Sepsis: New Evidence and Best Practice to Improve Patient Outcomes

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Talk Objectives

• Review the Epidemiology of Sepsis
• Describe Treatment Guidelines for Patients with Sepsis
• Highlight New Studies
• Review the Evidence Supporting Use of Guidelines in Severe Sepsis

Disclosures

• Financial
  • Abbott Laboratories Provided Support to Emory for a Sepsis Biomarker Discovery Project (NCT01746407)

• Intellectual
  • I believe that protocols can help the care of critically ill patients, and am the PI of a multicenter study to test this hypothesis (NCT01109719)

Patient JM

• 66 year old with CML- extra lymphatic involvement S/P ABMT 60 days prior to admission
  – Admitted with GVHD with GI symptoms
    • Increased steroids
  – Noted to have tachypnea to 30’s B/P 90/55 pulse 108 T 38.5 wbc 1.2
  – Blood cultures oxidase positive gram negative rods
  – Started on ceftazidime
  – Transferred to ICU when required non rebreather
Patient JM

• Tunneled catheter removed
• Antibiotics broadened to cover most likely organisms based on previous sensitivities

Sepsis Diagnosis - Not Always Simple

• Incidence 2.40/1000
• Increasing incidence with increasing age
• May be gender and racial differences in incidence
• Mortality rate 17-50%
• Patients with septic shock have mortality rates >50%
• Second most common cause of death in medical and surgical intensive care units
• Syndrome Not a Disease - no Biomarker

Sepsis Syndrome

• T > 38 or <36
• HR >90
• RR> 20 or pCO2 <32
• wbc >12,000 or < 4000 or >10% band forms
• Evidence infection
• Severe Sepsis = Sepsis + Organ Failure
• Septic Shock = Sepsis + Organ Failure + Hypotension Refractory to Fluid Resuscitation

Sepsis Epidemiology

- Increasing Incidence
- Decreasing Case Fatality Rates

Treatment Goals for Sepsis

- Identify Patient
- Give early appropriate antibiotics!!!
  - Send cultures first, but do not wait for culture results to start therapy for a patient with severe sepsis
  - Direct antibiotics at most likely organisms based on where patient is from (nursing home, hospital floor, or community) and local resistance patterns
- If you start with broad antibiotic coverage, narrow when culture results are available
- Pick a treatment goal and then reach it (lactate or SvO2)

Prevention of Nosocomial Complications

- Minimize Catheter Associated Bacteremia
- Use Lung Protective Ventilation (especially in sepsis induced ALI)
- Minimize VAP
  - Weaning Protocols
  - Sedation Limiting Protocols
- Minimize Critical Illness Weakness
- Glucose Control
- DVT, Stress Ulcer Prophylaxis

R. Phillip Dellinger, MD, Mitchell M. Levy, MD, Andrew Rhodes, MB BS, David Angus, MD, PhD, Harvey Gelatt, MD, PhD, Steve M. Opal, MD, Jonathan E. Sevransky, MD, Charles L. Sprung, MD, John S. Douglas, MD, Roman Jochle, MD, Tiffany M. Obrosky, MD, MPH, Mark E. Nunnally, MD, Sara R. Turecek, MD, Konrad Reinhart, MD, Ruth M. Kips, PhD, EN-CSL; Derek C. Angus, MD, MPH; Charles S. Deutschman, MD, MPH; Flavia R. Machado, MD, PhD; Gordon D. Rubenstein, MD, PhD; Steven A. Webb, MB, BS, PhD; Richard J. Bank, MD, PhD; Jean-Louis Vincent, MD, PhD; Ita Moreira, MD, PhD; and for the Surviving Sepsis Campaign Guidelines Committee including the Pediatric Subgroup

Guidelines Development

• Grading of Recommendations Assessment, Development and Evaluation (GRADE)
• 68 international experts, including methodologists
• No industry funding

