Sepsis 2015: You say you wanted a revolution

R. Phillip Dellinger, MD, MCCM
*Professor and Chair, Department of Medicine Cooper Medical School of Rowan University Medical Director, Adult Health Institute Senior Attending, Critical Care Medicine Cooper University Health Care*

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SEPSIS 2015:
YOU SAY YOU WANT A REVOLUTION

R. Phillip Dellinger MD, MSc, MCCM
Professor and Chair of Medicine
Cooper Medical School of Rowan University
Medical Director Adult Health Institute
Senior Critical Care Attending
Cooper University Hospital
Camden NJ USA
POTENTIAL CONFLICTS OF INTEREST

• Hold leadership position in Surviving Sepsis Campaign

• Cooper University Hospital receives consultant fees and research funding from Spectral Inc. for work with the EUPHRATES trial.
Burden of Severe Sepsis

Sepsis Performance Improvement Revolution

Research: New or Ongoing Clinical Trials
SEVERE SEPSIS

• Severe Sepsis is the Leading Cause of Hospital Death

• Admissions with severe sepsis 8X > chance of death than other conditions

• Most expensive condition treated in the hospital (23 billion dollars per annum)

• Enormous economic burden that can be lessened with early identification and early appropriate evidence based medicine care

NCHS data brief #62, 2011
US National Lib Med, NIH, 2010
HCUP Statistical Brief #160
Causes of death in New Jersey in 2011, according to the most recent data available.
New Jersey Department of Health posted January 8, 2015
“Houston, we have a problem.”

APOLLO 13
“HEALTHCARE, WE HAVE A PROBLEM.”
CURRENTLY FUNDED WITH A GORDON AND BETTY MOORE FOUNDATION GRANT (INTEL FAMILY).

NO DIRECT OR INDIRECT INDUSTRY SUPPORT FOR GUIDELINES REVISION
SURVIVING SEPSIS CAMPAIGN: INTERNATIONAL GUIDELINES FOR MANAGEMENT OF SEVERE SEPSIS AND SEPTIC SHOCK: 2012


Crit Care Med 2013; 41:580-637
Intensive Care Medicine 2013; 39: 165-228
CURRENT SURVIVING SEPSIS CAMPAIGN GUIDELINE SPONSORS

- American Association of Critical-Care Nurses
- American College of Chest Physicians
- American College of Emergency Physicians
- Australian and New Zealand Intensive Care Society
- Asia Pacific Association of Critical Care Medicine
- American Thoracic Society
- Brazilian Society of Critical Care (AIMB)
- Canadian Critical Care Society
- Chinese Society of Critical Care Medicine
- Emirates Intensive Care Society
- European Respiratory Society
- European Society of Clinical Microbiology and Infectious Diseases
- European Society of Intensive Care Medicine
- European Society of Pediatric and Neonatal Intensive Care
- Infectious Diseases Society of America
- Indian Society of Critical Care Medicine
- International Pan Arab Critical Care Medicine Society
- Japanese Association for Acute Medicine
- Japanese Society of Intensive Care Medicine
- Pediatric Acute Lung Injury and Sepsis Investigators
- Society Academic Emergency Medicine
- Society of Critical Care Medicine
- Society of Hospital Medicine
- Surgical Infection Society
- World Federation of Critical Care Nurses
- World Federation of Pediatric Intensive and Critical Care Societies
- World Federation of Societies of Intensive and Critical Care Medicine

Participation and endorsement:
- German Sepsis Society
- Latin American Sepsis Institute
GUIDELINES ARE NOT ENOUGH

• Protocols
• Performance Improvement Programs
  • Audit and Feedback
Early Screening and a Hospital Based Performance Improvement Program
Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock

B. Philip Defeiver, MD; Jean M. Carlet, MD; Henry Maurer, MD; Bernhard Greischar, MD, PhD; Thierry Colin, MD; Jonathan Cohen, MD; Jean-Georges Biston, MD, PhD; Dieter Kem, MD; John C. Marshall, MD; Margaret M. Parry, MD; Graham Ramsay, MD; Janice E. Zimmerman, MD; Jean-Louis Vincent, MD, PhD; Malcolm R. Levy, MD; for the Surviving Sepsis Campaign Management Guidelines Committee

Sponsoring Organizations: American Association of Critical-Care Nurses; American College of Chest Physicians; American College of Emergency Physicians; American Thoracic Society; Australian and New Zealand Intensive Care Society; European Society of Critical Care Medicine; European Society of Intensive Care Medicine; European Respiratory Society; International Sepsis Forum; Society of Critical Care Medicine; Surgical Infection Society.

