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)†
  - 10th leading cause of death overall (US)†
- In the US, more than 700 patients die of severe sepsis daily

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, CHN, placental abruption and placenta accreta
    - Assistive reproductive technology and multi-fetal gestation
  - Obesity
    - CHN, DM, Cesarean, cardiopulmonary complications

Maternal Sepsis Mortality and Morbidity During Hospitalization for Delivery

- 44,999,260 hospitalizations for delivery
  - Septic complications 1:3333 deliveries
  - Severe sepsis 1:10,823 deliveries
  - Sepsis related death 1:105,384 deliveries
  - Overall frequency of sepsis stayed the same during the study period
- Severe sepsis and death odds increased 10% per year
Maternal Sepsis Mortality and Morbidity During Hospitalization for Delivery

- Independent risk factors for severe sepsis
  - Age >35
  - AA Race
  - Medicaid
  - Retained POCs*
  - PROM**
  - CHF

- Chronic renal failure
- HIV infection
- Multiple gestation
- Cervical Cerclage
- Chronic liver failure

*products of conception
**preterm = less than 37 weeks
***Systemic Lupus Erythematosus

Bauer et al. Anesth Analg 2013

Maternal Sepsis Mortality and Morbidity During Hospitalization for Delivery

- 1680 Women with severe sepsis had an ICD9 code for a known organism
  - E. coli septicemia 27%
  - Staphylococcal septicemia 22%
  - Gram negative septicemia 20%
  - Pneumococcal septicemia 4%
  - Pseudomonal septicemia 2.4%
  - Anaerobic septicemia 2%

Bauer et al. Anesth Analg 2013

Maternal Sepsis Mortality and Morbidity During Hospitalization for Delivery

- Concurrent infections in women with severe sepsis
  - Pneumonia 30%
  - GU infections 30%
  - Chorioamnionitis 18%
  - Endometritis 9%
  - Pyelonephritis 6%
  - Wound Infection 5%
  - Endocarditis 2%
  - Meningitis 1%

Bauer et al. Anesth Analg 2013

Lower Mortality in the Obstetric Patient

- 0-28 % versus 10-81% in the non-pregnant population
- Factors associated with the decreased mortality
  - Younger age
  - Types of organisms
  - Overall healthy population
  - Pelvis amenable to surgical and medical intervention
  - Transient bacteremia

Creasy, Resnick and Iams 2008

Bacterial Infections in Obstetrics

- Postpartum endometritis
  - Cesarean delivery 15-87%
  - Vaginal delivery 1-4%
- Lower tract UTI 1-4%
- Septic abortion 1-2%
- Pyelonephritis 1-2%
- Chorioamnionitis 0.5 - 1%
- Necrotizing fasciitis < 1%
- Toxic shock syndrome < 1%

Slides courtesy of Jonnie S. Sheffield, M.D.
Maternal Fetal Medicine
University of Texas Southwestern/2013

Newborn/Neonatal/Pediatric Sepsis

Newborn/Neonatal
- Early onset or late onset
- Early-95% present within 24hrs
- 5%-24-48hrs
- 5% -72hrs
- Early-associated with premature neonates
- Early=Maternal acquisition
  - GBS trends lowering n/prenatal screening & tx protocol for GBS
- Late onset-caregiving environment

Untreated sepsis mortality around 50%-
Tx often initiated before culture results

Pediatric Sepsis
- 20,000 to 40,000 develop septic shock annually
- Incidence is increasing

Anderson Barry et al. Neonatal sepsis,
Sepsis Impact on Mortality in Hospitals

Table 1. Patients with Sepsis/Septic Shock in the Kaiser Permanente Northern California Current and the Healthcare Cost and Utilization Project National Inpatient Sample

<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 of origin in ED, %</td>
<td>30.9</td>
<td>26.0</td>
<td>0.001</td>
</tr>
<tr>
<td>Hospital mortality of origin in Ward, %</td>
<td>45.3</td>
<td>36.7</td>
<td>0.001</td>
</tr>
<tr>
<td>Hospital mortality of origin in 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

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</td>
<td>895,000</td>
<td>171,000</td>
<td>19%</td>
</tr>
<tr>
<td>Stroke</td>
<td>700,000</td>
<td>157,800</td>
<td>23%</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>1,300,000</td>
<td>61,800</td>
<td>4.8%</td>
</tr>
<tr>
<td>Severe Sepsis</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-Resusculation 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>Lactate</td>
<td>0.80</td>
<td>0.73-0.89</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lactate ≥ 2</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 Admin.</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
Implementation of Early Screening Tools and Triggers

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

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/petechia


Severe Sepsis: Defining a Disease Continuum

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


SIRS = Systemic Inflammatory Response Syndrome
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

