Surviving Sepsis: Improving Mortality With New Therapies

Sepsis remains the leading cause of death in critically ill patients in the US. Each year, 750,000 people will develop sepsis and more than 210,000 of them will die. As increasing numbers of septic patients present to EDs, identifying those who will benefit from early implementation of selected therapies is important. The speaker will review sepsis pathophysiology and discuss the latest updates in sepsis and SIRS therapies.

- Review the criteria defining sepsis and SIRS.
- Discuss the newest strategies on sepsis and SIRS.
- Define time-dependent ED management of septic shock through early goal-directed therapy.
- Discuss the financial impact of early goal-directed therapy.

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Surviving Sepsis: Improving Mortality With New Therapies

Peter DeBlieux, MD
LSUHSC Emergency Medicine
Pulmonary and Critical Care Medicine
New Orleans
pdebli@lsuhsc.edu

Objectives
At the end of this presentation participants should be able to:
• Review the criteria defining sepsis and SIRS
• Discuss the newest strategies on sepsis and SIRS
• Define time-dependent ED management of septic shock through early goal-directed therapy
• Discuss the financial impact of early goal-directed therapy

Why EM?
• Severe Sepsis and Septic Shock account for 2.9% of hospital admissions and 10% of admissions to ICUs
• Estimated 50% of these cases came from the ED
• Early Goal Directed Therapy has focused on the initial 6 hours of patient care
• Surviving Sepsis Campaign has incorporated EM as a key component

Challenges
• Fighting our practice habit
  – It does not make a difference
  – Intensivist's job
  – Way too complicated
• Goals
  – Show outcomes differences
  – Early intervention is essential
  – Keep it simple

Steps to Treating Sepsis
• Simple approach
• Logical format
• Fast recall

Steps to Treating Sepsis
Diagnosis Suspected
**Diagnosis**

**SIRS**
Two or more of the following:
- Temp >38°C or <36 °C
- Heart rate > 90 bpm
- Resp rate > 20 bpm or PCO₂ < 32 mm Hg
- WBC >12k or < 4k or >10% bands

**Early LAB Clues**
- Glucose > 120 mg/dL
- Creatinine increase > 0.5 mg/dL
- INR > 1.5 or aPTT > 60s
- Thrombocytopenia < 100,000
- Hyperbilirubinemia > 4 mg/dL
- Lactate level > 1mmol/L

**Sepsis**
SIRS with documented or presumed infection

**Severe Sepsis**
Sepsis and organ dysfunction: may include but not limited to lactic acidosis, oliguria, AMS

**Septic Shock**
Sepsis induced hypotension SBP < 90 mm Hg or > 40 mm Hg drop from baseline not relieved with fluids
Steps to Treating Sepsis

Diagnosis Suspected

Antibiotics

Sites of Infection

- Lung - 45%
- Abdomen - 17%
- Urinary tract - 10%
- Undetermined - 20-30%

Outcomes

In a series of patients with Gram negative sepsis those treated with appropriate antibiotics had a mortality of 18% compared to the inappropriate group - 34%


Goals

- Search for a source and control it ASAP
- Drain any infected fluid
- Debride infected tissue
- Remove infected devices


Recommendations

- Administer antibiotics in the ED within 1 hour of sepsis diagnosis
- Initial broad coverage tailored to the potential source
- Consider resistance patterns in nursing home patients and patients on prior antibiotics


Steps to Treating Sepsis

Hemodynamic

Antibiotics

Diagnosis Suspected
Outcomes

• No improved organ function or survival as a result of increasing mean arterial blood pressure above 65 mm Hg
• Early Goal Directed Therapy utilized these criteria to achieve a mortality reduction of 16.5%:
  • Central Venous Pressure 8-12 mm Hg
  • Urine output ≥ 0.5 cc/kg/hr
  • SCVO₂ ≥ 70%
  • MABP ≥ 65 mm Hg


Pathophysicsology

• Oxygen delivery and utilization can be measured by pulmonary artery catheter mixed venous oxygen saturation SVO₂ or central venous oxygen saturation SVCO₂
• A normal SVO₂ > 65% or normal SVCO₂ > 70% with a normal serum lactate suggests that oxygen delivery meets demand


Pathophysicsology

Global tissue hypoxia results when systemic oxygen delivery cannot meet tissue demands resulting in:
  • Low SCVO₂ < 70%
  • Increased/increasing serum lactate levels


