Sepsis: What do we do now?

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Evidence Based Treatment of Sepsis

- Epidemiology
- Surviving Sepsis Campaign; Institute for Healthcare Improvement
- Early Goal Directed Therapy
- BP Target and Pressors
- Steroids
- Activated Protein C
- Implementation of Standard Operating Procedures
Incidence of Sepsis in US 1979-2000

Martin et al, NEJM 2003; 348: 1546-1554
Sepsis Incidence in US 1979-2000

Martin et al, NEJM 2003; 348: 1546-1554
Mortality from Sepsis 1979-2000

Proportion of Patients with Sepsis Who Died

Martin et al, NEJM 2003; 348: 1546-1554
Surviving Sepsis Campaign

- Initiative of the European Society of Intensive Care Medicine, the International Sepsis Forum, and the Society of Critical Care Medicine
- Global program to reduce mortality rates in severe sepsis
- Publication of evidence based guidelines in 2004
- 11 international critical care and infectious disease societies represented
- International guidelines updated in 2008
Surviving Sepsis Campaign

• New grading system
  – Continues to categorize quality of evidence graded from A to D (A is highest)
  – Adds a numerical score
    • 1 means “recommend,” “strong recommendation,” or “do it”
    • 2 means “suggest,” “weak recommendation,” or “probably do it”
Institute for Healthcare Improvement (IHI) Sepsis Bundles

1. Sepsis Resuscitation Bundle

2. Sepsis Management Bundle
Institute for Healthcare Improvement (IHI) Sepsis Bundles

1. Resuscitation Bundle
   - Measure serum lactate (Grade 1C)
   - Obtain blood cultures prior to antibiotic administration (Grade 1C)
   - Administer early broad spectrum antibiotics (Grade 1B)
     - Treat hypotension and/or elevated lactate with fluids (Grade 1B)
   - Apply vasopressors for persistent hypotension (Grade 1C)
   - Maintain adequate CVP (Grade 1B)
   - Maintain adequate ScVO2 (Grade 1B)
Institute for Healthcare Improvement (IHI) Sepsis Bundles

2. Management Bundle

- Administer low dose steroids by standard policy (Grade 2C)
- Administer activated protein C by standard policy (Grade 2B; 2C for post-operative patients)
- Maintain adequate glycemic control BG < 150 mg/dL (Grade 2C)
- Prevent excessive inspiratory plateau pressures (limit to < 30 cmH₂O) (Grade 1B)
Early Goal-Directed Therapy
• Background:
  – Purpose of study to evaluate efficacy of early goal-directed therapy before ICU admission
  – Approach involves adjusting preload, afterload, and contractility to balance oxygen delivery and demand

Rivers et al, NEJM, 2001; 345:1368-77
• Randomized, prospective trial
• 260 patients randomized; 2/4 SIRS criteria and SBP ≤ 90 mmHg or lactate ≥ 4 mmol/L
• Patients randomized to 6 hours of goal-directed therapy vs. standard therapy

Rivers et al, NEJM, 2001;345:1368-77
Supplemental oxygen + endotracheal intubation and mechanical ventilation

Central venous and arterial catheterization

Sedation, paralysis (if intubated), or both

Crystalloid

Colloid

Vasoactive agents

Transfusion of red cells Until hematocrit > 30%

Inotropic agents

Hospital admission

Yes

Goals Achieved

Rivers et al, NEJM, 2001;345:1368-77
Early Goal-Directed Therapy in Patients with Severe Sepsis


- In-hospital mortality 30.5% with EGDT vs. 46.5% with standard therapy
- 42% ↓ in relative risk of in-hospital and 28-day mortality (P=0.009, P=0.01)
- 33% ↓ in relative risk of death at 60 days (P=0.03)
Intensive Insulin Therapy and Pentastarch Resuscitation in Severe Sepsis