Resources to Validate

- Barton & Sibai publication, Sept 2012, Severe sepsis and septic shock in pregnancy (Obstet Gynecol, 2012;120:689-706)
  - Validated our screening parameter selections
  - Guided our HR parameter decision
  - Guidelines updated: added altered mental status; deleted chills/rigors; changed BG to 140

Slides courtesy of Jeanne S. Sheffield, M.D.
Maternal Fetal Medicine
University of Texas Southwestern/2013

Screening Tool

- Is there a suspected or confirmed infection?
- Are there 2 or more altered general variables?
  - Temp > 38 C or < 36 C
  - FHR > 160 bpm (gestational age >20wks)
  - Maternal HR >110 bpm
  - RR > 24 bpm
  - WBC >15,000 or <4000 or >10% bands with normal WBC
  - AMS
  - BG > 140 (in absence of DM)
Screening Tool

- Is at least one of the following acute organ dysfunctions present?
  - Decreased Cap refill/mottling skin
  - Lactic acid above normal values
  - Bilirubin >2mg/dl
  - Urine output < 0.5ml/kg/hr x2 hrs
  - Serum creatinine > 1.5 mg/dl or increase >0.5mg/dL from baseline
  - INR >1.5 or PTT >60 w/o meds
  - SBP decrease >40mmHg from baseline
  - MAP <65 mmHg
  - Acute lung injury with PaO2/FiO2 ratio <250 (RT can calculate with ABG)

Pregnancy Sepsis Score

- Sepsis in Obstetrics Score (SOS)
  - Combines the Rapid emergency medicine score with SIRS criteria with OB adjustments
  - Score ranges from 0-28
  - Retrospective review of 850 pregnant or recently postpartum women who had blood cultures or Flu swab in the ED
  - Results:
    - 43 women score>6 & 8 admissions to ICU
    - 802 women score < 6 & 1 admission to ICU
    - Score > 6 88.9% sensitivity, 95.2% specificity, NPP 99.9%

Neonatal/Newborn-Not Well Defined

- Evaluating for Sepsis Risk In the following situations, the infant should have a complete diagnostic evaluation and empiric antibiotic therapy:
  - History of a prior infant with GBS sepsis
  - Preterm premature rupture of membranes
  - Maternal clinical chorioamnionitis
  - Infants in a multiple birth group if one is diagnosed with GBS sepsis

Perform a Risk Assessment.

- The following is one way to assess common risk factors, based on odds ratios (O.R.) for developing neonatal sepsis when a single factor is present. (Only a guide)
  - Any newborn infant with clinical signs of sepsis should be considered for admission for full sepsis evaluation.
  - CRP has good positive predictive value only at levels >5 mg/L and good negative predictive value if tested serially and level is <1 mg/L each time.

Low Risk Criteria for Sepsis (OR < 3.0)

- Cyanosis
- Tachypnea
- Hypotonia
- Hyperreflexia
- Mec stained fluid
- Preterm onset labor
- Shunting
- Hyperbilirubinemia >24h
- Seizures
- Retractions
- Lethargy
- Poor feeding

Moderate Risk Criteria for Sepsis (OR >3.0 but <6.0)

- Diarrhea
- Agar <= 5 minutes
- Apnea
- Splenomegaly
- Maternal fever >37.5 C
- Rash
- Distended Abdomen
- Hypertension
- Hypotension
- Bulging Fontanel
- EGA 34-36 weeks

High risk Criteria for Sepsis (OR >6)

- Pusules
- Bleeding
- PROM >18 hours
- Decreased perfusion
- Tachycardia
- Arthrythmia
- Vasomotor instability
- Hyperbilirubinemia <24h
- Pallor
- Fetal tachycardia in the 10 minutes prior to delivery
- Persistent neonatal tachycardia
- Cord blood pH <7.18
- Twin with sepsis
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.

- 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.

Chain of Command

- When to use it?
- Who is it?
- How to implement the chain of command?

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.

WHEN FULLY COMPUTERIZE....

AUTOMATED SEPSIS AWARENESS?
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

Inflammation, Coagulation and Impaired Fibrinolysis In Severe Sepsis

Pathophysiologic Characteristics in Severe Sepsis

• Maldistribution of blood flow
• Imbalance of oxygen supply & demand
• Metabolic alterations & activation of the stress response

HOMEOSTASIS IS UNBALANCED IN SEVERE SEPSIS

MICROCIRCULATION: SUBLINGUAL BLOOD FLOW

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

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
Imbalance of Oxygen Supply & Demand

O₂ Supply Debt

Metabolic Alterations & The Stress Response

Metabolic Alterations & The Stress Response

Early Management
Grade System

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (high) RCTs</td>
<td>Upgraded observational studies with control RCTs</td>
</tr>
<tr>
<td>B (moderate) Downgraded RCTs</td>
<td>Moderate observational studies with control RCTs</td>
</tr>
<tr>
<td>C (low) Well-done observational studies</td>
<td>Control RCTs</td>
</tr>
<tr>
<td>D (very low) Downgraded controlled studies or expert opinion based on other evidence</td>
<td></td>
</tr>
</tbody>
</table>

