Clinical Practice Guideline:

Do Steroids Administered in the Emergency Room Improve Mortality or Shock Reversal in Patients with Septic Shock? (2/14/10)

Reviewed and approved by the AAEM Clinical Practice Committee.

Chair: Steven Rosenbaum, MD

Author: Robert Sherwin, MD

Reviewers: A. Joseph Garcia, MD

Robert Bilkovski, MD

Lisa Mills, MD

Richard Shih, MD

Brian O'Neil, MD

Robert Welch, MD

Jack Perkins, MD

Steve Rosenbaum, MD

Reviewed and approved by the AAEM Board of Directors 2/14/2010.

1. Define the Issue and State the Question

A. Topic Area: Sepsis

B. General Issue: Steroid administration in septic shock

C. Clinical Question:

Do steroids administered in the emergency room improve mortality or shock reversal in patients with septic shock?

D. Executive Summary:

Answer: Overall Benefit: Yes. Although the literature is heterogeneous, underlying themes remain in distinct favor of steroid administration in patients with refractory septic shock. (Level of Recommendation: B1)
28-Day Mortality: No (Level of Recommendation: C)
Shock Reversal: Yes (Level of Recommendation: A)

The sepsis sub-committee reviewed seven trials formulated into this

recommendation.[1-7] All the included trials used hydrocortisone as the steroid of choice, and six of seven studies used a long protocol, which was defined as steroid treatment for ≥ 5 days.[8, 9]

Six of the seven trials reported a mortality outcome of patients in septic shock.[1-4, 6, 7] Pooled results from these six reports yielded 965 patients: 485 patients in the treatment group and 480 in the control group. Analysis of the data revealed that the relative risk (RR) of 28-day all-cause mortality in septic shock patients who received steroids was 0.92 (95% confidence interval (CI) 0.79–1.07). All seven trials reported data concerning *shock reversal* or the withdrawl of vasopressors. These seven trials had 1005 patients, with 503 and 502 patients in the intervention and control arms, respectively. Pooled results revealed that the RR of shock reversal is 1.17 (95% CI 1.07–1.28), which suggests a significant improvement in shock reversal following steroid administration.

It is important to understand that two of the seven studies reviewed were disproportionately represented and accounted for 799 of 1005 patients (80%) considered for this recommendation.[1, 7] Sprung et al reported no significant improvement in mortality from steroids in septic shock, regardless of the patient's response to a corticotropin stimulation test (CST). Though the proportion of patients who had shock reversal was not significantly different, the time to shock reversal was shorter in the treatment group (3.3 days, 95% CI, 2.9–3.9 versus 5.8 days, 95% CI 5.2–6.9). The authors concluded that hydrocortisone could *not* be recommended as a general adjuvant therapy for septic shock. In 2002, Annane et al[1] reported that mortality was not significantly improved overall, but they found a significant mortality reduction for patients not responding to a CST odds ratio (OR, 0.54, 95% CI 0.31–0.97) in addition to a two-day improvement in vasopressor withdrawl for all patients (hazard ratio 1.54, 95% CI, 1.10–2.16; p = 0.01). There were important design differences between these two studies, most notably the enrolment window (8 vs. 72 hours for Annane et al and Sprung et al, respectively) that may explain the divergent results between these two trials.

The heterogeneity of the studies can appear to yield conflicting results concerning the benefit of steroid administration in patients with septic shock. With respect to this, it is necessary to perform a risk-benefit analysis to weigh the benefit of an expedited shock reversal with the risks of hyperglycemia and other reported steroid risk. It appears that the evidence supports the notion that steroids reverse shock faster. However, mortality is not improved for the overall population..

2. Search

- Define separate strategy for each database / search process used in this review.
- Attach additional search strategies for other database / search processes in this review.

