Steroids Should be Used to Treat Patients With Septic Shock Pro

John J. Marini
Professor of Medicine
University of Minnesota
Minneapolis / St. Paul (USA)
The Ideal Clinical Trial

• **Sharply defined population**
• Testable questions... Defined mechanism, appropriate outcome variables, solid preliminary data, high impact likely
• Well designed, *mechanism-driven* protocol
• Targeted dosing and duration
• Flawless methodology
• Tight co-intervention control
• Unbiased data collection and analysis
• Relevant to the practice of the *individual* caregiver and *individual* patient
Clinical Trials in Critical Care

What Have We Really Learned?

- Precise definitions are needed before an RCT can be usefully translated into practice.

- Complexity of critical illness and variation of practice environments render RCTs difficult to execute and limit their relevance to bedside management.

- RCTs are a potentially dangerous methodology when misapplied or misinterpreted.
  - Most questions cannot or should not be “trialed.”
GOOD INTENTIONS
bad results
Use Steroids in Septic Shock?
High or Low Dose?
Corticosteroids For Septic Shock—Yes!

A Few Questions

- Why *should* they work?
- Which Patients?
- When?
- Which Drug?
- Which Dose?
- Duration?
- Risk?
Corticosteroids For Septic Shock—Yes!

A Few Questions

• Why *should* they work?
  – Suppression of dysfunctional inflammation
  – Restoration of vasomotor receptivity
Sequence of Mediator Responses
Cortisol Operates At Multiple Points to Modify Mediator Output

[Diagram showing interactions between stress, CRH, IL-1, TNF, IL-6, LIF, IL-11, TNF, TGF-beta, endotoxin, Cortisol, ACTH, CRH, LIF, and related gene transcription.]
Effects of Hydrocortisone on the Microcirculation in Septic Shock

Immunologic and Hemodynamic Effects of "Low-Dose" Hydrocortisone in Septic Shock
A Double-Blind, Randomized, Placebo-controlled, Crossover Study

Didier Keh, Thomas Boehnke, Steffen Weber-Cartens, Christina Schulz, Olaf Ahlers, Sven Bercker, Hans-Dieter Volk, Wolf-Dietrich Doecke, Konrad J. Falke, and Herwig Gerlach
Steroids do NOT suppress Anti-inflammatory IL-10

IL-6
Pro-Inflammatory

IL-10
Anti-Inflammatory
Corticosteroids For Septic Shock—Yes!

A Few Questions

- Which Patients?
Hydrocortisone Therapy for Patients with Septic Shock

Charles L. Sprung, M.D., Djillali Annane, M.D., Ph.D., Didier Keh, M.D., Rui Moreno, M.D., Ph.D., Mervyn Singer, M.D., F.R.C.P., Klaus Freivogel, Ph.D., Yoram G. Weiss, M.D., Julie Benbenishty, R.N., Armin Kalenka, M.D., Helmuth Forst, M.D., Ph.D., Pierre-Francois Laterre, M.D., Konrad Reinhart, M.D., Brian H. Cuthbertson, M.D., Didier Payen, M.D., Ph.D., and Josef Briegel, M.D., Ph.D., for the CORTICUS Study Group

CONCLUSIONS

Hydrocortisone did not improve survival or reversal of shock in patients with septic shock, either overall or in patients who did not have a response to corticotropin, although hydrocortisone hastened reversal of shock in patients in whom shock was reversed. (ClinicalTrials.gov number, NCT00147004.)
MEDICAL GRAND ROUNDS

EDUCATIONAL OBJECTIVE: Readers will consider the recommendations of the Surviving Sepsis Campaign when treating patients with sepsis

R. PHILLIP DELLINGER, MD, MSc, MCCM
Professor and Chair of Medicine, Cooper Medical School of Rowan University, Camden, NJ; Director, Adult Health Institute, and Senior Critical Care Attending, Cooper University Hospital, Camden, NJ; Steering Committee, Surviving Sepsis Campaign

The Surviving Sepsis Campaign: Where have we been and where are we going?

Corticosteroids should be considered only for patients who remain unstable despite adequate fluid resuscitation and vasopressor therapy.
Recommendation. Intravenous corticosteroids should not be used in adults with septic shock if adequate fluid resuscitation and vasopressor therapy restore hemodynamic stability (grade 2C). However, a patient on high doses of multiple vasopressors after adequate fluid resuscitation would likely benefit.
The Japanese guidelines for the management of sepsis

Shigeto Oda1*, Mayuki Aibiki2, Toshiaki Ikeda3, Hitoshi Imazumi4, Shigeatsu Endo5, Ryoichi Ochi6, Joji Kotani7, Nobuaki Shime8, Osamu Nishida9, Takayuki Noguchi10, Naoyuki Matsuda11, Hiroyuki Hirasawa12 and Sepsis Registry Committee of The Japanese Society of Intensive Care Medicine

Steroid

CQ1: What is the indication of steroid therapy in sepsis?