2012 Guidelines- Recommendations Level 1 Evidence

• Early Quantitative Resuscitation of the Septic Patient (1C)
• Antimicrobial Therapy within 1 hour of recognition of septic shock (1B)
• Infection Source Control ..., within 12 hours of diagnosis (1C)
• Reassessment daily of antimicrobial therapy for potential de-escalation (1C)
• Initial Fluid resuscitation with Crystallloid (1B)
• Avoidance of hetastarch formulation (1C)
• Initial Fluid challenge of > 30 cc/kg (1C)
• Norepinephrine as 1st choice vasopressor (1B)
• Dobutamine for hypoperfusion in appropriate patients (1C)
• Hemoglobin target of 7.5 in absence of tissue hypoperfusion or cardiac ischemia (1B)
• Low tidal volume ventilation and limitation of plateau pressure in patients with sepsis induced ARDS (1A and 1B, respectively)
• Conservative fluid management for patients with sepsis induced ARDS without tissue hypoperfusion (1C)
2012 Guidelines- Recommendations
Level 1 Evidence

- Protocols for sedation (1A)
- Minimizing use of sedation (1B)
- Targeting blood Glucose <= 180 mg/dL (1A)
- DVT prophylaxis (1B)
- Stress ulcer prophylaxis (1B)
- Goals of care discussions within 72 hours ICU (1B)

Crit Care Med 2013:41:580-637

Sepsis Bundles

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

From Surviving Sepsis Campaign  www.survivingsepsis.org

Sepsis Bundles

6 HOUR BUNDLE:
5) Apply vaspressors (for hypotension that does not respond to initial fluid resuscitation) to maintain a mean arterial pressure (MAP) ≥65 mm Hg
6) In the event of persistent arterial hypotension despite volume resuscitation (septic shock) or initial lactate ≥4 mmol/L (36 mg/dL):
   -- Measure central venous pressure (CVP)*
   -- Measure central venous oxygen saturation (ScvO2)*
7) Remeasure lactate if initial lactate was elevated*

From Surviving Sepsis Campaign  www.survivingsepsis.org

Sepsis Bundles

- Each hospital’s sepsis protocol may be customized, but it must meet the standards created by the bundle

From Surviving Sepsis Campaign  www.survivingsepsis.org
Evidence Supporting Guidelines

- Antibiotics
- Fluids
- Resuscitation
- Vasopressors

Antibiotics in Severe Sepsis and Septic Shock

- Antimicrobial Therapy within 1 hour of recognition of septic shock (1B)

Timing of Antibiotics in Sepsis Induced Hypotension

- 2731 Patients with septic shock
- 44% Admissions From ED
  - Lung, Intra-abdominal and Urine most common sites of infection
- Mortality Rate 21% if Effective Antibiotics given within 1 hour
- Mortality Rate 58% if Effective Antibiotics given within 6 hours

Kumar et al Crit Care Med 2006;34:1589-1596
**Timing of Antibiotics in Shock**

Kumar et al. Crit Care Med 2006;34:1589-1596

**Fluid Resuscitation**

- Initial Fluid resuscitation with Crystalloid (1B)
- Avoidance of hetastarch formulation (1C)


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**Volume Resuscitation**

- Crystalloids – Easily accessible, cheap, potential rapid distribution into extravascular compartment.
- Colloids: Less volume needed, potentially increase oncotic pressure with less distribution into extravascular compartment, more expensive.
- Blood – Potential increase in oxygen delivery.
- Risk of TRALI infection, and no proven benefit.
- Routine Use of Pentastarch Harmful in Patients with Severe Sepsis: Increased renal failure and mortality with dose effect.

- Need to Aggressively volume resuscitate patients with shock.
  - Mean 5 L crystalloid immediately.
  - 8-9 L over 24 hour.
  - Less if giving colloid or blood.
  - Safe Trial.
  - 6997 patients requiring fluid resuscitation.
  - 4% albumin.
  - 3.9% NS.
  - No difference in new incidence of organ failure.
  - No difference in length of ICU or hospital stay.
  - Overall no mortality difference.
  - Subgroups:
    - Sepsis maybe better outcome.
    - Trauma maybe worse.