Frank M. Brunkhorst, M.D., Christoph Engel, M.D., Frank Bloos, M.D., Ph.D., Andreas Meier-Hellmann, M.D., Max Ragaller, M.D., Norbert Weiler, M.D., Onnen Moerer, M.D., Matthias Gruendling, M.D., Michael Oppert, M.D., Stefan Grond, M.D., Derk Olthoff, M.D., Ulrich Jaschinski, M.D., Stefan John, M.D., Rolf Rossaint, M.D., Tobias Welte, M.D., Martin Schaefer, M.D., Peter Kern, M.D., Evelyn Kuhnt, M.Sc., Michael Kiehntopf, M.D., Christiane Hartog, M.D., Charles Natanson, M.D., Markus Loeffler, M.D., Ph.D., and Konrad Reinhart, M.D., for the German Competence Network Sepsis (SepNet)

Brunkhorst et al, NEJM 2008; 358 (2): 125-139
Intensive Insulin Therapy and Pentastarch Resuscitation in Severe Sepsis

- Multicenter, two-by-two factorial trial
- 537 patients
- Intensive versus conventional insulin therapy
- 10% pentastarch versus Ringer’s lactate
- Results:
  - Patients with sepsis are at increased risk of adverse events with the use of intensive insulin therapy
  - Pentastarch therapy associated with higher rates of renal failure and RRT

Brunkhorst et al, NEJM 2008; 358 (2): 125-139
A Comparison of Albumin and Saline for Fluid Resuscitation in the Intensive Care Unit

The SAFE Study Investigators*

NEJM 2004; 350:2247-56
Is albumin administration in the acutely ill associated with increased mortality? Results of the SOAP study

Jean-Louis Vincent¹, Yasser Sakr¹, Konrad Reinhart², Charles L Sprung³, Herwig Gerlach⁴, V Marco Ranieri⁵ for the 'Sepsis Occurrence in Acutely Ill Patients' investigators

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Received: 9 May 2005  Revisions requested: 24 Jun 2005  Revisions received: 13 Sep 2005  Accepted: 7 Oct 2005  Published: 7 Nov 2005

This article is online at: http://ccforum.com/content/9/6/R745
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Pressors
Blood Pressure Target

- BP targets are arbitrary
- Autoregulation lost below MAP 55-60 mmHg
- What is the data that we should target a MAP of 65 mmHg?
Increasing mean arterial pressure in patients with septic shock: Effects on oxygen variables and renal function

Aurélie Bourgoin, MD; Marc Leone, MD; Anne Delmas, MD; Franck Garnier, MD; Jacques Albanèse, MD; Claude Martin, MD, FCCM

Increasing Mean Arterial Pressure

Blood Lactate (meq/l)

Oxygen Consumption (ml/min/m²)

Oxygen Delivery (ml/min/m²)

Oxygen Extraction Ratio (%)

* p < 0.01 versus baseline

* p < 0.05 versus baseline
Increasing Mean Arterial Pressure

Urine Output (ml/h)
Creatinine Clearance (ml/min)

Table 3. Biochemical variables, median (range)

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n = 14) MAP, 65 mm Hg</th>
<th>Group 2 (n = 14) MAP, 85 mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>8 Hrs</td>
</tr>
<tr>
<td>Arterial Pao\textsubscript{2}, mm Hg</td>
<td>70 (57–115)</td>
<td>75 (54–117)</td>
</tr>
<tr>
<td>Arterial Pco\textsubscript{2}, mm Hg</td>
<td>35 (30–42)</td>
<td>35 (31–44)</td>
</tr>
<tr>
<td>Hemoglobin, g · 100 mL\textsuperscript{−1}</td>
<td>10.0 (7.9–13.4)</td>
<td>9.8 (7.7–13.1)</td>
</tr>
</tbody>
</table>

MAP, mean arterial pressure.
Dopamine

- Does not confer clinically significant protection against renal dysfunction
- Tachycardia more common than with norepinephrine
- May impair splanchnic blood flow
Does dopamine administration in shock influence outcome? Results of the Sepsis Occurrence in Acutely Ill Patients (SOAP) Study

