DECISION DILEMMA

STEROID IN SEPTIC SHOCK

Dr Punit D. Ghetia

MD,IDCCM

Consultant intensivist

Bankers Heart Institute

Sepsis and septic shock

- **Mortality is ~ 30%: usually its hypotension + coagulopathy**
- **Hypotension**
  - **Prostaglandins synthesised by COX-2** cause vasodilation
- **Coagulopathy**
  - **Cytokines TNF-Alpha, IL-1** cause endothelial cell activation
- Multiple other factors… reactive oxygen species, metabolic abnormalities eg. hyperglycaemia and acidosis, decreased myocardial contractility, end organ failure,

Kumar et al. **Robbins and Cotran Pathological Basis of Disease 8th ed. Ch 4** 2009

Steroids:

- **Inhibit the extravasation of leucocytes**

  (inhibit leucocyte adhesion molecules from interacting with endothelial cell adhesion molecules; **this raises the WCC**)
- **Increase the migration of lymphocytes to the lymphoid tissues (and out of the bloodstream)**
- **Inhibit the function of macrophages and antigen-presenting cells**
- **Inhibit phagocytosis by macrophages**
- **Inhibit production of TNF-alpha and interleukin-1**
- **Inhibit expression of cyclooxygenase-2: Thus, inhibit the synthesis of prostaglandins**
- **Inhibit synthesis of antibodies (in large doses)**

Katzung et al. **Basic and Clinical Pharmacology 11th ed. Ch 39** 2009

Steroids

- IN SUMMARY
  - **Less inflammatory cells**
  - **The remaining inflammatory cells are less active**
  - There are fewer inflammatory cytokines, there are fewer local mediators of inflammation, thus **both local and systemic inflammatory response is inhibited**
  - **Both specific and non-specific immunity is inhibited**

The promising role of steroids in septic shock

- Sepsis is a large-scale inflammatory response
- Most of the fatal features of sepsis are the results of inflammatory processes
- Steroids are anti-inflammatory
- Thus, steroids should reduce mortality in sepsis

Also…

- **Concept of "relative adrenal insufficiency"**
  - Adrenal glands respond to stress by producing corticostroids
  - "relative insufficiency" means the degree of response is not directly proportionate with the degree of stress
  - i.e that is is when they don't produce ENOUGH corticosteroids

LaNoue, K. F. et al **The Impairment of Glucogenesis by Gram Negative Infection**. Metabolism, 17:606, 1968.
Venkatesh et al **Relative adrenal insufficiency in sepsis: match point or deuce?** Critical Care and Resuscitation • Volume 8 Number 4 • December 380 er 2006

Relative adrenal insufficiency

- **But how much is "sufficient"?**
  - Whats an appropriate baseline level of a septic patient in ICU?
  - What would the laboratory reference range be ?

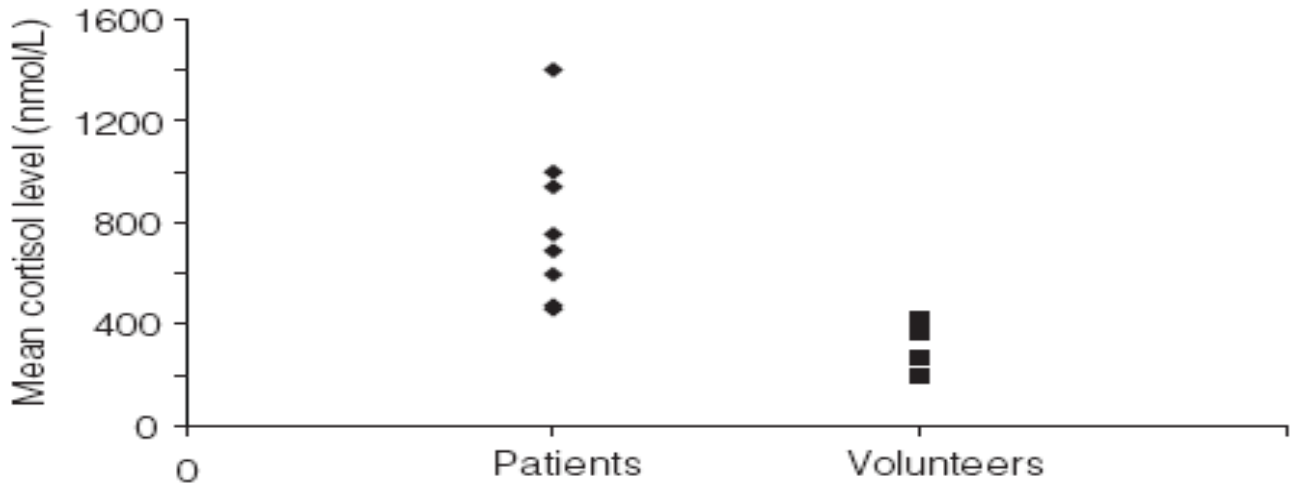
FREE CORTISOL is implicated to further complicate the issue

Septic patients have less globulin, thus more free cortisol… ?

