Surviving Sepsis: Is corticosteroid therapy beneficial in patients with severe sepsis and septic shock?

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**Why worry?**

- >750,000 cases of sepsis annually in US
- Leading cause of death in general ICUs
- Healthcare cost $16.7 billion annually
- Mortality rate for severe sepsis 10-30%; septic shock 30-50%
SIRS criteria (2 or more):

- Temp >38°C or < 36°C
- HR> 90
- RR> 20 or PaCO₂ < 32 mm Hg
- WBC> 12,000/mm³, < 4,000/mm³, or > 10% bands?
Established in 2002
Society of Critical Care Medicine, European Society of Intensive Care Medicine, International Sepsis Forum

Objective: reduce sepsis mortality
Producing evidence-based guidelines
“Care Bundles” – targets to be achieved at 6 and 24 hours
Goal: mortality reduction of 25% in five years
Criticism

- Based on results of a small, single-center studies not reproduced by multi-center studies
- Industry funding
- Majority of recommendations based on Grade E evidence
Recognize severe sepsis on arrival to ER
Maintain airway and establish IV access

Volume resuscitation with NS up to 30 cc/kg (2 L) over 30 minutes

Early empiric broad spectrum antimicrobial therapy

If MAP < 70 mmHg after 30 cc/kg
Insert Venous Access

Start norepinephrine @ 0.01ug/kg/min and titrate to MAP
Fluid boluses (500 ml LR)

If MAP < 70 mmHg despite 0.2 ug/kg/min norepinephrine
Consider hydrocortisone 50 mg q6 or 10mg/hr

SIRS Criteria
1. Temp > 38 or < 36
2. Heart rate > 90 beats/min
3. Resp rate > 20 breaths/min
4. WBC > 12000 or < 4000 or >10% bands

Severe Sepsis
1. Suspected infection
2. 2 or more SIRS Criteria
3. SBP < 90 after (30 cc/kg LR bolus (2 L) or
4. Lactate > 4 mmol/L

Tests:
Lab Tests: CBC, Lactate, Chem 7, PT, PTT, INR, LFTs, Ce, Mg, P, blood cultures, UA + culture.
Radiology: CXR and other

ECHO to determine global LV function

PPV to determine fluid responsiveness

Depressed-Normal LV function

Hypercontractile LV

Start dobutamine @ 2.5 ug/kg/min
Start vasopressin @ 0.03 U/min Continue norepinephrine titration

Persistant Shock

Shock resolution

Consider Recombinant Activated Protein C (24ug/kg/hr) IV for 9 hours if no contraindication

Fluid Responsive: Alternate 500 cc boluses of LR and 5% albumin

Monitor:
PaO2/FIO2
Arterial Satuations
Extravascular lung water

Monitor:
MAP
Lactis acid
Non-invasive CI/SI
Urine Output

Grade 2 C
HPA axis

SCN
Circadian information

CNS
Stressors

PVN
Hypothalamus

CRH and AVP release

Median eminence

Anterior pituitary

Corticotroph cells

ACTH release

Portal vein

Corticosterone

Adrenal cortex

Nature Reviews | Neuroscience
Adrenal dysfunction

• The incidence of adrenal dysfunction during severe sepsis and septic shock has been estimated to be as high as 50%.
• Caused by inappropriately low production of glucocorticoids or an impaired response to cortisol in the systemic circulation
• Medications - Fluconazole, Etomidate, Estrogens
• Systemic disease – HIV, liver failure, cancer
Definition

Adrenal insufficiency

• Random cortisol level <10 μg/dl or
• Less than a 9 μg/dl increase in cortisol 60 minutes after an ACTH stimulation test
Effect of Treatment With Low Doses of Hydrocortisone and Fludrocortisone on Mortality in Patients With Septic Shock

Djillali Annane, MD, PhD

JAMA, August 21, 2002—Vol 288, No. 7

The NEW ENGLAND JOURNAL of MEDICINE

Hydrocortisone Therapy for Patients with Septic Shock
Prospective, randomized, double-blind study

300 patients with septic shock

Dates: 1995 to 1999

Randomized within 8 hours of presentation

Either given 50 mg hydrocortisone IV q6H x7 days vs. placebo

Primary endpoint – 28 day survival

Days on vasopressor therapy, adverse events, overall mortality
Results

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

Djillali Annane, MD, PhD

Results

- 76.5% met criteria for non-responders
- 28 day mortality rate for steroid treatment vs. placebo was significantly different at 53% vs. 63%
- Median time to withdrawal of vasopressors 7 vs. 10 days
- No significant difference in adverse events
Multicenter, prospective, randomized, double-blind, placebo-controlled study

Dates: 2002 to 2005

499 patients with septic shock

50 mg hydrocortisone q6H x5 days vs. placebo

Primary endpoint – 28 day mortality rate in non-responders
Results

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Aka CORTICUS study

Hydrocortisone Therapy for Patients with Septic Shock

- 76.5% met criteria for non-responders
- 28 day mortality rate for steroid treatment vs. placebo was significantly different at 53% vs. 63%
- Median time to withdrawal of vasopressors 7 vs. 10 days
- No significant difference in adverse events
- NO difference in 28 day mortality 39% v 36% in non-responders
- Increased frequency of hyperglycemia, superinfections
- Shock reversal in 3.3 days vs. 5.8 days
Conclusions

• Despite decades of experimental animal and human trials, the role of corticosteroid therapy remains uncertain and controversial
• Early high-dose steroids not helpful, potentially harmful
• Low-dose steroids associated with improved blood pressure and shorter duration of vasopressor support in patients with septic shock
• No evidence to support survival benefit
• Possible increased infection risk
• Questions: What dose to use, when to initiate treatment, intermittent or continuous infusion therapy, duration of treatment, in what subgroup of patients are steroids beneficial
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