**TABLE 1: Factors Determining Strong vs. Weak Recommendation**

<table>
<thead>
<tr>
<th>What Should Be Considered</th>
<th>Recommended Process</th>
</tr>
</thead>
<tbody>
<tr>
<td>Y or N = Yes or No</td>
<td>Y or N = Yes or No</td>
</tr>
<tr>
<td>Y or N = Yes or No</td>
<td>Y or N = Yes or No</td>
</tr>
</tbody>
</table>

NQF/SSC Bundles
Initial Resuscitation

To be completed within 3 hours of time of presentation*

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

CMS Measures: Severe Sepsis/Septic Shock

**Numerator Statement:** Patients who received ALL of the following:

- Received within three hours of presentation of severe sepsis:
  - Initial lactate level measurement
  - Broad spectrum or other antibiotics administered
  - Blood cultures drawn prior to antibiotics
- AND received within six hours of presentation of septic shock:
  - Repeat lactate level measurement only if initial lactate level is elevated
  - Resuscitation with 30 ml/kg crystalloid fluids
  - AND ONLY IF hypotension persists after fluid administration, received within six hours of presentation of septic shock:
    - Vasopressors
    - Repeat volume status and tissue perfusion assessment consisting of either:
      - A focused exam including:
        - Vital signs, AND
        - Cardiopulmonary exam, AND
        - Capillary refill evaluation, AND
        - Peripheral pulse evaluation, AND
        - Skin examination
      - OR
      - Any two of the following four:
        - Central venous pressure measurement
        - Central venous oxygen measurement
        - Bedside Cardiovascular Ultrasound
        - Passive Leg Raise or Fluid Challenge

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    - A focused exam including:
      - Vital signs, AND
      - Cardiopulmonary exam, AND
      - Capillary refill evaluation, AND
      - Peripheral pulse evaluation, AND
      - Skin examination
    - OR
    - Any two of the following four:
      - Central venous pressure measurement
      - Central venous oxygen measurement
      - Bedside Cardiovascular Ultrasound
      - Passive Leg Raise or Fluid Challenge

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

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

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


Management of Septic Shock

- Overall goals
  - Treat the mother!
  - Resuscitating the mother will resuscitate the fetus
  - Delivery attempts increase maternal and fetal mortality assuming the source is not intrauterine
  - Improve functional intravascular volume
  - Establish and maintain an adequate airway
  - Determine the septic foci
  - Empircic antibiotic therapy : know the most common pathogens

Creasy and Resnick 2008

Management of Septic Shock

- Oxygenation/Ventilation
  - Mechanical ventilation usually required
  - ARDS : hypoxemia, normal PCWP, diffuse infiltrates and decreased pulmonary compliance
  - PEEP
  - Keep at or above 96% if possible during pregnancy
  - Blood transfusion can increase O₂ content : keep Hgb ~ 10 g/dl

Source Control

E. Source Control

1. A specific antimicrobial diagnosis of infection requiring consideration for emergent source control be sought and diagnosed as quickly as possible, and intervention be instituted for source control within the first 12 hr after the diagnosis is made, if feasible (Grade 1C).

2. When infected periparacolic membranes is identified as a potential source of infection, definitive intervention is expedited with adequate drainage or vaginal and culdocentesis (Grade B).

3. When source control in a severely septic patient is required, the effective intervention associated with the local physiology must be used, e.g., paracentesis rather than surgical drainage of abdominal (Grade C).

4. If intravascular access devices are a possible source of severe sepsis or septic shock, they should be removed promptly. If catheter source control has been established (Grade C).

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)

Mikkelsen, Mark  et al  CCM 2009 Vol 37 No 5

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

Mikkelsen, Mark  et al  CCM 2009 Vol 37 No 5
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