Yasser Sakr, MB, BCh, MSc; Konrad Reinhart, MD, PhD; Jean-Louis Vincent, MD, PhD, FCCP; Charles L. Sprung, MD; Rui Moreno, MD, PhD; V. Marco Ranieri, MD; Daniel De Backer, MD, PhD; Didier Payen, MD

- Cohort, multi-center, observational study
- 198 European Intensive Care Units
- All patients admitted to participating ICUs over 2 week period in 2002
- No interventions

Sakr et al, Crit Care Med 2006; 34 (3): 589-597
Kaplan-Meier survival curves at 30 days in patients with shock due to any cause. Sakr, CCM 2006; 34:589-597
Does dopamine administration in shock influence outcome? Results of the Sepsis Occurrence in Acutely Ill Patients (SOAP) Study*

Yasser Sakr, MB, BCh, MSc; Konrad Reinhart, MD, PhD; Jean-Louis Vincent, MD, PhD, FCCP; Charles L. Sprung, MD; Rui Moreno, MD, PhD; V. Marco Ranieri, MD; Daniel De Backer, MD, PhD; Didier Payen, MD

Results:

– No difference in ICU mortality rates with dopamine versus no dopamine
– 30 day survival decreased with dopamine and epinephrine
– Norepinephrine and dobutamine not associated with altered 30 day survival

Sakr et al, Crit Care Med 2006; 34 (3):589-597
Effect of norepinephrine on the outcome of septic shock

Claude Martin, MD, FCCM; Xavier Vivian, MD; Marc Leone, MD; Xavier Thirion, MD, PhD

- Prospective, observational cohort study
- 97 patients with septic shock
- Use of Norepinephrine associated with favorable outcome
  - ↓ hospital mortality
    - (62% vs. 82%, P < 0.001)

Crit Care Med 2000; 28:2758-2765
Comparison of Norepinephrine and Dobutamine to Epinephrine

- 30 adult patients with septic shock
- MAP $\leq$ 60 mm Hg
- Norepinephrine and Dobutamine vs Epinephrine to MAP $>80$ mm Hg

Results
- Similar effect on hemodynamics
- Epinephrine
  - ↑ Lactate
  - ↑ Lactate/pyruvate ratio
  - ↓ Gastric pH

Levy et al, Intens Care Med 1997; 23:282-287
Norepinephrine plus dobutamine versus epinephrine alone for management of septic shock: a randomised trial

Djillali Annane, Philippe Vignon, Alain Renault, Pierre-Edouard Bollaert, Claire Charpentier, Claude Martin, Gilles Troché, Jean-Damien Ricard, Gérard Nitenberg, Laurent Papazian, Elie Azoulay, Eric Bellissant, for the CATS Study Group*

Summary

Background International guidelines for management of septic shock recommend that dopamine or norepinephrine are preferable to epinephrine. However, no large comparative trial has yet been done. We aimed to compare the efficacy and safety of norepinephrine plus dobutamine (whenever needed) with those of epinephrine alone in septic shock.

Methods This prospective, multicentre, randomised, double-blind study was done in 330 patients with septic shock admitted to one of 19 participating intensive care units in France. Participants were assigned to receive epinephrine (n=161) or norepinephrine plus dobutamine (n=169), which were titrated to maintain mean blood pressure at 70 mm Hg or more. The primary outcome was 28-day all-cause mortality. Analyses were by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT00148278.

Findings There were no patients lost to follow-up; one patient withdrew consent after 3 days. At day 28, there were 64 (40%) deaths in the epinephrine group and 58 (34%) deaths in the norepinephrine plus dobutamine group (p=0.31; relative risk 0.86, 95% CI 0.65–1.14). There was no significant difference between the two groups in mortality rates at discharge from intensive care (75 [47%] deaths vs 75 [44%] deaths, p=0.69), at hospital discharge (84 [52%] vs 82 [49%], p=0.51), and by day 90 (84 [52%] vs 85 [50%], p=0.73), time to haemodynamic success (log-rank p=0.67), time to vasopressor withdrawal (log-rank p=0.09), and time course of SOFA score. Rates of serious adverse events were also similar.