SEARCH _1_

A. Keywords used in search: [Sepsis OR severe sepsis OR septic shock OR septic syndrome] AND Steroids

B. Database Searched / Process Performed (Ovid, BIOMEDNET, PubMed, Cochrane, EMBASE, Textbook / Article Reference Review, etc):
_____MEDLINE_____
_____

C. Dates searched: From 1950 to 2008 with # of references_708__

D. Limits applied

limit ____Adult____ with # of references_321__

limit ____Human and English__ with # of references__284__

limit __ randomized controlled trials, all clinical trials, controlled clinical trial, meta-analysis and multicenter trial __ with # of references__51__

E. Final Search Result with # of references_____51____

SEARCH _2_

A. Keywords used in search: [Sepsis OR severe sepsis OR septic shock OR septic syndrome] AND Glucocorticoids

B. Database Searched / Process Performed (Ovid, BIOMEDNET, Pubmed, Cochrane, EMBASE, Textbook / Article Reference Review, etc): _____MEDLINE_____

C. Dates searched: From _1950 to 2008 with # of references__520__

D. Limits applied

limit ____Adult____ with # of references_126__

limit ____Human and English__ with # of references__106__

limit __ randomized controlled trials, all clinical trials, controlled clinical trial, meta-analysis and multicenter trial __ with # of references_____

E. Final Search Result with # of references___20___

SEARCH _3_

A. Keywords used in search: [Sepsis OR severe sepsis OR septic shock OR septic syndrome] AND [Prednisone OR Methylprednisolone OR Hydrocortisone OR Dexamethasone]

B. Database Searched / Process Performed (Ovid, BIOMEDNET, Pubmed, Cochrane, EMBASE, Textbook / Article Reference Review, etc): _____MEDLINE_____

C. Dates searched: From 1950 to 2008 with # of references_1218__

D. Limits applied

limit ____Adult____ with # of references_565__

limit ____Human and English__ with # of references__496__
limit __ randomized controlled trials, all clinical trials, controlled clinical trial, meta-analysis and multicenter trial __ with # of references_162_

E. Final Search Result with # of references_____162___

3. Final Evidence Database – Grade of Evidence Review

- For each reference from Step 2, assign a grade of evidence using reference focus, design, and methodology.
- Attach list of final evidence database with assigned grade of evidence.

Grade A Randomized clinical trials or meta-analyses (multiple clinical trials) or randomized clinical trials (smaller trials), directly addressing the review issue
Grade B Randomized clinical trials or meta-analyses (multiple clinical trials) or randomized clinical trials (smaller trials), indirectly addressing the review issue
Grade C Prospective, controlled, non-randomized, cohort studies
Grade D Retrospective, non-randomized, cohort or case-control studies
Grade E Case series, animal / model scientific investigations, theoretical analyses, or case reports
Grade F Rational conjecture, extrapolations, unreferenced opinion in literature, or common practice

4. Final Evidence Database – Quality Ranking

- Critically assess each reference with regard to design and methodology.
- Design Consideration – of the reference under review, consider the focus, model structure, presence of controls, etc.
- Methodology Consideration – of the reference under review, consider the methodology.
- Attach list of final evidence database with assigned quality of evidence

Ranking Design Consideration

Present
Methodology Consideration
Present
Both Considerations
Present
Outstanding Appropriate Appropriate Yes, both present
Good Appropriate Appropriate No, either present
Adequate Adequate with
Possible Bias
Adequate No, either present
Poor Limited or Biased Limited No, either present
Unsatisfactory Questionable / None Questionable / None No, either present

5. Assign the Reference Support of the Question

- Separate the references into three categories: supportive, neutral, opposed.
- Construct three tables assigning the references to the appropriate location using both Grade of Evidence and Quality of Evidence.
- Use lead author name, journal abbreviation, and year of publication as reference.

Supportive Evidence (MORTALITY)

Quality / Grade

A B C D E F
Outstanding
- Annane JAMA 2002[1]

Good
Adequate
Poor
Unsatisfactory
Neutral Evidence (MORTALITY)
Quality / Grade
A B C D E F
Outstanding
- Sprung NEJM 2008[7]
- Bollaert CCM 1998[2]
- Briegel CCM 1999[3]

Good
- Oppert CCM 2005[6]

Adequate
- Chawla CCM 1999[4]

Poor
Unsatisfactory
Opposing Evidence (MORTALITY)
Quality / Grade
A B C D E F
Outstanding
Good
Adequate
Poor
Unsatisfactory
Supportive Evidence (SHOCK REVERSAL)
Quality / Grade
A B C D E F
Outstanding
- Annane JAMA 2002[1]
- Bollaert CCM 1998[2]
- Keh CCM 2003[5]

Good
Adequate
- Chawla CCM 1999[4]