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**Effect of Fluid Choice and Pentastarch Dose on Survival: VISEP**

- Fluid Choice and Survival.
  - Dose Dependent Increase in RRT and 90 day mortality with HES.

6% Hydroxyethyl Starch Worsens Outcomes in Severe Sepsis

Patients treated with HES were 17% more likely to die and 35% more likely to require renal replacement therapy.


Which Vasopressor in Septic Shock?

- Norepinephrine as 1st choice vasopressor (1B)

Crit Care Med 2013; 41:580-637

Vasopressor Of Choice: Use Clinical Judgment in Septic Shock

SOAP II Study

- 1679 Patients with Shock
- Dopamine vs. Norepinephrine
  - Predominantly septic shock (61.7%)
  - In septic shock patients no difference in mortality between dopamine and norepinephrine (59.4% vs 56.5% in hospital)
  - More arrhythmias with dopamine
  - Longer duration of vasopressors on norepi (1 day)

Dopamine worse in cardiogenic shock


Vasopressin In Septic Shock

Strong Biological and Clinical Rationale

- Plasma Levels of Vasopressin Low in Septic shock Patients
- Exogenous Vasopressin Improves Blood Pressure and Decreases Catecholamine Requirements
- Small Trial Suggests Improved Urine Output

Does Not Alter Outcome

VASST trial -778 patients with septic shock on norepinephrine – No difference in mortality rates between groups

N Engl J Med 2008;358;877-87
Resuscitation of the Severe Sepsis Patient

- Early Quantitative Resuscitation of the Septic Patient (1C)

Early Goal Directed Therapy for Patients with Severe Sepsis

Improved Mortality Rate with Complicated algorithm in Single Center Trial

- 263 patients presenting to the ED with severe sepsis or septic shock
  - 2/4 SIRS criteria
  - SBP < 90
  - Lactate > 4

Early goal-directed therapy in the treatment of severe sepsis and septic shock

- EGDT subjects more fluids early, more inotropes early, more prbc transfusions early (1st 6 h)
- Improved in-hospital, 28 day and 60 day mortality

EGDT

- EGDT subjects more fluids early, more inotropes early, more prbc transfusions early (1st 6 h)
- Improved in-hospital, 28 day and 60 day mortality
Methods of Early Resuscitation: Lactate Clearance

SVO2 vs Lactate Clearance
- 300 ED Patients with Severe Sepsis
  - Randomized to EGDT vs. Lactate Clearance
  - Similar Amounts of Fluids, Vasopressors, Dobutamine, PRBC Transfusion

No Difference In Mortality

JAMA 2010;303:739-746.

Goal-Oriented Hemodynamic Therapy in Critically Ill Patients

Goal Directed Therapy In ICU
- 762 Patients with critical illness measured by SAPS scores > 11 admitted to ICU > 48 h
  - Randomized to
    - Normal cardiac index (> 2.5)
    - Supranormal cardiac index (> 4.5)
    - Normal mixed venous O2 sat (> 70%)

ALL RECEIVED
- MAP > 60 mm Hg
- PCWP <= 18 mm Hg
- CVP > 8 < 12 mm hg
- Urine output > 0.5 cc/kg
- pH > 7.3 < 7.5

GOAL DIRECTED
- Dobutamine
- PRBC
- Colloids
- Vasopressors
- Vasodilators

ProCESS NCT00510835
ARISE NCT00975793

Goal-Oriented Hemodynamic Therapy in Critical Illness

- Between three groups
  - No difference in mortality rates
  - No difference in organ dysfunction
  - No difference in length of stay
- Could increase oxygen delivery and cardiac output, but also had increased oxygen consumption