Interpretation There is no evidence for a difference in efficacy and safety between epinephrine alone and norepinephrine plus dobutamine for the management of septic shock.

Lancet 2007; 370:676-684
Norepinephrine plus dobutamine versus epinephrine alone for management of septic shock: a randomised trial

- Prospective, multicenter, randomised, double-blind study
- 330 patients
- Epinephrine or norepinephrine plus dobutamine
- Primary outcome was 28-day all-cause mortality
- No significant difference in mortality rates
- Similar rates of adverse events

Lancet 2007; 370:676-684
Arginine vasopressin in 316 patients with advanced vasodilatory shock

Günter Luckner, MD; Martin W. Dünser, MD; Stefan Jochberger, MD; Viktoria D. Mayr, MD; Volker Wenzel, MD; Hanno Ulmer, PhD; Stefan Schmid, MD; Hans Knotzer, MD; Werner Pajk, MD; Walter Hasibeder, MD; Andreas J. Mayr, MD; Barbara Friesenecker, MD

**Objective:** To assess the effects of arginine vasopressin (AVP) on hemodynamic, clinical, and laboratory variables and to determine its adverse side effects in advanced vasodilatory shock.

**Design:** Retrospective study.

**Patients:** A total of 316 patients.

**Interventions:** AVP infusion (4 units/hr).

**Measurements and Main Results:** Cardiocirculatory, laboratory, and clinical variables were evaluated before, 0.5, 1, 4, 12, 24, 48, and 72 hrs after administration of AVP. AVP increased mean arterial pressure, systemic vascular resistance, and stroke volume index. Heart rate, central venous pressure, mean pulmonary arterial pressure, norepinephrine, milrinone, and epinephrine requirements decreased. There was no difference in the hemodynamic response between patients with septic shock, postcardiotomy shock, or systemic inflammatory response syndrome. Cardiac index decreased in 41.1% of patients during AVP treatment. In patients with hyperdynamic circulation before AVP, cardiac index decreased, whereas it remained unchanged or tended to increase in patients with normodynamic or hypodynamic circulation. During the course of AVP treatment, liver enzymes (28.5% of patients) and total bilirubin concentrations (69.3% of patients) increased, whereas platelet count decreased (73.4% of patients). Simultaneous hemofiltration significantly contributed to the decrease in platelet count ($p < .001$) and increase in bilirubin ($p < .001$). Whereas patients with an increase in bilirubin were more likely to die, a decrease in cardiac index or platelet count and an increase in liver enzymes did not affect mortality. Systemic inflammatory response syndrome as admission diagnosis, a high degree of multiple organ dysfunction, and norepinephrine requirements of $>0.5 \, \mu g \cdot kg^{-1} \cdot min^{-1}$ before AVP treatment were independent risk factors for death from advanced vasodilatory shock treated with AVP. If norepinephrine dosages exceeded 0.6 $\mu g \cdot kg^{-1} \cdot min^{-1}$ before AVP treatment, a substantial increase in mortality occurred.

**Conclusions:** Supplementary AVP infusion improved cardiocirculatory function in advanced vasodilatory shock, but an increase in liver enzymes and bilirubin, and a decrease in platelet count occurred during AVP therapy, particularly during simultaneous hemofiltration. Initiation of AVP infusion before norepinephrine requirements exceeding 0.6 $\mu g \cdot kg^{-1} \cdot min^{-1}$ may improve outcome. (Crit Care Med 2005; 33:2659–2666)

**Key Words:** arginine vasopressin; norepinephrine; side effects; mortality; septic shock; vasodilatory shock; cardiac index; liver enzymes; bilirubin; platelets

Crit Care Med 2005; 33:2659-2666
Vasopressin in Shock

- Retrospective study 316 patients with shock
- Vasopressin infusion at 4 units/hour
- Reviewed hemodynamics, lab parameters