A1:
- The use of steroids is aimed at early recovery from shock in adult patients with septic shock who do not respond to initial fluid resuscitation and vasoactive drugs (2B).
- Adrenocorticotropic hormone (ACTH) testing is not required to determine the indication for steroid therapy (2B).
Corticosteroids For Septic Shock—Yes!

A Few Questions

• When?
  – It is important to *avoid and reverse hypotension quickly* in sepsis!
Anti-Inflammatory Steroid Effects Are Seen Early

(CHEST 2007; 131:954–963)
Low Dose Steroids Improve Hemodynamics Quickly

**Figure 3.** Kaplan–Meier Curves for the Time to Reversal of Shock.
The Earlier The Better For Low Dose Steroids in Septic Shock
### The Evidence Favors Shock Reversal

Table 3. Summary of Included Studies

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>n</th>
<th>28-day Mortality Relative Risk (95% CI)</th>
<th>Shock Reversal Relative Benefit (95% CI)</th>
<th>Grade</th>
<th>Quality</th>
<th>Reference Support Mortality</th>
<th>Reference Support Shock Reversal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annane et al., 2002 (10)</td>
<td>300</td>
<td>0.89 (0.73–1.08)</td>
<td>1.28 (1.01–1.62)</td>
<td>A</td>
<td>Outstanding</td>
<td>Supportive</td>
<td>Supportive</td>
</tr>
<tr>
<td>Sprung et al., 2008 (29)</td>
<td>499</td>
<td>1.09 (0.85–1.40)</td>
<td>1.07 (0.98–1.18)</td>
<td>A</td>
<td>Outstanding</td>
<td>Neutral</td>
<td>Neutral</td>
</tr>
<tr>
<td>Bollaert et al., 1998 (12)</td>
<td>41</td>
<td>0.50 (0.25–1.02)</td>
<td>3.24 (1.30–8.10)</td>
<td>A</td>
<td>Outstanding</td>
<td>Neutral</td>
<td>Supportive</td>
</tr>
<tr>
<td>Keh et al., 2003 (19)</td>
<td>40</td>
<td>Not reported</td>
<td>2.33 (1.12–4.83)</td>
<td>A</td>
<td>Outstanding</td>
<td>Not reported</td>
<td>Supportive</td>
</tr>
<tr>
<td>Biegerl et al., 1999 (13)</td>
<td>40</td>
<td>0.75 (0.19–2.93)</td>
<td>1.13 (0.87–1.46)</td>
<td>A</td>
<td>Outstanding</td>
<td>Neutral</td>
<td>Neutral</td>
</tr>
<tr>
<td>Chawla et al., 1999 (14)</td>
<td>44</td>
<td>0.55 (0.24–1.25)</td>
<td>2.09 (1.08–4.05)</td>
<td>B</td>
<td>Adequate</td>
<td>Neutral</td>
<td>Supportive</td>
</tr>
<tr>
<td>Oppert et al., 2005 (25)</td>
<td>41</td>
<td>0.81 (0.40–1.67)</td>
<td>0.61 (0.37–0.99)</td>
<td>A</td>
<td>Good</td>
<td>Neutral</td>
<td>Neutral</td>
</tr>
<tr>
<td>Overall</td>
<td>1005</td>
<td>0.92 (0.79–1.07)</td>
<td>1.17 (1.07–1.28)</td>
<td>A</td>
<td>Outstanding</td>
<td>Neutral</td>
<td>Supportive</td>
</tr>
</tbody>
</table>
Early Dexamethasone for Inflammation Suppression in Pneumonia