Monitoring Goals

• CVP – 8-12 mm Hg
• CVP – SCVO₂ > 70%
• Urine output – 0.5 cc/kg/hr
• Arterial blood pressure MABP >65 mm Hg
• Normal serum lactate levels

Monitoring Goals

• Trends of vital signs are not sufficient endpoints to resuscitation
• Persistently elevated lactate levels is associated with increased mortality


Fluids

• No superiority of colloids to crystalloids regarding; pulmonary edema, length of stay or survival
• Serial crystalloid bolus of 500 cc or serial colloid bolus of 300 cc
  • Balk RA - Dis Mon - 01-APR-2004; 50(4): 168-213
**Blood Controversy**

EGDT promotes increasing oxygen carrying capacity in patients with evidence of oxygen debt:
- Transfusion with PRBC to a goal H/H of 10/30
- Maximize oxygenation with mechanical ventilation or high level oxygen
- Improve cardiac output with inotropes

**Blood Controversy**

- Lack of significant outcome benefit to raising hemoglobin above 10 g/dL in non-bleeding critically ill patients without active coronary/cerebral ischemia
- Suggests a conservative strategy maintaining an H/H


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**Vasoactive agents**

- Both dopamine and norepinephrine are considered first line therapy for MABP < 65 mm Hg with a CVP 8-12 mm Hg
- Consider agents with less of a beta agonist effect in those patients with tachycardia or coronary artery disease - norepinephrine or phenylephrine


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**Vasoactive agents**

In those patients with persistent SCVO$_2$ < 70% with MABP > 65 mm Hg and CVP within the 8-12 mm Hg range consider inotropic therapy:
- Dobutamine titrated 2.5 $\mu$g/kg/min every 20-30 minutes to a SCVO$_2$ > 70%
- Consider a phosphodiesterase inhibitor, Milrinone, in tachycardic patients


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**Vasoactive agents**

**Early Goal Directed Therapy**

- #1 CVP Goal 8-12 mmHg
- #2 MABP Goal 65 mmHg
- #3 SCVO$_2$ Goal > 70%

Crystalloids Levophed/Dopamine Dobutamine

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**Steps to Treating Sepsis**

- Airway
- Hemodynamic
- Antibiotics
- Diagnosis Suspected
Airway

Indications for intubation:
• Airway protection
• Oxygenation/Ventilation
• Expected clinical course

Pathophysiology

• Cardiac output can be increased ten fold during respiratory compromise and this cardiac output can be redirected to brain, liver, kidney, and heart with intubation, mechanical ventilation and sedation.
• As many as 35% of patients with sepsis demonstrate ARDS

Outcomes

• The Acute Respiratory Distress Syndrome Network ARDSNet compared traditional ventilation utilizing a tidal volume of 12 cc/kg of ideal body weight to 6 cc/kg/IBW
• Maintenance of plateau pressures less than 30 cm H₂O
• Decrease of 22% in hospital mortality and an increase in ventilator-free and organ failure-free days

Goals

• Early institution of mechanical ventilation in patients with hemodynamic instability and sepsis
• Utilization of ARDSNet protocol- tidal volume of 6 cc/kg/IBW and plateau pressures < 30 cm H₂O
• Maintain patients in a semi recumbent position

Steps to Treating Sepsis

Metabolic
Airway
Hemodynamic
Antibiotics
Diagnosis Suspected
Outcomes

• Tight glycemic control when compared to conservative glycemic control yielded a reduction in mortality from 8.0% to 4.6%.
• Compared with placebo, the administration of low doses of hydrocortisone to patients with septic shock decreased their mortality 10% and decreased their requirements for vasopressors.


Outcomes

Indication and practical use of intensive insulin therapy in the critically ill:
• Pooled analysis (n = 2748) revealed a significantly reduced morbidity and mortality in critically ill patients for all subgroups, except those with a prior history of diabetes.
• An absolute reduction in risk of hospital death of 3-4% is to be expected from this therapy in an intention-to-treat analysis.
• When patients are treated for more than 3 days, the absolute reduction in risk of death increases to approximately 8%.
• Risk for hypoglycemia remains and close monitoring is essential.

Current Opinion in Critical Care: 13(4):392-398, August 2007

Outcomes

Goal of 80-110 mg/dL is too dangerous:
• (n = 480) VISEP trial goal 180-200 mg/dL stopped early
• Revealed a significantly increased incidence of hypoglycemia in the intensive (80-110 mg/dL) group 17.6% vs 4.5%
• Hypoglycemia as a life threatening event 5.3% in the intensive group compared to 2.1%
• Any patient placed on an insulin drip should be monitored closely
• Ideal range has yet to be established- perhaps 140-180 mg/dL.