Luckner et al, Crit Care Med 2005; 33:2559-2666
# Adverse Effects of Vasopressin

<table>
<thead>
<tr>
<th>Effect Description</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>p Value</th>
</tr>
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<tbody>
<tr>
<td><strong>Decrease in cardiac index (I = 41.1%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac index before AVP, L/m²/min</td>
<td>6.76</td>
<td>1.06–47.69</td>
<td>.048</td>
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<tr>
<td><strong>Increase in bilirubin concentrations (I = 69.3%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severest MODS during ICU stay, patients</td>
<td>135</td>
<td>1.09–1.67</td>
<td>.007</td>
</tr>
<tr>
<td>Norepinephrine dosage before AVP, µg/kg/min</td>
<td>1.55</td>
<td>1.02–2.34</td>
<td>.038</td>
</tr>
<tr>
<td>Arterial lactate before AVP, mmol/L</td>
<td>1.02</td>
<td>1–1.03</td>
<td>.02</td>
</tr>
<tr>
<td><strong>Increase in serum transaminases L = 28.5%</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAP Before AVP, mm Hg</td>
<td>0.97</td>
<td>0.95–1</td>
<td>.021</td>
</tr>
<tr>
<td><strong>Decrease in platelet count (I = 73.4%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelet count before AVP, 1,000 cells/µL</td>
<td>1.003</td>
<td>1.001–1.005</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Severest MODS during ICU stay, patients</td>
<td>1.29</td>
<td>1.06–1.57</td>
<td>.012</td>
</tr>
<tr>
<td>Norepinephrine dosage before AVP, µg/kg/min</td>
<td>1.69</td>
<td>1.12–2.54</td>
<td>.012</td>
</tr>
</tbody>
</table>

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Luckner et al, Crit Care Med 2005; 33:2559-2666
Vasopressin versus Norepinephrine Infusion in Patients with Septic Shock

Vasopressin versus Norepinephrine Infusion in Patients with Septic Shock

- Multi-center randomized controlled trial
- Several ICUs across Canada and Australia
- Determine effectiveness of Vasopressin compared to Norepinephrine in increasing 28-day and 90-day survival
- 778 patients in septic shock requiring vasopressors randomized to receive NE or vasopressin
- No difference in survival

Russell et al, NEJM 2008; 358 (9): 877-887
Steroids
Effect of Treatment With Low Doses of Hydrocortisone and Fludrocortisone on Mortality in Patients With Septic Shock

Djillali Annane, MD, PhD
Veronique Sibilla, PhD
Claire Charpentier, MD
Pierre-Ericard Belissant, MD, PhD
Bruno François, MD
Jean-Michel Kouril, MD
Gilles Capellier, MD, PhD
Yves Cohen, MD
Elie Arenday, MD
Gilles Troche, MD
Philippe Chaumet-Riffault, MD
Eric Bellissant, MD, PhD

Context Septic shock may be associated with relative adrenal insufficiency. Thus, a replacement therapy of low doses of corticosteroids has been proposed to treat septic shock.

Objective To assess whether low doses of corticosteroids improve 28-day survival in patients with septic shock and relative adrenal insufficiency.


Patients Three hundred adult patients who fulfilled usual criteria for septic shock were enrolled after undergoing a short corticotropin test.

Intervention Patients were randomly assigned to receive either hydrocortisone (50 mg intravenous bolus every 6 hours) and fludrocortisone (50 μg tablet once daily) (n=151) or matching placebo (n=149) for 7 days.

Main Outcome Measure Twenty-eight-day survival distribution in patients with relative adrenal insufficiency (nonresponders to the corticotropin test).

Results One patient from the corticosteroid group was excluded from analyses because of consent withdrawal. There were 229 nonresponders to the corticotropin test (placebo, 115; corticosteroids, 114) and 70 responders to the corticotropin test (placebo, 94; corticosteroids, 36). In nonresponders, there were 73 deaths (63%) in the placebo group and 60 deaths (53%) in the corticosteroid group (hazard ratio, 0.67; 95% confidence interval, 0.47-0.95; P=.02). Vasopressor therapy was withdrawn within 23 days in 46 patients (40%) in the placebo group and in 55 patients (57%) in the corticosteroid group (hazard ratio, 1.91; 95% confidence interval, 1.29-2.84; P=.001). There was no significant difference between groups in responders. Adverse events rates were similar in the 2 groups.