Does this matter? It seems to correspond to sepsis severity

Venkatesh et al. **Evaluation of random plasma cortisol and the low dose corticotropin test as indicators of adrenal secretory capacity in critically ill patients: a prospective study.**
Anaesth Intensive Care 2005; 33: 201-9.
Venkatesh et al **Relative adrenal insufficiency in sepsis: match point or deuce?** Critical Care and Resuscitation • Volume 8 Number 4 • December 380 er 2006

Figure 1. Mean plasma cortisol levels in critically ill patients (eight studies[15-22]) and control volunteers (four studies[23-26])



Which ones are "insufficient"?

- Corticotropin stimulation test:
  - Measures the 60 minute response to 250 mcg of synthetic corticotropin;
  - You pass if your cortisol levels go above 500-550 nmol/L, or if you go more than 250 nmol/L above your baseline

- However- **250 mcg is a HUGE dose** of synacthen, compared to normal corticotropin levels
- Also: Do you measure the total cortisol, or the active free cortisol?

And sadly…

- All European studies of this are suspect because they use ETOMIDATE, a sedating drug which is not approved in Australia, which causes adrenal suppression

For **Corticotropin stimulation test:** which ways : so much confusion !!!

History of steroids in sepsis

Stott (1924):

" **Adrenalectomized rats dealt rather poorly** with the effects of having killed bacteria injected into them, compared to the ones I didnt adrenalectomize"

Hahn (1951): first ever trial of steroids in infection;

174 air force officers with pharyngitis, 87 given cortisone acetate

No useful effect was observed.

Kass (1958): "It was a clinical observation without an adequate theoretical framework for predicting the observed effects. "

Scott, WJ. **The influence of the adrenal glands on resistance: II. The toxic effect of killed bacteria in adrenalectomized rats.** J Exp Med 1924; 39:457.

Hahn EO, et al. **Effect of cortisone on acute streptococcal infections and poststreptococcal complications.** *J Clin Invest 1951; 30: 274-81.*

Kass, EH. **Adrenocorticosteroids and the Management of Infectious Diseases** *AMA Arch Intern Med.* 1958;102(1):1-4.

In the 70s we liked the steroids

Schumer, 1976:

- Double blind randomized trial. 328 patients, 172 prospective
- 1/3rd got dex, 1/3rd got methylprednisone, 1/3rd got saline
  - Dex group: 9.3% mortality
  - Methylprednisone group: 11.5 % mortality
  - Saline group: 38.4% mortality

Schumer W: **Steroids in the treatment of clinical septic shock.** *Ann Surg* 1976

In the 80s, we loved the steroids

High dose steroids came into popularity

Beller et al, Brigham et al,

- Massive doses or constant infusions of steroids
- Interest arising from animal studies

Doses as large as 30mg/kg of methylprednisone were used

Beller BT, et al **Effectiveness of Modified Steroid-Antibiotic Therapies for Lethal Sepsis in the Dog** *Arch Surg.* 1983;118(11):1293-1299.
Brigham et al. **Methylprednisolone Prevention of Increased Lung Vascular Permeability following Endotoxemia in Sheep** J Clin Invest. 1981 April; 67(4): 1103–1110.

In the 80s, we abandoned the use of steroids

1987: Multicenter randomized, double-blind, placebo-controlled trial

- Testing high dose methylprednisone on conscious septic patients
- 223 patients
- **No reduction in mortality**

1987: prospective, randomized, double-blind, placebo-controlled trial

- Strict entry criteria; high dose 30mg/kg methylprednisone
- 136 patients
- **INCREASE in 14-day mortality (secondary infection)**

Veterans Administration Systemic Sepsis Cooperative Study Group: **Effect of high-dose glucocorticoid therapy on mortality in patients with clinical signs of systemic sepsis.** *N Engl J Med* 1987 , **317:**659-665

Bone RC, et al **A controlled clinical trial of high-dose methylprednisolone in the treatment of severe sepsis and septic shock.** N Engl J Med. 1987;317:653–658.