-Gattinoni et. al NEJM 1995;333:1025-1032

Things Not to Routinely Do in Severe Sepsis or Septic Shock

- Stress Dose Steroids
- Tight Glycemic Control
Stress Dose Steroids

- Avoid use of intravenous hydrocortisone in adult septic shock patients if adequate fluid resuscitation and vasopressor therapy are able to restore hemodynamic stability (2C)

Corticus

- 499 Patients with septic shock who did not respond to short cosyntropin tests
  - Hydrocortisone versus placebo
  - More shock reversal in hydrocortisone patients
  - More superinfection in hydrocortisone patients
  - Substantial variability in results from short cosyntropin tests

Glycemic Control in Sepsis

- Target an upper blood glucose ≤ 180 mg/dL (1A)
Glycemic Control in Sepsis

NICE-SUGAR
6014 Patients with Critical Illness
Intensive (80-108 mg/dL) versus conventional insulin therapy (<180 mg/dL)
Roughly 20% with preexisting DM
Roughly 20% with severe sepsis
Initial glucose in 140’s both groups
Intensive median am glucose 118+25 versus 145+26
1% higher mortality in tight glycemic control patients


New Studies

• Process
• Albios
• Chloride Restriction
• SEPSISPAM N Engl J Med 2014; 370(17):1683-93

A Randomized Trial of Protocol-Based Care for Early Septic Shock

• Patients with severe sepsis in ED
  – With Refractory hypotension or lactate > 4
  – 1351 patients, 32 centers 1:1:1 randomization
– Randomized to
  • 1 River’s EGDT protocol
  • 2 Investigators Consensus Sepsis Protocol
  • 3 Wild type care
– Primary outcome measure 60 day mortality


Process Trial

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Protocol-based EGDT (N=453)</th>
<th>Protocol-based Standard Therapy (N=450)</th>
<th>Usual Care (N=452)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-hospital death by 60 days; primary outcome</td>
<td>10,492 (23.0)</td>
<td>8,446 (18.8)</td>
<td>8,414 (18.9)</td>
<td>0.03</td>
</tr>
<tr>
<td>Death by 90 days</td>
<td>11,645 (25.8)</td>
<td>10,605 (23.3)</td>
<td>10,412 (23.7)</td>
<td>0.46</td>
</tr>
<tr>
<td>Cardiac-Related Morbidity and Mortality</td>
<td>260 (58.3)</td>
<td>264 (58.7)</td>
<td>264 (58.6)</td>
<td>0.96</td>
</tr>
<tr>
<td>Neurology</td>
<td>105 (23.0)</td>
<td>105 (23.0)</td>
<td>105 (23.0)</td>
<td>0.78</td>
</tr>
<tr>
<td>Renal</td>
<td>124 (26.9)</td>
<td>124 (26.9)</td>
<td>124 (26.8)</td>
<td>0.90</td>
</tr>
<tr>
<td>Duration of organ support—days</td>
<td>1.5±0.8</td>
<td>1.5±0.8</td>
<td>1.5±0.8</td>
<td>0.52</td>
</tr>
<tr>
<td>Length of stay in ICU</td>
<td>6.6±4.6</td>
<td>7.3±5.4</td>
<td>6.9±4.2</td>
<td>0.41</td>
</tr>
<tr>
<td>Length of stay in hospital</td>
<td>12.1±12.1</td>
<td>13.4±12.1</td>
<td>13.3±12.9</td>
<td>0.25</td>
</tr>
</tbody>
</table>

Albios

1818 Patients
Albumin + crystalloid vs crystalloid
Albumin
Higher MAP
Lower net fluid balance
No mortality difference

Chloride Restriction

Use of Lower Chloride Solutions
Pre-Post Trial
Single Center Trial
Intervention Arm
Only faculty could prescribe chloride rich fluids

Protocols/Bundles For Sepsis

One Size Fits All? Cookbook Medicine?

Do Sepsis Guidelines Help Patients?