Poor
Unsatisfactory

Neutral Evidence (SHOCK REVERSAL)
Quality / Grade
A B C D E F
Outstanding
• Sprung NEJM 2008[7]
• Briegel CCM 1999[3]
Good
Adequate
Poor
Unsatisfactory
Opposing Evidence (SHOCK REVERSAL)
Quality / Grade
A B C D E F
Outstanding
Good
• Oppert CCM 2005[6]
Adequate
Poor
Unsatisfactory

6. Recommendation

- Answer the clinical question if possible
- Assign a level of recommendation
- Make a recommendation

A. Recommendation:

Overall Benefit: Yes. Although the literature is heterogeneous, underlying themes remain in distinct favor of steroid administration in patients with refractory septic shock. It is not clear that there is a distinct mortality benefit, but improvement of shock reversal is a consistent result.
(Level of Recommendation: B1)

28-Day Mortality: No (Level of Recommendation: C)

Shock Reversal: Yes (Level of Recommendation: A)

B. Level of recommendation:_____

Level of Recommendation Criteria for Level of Recommendation
Mandatory Evidence
Class A
recommended with outstanding evidence
• Acceptable
• Safe
• Useful
• Established / definitive

• Level A / B grade
• Outstanding quality
• Robust
• All positive

Class B

acceptable & appropriate with good evidence

• Acceptable
• Safe
• Useful
• Not yet definitive
• Level A / B grade lacking
• Adequate to Good quality
• Most evidence positive
• No evidence of harm

Class B 1

• Standard approach
• Higher grades of evidence
• Consistently positive

Class B 2

• Optional or alternative approach
• Lower grades of evidence
• Generally, but not consistently, positive

Class C

not acceptable or not appropriate

• Unacceptable
• Unsafe
• Not useful
• No positive evidence
• Evidence of harm

Class Indeterminate

Unknown

• Minimal to no evidence
• Minimal to no evidence

7. List all conflicts of interest:

_____
_____
_____

8. Discussion

- Discuss the clinical question – Address the issue
- Make a recommendation – Succinctly discuss the rationale and evidence supporting the recommendation.

Introduction

Basic elements of sepsis pathophysiology include hypovolemia, vasodilation,[10] myocardial suppression,[11, 12] microcirculatory dysfunction, and mitochondrial dysfunction.[13] Additionally, it is important to appreciate the intimate interwoven cascades of pro-inflammation, anti-inflammation, apoptosis, coagulation, and

complement activation.[14] It is clear, however, that there exists both a balance *and* an evolution of pro- and anti- inflammatory responses in sepsis.[14, 15] Although the steroid controversy can be traced back sixty years,[16] the association between hypothalamicpituitary-adrenal (HPA) dysfunction and sepsis is approaching a centennial.[17] In the 1980s, negative studies using "high-dose, industrial strength doses" were published.[18, 19] Further research demonstrated positive immunologic and clinical results from low-dose steroids.[20] The objective of this guideline is to provide an evidence-based recommendation for the administration of low-dose steroids (less than 300 mg of hydrocortisone or equivalent dose daily) in patients with septic shock to improve patient outcomes (mortality and shock reversal).

Clinical Question:
Does steroid administration improve either mortality or shock reversal in adult patients with septic shock?

Overall Benefit: Yes. Although the literature is heterogeneous, underlying themes remain in distinct favor of steroid administration in patients with refractory septic shock.
It is not clear that there is a distinct mortality benefit, but improvement of shock reversal is a consistent result. (Level of Recommendation: B1)
28-Day Mortality: No (Level of Recommendation: C)
Shock Reversal: Yes (Level of Recommendation: A)

Methods

A comprehensive MEDLINE search was performed using data from January 1950 through June 2009. The primary search included the following keywords: sepsis, severe sepsis, septic shock, septic syndrome, steroids, glucocorticoids, hydrocortisone, methylprednisolone, dexamethasone, and prednisone. Results were limited to studies involving all adult (19 plus years), human subjects written in the English language. The additional publication-type limits were set to include randomized controlled trials, all clinical trials, controlled clinical trials, meta-analysis and multicenter trials. These results were supplemented by manual review of key journals, bibliographies, and relevant source material to collect all identifiable evidence available to provide the final list of potential papers applicable to this recommendation. Only randomized controlled, original research trials, which utilized low-dose steroids and reported either mortality and/or time to shock reversal in adult patients diagnosed with septic shock were included. For trials which included non-adult, non-shock patients, only data from adult septic shock patients was considered. The search strategy yielded 28 unique articles focused on providing evidence specific to the efficacy of steroids in adult patients with septic shock.[1-7, 21-41] Twenty-one of the twenty-eight trials were excluded due to the pre-specified criteria including the use high dose steroids (seven trials), non-adult population (one trial), outcome of interest (mortality or shock reversal) not reported (four trials), reported only in abstract form (two trials), and non-septic shock population or septic shock data not separately reported (seven trials). Seven trials, were then subsequently reviewed by the sepsis subcommittee and formulated into this recommendation.[1-7, 24] All the included trials used hydrocortisone as the steroid of choice. Six of seven studies used a long protocol, previously defined as ≥ 5 days; however, it is a general consensus that steroids be tapered once the patient has been permanently weaned from vasopressors.[8, 9]