Resurgent interest: late 1990s

Small, "stress" doses of steroids

- **aim is to reduce vasopressor requirements**
- Theory is that the stress doses of steroids supplement endogenous steroid release in "relative adrenal insufficiency"

- patients had their cortisol levels cortisol response and norad dose-response curves measured by Annane et.al; patients with sepsis had impaired response to cortisol and to noradrenaline

Annane et al. **Impaired pressor sensitivity to noradrenaline in septic shock patients with and without impaired adrenal function reserve**. Br J Clin Pharmacol. 1998;46:589–597.

"Stress dose" steroids in the late 90s

- So do low dose long course steroids improve the effectiveness of inotropes in sepsis?
- For Briegel et.al (40 pts) the steroids reduced time until cessation of inotropes, but had no effect on mortality
- For Bollaert et.al (41 pts) the steroids improved mortality and "early shock reversal" (off inotropes within 7 days)

Bollaert et al. **Reversal of late septic shock with supraphysiological doses of hydrocortisone** Crit Care Med 1998 26:645-50
Briegel J et al. **Stress doses of hydrocortisone reverse hyperdynamic septic shock: a prospective, randomized, double-blind, single-center study.** Crit Care Med. 1999;27:723–732.

Limitation of trial…

- A study by **Bollaert *et al*.,**

  in which septic patients requiring catecholamines were randomized to receive hydrocortisone(100 mg intravenously three times a day for 5 days) or placebo, found **a significant reduction in the time it took to reverse shock, and a trend towards improved survival .**

  While the results of this trial were impressive, care must be taken not to **overinterpret** the results;

  it was **a small clinical trial with only about 20 patients in each arm,** and there was a relatively high mortality rate in the placebo arm (63%) for patients with septic shock.

Limitation of trial…

- In a similar small trial by **Briegel *et al.,*** *septic shock patients* were randomized to receive either a placebo or hydrocortisone (100 mg intravenous bolus), followed by continuous infusion until septic shock resolved [8].
- The **length of time for which vasopressor support** was required was **significantly reduced**
- **Mean arterial pressure was increased** in patients treated with steroids.
- In addition, there were trends toward earlier reversal of organ dysfunction.
- However, There was **not a mortality difference between the two groups .**
- It may be reflection to recognize that all benefit of immunomodulatory therapy in adequately powered, randomized, controlled trials is confined to the most severely ill.

Above two studies

(that suggest low-dose steroids are beneficial),

BUT,,,

The question becomes one Of whether steroid-induced reversal of vasopressor support confers any outcome benefits.

Unfortunately, no definitive work has been published.

"Stress dose" steroids in the early 2000s

Most studies demonstrated no benefit to 28day survival.

This didn't stop "stress dose" steroids from being recommended:

"SURVIVING SEPSIS" guidelines (2004):

- **250 mics of synacthen is the standard amount to use for the corticotropin response test**
- **IV hydrocortisone up to 300mg**
- **Also add 50 mcg fludrocortisone**

AVOID high dose steroids (everybody in agreement)

Dellinger et.al, 2004, **Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock.** Crit Care Med. 2004 Mar;32(3):858-73

Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016

H. CORTICOSTEROIDS

1. We suggest against using IV hydrocortisone to treat septic shock patients if adequate fluid resuscitation and vasopressor therapy are able to restore hemodynamic stability. If this is not achievable, we suggest IV hydrocortisone at a dose of 200 mg per day (weak recommendation, low quality of evidence).

Why was this recommended?

COCHRANE review: 2004

Annane, Bellisant, Bollaert, Briegel, Keh and Kupfer : Names recognizable from previously mentioned studies

Corticosteroids for treating severe sepsis and septic shock

15 trials identified (N = 2023)

- **Corticosteroids did not improve 28 day mortality from all causes**
- **Corticosteroids DID improve ICU mortality**
- **Corticosteroids DID increase the proportion of shock reversal by day 7**

Low dose steroids over > 5 days recommended

RECENT PAST: 2008

- CORTICUS study: Corticosteroid Therapy of Septic Shock
- multicenter, randomized, double-blind, placebo-controlled trial
- Close to 500 pts
- Major outcome measure: death at 28 days
- CONCLUSION:
  - **No survival benefit**
  - Hydrocortisone reverses shock faster, but increases the rate of secondary infections
  - **Shock is reversed faster IN THOSE IN WHO SHOCK WAS REVERSED**
  - **i.e. if you were going to get better… You would get better faster with steroids**

Sprung et al, **Hydrocortisone therapy for patients with septic shock.** N Engl J Med. 2008 Jan 10;358(2):111-24.