• Yes
Educational Campaign to Improve Process Measures in Sepsis

Process Measures

• 1st 6 hours
  – Measure lactate
  – Blood Cultures Prior to AB
  – Broad Spectrum Antibiotics
  – Fluid and Vasopressors
  – CVP Measurement > 8
  – SvO2 > 10%

• 1st 24 hours
  – Consider low dose steroids
  – Consider APC
  – Glucose Control
  – Ppl control

Performance of Outcome Measurements: Did the Campaign Work?

Small Increase in Process Measures

Decreased Mortality Rate

• Increasing Compliance with Sepsis Bundle is Associated with Decreasing Patient Mortality
• Compliance with early bundles was associated with decreased need for later intervention
• Lung protective Mechanical Ventilation, inotropes, and steroids were interventions independently associated with mortality

Surviving Sepsis Performance Improvement

17990 patients in surviving sepsis database from 2005-2010
25% antibiotics <= hour 52% <= 2 hours 68% <= 3 hours

Emory Performance Improvement Project: Treatment of Severe Sepsis

Baseline Performance
- Low baseline compliance with recommended therapy
- Delays in ED triage leading to delays in antibiotic and fluid therapy
- Different Ordersets in ED and Hospital

Response
- System wide computer orderset
- Nurse screening for possible sepsis
  - Blood cultures sent, 500 cc fluids given
  - Flagged for physician to see within 30 min
  - Opt out for specific patient groups (heart failure, post partum)

Emory Performance Improvement Project: Treatment of Severe Sepsis

<table>
<thead>
<tr>
<th>Group</th>
<th>Concept</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Information technology</td>
<td>Better decision support</td>
<td>Electronic sepsis trigger</td>
</tr>
<tr>
<td></td>
<td>Better documentation process</td>
<td>View flowsheet revisions</td>
</tr>
<tr>
<td></td>
<td>Better performance evaluation</td>
<td>Operationalize metrics</td>
</tr>
<tr>
<td>Lab</td>
<td>More timely and informative</td>
<td>Turnaround time</td>
</tr>
<tr>
<td></td>
<td>diagnostics</td>
<td></td>
</tr>
<tr>
<td>Supplies / Equipment</td>
<td>Have what is needed when needed</td>
<td>Hemodynamic monitors</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Procedure carts/kits</td>
</tr>
<tr>
<td>Education</td>
<td>Know what need to do</td>
<td>Professional education</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Patient/family education</td>
</tr>
<tr>
<td>Process standardization</td>
<td>Standardize approach as</td>
<td>Code Sepsis team</td>
</tr>
<tr>
<td></td>
<td>appropriate</td>
<td>Progressive mobility</td>
</tr>
<tr>
<td>Antibiotic management</td>
<td>Start right antibiotics faster</td>
<td>Antibiotics in Omnicell</td>
</tr>
<tr>
<td></td>
<td>Stop wrong antibiotics faster</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Antibiotic targeting protocol</td>
</tr>
<tr>
<td>Transitions of care</td>
<td>Improve coordination of care</td>
<td>Shift reports</td>
</tr>
<tr>
<td></td>
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<td>Inter-unit transfers</td>
</tr>
</tbody>
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Emory Performance Improvement Project: Treatment of Severe Sepsis

- Further work needed
  - Roll out Across System
- Quantify antibiotic use to ensure that inappropriate antibiotics usage does not increase
- Follow up patient outcomes
Summary Severe Sepsis Therapy

- Appropriate antibiotics given early - within first hour for hypotensive patient (often have to give empirically)
- Adequate fluids (start early give lots)
- Use a treatment goal in first 6 hours - lactate versus SVO2 > 70%
- Use crystalloids for fluid resuscitation - no proven benefit to giving albumin, and harm for pentastarch and hetastarch

Summary Severe Sepsis Therapy

- Norepinephrine first line vasopressor choice in septic shock
- A Protocol/Pathway/Orderset may help remind clinicians of treatment goals
- Use of a Protocol/Pathway/Orderset improves process measures and patient outcomes
- Steroids for patients on vasopressors with refractory shock, but not routine shock

Thank you

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