Six of the seven trials reviewed reported a mortality outcome of patients in septic shock.[1-4, 6, 7] Only two trials were powered for a mortality outcome.[1, 7] Pooled results from these six reports yielded 965 patients: 485 patients in the treatment group and 480 in the control group (Table 1). An analysis of the data revealed that the relative risk (RR) of 28-day all-cause mortality in septic shock patients receiving steroids was 0.92 (95% confidence interval (CI) 0.79–1.07).

All seven trials reported *shock reversal* or the withdrawl of vasopressors. The definition of shock reversal was heterogeneous throughout the literature. Trials ranged from shock reversal at day three to day twenty-eight and varied in the specific definition of shock reversal. Five trials reported shock reversal as a primary outcome measure.[2-6] These seven trials had 1005 patients, with 503 and 502 patients in the intervention and control arms, respectively. Pooled results reveal that the RR of shock reversal is 1.17 (95% CI 1.07–1.28), which suggests a significant improvement in shock reversal following steroid administration.

It is important to understand that two of the seven studies reviewed were disproportionately represented and accounted for 799 of 1005 patients (80%) considered for this recommendation.[1, 7] The most recent of these two trials, Sprung et al[7], reported no significant improvement in mortality from steroids in septic shock regardless of the patient's response to a corticotropin stimulation test (CST). Furthermore, though the proportion of patients who had shock reversal was not significantly different, the time to shock reversal was shorter in the treatment group (3.3 days, 95% CI, 2.9–3.9 versus 5.8 days, 95% CI 5.2–6.9). The authors further reported increased episodes of *new* septic shock in the treatment group, and concluded that hydrocortisone could *not* be recommended as a general adjuvant therapy for septic shock. Though the design and methods of the study were excellent, it must be clarified that patients were allowed to be enrolled into the study up to 72 hours after the onset of shock, which may arguably have negated any potential benefit steroids may have incurred.

The second largest study from Annane et al[1]n 2002 reported that the mean time on a vasopressor prior to treatment was 4.1 ± 3.0 and 4.1 ± 3.4 hours for the control and treatment groups, respectively. Though mortality was not significantly improved overall, they

Author, Year N
28-day Mortality
Relative Risk (95% CI)
Shock Reversal
Relative Benefit (95% CI)
Grade Quality
Reference Support
Mortality
Reference Support
Shock Reversal
Annane et al JAMA 2002[1] 300 0.89 (0.73-1.08) 1.28 (1.01-1.62) A Outstanding Supportive Supportive
Sprung et al NEJM 2008[7] 499 1.09 (0.85-1.40) 1.07 (0.98-1.18) A Outstanding Neutral Neutral
Bollaert et al CCM 1998[2] 41 0.50 (0.25-1.02) 3.24 (1.30-8.10) A Outstanding Neutral Supportive
Keh et al Am J Resp CCM 2003[5] 40 Not reported 2.33 (1.12-4.83) A Outstanding Not reported Supportive
Briegel et al CCM 1999[3] 40 0.75 (0.19-2.93) 1.13 (0.87-1.46) A Outstanding Neutral Neutral

Chawla et al CCM 1999[4] 40 0.55 (0.24-1.25) 2.09 (1.08-4.05) B Adequate Neutral Supportive
Oppert et al CCM 2005[6] 41 0.81 (0.40-1.67) 0.61 (0.37-0.99) A Good Neutral Opposed
Overall 965 0.92 (0.79-1.07) 1.17 (1.07-1.28) Outstanding Neutral Supportive

Table 1: Summary of included studies. SR, shock reversal; NR, nonresponders to a cortictropin stimulation test

reported significant mortality reduction for patients not responding to a CST (OR, 0.54, 95% CI 0.31–0.97) and also a two-day improvement in vasopressor withdrawl for all patients (hazard ratio 1.54, 95% CI 1.10– 2.16; p = 0.01). There were important design differences between these two trials, most notably the enrolment window (8 vs. 72 hours for Annane et al and Sprung et al, respectively) that may explain the divergent results between these two trials.

