Sepsis 2013 - New Management Strategies

Michael J. Apostolakos, MD
Professor of Medicine
Director of Adult Critical Care
University of Rochester

Sepsis: Epidemiology

- ~ 750,000 cases per year
- ~200,000 deaths per year
- Increased incidence and mortality with age and co-morbidity
- 2/3 occur in hospitalized patients
- Incidence increasing in the North America

Systemic Inflammatory Response Syndrome (SIRS)

- A complex systemic response which includes two or more of the following manifestations:
  - fever or hypothermia (≥38°C or ≤ 36°C)
  - tachycardia (> 90 beats/min)
  - tachypnea (> 20 breaths/min)
  - WBC count of > 12,000 or < 4,000 cells/mm$^3$ or 
    > 10% immature neutrophils
- CCM 20:864-874, 1992

Sepsis

- Confirmed or suspected infection, plus
- > 2 SIRS criteria

Severe Sepsis

- Sepsis
- ≥ 1 organ dysfunction

Sepsis: A Complex Disease

- This Venn diagram provides a conceptual framework to view the relationships between various components of sepsis.
- The inflammatory changes of sepsis are tightly linked to disturbed hemostasis.

Septic Shock

- Sepsis with hypotension (SBP < 90 mm Hg or a reduction of > 40 mm Hg from baseline) despite adequate fluid resuscitation along with perfusion abnormalities:
  - lactic acidosis
  - oliguria
  - altered mental status
- CCM 20:864-874, 1992

Accuracy of Procalcitonin for Sepsis Diagnosis in Critically Ill Patients: Systematic Review and Meta-analysis

- Systematic review of 18 studies evaluating the diagnostic accuracy of procalcitonin in sepsis diagnosis in critically ill patients
- Sensitivity and specificity was 71%
- Conclusion: Procalcitonin cannot reliably differentiate sepsis from other non-infectious causes of systemic inflammatory response syndrome in critically ill adult patients.

Sepsis: Etiology

- ~1/2 culture positive cases are gram negative organisms
- ~1/2 gram positive organisms
- 2-5% fungi or mixed infections
- Mycobacteria, rickettsiae, viruses and protozoans may cause sepsis
- 1/3 of cases culture negative

Sepsis: A Network of Cascading Events

- Fibrinolysis
- Proinflammatory mediators
- Inflammation
- Infection
- Anti-inflammatory mediators
- Endothelial injury
- Coagulation
- |

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

- Retrospective cohort design
- 2,731 adult patients with septic shock
- Administration of effective abx for isolated or suspected pathogen was associated with 80% survival
- Each hour delay associated with 8% reduction in survival
- Only 50% of septic shock patients received abx with 6 hours of hypotension

Sepsis: Treatment

- Removal of source of infection
- Antimicrobials
- Fluid resuscitation
- Hemodynamic support
- General supportive care
- ? Attack inflammatory response

- Kumar et al, CCM 34:1580-1596, 2006
Septic Shock: Hemodynamic Therapy

- Adequate volume resuscitation (colloids vs crystalloid)
  - CVP 8-12 (12-16 if intubated)
- Pressors to goal MAP > 65
  - Norepinephrine 1st line
  - Epinephrine 2nd line
  - Phenylephrine if tachyarrhythmias
  - Dopamine if bradyarrhythmias
  - Vasopressin in refractory hypotension

Association Between a Chloride-Liberal vs Chloride-Restrictive Intravenous Fluid Administration Strategy and Kidney Injury in Critically Ill Adults

- Prospective study of 1500 patients
- Compared chloride rich (ie NS), vs chloride poor (ie LR, Plasmalyte)
- Chloride rich fluids associated with significantly higher serum creatinine
- Risk of RRT 10% vs 6%
  - JAMA, 2012;308:1566-1572

Quotables

"You have to swell to get well"
Don Smith, MD circa 1994

Norepinephrine or Dopamine for the Treatment of Hyperdynamic Septic Shock?

- 32 patients with hyperdynamic septic shock randomized to receive dopamine (2.5-25 mcg/kg/min) or NE (0.5 - 5.0 mcg/min)
- Goal to achieve at 6 hours (1) SVR > 1,100 dynes and/or MAP > 80 mm Hg (2) CI > 4.0 L/min/m2 (3) DO2 > 550 ml/min/m2 (4) VO2 > 150 ml/min/m2
- Dopamine 5/16 achieved goal, NE 15/16 reached goal
- 10/11 Dopamine patients who failed, met goal when NE started
- NE more reliable at reversing septic shock hemodynamics
  - Martin et al, CHEST 1993;103:1826-31

Comparison of Dopamine and Norepinephrine in the Treatment of Shock
Vasopressin Deficiency Contributes to the Vasodilation of Septic Shock