Objectives: In 2004, critical care and infectious disease experts representing 11 international organizations developed management guidelines for severe sepsis and septic shock that were to be published simultaneously for the first time. Subsequently, these guidelines were incorporated into the Surviving Sepsis Campaign, an international effort to improve awareness and improve outcomes in severe sepsis.

The purpose of this document is to identify the recommendations that were developed during the Surviving Sepsis Campaign. The recommendations are intended for critical care physicians, who are in the critical care setting and are available as such for the purpose of managing patients with severe sepsis.

Severe Sepsis Bundles:

Sepsis Resuscitation Bundle

1. Hemodynamic monitoring
2. Broad-spectrum antibiotics administered in 3 hours for sepsis and 6 hours for severe sepsis
3. Sepsis-related hypotension treated with norepinephrine
4. Hypertensive response to fluid resuscitation
5. Blood glucose maintained between 80 and 110 mg/dL

Sepsis Management Bundle

1. Low-dose steroids administered in 6 hours
2. Continuous renal replacement therapy
3. Blood glucose maintained between 80 and 110 mg/dL

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CONVERTING GOALS TO MEASURABLE INDICATORS
Severe Sepsis Resuscitation Bundle

Complete tasks within 6 hours of identifying severe sepsis.

1. Measure serum lactate.
2. Obtain blood cultures prior to antibiotic administration.
3. Administer broad-spectrum antibiotic within 3 hours of ED admission and within 1 hour of non-ED admission.
4. In the event of hypotension and/or serum lactate > 4 mmol/L:
   a. Deliver an initial minimum of 20 mL/kg of crystalloid or equivalent.
   b. Begin vasopressors for hypotension not responding to initial fluid resuscitation to maintain MAP > 65 mm Hg.
5. In the event of persistent hypotension despite fluid resuscitation (septic shock) and/or lactate > 4 mmol/L:
   a. Achieve a central venous pressure (CVP) of > 8 mm Hg
   b. Achieve a central venous oxygen saturation (ScvO₂) > 70% or mixed venous oxygen saturation (ScvO₂) > 65%

Implement the 6-hour bundle. Available at: http://ssc.sccm.org/8hr_bundles.
Severe Sepsis Management Bundle

Complete tasks within 24 hours of identifying severe sepsis.

1. Administer low-dose steroids for septic shock in accordance with a standardized hospital policy.
   - If not administered, document why the patient did not qualify for low-dose steroids based upon the standardized protocol.

2. Administer recombinant human activated protein C (rhAPC) in accordance with a standardized hospital policy.
   - If not administered, document why the patient did not qualify for rhAPC.

3. Maintain glucose control 80-150 mg/dL.

4. Maintain a median inspiratory plateau pressure (IPP) ≤ 30 cm H2O for mechanically ventilated patients.

Implement the 24-hour bundle. Available at: http://ssc.sccm.org/24hr_bundles.
CHANGE IN COMPLIANCE OVER TIME

Levy MM, Dellinger, RP, Townsend SA et al.
CHANGE IN MORTALITY OVER TIME

SSC MORTALITY

WHY?
Recommend
Insertion central venous catheter

Recommended goals:
• Central venous pressure: 8–12 mm Hg
  • Higher with altered ventricular compliance or increased intrathoracic pressure
• ScvO2 saturation (SVC) ≥ 70%

Grade 1C
The Starling principle relates to the fact that the more a myocardial fibril is stretched the greater the contraction.
EXPECTED RESULT OF VOLUME Expansion

Diagram showing the relationship between Stroke Volume and Ventricular preload, with points A and B.