Annane *Annals of Intensive Care* 2011, **1**:7
http://www.annalsofintensivecare.com/content/1/1/7

Annals of Intensive Care
a SpringerOpen Journal

REVIEW Open Access

Corticosteroids for severe sepsis: an evidence-based guide for physicians

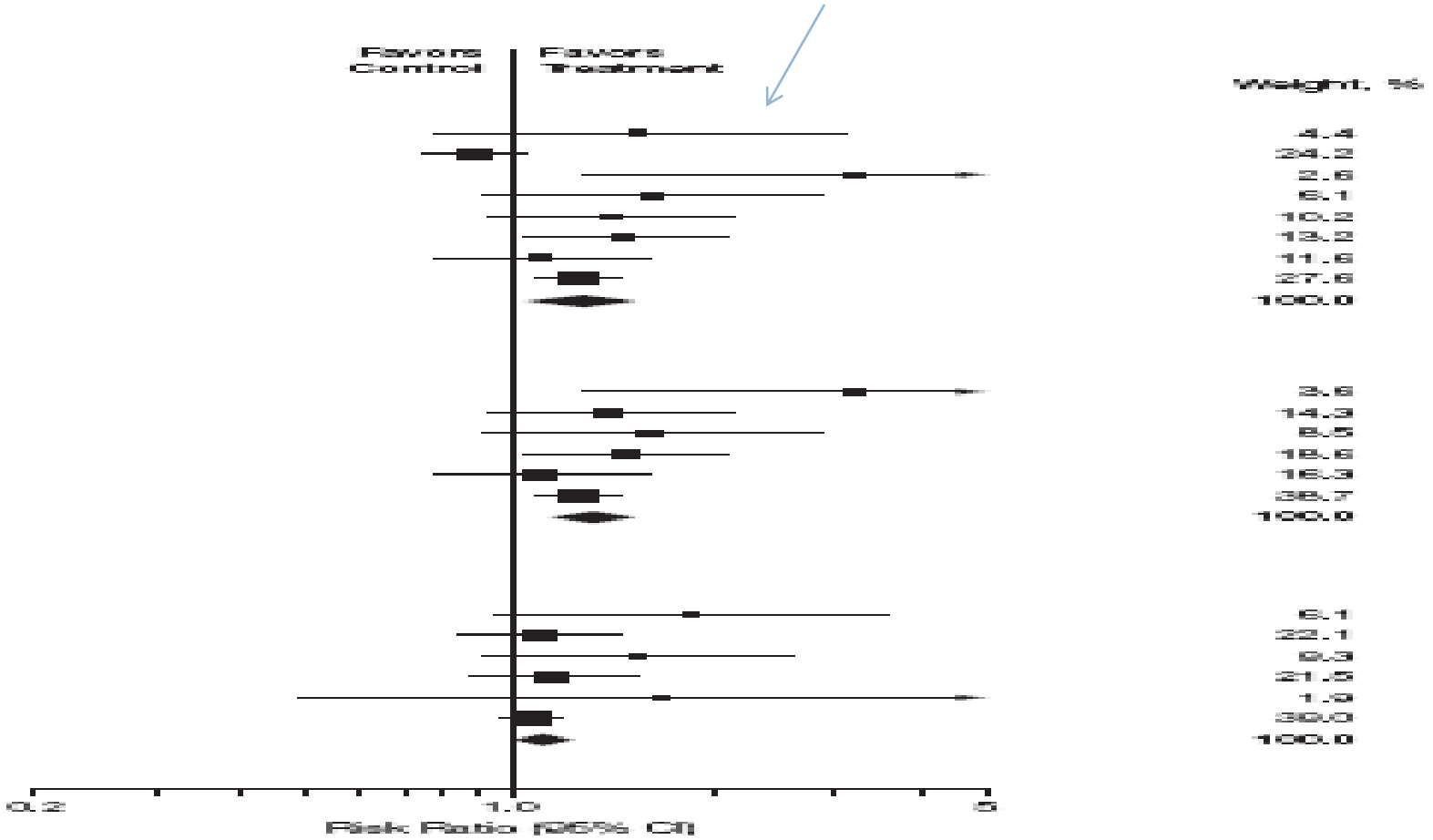
Djillali Annane

Abstract

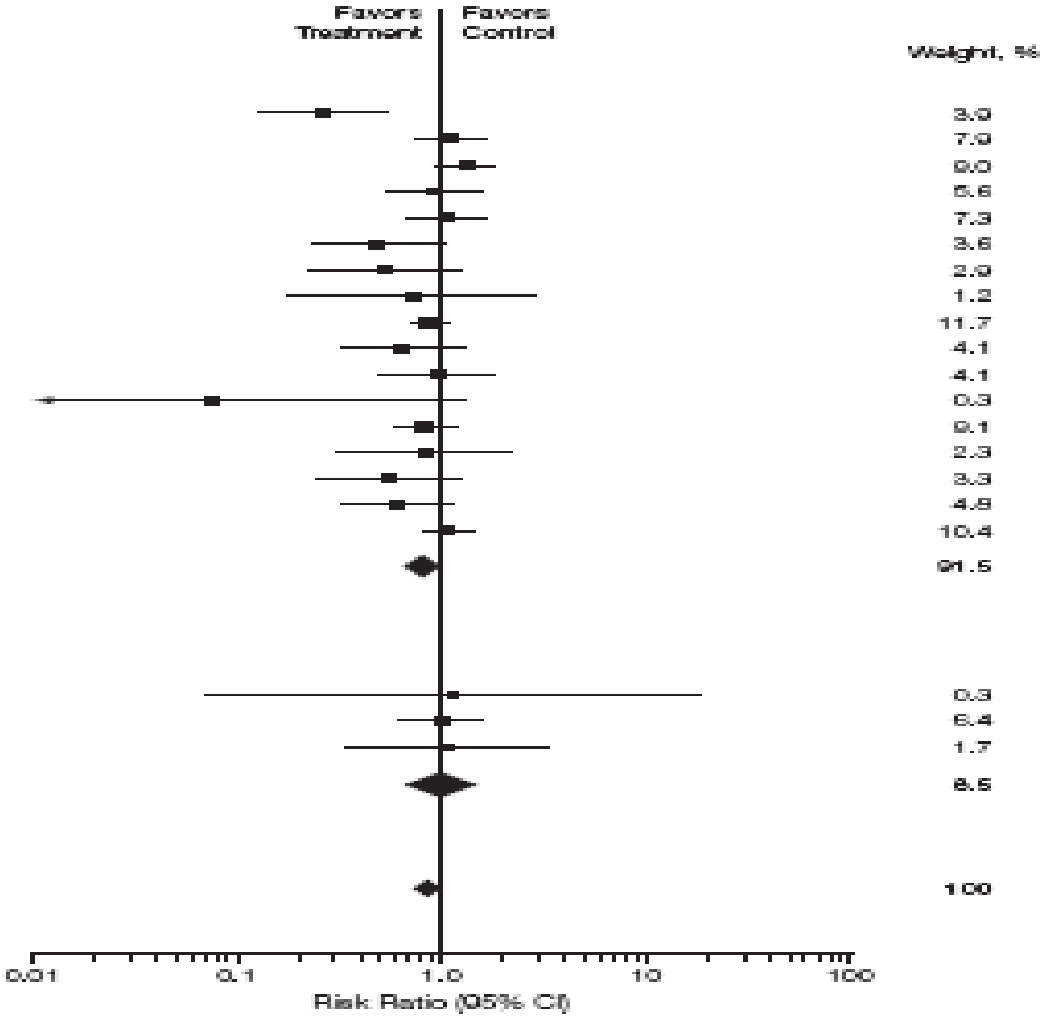
Septic shock is characterized by uncontrolled systemic inflammation that contributes to the progression of organ failures and eventually death. There is now ample evidence that the inability of the host to mount an appropriate hypothalamic-pituitary and adrenal axis response plays a major in overwhelming systemic inflammation during infections. Proinflammatory mediators released in the inflamed sites oppose to the anti-inflammatory response, an effect that may be reversed by exogenous corticosteroids. With sepsis, via nongenomic and genomic effects, corticosteroids restore cardiovascular homeostasis, terminate systemic and tissue inflammation, restore organ function, and prevent death. These effects of corticosteroids have been consistently found in animal studies and in most recent frequentist and Bayesian meta-analyses. Corticosteroids should be initiated only in patients with sepsis who require 0.5 μg/kg per minute or more of norepinephrine and should be continued for 5 to 7 days except in patients with poor hemodynamic response after 2 days of corticosteroids and with a cortisol increment of more than 250 nmol/L after a standard adrenocorticotropin hormone (ACTH) test. Hydrocortisone should be given at a daily dose of 200 mg and preferably combined to enteral fludrocortisone at a dose of 50 μg. Blood glucose levels should be kept below 150 mg/dL.