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


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


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>
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<td>&lt;0.001</td>
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</tr>
<tr>
<td>2</td>
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<td>1.10</td>
<td>1.32</td>
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<td>17.2</td>
</tr>
<tr>
<td>3</td>
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<tr>
<td>4</td>
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<tr>
<td>5</td>
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<td>1.20</td>
<td>2.01</td>
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<td>20.3</td>
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<td>1.34</td>
<td>2.31</td>
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<td>21.9</td>
<td>18.8</td>
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</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>
<th>CI</th>
<th>P Value</th>
<th>Prob of Death</th>
<th>CI</th>
<th>CI</th>
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<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>
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<tr>
<td>1</td>
<td>1.03</td>
<td>1.00</td>
<td>1.06</td>
<td>&lt;0.046</td>
<td>22.7</td>
<td>21.4</td>
<td>24.5</td>
</tr>
<tr>
<td>2</td>
<td>1.06</td>
<td>1.00</td>
<td>1.12</td>
<td>&lt;0.046</td>
<td>23.2</td>
<td>22.0</td>
<td>24.5</td>
</tr>
<tr>
<td>3</td>
<td>1.09</td>
<td>1.00</td>
<td>1.19</td>
<td>&lt;0.046</td>
<td>23.7</td>
<td>22.5</td>
<td>25.1</td>
</tr>
<tr>
<td>4</td>
<td>1.12</td>
<td>1.00</td>
<td>1.26</td>
<td>&lt;0.046</td>
<td>24.3</td>
<td>22.7</td>
<td>25.9</td>
</tr>
<tr>
<td>5</td>
<td>1.16</td>
<td>1.00</td>
<td>1.33</td>
<td>&lt;0.046</td>
<td>24.8</td>
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<tr>
<td>6</td>
<td>1.19</td>
<td>1.00</td>
<td>1.41</td>
<td>&lt;0.046</td>
<td>25.4</td>
<td>23</td>
<td>27.9</td>
</tr>
</tbody>
</table>

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)

Empiric antibiotic therapy in Maternal Sepsis

- Find the underlying etiology of the sepsis
- Start broad spectrum antibiotics immediately after drawing cultures
  - Penicillin (if Staphylococcus aureus suspected, consider Vancomycin) or derivative PLus aminoglycoside PLUS Clindamycin
  - Vancomycin and Piperacillin/Tazobactam
- Alter regimen as culture and sensitivity results available

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

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


Clinical Investigations

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

Alan E, Jones, MD; Michael C. Brown, MD, MS; Stephen Travers, MD, MPH; Nathan A. Shapiro, MD, MPH; John S. Garrett, MD; Alan C. Hether, MD; Jeffrey A. Kline, MD; on behalf of the EMERGENT 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.

CCM, October 2008

Abstracts and Publications

- 1 of every 6 Patients

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

**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

**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 5yrs, roughly 8 patients per center
- All groups in the study received on average >2L 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

<table>
<thead>
<tr>
<th></th>
<th>EGDT</th>
<th>Usual Care</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluids</td>
<td>1964 ± 1415</td>
<td>1713 ± 1401</td>
</tr>
<tr>
<td>Vasopressor infusion</td>
<td>56.6%</td>
<td>57.8%</td>
</tr>
<tr>
<td>red-cell transfusions</td>
<td>13.6%</td>
<td>7.0%</td>
</tr>
<tr>
<td>Dobutamine</td>
<td>15.4% vs.</td>
<td>2.6%</td>
</tr>
<tr>
<td>Mortality</td>
<td>18.6%</td>
<td>18.8%</td>
</tr>
</tbody>
</table>

Authors state it was not a replication of the EGDT Trial

ProCESS Investigators, NEJM, Mar 18, 2014

AND ONLY IF hypotension persists after fluid administration, received within six hours of presentation of septic shock:

- Vasopressors
- Repeat volume status and tissue perfusion assessment consisting of either
  
  A focused exam including:
  
  - Vital signs, AND
  - Cardiopulmonary exam, AND
  - Capillary refill evaluation, AND
  - Peripheral pulse evaluation, AND
  - Skin examination
  
  OR
- Any two of the following four:
  
  - Central venous pressure measurement
  - Central venous oxygen measurement
  - Bedside Cardiovascular Ultrasound
  - Passive Leg Raise or Fluid Challenge

---

### Compliance with Measures & Outcomes

**SSC: Change in Compliance Over Time**

[Graph showing compliance over time with labels: Site Quarter, Bundle Compliance (%).]

**SSC: Change in Mortality Over Time**

[Graph showing mortality over time with labels: Site Quarter, Hospital Mortality (%).]


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### Intermountain Health

**Sepsis Bundle System**

[Graphs illustrating bundle compliance with labels: Serum Lactate, Blood Cultures, Broad-Spectrum Antibiotics, CVP and ScvO2, Intravenous and/or PIBC's, Glucose Control, Steroids, Dose through Arts Eligibility, Lung Protective Strategy.]
Intermountain Health: SS and Shock

![Graph showing mortality rates for Intermountain Health: SS and Shock](image1)

Intermountain Health: Shock

![Graph showing mortality rates for Intermountain Health: Shock](image2)

Northern Kaiser Combine Sepsis Mortality Rate 13%

![Image showing Northern Kaiser Combine Sepsis Mortality Rate](image3)

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.
Forbid Yourself to be Deterred by Poor Odds Just Because your Mind has Calculated that the Opposition is to Great. If it Were Easy Everyone Would be Do It.

THANK YOU!!

QUESTIONS???