- 19 patients with vasodilatory septic shock
- Administered 0.04 U/min continuous infusion AVP
- BP increased from 92/52 to 146/66 (p<0.001)
- SVR increased from 644 to 1187 dynes (p<0.001)
- Mean vasopressin level 3.1 pg/mL vs 22.7 in patients with cardiogenic shock
- Vasopressin levels normalized with infusion
  - Landry et al 1997;95:1122-1125

Vasopressin versus Norepinehrine Infusion in Patients with Septic Shock

- 778 patients on minimum of 5 mcg/min NE were randomized to receive low dose vasopressin (0.01 to 0.03 units/min) or NE 5-15 mcg/min
- Mortality rates 35% vs 39% (non-significant)
  - NEJM 2008;358:877-887.

Oxygen Consumption/Delivery

\[ \text{VO}_2 = \text{CO} \times (\text{CaO}_2 - \text{CvO}_2) \]

\[ \text{DO}_2 = \text{CO} \times (\text{CaO}_2) \]

\[ \text{CaO}_2 = \{\text{O}_2 \text{ sat} \times \text{Hg (gm/dL)} \times 1.34 \text{ ml O}_2/\text{gm Hg}\} + \text{PaO}_2 (0.003 \text{ ml O}_2/\text{mm Hg}) \]

A Trial of Goal-Oriented Hemodynamic Therapy in Critically Ill Patients

- Randomly assigned 756 critically ill patients to control, cardiac-index group and oxygen-saturation group
- Mortality rates were 48.4%, 48.6% and 52.1% respectively
- Number of organ dysfunctions and ICU length of stay were similar

Early Goal-Directed Therapy in the Treatment of Severe Sepsis and Septic Shock

- Assigned 263 patients with severe sepsis or septic shock to six hours of conventional or goal directed therapy
- Standard: CVP 8-12, MAP > 65, U/O > 0.5 ml/hr
- Goal directed: Standard + SVO2 > 70% using blood trx to Hct > 30 and dobutamine
- In-hospital mortality 30.5% (Goal directed) vs. 46.5% standard therapy (p=0.009)
- Over first 72 hours goal directed therapy group had lower lactate levels, higher pH and lower APACHE II scores
  - Rivers et al, NEJM 2001
The effect of a quantitative resuscitation strategy on mortality in patients with sepsis: A meta-analysis.

Jones, Alan; Brown, Michael; MD, MSc; Trzeciak, Stephen; MD, MPH; Shapiro, Nathan; MD, MPH; Garrett, John; Heffner, Alan; Kline, Jeffrey

DOI: 10.1097/CCM.0b013e318186f839


Surviving Sepsis Campaign: Results of an international guideline-based performance improvement program targeting severe sepsis

DOI: 10.1097/CCM.0b013e3181cb0cdc

General Supportive Care

- Protective ventilatory strategies (low tidal volume ventilation)
- Electrolytes, glucose (goal less than 180)
- Renal dysfunction
- Nutritional support
- GI/DVT prophylaxis
Limiting the Sepsis Response

- Endotoxin blockade
- Anti-TNF
- Anti-IL-1
- Anti-PAF
- Corticosteroids
- Anti-oxidants
- Coagulation system interference
- NO interference
- Hemofiltration

Effect of Treatment with Low Doses of Hydrocortisone and Fludrocortisone on Mortality in Patients with Septic Shock

- 300 patients with septic shock, unresponsive to IVF and low dose pressors as well as organ dysfunction
- All underwent co-syntropin stim test
- Hydrocortisone 50 mg iv q 6h and fludrocortisone 50 µg daily or placebos x 7days
- 28 day survival distribution in patients with relative adrenal insufficiency

Effect of Treatment with Low Doses of Hydrocortisone and Fludrocortisone on Mortality in Patients with Septic Shock: Results

- 229 nonresponders and 70 responders to the cosyntropin
- Nonresponders:
  - 73 (63%) deaths in placebo group; 60 (53%) deaths in treatment group (p=0.02)
  - Vasopressor therapy withdrawn within 28 days in 46 (40%) in the placebo group and in 65 (57%) in the treatment group (p=0.001)
- Responders: No significant difference
- Adverse event rates similar
Corticosteroid Therapy of Septic Shock (CORTICUS)

- Included all patients in septic shock no matter how they responded to pressors
- Faster resolution of septic shock in those that received steroids
- ACTH response did not predict responders
- No mortality benefit
  

Steroids in Sepsis: Conclusions

- Altered HPA axis function common in septic shock
- Candidates for steroid replacement are those hypotensive (SBP<90) despite 1 hour of pressors
- Replacement of steroids in such patients is associated with improved survival
- No routine ACTH tests or steroids in most sepsis patients