The question of steroid administration in septic shock is complicated. A thorough review of all of the clinical trials encompasses more than sixty years of research. The heterogeneity of the studies can appear to yield conflicting results; however, the literature must be distilled down to the specific question at hand: *Does steroid administration improve either mortality or shock reversal in adult patients with septic shock?* Considering this issue, it appears that the evidence supports the notion that steroids reverse shock faster, potentially freeing up valuable resources in the intensive care unit. Furthermore, though mortality may not be improved for the overall population, a portion of patients, who would otherwise be classified as nonresponders, may still benefit from steroids with minimal risk involved. However, mortality is not improved for the overall population..

References

1. Annane D, Sebille V, Charpentier C, et al. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. *JAMA*. 2002;288:862-71.
2. Bollaert PE, Charpentier C, Levy B, Debouverie M, Audibert G, Larcan A. Reversal of late septic shock with supraphysiologic doses of hydrocortisone. *Crit Care Med*. 1998;26:645-50.
3. Briegel J, Forst H, Haller M, et al. Stress doses of hydrocortisone reverse hyperdynamic septic shock: a prospective, randomized, double-blind, singlecenter study. *Crit Care Med*. 1999;27:723-32.
4. Chawla K, Kupfer Y, Goldman I, Tessler S. Hydrocortisone Reverses Refractory Septic Shock. *Critical Care Medicine*. 1999;27:33A.
5. Keh D, Boehnke T, Weber-Cartens S, et al. Immunologic and hemodynamic effects of "low-dose" hydrocortisone in septic shock: a double-blind, randomized, placebo-controlled, crossover study. *Am J Respir Crit Care Med*. 2003;167:512-20.
6. Oppert M, Schindler R, Husung C, et al. Low-dose hydrocortisone improves shock reversal and reduces cytokine levels in early hyperdynamic septic shock. *Crit Care Med*. 2005;33:2457-64.
7. Sprung CL, Annane D, Keh D, et al. Hydrocortisone therapy for patients with septic shock. *N Engl J Med*. 2008;358:111-24.
8. Annane D, Bellissant E, Bollaert PE, Briegel J, Keh D, Kupfer Y. Corticosteroids for severe sepsis and septic shock: a systematic review and meta-analysis. *BMJ*. 2004;329:480.
9. Dellinger RP, Levy MM, Carlet JM, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008.

