Sepsis: Update on Diagnosis, Evaluation and Management

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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

Angus et al., CCM 2001;29:103-1310

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/mm³ or > 10% immature neutrophils
- CCM 20:864-874, 1992

Sepsis

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

Severe Sepsis

- Sepsis
- ≥ 1 organ dysfunction

CCM 20:864-874, 1992

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

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.

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

Sepsis: Current Treatment

- Removal of source of infection
- Antimicrobials
- Fluid resuscitation
- Hemodynamic support (new role for vasopressin?)
- General supportive care
- ? Attack inflammatory response

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

- Kumar et al, CCM 34:1589-1596, 2006
Septic Shock: Hemodynamic Therapy

- Adequate volume resuscitation (colloids vs crystalloid)
- ? Swan-Ganz Catheter
- ? SVO2 monitor
- Dopamine
- Norepinephrine
- Phenylephrine if tachyarrhythmias
- Vasopressin in refractory hypotension

Quotables

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

Comparison of Dopamine and Norepinephrine in the Treatment of Shock


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

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<.001)
- SVR increased from 644 to 1187 dynes (p<.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

- $\text{VO}_2 = \text{CO} \times (\text{CaO}_2 - \text{CvO}_2)$
- $\text{DO}_2 = \text{CO} \times (\text{CaO}_2)$
- $\text{CaO}_2 = \{\text{O}_2 \text{ sat x Hg (gm/dL)} \times 1.34 \text{ ml O}_2/\text{gm Hg}\} + \frac{\text{PaO}_2}{0.003 \text{ ml O}_2/\text{mm Hg}}$

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

Patients Treated with EG T Received More Fluids, RBCs and Dobutamine
The effect of a quantitative resuscitation strategy on mortality in patients with sepsis: A meta-analysis.
Jones, Alan; Brown, Michael; MD; Trzeciak, Stephen; MD; Shapiro, Nathan; MD; MPH; Garrett, John; Heffner, Alan; Eline, Jeffrey
DOI: 10.1097/CCM.0b013e318186f839

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General Supportive Care
- Protective ventilatory strategies (low tidal volume ventilation)
- Electrolytes, glucose
- 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 ug daily or placebos x 7days
- 28 day survival distribution in patients with relative adrenal insufficiency
  - Annane et al JAMA 288:862-871, 2002

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 (46%) 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

Quotables

“We in critical care medicine have deep pockets…”
Michael J. Apostolakos, circa 1995

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

Quotables

“… That’s more than made up for by your superficial thoughts”
Paul C. Levy, circa 1995
(now Paul V.C. Levy)
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: 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 Evolving Trends in the Evaluation and Management: Conclusions

- Sepsis represents a complex host reaction to severe infection involving coagulation and inflammation
- MUST remove source of infection(drainage/abx)
- MUST use early, effective antibiotics
- Early, aggressive volume resuscitation to predetermined goals is beneficial
- 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!