Diagram:
- Vertical axis: Stroke Volume
- Horizontal axis: Ventricular preload
- Curve showing the expected result of volume expansion
CENTRAL VENOUS PRESSURE POORLY PREDICTS CARDIAC PRELOAD AND VOLUME STATUS

INTRAVASCULAR VOLUME STATUS AND PERFUSION PARAMETERS

- Limitation of pressure measurement to predict fluid responsiveness
- There are alternatives to CVP for judging fluid responsiveness that are in general more reliable
ARTERIAL SYSTOLIC PRESSURE VARIATION

EFFECT ON CARDIAC FILLING

Ultrasound
Inferior
Vena Cava
Long Axis
EFFECT ON STROKE VOLUME
EFFECT ON STROKE VOLUME
## Surviving Sepsis Campaign Bundles 2012

<table>
<thead>
<tr>
<th>To be accomplished as soon as possible and scored over first 3 hrs:</th>
<th>To be accomplished as soon as possible and scored over first 6 hrs:</th>
</tr>
</thead>
<tbody>
<tr>
<td>✓ Serum lactate measured.</td>
<td>✓ Apply vasopressors for hypotension not responding to initial fluid resuscitation to maintain MAP ≥ 65 mm Hg.</td>
</tr>
<tr>
<td>✓ Blood cultures obtained prior to antibiotics administered.</td>
<td>✓ In the event of persistent arterial hypotension despite volume resuscitation (septic shock) or initial lactate &gt; 4 mmol/L (36 mg/dL):</td>
</tr>
<tr>
<td>✓ Administer broad-spectrum antibiotics.</td>
<td>✓ Measure CVP*</td>
</tr>
<tr>
<td>✓ For hypotension and/or lactate &gt; 4 mmol/L:</td>
<td>✓ Measure ScvO₂*</td>
</tr>
<tr>
<td>✓ Deliver an initial minimum of 30 ml/kg of crystalloid</td>
<td>✓ Remeasure lactate if initial lactate is elevated*</td>
</tr>
</tbody>
</table>

You say you want a revolution

The BEATLES

Revolution
1. Measure lactate level
2. Obtain blood cultures prior to administration of antibiotics
3. Administer broad spectrum antibiotics
4. Administer 30ml/kg crystalloid for hypotension or lactate $\geq$4mmol/L
2012 NQF: SEPSIS 0500

TO BE COMPLETED WITHIN 6 HOURS OF TIME OF PRESENTATION:

5. Apply vasopressors (for hypotension that does not respond to initial fluid resuscitation to maintain a mean arterial pressure (MAP) ≥65mmHg)

6. In the event of persistent arterial hypotension despite volume resuscitation (septic shock) or initial lactate ≥4 mmol/L (36mg/dl):
   - Measure central venous pressure (CVP)
   - Measure central venous oxygen saturation (ScvO2)

7. Remeasure lactate if elevated.
A Randomized Trial of Protocol-Based Care for Early Septic Shock

The ProCESS Investigators*


Over 1500 Patients

Goal-Directed Resuscitation for Patients with Early Septic Shock

The ARISE Investigators and the ANZICS Clinical Trials Group*


1600 Patients
Both the ProCESS and ARISE trials demonstrated the lack of necessity of using central venous oxygen saturation and central venous pressure monitoring as resuscitation targets when compared to the usual care group.
Table 2 - NQF 0500(revised)

A. Measure lactate level
B. Obtain blood cultures prior to antibiotics
C. Administer broad spectrum antibiotics
D. Administer 30 ml/kg crystalloid for hypotension or lactate = 4 mmol/L
E. Apply vasopressors (for hypotension that does not respond to initial fluid resuscitation to maintain a mean arterial pressure = 65)
F. In the event of persistent hypotension after initial fluid administration (MAP < 65 mm Hg) or if initial lactate was = 4 mmol/L, re-assess volume status and tissue perfusion and document findings.