Current Opinion Clin Nutr Metab Care 2007;10(2):206-209

Outcomes

• ACTH test is capable of diagnosing adrenal insufficiency in sepsis.
• Inaccuracies in free cortisol measurements prevent its use as a sole determinant for steroid treatment.
• Steroids should be considered in the subset of septic patients with vasopressor-refractory hypotension.

Ann Pharmacother 2007;41:1456-1465

Outcomes

• In the PROWESS study Activated Protein C reduced mortality from severe sepsis or septic shock 6% compared to placebo. Number needed to treat is 16.
• Greatest benefit in the sickest patients.


Goals

• Utilize continuous Insulin Drip and glucose administration to maintain glucose <180-200 mg/dL with frequent accuchecks.
• IV Hydrocortisone 50 mg every 6 hours for patients requiring vasopressor therapy to maintain MABP > 65 mm Hg.

Balk RA - Dis Mon - 01-APR-2004; 50(4): 168-213
Current Opinion Clin Nutr Metab Care 2007;10(2):206-209
Goals

Patients receiving Activated Protein C within the first 24 hours of onset of severe sepsis had a better outcome compared with patients administered APC in the 24-48 hr time frame.

Balk RA - Dis Mon - 01-APR-2004; 50(4): 168-213

Steps to Treating Sepsis

Diagnosis Suspected

Hemodynamic

Metabolic

Airway

Antibiotics

Sepsis/Sirs Diagnosis Suspected

Antibiotics Initiated

HEMODYNAMICS

- Central line and serial fluid resuscitation to reach Goal CVP 8-12 mmHg
- Goal MAP 65 mmHg - if MAP < 65 mmHg then
  - Levophed or Dopamine to reach goal MAP 65 mmHg
- Goal SCVO2 > 70% and normal lactate - if SCVO2 < 70% and lactate > 4 mmol
  - Dobutamine infusion and/or
  - Maximized oxygenation and consideration for mechanical ventilation
  - Consideration for RBC transfusion to H/H 10/30

Metabolic if patient requires vasopressors to maintain goals consider:
- Activated Protein C administration
- Glycemic control Goal blood sugar 110-150 mg/dL
- Adrenal replacement therapy Hydrocortisone 50mg IV Q 6 hours

Sepsis Bundles

Successfully translating EGDT from the research bench to the bedside:
- Requires collaboration between Critical Care Medicine and EM
- Can be a Quality Improvement initiative
- Associated with decreased in-hospital mortality

Nathan Shapiro et al Acad Em Med 2005;12:352-359

Sepsis Bundles

Financial Impact of EGDT:
- Reduced hospitalization days, ICU days and complications
- Reduced ICU costs
- Associated with decreased in-hospital mortality

Rupert Pearse et al. Critical Care 2005, 9:B687-R693
David Huang Critical Care 2004, 8:498-502

Case One

A 38 year old female presents with a complaint of URI symptoms resolving after 5 days followed by high fever, cough, body aches, nausea, vomiting and diarrhea. BP 90/50 responding quickly to 1 liter IVF. Lab values: K 3.2, serum CO2 15, Lactate level 5 mmol.
Case One

Consideration for:
• Early antibiotic therapy
• Placement of central venous catheter
• Early Goal Directed Therapy
• ICU admission and intensive monitoring

Case Two

A 69 year old male presents with fever, cough, and confusion. Chest x-ray reveals multilobar pneumonia. Blood pressure of 80/40 mmHg and heart rate of 132. His blood pressure remains 80/40 after three liters of IVF over one hour. Central line is placed and CVP reading is 5 cm H2O.

Consideration for:
• Serial crystalloid boluses
• If CVP goal 8-12 mmHg is attained and patient remains hypotensive initiate vasopressor therapy to reach goal MAP of ≥ 65 mmHg
• If goal MAP is attained and lactate remains elevated or increasing or SCVO₂ < 70% then add Dobutamine or Milrinone to improve cardiac output

Case Three

A 60 year old female presents with EMS intubated, febrile and comatose. P122, BP 96/58, RR 32. Lab values: UA WBC TNTC with Gram negative bacteria, CBC WBC 26K with left shift, Creatinine 5.5, Glucose 360, Lactate is 0.5 mmol, Coag panel normal, CXR is clear.

Consideration for:
• Central line placement for intensive monitoring purposes
• Glycemic control
• Activated Protein C administration