providers recommending the appropriate antibiotic based on whether hospital or community acquired, source and your hospital's antibiogram
- Turnaround time---from indication to hanging
  - ED vs ICU vs Floor
- Understand your current process and where the gaps are
- Make antibiotics rapidly available

**Fluid Boluses**

- How fast should they be given?
  - gravity or pressure bag not by infusion pump
- What about dialysis patients?
- What about patients with CHF or low EF?
Tools to Assist with Consistent Application of the Evidence

- Identify tools to assist bedside staff to implement bundles
  - algorithm, pathway, checklist, pocket cards, green folder etc
- Create protocols
  - For positive screen: lactate, blood cultures and fluids
  - When patients need ICU level care
- Multidisciplinary Rounds
- Handoffs
- Real time review and feedback

Clinical Scenario 1: Early identification and intervention

- **88 year old**, 51.6kg, white, female presented to ED at 1345 from ECF
- **History**: CAD, COPD, dementia, Alzheimer disease, depression, SVT
- **Chief Complaint**: rib pain, chest congestion and SOB
- Awake, alert and oriented, slight combative (history of combative behavior)
Clinical Scenario 1: Early Identification and Intervention

- **Initial VS: 0900**
  - Temp: 101.6 F
  - RR: 31
  - HR: 109, atrial fib with occasional SVT
  - BP: 79/51
  - 2L of O2, O2 sat of 96%
- Does this patient screen positive for severe sepsis?
  - Positive Screen for severe sepsis:
    - SIRS: HR >90; RR > 20; Temp > 38
    - Organ dysfunction: SBP<90mmHg

**WHAT ARE THE NEXT STEPS?**
- IV started
- Received 1500cc NS bolus over 30-60 minutes
- Labs drawn

---

Clinical Scenario 1: Early Identification and Intervention

**Vital Signs: 1000**
BP: 100/50; HR 100; RR 20; O2 sat: 92

- **Labs: (resulted at 10am)**
  - WBC: 11.5
  - Hgb: 15.8
  - Hct: 47.4
  - BUN: 28  Creatinine: 1.6
  - Glucose: 158
  - BNP: 78 (moderate CHF); troponin: 0.03
  - Lactic acid: 4.6
  - U/A: positive for bacteria
  - Blood cultures X 2 drawn

**What are the next steps?**
Clinical Scenario 1: Early Identification and Intervention

• **CXR:** RLL consolidation

• **Additional Interventions:**
  – Broad spectrum antibiotics hung within 1 hour of screening positive for severe sepsis
  – Lactic acid >4mmol/L so CVP inserted
  – Fluid resuscitation continued
  – Initial ScvO2: 49.1%
  – Foley inserted

• Code sepsis called at 1030
• Received total of 3 Liters of NS during 3 hour ED stay
• **ED diagnosis:** Severe sepsis, Pneumonia, UTI, CHF

Transferred to MICU

Clinical Scenario 1: Early Identification and Intervention--MICU

• 1200: (arrived in MICU—pre brief done by senior resident)
  – 88/55; HR 98, RR 22, O2 sat 96%
  – CVP: 5, ScvO2 60% (patient not intubated)—

What is the next step?
Fluid optimization: 500ml bolus until CVP > 8
Gave 4L in next 3 hours

1500: 98/55, HR 90, RR 20, sat 95%

What are your next steps?
More data: CVP: 6, ScvO2: 65% LA: 3.2

WHAT ARE YOUR NEXT STEPS??
Clinical Scenario 1:

- **HOURS 6-24**
- **Labs:**
  - Lactic acid: 4 hours after time zero: 6.7
  - 8 hours after ICU admission: 2.3

**VS:**
- Continue monitoring VS, CVP, ScvO2, every 2hrs for first 24 hours to ensure goals of resuscitation are maintained
- Monitor urine output every 1-2 hrs for 24hrs

**WHAT WE DO AND HOW WELL WE DO IT MAKES A SIGNIFICANT DIFFERENCE IN MORTALITY!**
The Nurses Role

- Early recognition of patients with signs of sepsis
- Early initiation of evidence based practice therapies appropriate for your area of practice (antibiotics, fluids/blood & pressors)
- Swift disposition to care areas where the rest of the bundle can be started.

THANK YOU!!

QUESTIONS???