Crit Care Med. 2008;36:296-327.
10. Rackow EC, Astiz ME. Pathophysiology and treatment of septic shock. *N Engl J Med*. 548-54, 1991 Jul 24-31.
11. Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med*. 1368-77, 2001 Nov 8.
12. Dellinger RP, Carlet JM, Masur H, et al. Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock. *Crit Care Med*. 536-55, 2004 Apr.
13. Brealey D, Brand M, Hargreaves I, et al. Association between mitochondrial dysfunction and severity and outcome of septic shock. *Lancet.* 219-23, 2002 Jul 20.
14. Hotchkiss RS, Karl IE. The pathophysiology and treatment of sepsis. *N Engl J Med*.138-50, 2003 Jan 9.
15. Antonelli M. Sepsis and septic shock: pro-inflammatory or anti-inflammatory state? *J Chemother*. 1999;11:536-40.
16. Perla D, Marmorston J. Suprarenal corticol hormone and salt in the treatment of pneumonia and other severe infections. *Endocrinology*. 1940;27:367-74.
17. Waterhouse R. Case of suprarenal apoplexy. *Lancet.* 1911;1:577.
18. Bone RC, Fisher CJ, Jr., Clemmer TP, Slotman GJ, Metz CA, Balk RA. A controlled clinical trial of high-dose methylprednisolone in the treatment of severe sepsis and septic shock. *N Engl J Med.* 653-8, 1987 Sep 10.
19. Sprung CL, Caralis PV, Marcial EH, et al. The effects of high-dose corticosteroids in patients with septic shock. A prospective, controlled study. *N Engl J Med*. 1137-43, 984 Nov 1.
20. Barber AE, Coyle SM, Marano MA, et al. Glucocorticoid therapy alters hormonal and cytokine responses to endotoxin in man. *J Immunol*. 1993;150:1999-2006.
21. Aboab J, Polito A, Orlikowski D, Sharshar T, Castel M, Annane D. Hydrocortisone effects on cardiovascular variability in septic shock: a spectral analysis approach. *Crit Care Med*. 2008;36:1481-6.
22. Bennett I, Finland M, Hamburger M, Kass E, Lepper M, Waisbren BA. The effectiveness of hydrocortisone in the management of severe infection. *JAMA*. 1963;183:462-5.
23. Bone RC, Fisher CJ, Jr., Clemmer TP, Slotman GJ, Metz CA, Balk RA. A controlled clinical trial of high-dose methylprednisolone in the treatment of severe sepsis and septic shock. *N Engl J Med*. 1987;317:653-8.
24. Cooperative Study Group. The effectiveness of hydrocortisone in the management of pateints with severe infections. *JAMA*. 1963;183:462-5.
25. Hahn EO, Houser HB, Rammelkamp CH, Jr., Denny FW, Wannamaker LW. Effect of cortisone on acute streptococcal infections and poststreptococcal complications. *J Clin Invest*. 1951;30:274-81.
26. Hughes GS, Jr. Naloxone and methylprednisolone sodium succinate enhance sympathomedullary discharge in patients with septic shock. *Life Sci*. 1984;35:2319-26.
27. Kaufmann I, Briegel J, Schliephake F, et al. Stress doses of hydrocortisone in septic shock: beneficial effects on opsonization-dependent neutrophil functions. *Intensive Care Med*. 2008;34:344-9.
28. Klastersky J, Cappel R, Debusscher L. Effectiveness of betamethasone in management of severe infections. A double-blind study. *N Engl J Med*. 1971;284:1248-50.
29. Lucas CE, Ledgerwood AM. The cardiopulmonary response to massive doses of steroids in patients with septic shock. *Arch Surg*. *Bulletin of Johns Hopkins Hospital*. 1984;119:537-41.

30. Luce JM, Montgomery AB, Marks JD, Turner J, Metz CA, Murray JF. Ineffectiveness of high-dose methylprednisolone in preventing parenchymal lung injury and improving mortality in patients with septic shock. *Am Rev Respir Dis*. 1988;138:62-8.
31. McKee JI, Finlay WE. Cortisol replacement in severely stressed patients. *Lancet*. 1983;1:484.
32. Meduri GU, Chrousos GP. Effectiveness of prolonged glucocorticoid treatment in acute respiratory distress syndrome: the right drug, the right way? *Crit Care Med*. 2006;34:236-8.
33. Rogers J. Large doses of steroids in septicaemic shock. *Br J Urol*. 1970;42:742.
34. Schumer W. Steroids in the treatment of clinical septic shock. *Ann Surg*. 1976;184:333-41.
35. Slusher T, Gbadero D, Howard C, et al. Randomized, placebo-controlled, double blinded trial of dexamethasone in African children with sepsis. *Pediatr Infect Dis J*. 1996;15:579-83.
36. Sprung CL, Caralis PV, Marcial EH, et al. The effects of high-dose corticosteroids in patients with septic shock. A prospective, controlled study. *N Engl J Med. 1984*;311:1137-43.
37. Thompson W, Gurley H, Lutz B, Jackson D, Kylos L, Morris I. Inefficacy of glucocorticoid therapy in shock (double-blind study) [Abstract]. *Clin Res*. 1976;24:258A.
38. 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;317:659-65.
39. Wagner H, Bennett I, Lasagna L, Cluff L, Rosenthal M, Mirick G. The effect of hydrocortisone upon the course of pneumococcal pneumonia treated with penicillin. Bull Johns Hopkins Hosp 1955;98:197-215.
40. Weigelt JA, Norcross JF, Borman KR, Snyder WH, 3rd. Early steroid therapy for respiratory failure. *Arch Surg*. 1985;120:536-40.
41. Yildiz O, Doganay M, Aygen B, Guven M, Kelestimur F, Tutuu A. Physiologicaldose steroid therapy in sepsis [ISRCTN36253388]. *Crit Care*. 2002;6:251-9.