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Dexamethasone group (n=151)</th>
<th>Placebo group (n=153)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length of stay (days)</td>
<td>6.5 (5.0–9.0)</td>
<td>7.5 (5.3–11.5)</td>
<td>0.0480</td>
</tr>
<tr>
<td>In-hospital mortality</td>
<td>8 (5%)</td>
<td>8 (5%)</td>
<td>0.98</td>
</tr>
<tr>
<td>Time to death (days)</td>
<td>5.5 (2.6–18.9)</td>
<td>8.8 (3.8–12.8)</td>
<td>0.64</td>
</tr>
<tr>
<td>30-day mortality</td>
<td>9 (6%)</td>
<td>11 (7%)</td>
<td>0.68</td>
</tr>
<tr>
<td>ICU admission</td>
<td>7 (5%)</td>
<td>10 (7%)</td>
<td>0.47</td>
</tr>
<tr>
<td>Time to ICU admission (days)</td>
<td>2.5 (1.5–6.5)</td>
<td>1.8 (1.5–2.6)</td>
<td>0.34</td>
</tr>
<tr>
<td>Length of stay in ICU (days)</td>
<td>21.5 (14.5–28.5)</td>
<td>15.5 (10.1–28.5)</td>
<td>0.23</td>
</tr>
<tr>
<td>Empyema or pleural effusion</td>
<td>7 (5%)</td>
<td>5 (3%)</td>
<td>0.54</td>
</tr>
<tr>
<td>Readmission within 30 days</td>
<td>7 (5%)</td>
<td>7 (5%)</td>
<td>0.98</td>
</tr>
</tbody>
</table>

Data are median (IQR) or n (%), unless otherwise stated. ICU-intensive-care unit.

Table 2: Outcomes for all enrolled patients

Interpretation

Our study shows that a 4-day course of 5 mg dexamethasone reduces length of hospital stay in patients admitted for community-acquired pneumonia. The faster decline in concentrations of C-reactive protein and interleukin-6 that we noted in patients given dexamethasone compared with controls support the notion that dexamethasone reduces the systemic inflammatory response. Although serious adverse events were rare, the benefits of corticosteroids should be weighed against the potential side-effects.
Dexamethasone and length of hospital stay in patients with community-acquired pneumonia: a randomised, double-blind, placebo-controlled trial

Sabine C A Meijvis, Hans Hardeman, Hilde H F Remmelts, Rik Heijligenberg, Ger T Rijkers, Heleen van Velzen-Blad, G Paul Voorn, Ewoudt M W van de Garde, Henrik Endeman, Jan C Grutters, Willem Jan W Bos, Douwe H Biesma

Summary
Background Whether addition of corticosteroids to antibiotic treatment benefits patients with community-acquired pneumonia who are not in intensive care units is unclear. We aimed to assess effect of addition of dexamethasone on length of stay in this group, which might result in earlier resolution of pneumonia through dampening of systemic inflammation.

Procedures
Patients in the dexamethasone group were given a bolus of 5 mg (1 mL) of dexamethasone (dexamethasone-disodiumphosphate 5 mg. Centrafarm BV, Etten-Leur, Netherlands) intravenously and patients in the placebo group were given 1 mL of sterile water for injection (Centrafarm BV) intravenously at the emergency unit, within a maximum of 12 h from admission. All patients received antibiotics before study treatment was given. For the subsequent 3 days, patients received either intravenous dexamethasone 5 mg (1 mL) or sterile water (1 mL) once a day. Selection, duration, and administration

Interpretation Dexamethasone can reduce length of hospital stay when added to antibiotic treatment in non-immunocompromised patients with community-acquired pneumonia.
Early Severe ARDS Survival

(CHEST 2007; 131:954–963)
High Dose (Anti-inflammatory) Steroids Hasten Ventilator Independence in *Second Phase* ARDS
Corticosteroids For Septic Shock—Yes!

A Few Questions

• Which Drug and which Dose?
  – Replacement?
  – Immune Suppression?
Immunologic and Hemodynamic Effects of "Low-Dose" Hydrocortisone in Septic Shock
A Double-Blind, Randomized, Placebo-controlled, Crossover Study

Didier Keh, Thomas Boehnke, Steffen Weber-Cartens, Christina Schulz, Olaf Ahlers, Sven Bercker, Hans-Dieter Volk, Wolf-Dietrich Doecke, Konrad J. Falke, and Herwig Gerlach
The Surviving Sepsis Campaign: Where have we been and where are we going?

Recommendation. If corticosteroid therapy is used, hydrocortisone 200 mg should be given over 24 hours, preferentially by continuous intravenous infusion but alternatively 50 mg every 6 hours (grade 2D). This regimen can be continued for up to 7 days or tapered when shock resolves.
Corticosteroids For Septic Shock—Yes!