   *To meet the requirements, a focused exam† by a licenses independent practitioner (LIP) to include vital signs, cardiopulmonary, capillary refill, pulse and skin findings, or any 2 other items below are required:
   - Measure CVP
   - Measure ScvO2
   - Bedside cardiovascular ultrasound
   - Dynamic assessment of fluid responsiveness with passive leg raise or fluid challenge

G. Re-measure lactate if initial lactate is elevated
Table 2 - NQF 0500 (revised)

A. Measure lactate level
B. Obtain blood cultures prior to antibiotics
C. Administer broad spectrum antibiotics
D. Administer 30 ml/kg crystalloid for hypotension or lactate = 4 mmol/L
E. Apply vasopressors (for hypotension that does not respond to initial fluid resuscitation to maintain a mean arterial pressure = 65)
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- Measure CVP
- Measure ScvO2
- Bedside cardiovascular ultrasound
- Dynamic assessment of fluid responsiveness with passive leg raise or fluid challenge

G. Re-measure lactate if initial lactate is elevated
You say you got a real solution
Well, you know
We’d all love to see the plan

Revolution
You ask me for a contribution
Well, you know
We’re all doing what we can

The BEATLES

Revolution
You tell me it’s (for) the institution

Revolution
A Randomized Trial of Protocol-Based Care for Early Septic Shock

The ProCESS Investigators*


Over 1500 Patients

Goal-Directed Resuscitation for Patients with Early Septic Shock

The ARISE Investigators and the ANZICS Clinical Trials Group*


1600 Patients
<table>
<thead>
<tr>
<th></th>
<th>ProCESS</th>
<th>ARISE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enrollment</td>
<td>&lt;2 hours from detection of shock</td>
<td>2.8 hours (median) from presentation to ED</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>75% received prior to enrollment</td>
<td>70 minutes (median) from presentation to ED</td>
</tr>
<tr>
<td>Fluids</td>
<td>&gt;2 liters prior to enrollment</td>
<td>2515ml (mean) prior to enrollment</td>
</tr>
</tbody>
</table>
• SSC 2006 six hour bundle
• SSC 2012 three hour bundle
• NQF 0500
• ProCESS/ARISE/PROMISE
• NQF 0500 (revised)
• CMS SEP 1
TO SAVE LIVES.....

Early identification

Early antibiotics

Early fluid resuscitation
Table 2 - NQF 0500(revised)

A. Measure lactate level
B. Obtain blood cultures prior to antibiotics
C. Administer broad spectrum antibiotics
D. Administer 30 ml/kg crystalloid for hypotension or lactate = 4 mmol/L
E. Apply vasopressors (for hypotension that does not respond to initial fluid resuscitation to maintain a mean arterial pressure = 65)
F. In the event of persistent hypotension after initial fluid administration (MAP < 65 mm Hg) or if initial lactate was = 4 mmol/L, re-assess volume status and tissue perfusion and document findings.

*To meet the requirements, a focused exam† by a licenses independent practitioner (LIP) to include vital signs, cardiopulmonary, capillary refill, pulse and skin findings, or any 2 other items below are required:

- Measure CVP
- Measure ScvO2
- Bedside cardiovascular ultrasound
- Dynamic assessment of fluid responsiveness with passive leg raise or fluid challenge

G. Re-measure lactate if initial lactate is elevated
IMPORTANCE OF REASSESSMENT
• Sepsis is a big problem
• Logic of indicators is good
• Benchmarked performance
Don’t you know it’s gonna be alright, alright, alright
Research / New or Ongoing Clinical Trials
SELEPRESSIN
The Selective Vasopressin Type 1a Receptor Agonist Selepressin (FE 202158) Blocks Vascular Leak in Ovine Severe Sepsis*

Marc O. Maybauer, MD, PhD, EDIC, FCCP,1,2; Dirk M. Maybauer, MD, PhD1,2; Pernenlei Enkhaatar, MD, PhD3; Régent Laporte, DVM, MSc, PhD3; Halina Wiśniewska, MS3; Lillian D. Traber, RN1; ChiiDean Lin, PhD4; Juanjuan Fan, PhD5; Hal K. Hawkins, MD, PhD6; Robert A. Cox, PhD5; Kazimierz Wiśniewski, PhD5; Claudio D. Schteingart, PhD5; Donald W. Landry, MD, PhD6; Pierre J.-M. Rivière, PhD5; Daniel L. Traber, PhD, FCCM1†

Objective: To determine if the selective vasopressin type 1a receptor agonist selepressin (FE 202158) is as effective as the mixed vasopressin type 1a receptor/vasopressin V2 receptor agonist vasopressin hormone arginine vasopressin when used as a titrated first-line vasopressor therapy in an ovine model of Pseudomonas aeruginosa pneumonia-induced severe sepsis.