Conclusion In our trial, a 7-day treatment with low doses of hydrocortisone and fludrocortisone significantly reduced the risk of death in patients with septic shock and relative adrenal insufficiency without increasing adverse events.

For editorial comment see p 386.
Effect of Treatment with Low Doses of Hydrocortisone and Fludrocortisone on Mortality in Patients with Septic Shock

- **Objective:** To assess whether low doses of corticosteroids improve 28-day survival in patients with septic shock and relative adrenal insufficiency
- **Design:** Placebo-controlled, randomized, double-blind trial on two parallel groups
- **Setting:** 19 intensive care units in France from October 9, 1995 to February 23, 1999
- **Patients:** 300 adult patients who fulfilled the usual criteria for septic shock enrolled; half received low dose hydrocortisone and fludrocortisone and half received placebo

Annane, D. JAMA, 2002; 288 (7): 862-871
Effect of Treatment with Low Doses of Hydrocortisone and Fludrocortisone on Mortality in Patients with Septic Shock

• Conclusion:
  – Low doses of hydrocortisone and fludrocortisone reduced the risk of death in patients with septic shock and relative adrenal insufficiency without increasing adverse events
  – Patients with relative adrenal insufficiency (those who did not respond to corticotropin) had a higher probability of survival if they received steroids

Annane, D. JAMA, 2002; 288 (7): 862-871
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-François 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*
CORTICUS Study

- Objective: To assess whether low doses of corticosteroids improve 28-day survival in patients with septic shock and relative adrenal insufficiency
- Primary Objective: 28-day mortality in non-responders to ACTH stimulation test
- Design: Placebo-controlled, randomized, double-blind, multinational European study
- Setting: 52 intensive care units in multiple European countries from March 2002 to November 2005
- Patients: 500 patients enrolled; half received low dose hydrocortisone and half received placebo

Sprung et al, NEJM 2008; 358 (2):111-124
CORTICUS Study

• Results:
  – No significant difference in overall 28-day mortality
  – No significant difference in rates of shock reversal
    • Duration of time to shock reversal shorter in pts who had a response to corticotropin

Sprung et al, NEJM 2008; 358 (2):111-124
Activated Protein C
The New England Journal of Medicine

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VOLUME 344  MARCH 8, 2001  NUMBER 10

EFFICACY AND SAFETY OF RECOMBINANT HUMAN ACTIVATED PROTEIN C FOR SEVERE SEPSIS

GORDON R. BERNARD, M.D., JEAN-LOUIS VINCENT, M.D., PH.D., PIERRE-FRANCOIS LATERRE, M.D., STEVEN P. LAROSA, M.D., JEAN-FRANCOIS DHAINAUT, M.D., PH.D., ANGEL LOPEZ-RODRIGUEZ, M.D., JAY S. STEINGRUB, M.D., GARY E. GARBER, M.D., JEFFREY D. HELTERBRAND, PH.D., E. WESLEY ELY, M.D., M.P.H., AND CHARLES J. FISHER, JR., M.D., FOR THE RECOMBINANT HUMAN ACTIVATED PROTEIN C WORLDWIDE EVALUATION IN SEVERE SEPSIS (PROWESS) STUDY GROUP*
Efficacy and Safety of Recombinant Human Activated Protein C for Severe Sepsis

- PROWESS study group
- Randomized, double blind, placebo controlled trial
- 1690 Patients with sepsis were given infusion of activated PC or placebo for 96 hours
- Primary end point was death by 28 days
- Also monitored complications and coagulation activation
Mortality Reduction in PROWESS

Primary analysis results:
- Placebo (n=840): 30.8%
- Drotrecogin alfa (activated) (n=850): 24.7%