A Few Questions

• Duration?
  – Long enough to meet the purpose!
Efficacy and Safety of Corticosteroids for Persistent Acute Respiratory Distress Syndrome

The National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network*

The methylprednisolone group had significantly more ventilator-free days than the placebo group during the first 28 days (Table 2) as well as at 180 days (Table 3). Patients given methylprednisolone were able to breathe without assistance sooner than patients given placebo (14.1 days vs. 23.6 days, P=0.006) (Fig. 2). As compared with the placebo group, the methylprednisolone group also had significantly fewer days in the intensive care unit (ICU) during the first 28 days.
What Happened?
Dose, Duration, Withdrawal?
CQ3: How should steroids be administered and what should be the duration of treatment?

A3:

- Low-dose and long-term steroid therapy, such as $\leq 300$ mg/day hydrocortisone for $\geq 5$ days, is recommended (1A).

- For hydrocortisone, an equivalent dose of 200 mg/day is divided into four doses, or a continuous infusion of 10 mg/h (240 mg/day) is administered after a bolus dose of 100 mg (2B).
TAKE HOME MESSAGE

Long courses of low-dose corticosteroids reduce mortality in septic shock at 28 days in ICUs and in the hospital. They also improve systemic hemodynamics and reduce the time on vasopressor treatment without significantly altering the risk of gastroduodenal bleeding, superinfections, or hyperglycemia.
Corticosteroids For Septic Shock—Yes!

A Few Questions

• Risk?
  – Dose dependent!
### Table 4. Adverse Events (Per-Protocol Population).*

<table>
<thead>
<tr>
<th>Event</th>
<th>Hydrocortisone (N = 234)</th>
<th>Placebo (N = 232)</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no. of patients (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Superinfection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Catheter-related</td>
<td>3 (1)</td>
<td>3 (1)</td>
<td>0.99 (0.20–4.86)</td>
</tr>
<tr>
<td>Lung</td>
<td>34 (15)</td>
<td>30 (13)</td>
<td>1.12 (0.71–1.77)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>22 (9)</td>
<td>19 (8)</td>
<td>1.15 (0.64–2.06)</td>
</tr>
<tr>
<td>Urinary tract</td>
<td>11 (5)</td>
<td>10 (4)</td>
<td>1.09 (0.47–2.52)</td>
</tr>
<tr>
<td>Wound</td>
<td>9 (4)</td>
<td>7 (3)</td>
<td>1.27 (0.48–3.37)</td>
</tr>
<tr>
<td>Other</td>
<td>16 (7)</td>
<td>8 (3)</td>
<td>1.98 (0.87–4.54)</td>
</tr>
<tr>
<td>New sepsis</td>
<td>6 (3)</td>
<td>2 (1)</td>
<td>2.97 (0.61–14.59)</td>
</tr>
<tr>
<td>New septic shock</td>
<td>14 (6)</td>
<td>5 (2)</td>
<td>2.78 (1.02–7.58)</td>
</tr>
<tr>
<td>Other adverse event</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anastomotic leak</td>
<td>4 (2)</td>
<td>4 (2)</td>
<td>0.99 (0.25–3.92)</td>
</tr>
<tr>
<td>Wound dehiscence</td>
<td>2 (1)</td>
<td>2 (1)</td>
<td>0.99 (0.14–6.98)</td>
</tr>
<tr>
<td>Repeat shock</td>
<td>72 (31)</td>
<td>57 (25)</td>
<td>1.25 (0.93–1.68)</td>
</tr>
<tr>
<td>Bleeding</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>21 (9)</td>
<td>16 (7)</td>
<td>1.30 (0.70–2.43)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>15 (6)</td>
<td>13 (6)</td>
<td>1.14 (0.56–2.35)</td>
</tr>
</tbody>
</table>
Efficacy and Safety of Corticosteroids for Persistent Acute Respiratory Distress Syndrome

The National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network*

PATIENTS
Patients who were intubated and receiving mechanical ventilation were eligible for enrollment 7 to 28 days after the onset of ARDS as previously defined.† The ratio of the partial pressure of arterial oxygen to fraction of inhaled oxygen (PO₂/FI₂O₂) was ≥300. Patients were stratified according to hospital. A single dose of 2 mg of methylprednisolone per kilogram of predicted body weight was followed by a dose of 0.5 mg per kilogram of predicted body weight every 6 hours for 14 days, a dose of 0.5 mg per kilogram of predicted body weight every 12 hours for 7 days, and then tapering of the dose. Study drug was tapered over a period of 4 days if 21 days of treatment had been completed and the patient was unable to breathe without assistance for a period of 48 hours. Tapering occurred over...
Corticosteroids for Severe Sepsis and Septic Shock

length of hospital stay in survivors and showed no difference between groups (data not shown).