A closer look

Shock reveresal by day 7 : more in steroid group



Reduction in Length of ICU stay favors steroid



MODERN DAY:

- Another more recent review by **Annane et. al (2009, JAMA)**

Corticosteroids in the Treatment of Severe Sepsis and Septic Shock in Adults

- This time, **N = 2138**
- Analysis of the since-1998 subgroup: consisently good quality, 12 trials with only low-dose long-course steroids (200-300mg daily), only in vasopressor-dependent adults

  In that subgroup, there is a survival benefit, but "the evidence is not particularly robust" according to the authors.
- **Uniformly, short courses of high dose steroids are not supported.**

Annane et al, **Corticosteroids in the Treatment of Severe Sepsis and Septic Shock in Adults A Systematic Review** *JAMA.* 2009;301(22):2362-2375.

Conclusion for short courses of high dose steroids : NO

What harm could they do?

- 7 trials: unanimous NO to high dose short course steroids
- No demonstrated increase in risk of GI bleeding
- Increased risk of hyperglycaemia
- Increased risk of hypernatremia
- No change in mortality, whether you wean or abruptly cease

Moral of the story:

- **Take home message**

Do we give steroids or don't we?

Yes, …but…who have **vasopressor-dependent septic shock (require 0.5 µg/kg per minute or more of norepinephrine)**

- Limit dose to **200-300mg of hydrocortisone per day**
- **Valuable to start in first 24 hours of shock**
- **Wean them as soon as the pt does not require inotropes**

- Short synacthen test may not identify the patients who will benefit because nobody can agree on what a "normal" response is in ICU so **not compulsory to do synacthen test.**

further questions, please.

Thanks you

References

- Schumer W: **Steroids in the treatment of clinical septic shock.** *Ann Surg* 1976
- Katzung et al. **Basic and Clinical Pharmacology 11th ed. Ch 39** 2009
- Kumar et al. **Robbins and Cotran Pathological Basis of Disease 8th ed. Ch 4** 2009
- Bollaert et al. **Reversal of late septic shock with supraphysiological doses of hydrocortisone** Crit Care Med 1998 26:645-50
- Scott, WJ. **The influence of the adrenal glands on resistance: II. The toxic effect of killed bacteria in adrenalectomized rats.** J Exp Med 1924; 39:457.
- LaNoue, K. F. et al **The Impairment of Glucogenesis by Gram Negative Infection.** Metabolism, 17:606, 1968.
- Schuler, J. J., Erve, P. R. and Schumer, W.: **Glucocorticoid Effect on Carbohydrate Metabolism in the Endotoxin-Shocked Monkey.** Ann. Surg. 183:345, 1976
- Veterans Administration Systemic Sepsis Cooperative Study Group: **Effect of high-dose glucocorticoid therapy on mortality in patients with clinical signs of systemic sepsis.** *N Engl J Med* 1987 , **317**:659-665
- Bone RC, et al **A controlled clinical trial of high-dose methylprednisolone in the treatment of severe sepsis and septic shock.** N Engl J Med. 1987;317:653–658.

References

- Beller BT, et al **Effectiveness of Modified Steroid-Antibiotic Therapies for Lethal Sepsis in the Dog** *Arch Surg*. 1983;118(11):1293-1299.
- Brigham et al. **Methylprednisolone Prevention of Increased Lung Vascular Permeability following Endotoxemia in Sheep** J Clin Invest. 1981 April; 67(4): 1103–1110.
- Briegel J et al. **Stress doses of hydrocortisone reverse hyperdynamic septic shock: a prospective, randomized, double-blind, single-center study.** Crit Care Med. 1999;27:723–732.
- Annane et al. **Impaired pressor sensitivity to noradrenaline in septic shock patients with and without impaired adrenal function reserve.** Br J Clin Pharmacol. 1998;46:589–597.
- Dellinger et.al, 2004, **Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock.** Crit Care Med. 2004 Mar;32(3):858-73
- Sprung et al, **Hydrocortisone therapy for patients with septic shock.** N Engl J Med. 2008 Jan 10;358(2):111-24.