Patients with APACHE II ≥25:
- 13% more survivors at 28 days
- P=0.0005

- Drotrecogin alfa (activated) (n=414)
  - 13% reduction
- Standard therapy (n=403)
  - 11% reduction
Drotrecogin Alfa (Activated) for Adults with Severe Sepsis and a Low Risk of Death

Edward Abraham, M.D., Pierre-François Laterre, M.D., Rekha Garg, M.D., Howard Levy, M.D., Ph.D., Deepak Talwar, M.D., Benjamin L. Trzaskoma, M.S., Bruno François, M.D., Jeffrey S. Guy, M.D., Martina Brückmann, M.D., Álvaro Rea-Neto, M.D., Rolf Rossaint, M.D., Dominique Perrotin, M.D., Armin Sablotzki, M.D., Ph.D., Nancy Arkins, R.N., Barbara G. Utterback, M.S., M.B.A., and William L. Macias, M.D., for the Administration of Drotrecogin Alfa (Activated) in Early Stage Severe Sepsis (ADDRESS) Study Group*
Figure 2. Kaplan–Meier Estimates of Survival among 1316 Patients with Severe Sepsis in the Drotrecogin Alfa (Activated) (DrotAA) Group and 1297 Patients in the Placebo Group. There was no significant difference between the treatment groups in survival at 28 days (P=0.31 by the log-rank test).
Implementation of an evidence-based “standard operating procedure” and outcome in septic shock

Andreas Kortgen, MD; Petra Niederprüm, MD; Michael Bauer, MD

Objective: To assess the impact of an algorithm defining resuscitation according to early goal-directed therapy, glycemic control, administration of stress doses of hydrocortisone, and use of recombinant human activated protein C (rhAPC) on measures of organ dysfunction and outcome in septic shock.

Design: Retrospective cohort study.

Setting: Multidisciplinary ten-bed intensive care unit of a university hospital.

Patients: Sixty patients were analyzed: 30 consecutive patients fulfilling criteria for diagnosis of septic shock, treated from September 2002 until December 2003 after implementation of a standard operating procedure (SOP) for severe sepsis and septic shock; and 30 patients with septic shock treated from January until August 2002 in the same unit, who served as controls.

Measurements and Results: Data for blood gas analysis, lactate, glucose, serum creatinine, bilirubin, white blood cells, platelets, and C-reactive protein were obtained from patient files on admission or at time of diagnosis of septic shock and at 7:00 a.m. on days 2 and 4; Sequential Organ Failure Assessment scores were calculated and 28-day survival was assessed. With implementation of the SOP, use of dobutamine (12/30 vs. 2/30), insulin (blood glucose <150 mg/dL, day 4: 26/28 vs. 13/25), hydrocortisone (30/30 vs. 13/30), and rhAPC (7/30 vs. 0/30) significantly increased, whereas volume for resuscitation and use of packed red blood cells were unaffected. Mortality was 53% in the historical control group and 27% after implementation of the SOP (p < .05).

Conclusion: The combined approach of early goal-directed therapy, intensive insulin therapy, hydrocortisone administration, and additional application of rhAPC in selected cases seems to favorably influence outcome. The implementation of a “sepsis bundle” can be facilitated by a standardized protocol while significantly reducing the time until the defined therapeutic measures are realized in daily practice. (Crit Care Med 2006; 34:943-949)

Key Words: standard operating procedure; quality management; early goal directed therapy; hydrocortisone; intensive insulin therapy; recombinant human activated protein C
Interventions

• Early goal directed therapy
• Intensive insulin therapy
• Hydrocortisone supplementation  
  – If shock progressed
• Administration of APC

Kortgen et al, CCM 2006; 34:943-9
Survival

30 patients in each group

p = 0.0305 log rank test

SOP group

control group

Kortgen et al, CCM 2006
Conclusions

• EGDT is likely effective in reducing mortality
• If pressors are necessary, use norepinephrine as first agent
• Low dose steroids are probably not indicated in septic shock
• Consider APC for patients with severe sepsis
• Follow standard guidelines and consider developing protocols for the treatment of sepsis