Serious Adverse Events. Data for adverse events for treated vs control patients, respectively, are as follows. Gastroduodenal bleeding (data available in 1594 patients) was observed in 65 of 827 (7.9%) vs 56 of 767 (7.3%) (RR, 1.12; 95% CI, 0.81-1.53; \( P = .50 \)), with no heterogeneity across the studies (\( I^2 = 0\% \)). Superinfections (data available for 1917 patients) were observed in 184 of 983 (18.7%) vs 170 of 934 (18.2%) (RR, 1.01; 95% CI, 0.82-1.25; \( P = .92 \)), with no heterogeneity across the studies (\( I^2 = 8\% \)). Neuromuscular weakness (data available for 811 patients) was observed in 4 of 407 (1%) vs 7 of 404 (1.7%) (RR, 0.63; 95% CI, 0.12-3.35; \( P = .58 \)), with some heterogeneity across studies (\( I^2 = 30\% \)). In contrast, hyperglycemia (data available for 1434 patients) was observed in 385 of 745 (51.7%) vs 314 of 689 (45.6%) (RR, 1.16; 95% CI, 1.07-1.25; \( P < .001 \)), with no heterogeneity across the studies (\( I^2 = 0\% \)). Hypernatremia (data avail-
The exact dose of glucocorticoids to use for patients with life-threatening asthma is largely based on expert opinion. A higher initial dose of methylprednisolone 60 to 80 mg every 6 to 12 hours is often chosen for patients who are admitted to the intensive care unit. A lower initial dose of 40 to 60 mg every 12 to 24 hours is likely adequate for patients who are admitted to the hospital, but do not require intensive care. A massive initial dose (eg, methylprednisolone 500 mg intravenous bolus) is no more effective than a large initial dose (125 mg).

Duration — As a rough guide, most severe attacks that require hospitalization will resolve (with return of lung function to baseline) in 10 to 14 days. Alternatively, patients can stop their oral glucocorticoids sooner based on resolution of their symptoms and self-monitored peak flow values (eg, when peak expiratory flow is greater than 70 percent of baseline). Tapering oral glucocorticoids is not necessary if the duration of glucocorticoid treatment is less than three weeks (a duration too brief to cause adrenal atrophy) and if inhaled glucocorticoids are concomitantly prescribed for ongoing therapy (to prevent relapse).
For Severely Ill Who Are Refractory To Fluids and Vasopressors

- Strong Physiologic Rationale
- Speeds Shock Reversal
- Accelerates Ventilator Weaning
- Fast Response Time
- Tolerable Side Effects and Complications

- Low Cost
- Simple to Implement
Corticosteroids For Septic Shock—Yes!

* A Few Questions & Answers

- **Why should they work?**
  - Rebalance inflammation & response
  - Restore appropriate cortisol output & vascular responsiveness
- **Which Patients?**
  - Refractory to fluids and vasopressors
- **Which Drug?**
  - Hydrocortisone
- **Which Dose?**
  - 200-300 mg/day by infusion or 50 mg q 6h
Corticosteroids For Septic Shock—Yes!

A Few Questions & Answers

• When?
  – Sooner is better

• Duration?
  – At least 5 days then taper over 3 days if helpful
  – At least 3 days then stop if not helpful

• Risk?
  – Hyperglycemia is routine but addressable
  – Infection (but hazard is low at low doses)
  – Surveillance and re-evaluation are keys to prevention
Figure 1: Decision tree for practical use of corticosteroids at bedside

1. **Septic shock**
   - Onset < 24 hours
     - **YES**
       - Norepinephrine dose > 0.5 μg/kg/min
         - **YES**
           - Perform a 250μg ACTH test
             - Start hydrocortisone 200mg per day and fludrocortisone 50 μg per day
             - At day 2:
               - Norepinephrine dose reduce by >50%
                 - **OR**
                   - Cortisol increment < 250 nmol/L
                     - **NO**
                       - Stop corticosteroids
                     - **YES**
                       - Continue for 5 days and then tapered off over 2 to 3 days
                         - **OR**
                           - Continue for 7 days at full dose and stop
               - **NO**
                 - Stop corticosteroids
     - **NO**
       - Don't give corticosteroids
I SHOULD HAVE BEEN DOING THIS THE WHOLE TIME!

IT'S A NO BRAINER
Glucocorticoids for ARDS

Just Do It!
Here’s to YOU, Charlie!