Efficacy and Safety of Recombinant Human Activated Protein C for Severe Sepsis

- 1690 randomized patients with severe sepsis
- Drotrecogin alfa (activated) vs placebo
- Both groups received general supportive care
- Mortality rate 30.8% in placebo group, 24.7% in treatment group at 28 days (p<0.01)
- Serious bleeding 3.5% treatment group vs 2.0% placebo (p=0.06)

- Bernard et al NEJM 2001;344:699-709
APC Follow Up Trials

- **ADDRESS (2005):** Low disease severity
  - 28-day mortality 18.5% APC vs 17.0% placebo (NS)
  - Severe bleeding 3.9% APC vs 2.2% placebo (p= 0.01)
- **XPRESS (2007):** Adjunctive heparin
  - 28-day mortality 28.3% heparin vs 31.9% placebo
  - Severe bleeding 5.2% heparin vs 3.9 % placebo (p=0.16)
- **ENHANCE (2005) (open label APC)**
  - Mortality 25.3%
  - Severe bleeding 6.5%

PROWESS-SHOCK

- However, conflicting data from subsequent studies eventually led to a new trial, the PROWESS-SHOCK trial. In this trial, 1696 patients with vasopressor-dependent septic shock were randomly assigned to receive rhAPC or placebo [61]. Preliminary analyses done by the maker of the drug indicated that rhAPC did not improve 28-day mortality (26.4 versus 24.2 percent for placebo, RR 1.09, 95% CI 0.92-1.28).

Sepsis: Care Improvement

- Early identification of severe sepsis and septic shock
- Early goal directed therapy
  - Culture before antibiotics
  - Serial blood lactates
  - IVF to predetermined goals
  - Pressors to predetermined MAP
  - Targeting improved oxygen delivery
Adult Suspected Sepsis Diagnosis

- Patient requires Culturing
- Suspected Sepsis Order panel used

Lactate ↓
- Notify Team
- Activate RRT
- Per Team
- Notify team/RRT of:
  - ↑ HR, ↑ RR, ↓ SBP
  - Mental Status

Lactate ≥2
- Q 4 hours x3
- Then per order
- Notify team/RRT of:
  - ↑ HR, ↑ RR, ↓ SBP
  - Mental Status

Lactate <2
- Per order
- Notify team/RRT of:
  - ↑ HR, ↑ RR, ↓ SBP
  - Mental Status

Adult Suspected Sepsis Algorithm - DRAFT

URMC – Adult Septic Shock Management Protocol

- URMC Adult Non-Invasive Septic Resuscitation Protocol

<table>
<thead>
<tr>
<th>Goal</th>
<th>Action</th>
<th>Plan for Improvement</th>
</tr>
</thead>
</table>
| MAP <65 | Consider inotropic therapy | Consider inotropic therapy
| SBP <90 | Consider vasopressor therapy | Consider vasopressor therapy
| Lactate ≥ 4 *** or <20% lactate clearance | Consider antibiotic therapy | Consider antibiotic therapy
| ScvO2 < 70 | Consider fluid resuscitation | Consider fluid resuscitation
| | | |

SMH Mortality Rate: Severe Sepsis/Septic Shock

- Year: 2011-2014
- Comparison: 2013 vs 2014
- Decrease in mortality rate

Action and Plans for Improvement

- Identify cases earlier with automatic lactate with initial blood cultures/new algorithm for identification
- Continue with Education
  - Bundle evidence based care for severe sepsis and septic shock
  - Guidelines and order sets
  - RRT
  - UM queries of SIRS patient for spectrum of sepsis
**DOH: Sepsis Regulations: 2013**

- Must implement evidence-based protocols for early recognition and treatment of patients with severe sepsis and septic shock
- Requires staff training in sepsis protocols
  - Grand rounds
  - On-line (Blackboard)
- Measures shall be reported annually (process and outcome data)

**Sepsis: Prognosis**

- Severe sepsis carries mortality of 30 - 70%
- Prognosis influenced by the presence of shock, nature of underlying disease, and the organisms causing sepsis
- Negative prognostic host factors include immune dysfunction and reduced cardiorespiratory reserve

**Sepsis 2013: Conclusions**

- Sepsis represents a complex host reaction to severe infection involving coagulation and inflammation
- MUST remove source of infection (drainage/abs)
- MUST use early, effective antibiotics
- Early, aggressive volume resuscitation (with pressors as needed) to predetermined goals is beneficial in patients with severe sepsis and septic shock
- Check lactate!
- Sepsis bundles are best way to assure best practice!
- Corticosteroids in pressor unresponsive septic patients may be associated with reduced mortality
- Like in MI and CVA, in Sepsis time is tissue! There is a golden treatment period in the first 6 hours...This requires a team effort!