Design: Prospective, randomized, controlled laboratory experiment.
Setting: University animal research facility.
Subjects: Forty-five chronically instrumented sheep.
Interventions: Sheep were anesthetized, insufflated with cooled cotton smoke via tracheostomy, and P. aeruginosa were instilled into their airways. They were then placed on assisted ventilation, awakened, and resuscitated with lactated Ringer’s solution titrated to maintain hematocrit ± 3% from baseline levels. If, despite fluid management, mean arterial pressure fell by more than 10 mm Hg from baseline level, an additional continuous IV infusion of arginine vasopressin or selepressin was titrated to raise and maintain mean arterial pressure within no less than 10 mm Hg from baseline level. Effects of combination treatment of selepressin with the selective vasopressin V2 receptor agonist desmopressin were similarly investigated.

Measurements and Main Results: In septic sheep, MAP fell by ~30 mm Hg, systemic vascular resistance index decreased by ~50%, and ~7 L of fluid were retained over 24 hours; this fluid accumulation was partially reduced by arginine vasopressin and almost completely blocked by selepressin; and combined infusion of selepressin and desmopressin increased fluid accumulation to levels similar to arginine vasopressin treatment.

Conclusions: Resuscitation with the selective vasopressin type 1a receptor agonist selepressin blocked vascular leak more effectively than the mixed vasopressin type 1a receptor/vasopressin V2 receptor agonist arginine vasopressin because of its lack of agonist activity at the vasopressin V2 receptor. (Crit Care Med 2014; 42:e525–e533)

*See also p. 1747.
1Investigational Intensive Care Unit, Department of Anesthesiology, University of Texas Medical Branch, Galveston, TX.
2Department of Anaesthesia and Intensive Care, Philippus University of Marburg, Marburg, Germany.
3Ferring Research Institute, San Diego, CA.
4Department of Mathematics and Statistics, San Diego State University, San Diego, CA.
5Department of Pathology, University of Texas Medical Branch, Galveston, TX.
6Department of Medicine, Columbia University, New York City, NY.
†Deceased.
Drs. Marc O. Maybauer, Dirk M. Maybauer, Enkhaatar, and Laporte contributed equally to this work.
Supported, in part, by Ferring Research Institute, San Diego, CA.
Drs. Marc O. Maybauer, Dirk M. Maybauer, Enkhaatar, Traber, Hawkins, Cox, and Traber were employees of the University of Texas Medical Branch at Galveston, which was contracted by the Ferring Research Institute to conduct the study reported here. Drs. Lin and Fan are employees of Forestal Consulting Group, which was contracted by the Ferring Research Institute to conduct the statistical analysis of the study reported here. Drs. Laporte, Wiśniewski, Schteingart, and Rivière and Ms. Wiśniewska were employees of the Ferring Research Institute. Dr. Lin consulted for Ferring Research Institute. Drs. Landry and Traber were consultants for Ferring Research Institute.
Gut Integrity in Shock
"SSAIL" TRIAL (TREATMENT OF SEPTIC SHOCK BY INHIBITING AUTODIGESTION AND PRESERVING GUT INTEGRITY WITH ENTERIC LB1148)

• LB1148 – broad-spectrum serine protease inhibitor delivered enterally to gut

• Inhibit the intraluminal pancreatic proteolytic enzymes (proteases) that leak due to loss of gut integrity
SOLUBLE THROMBOMODULIN
ANGIOTENSIN II
Intravenous angiotensin II for the treatment of high-output shock (ATHOS trial): a pilot study

Lakhmir S Chawla¹,³*, Laurence Busse², Ermira Brasha-Mitchell³, Danielle Davison³, Jacqueline Honiq³, Ziyad Alothabi⁴ and Michael G Seneff³

Abstract

Introduction: Patients with distributive shock who require high dose vasopressors have a high mortality. Angiotensin II (ATII) may prove useful in patients who remain hypotensive despite catecholamine and vasopressin therapy. The appropriate dose of parenteral angiotensin II for shock is unknown.

Methods: In total, 20 patients with distributive shock and a cardiovascular Sequential Organ Failure Assessment score of 4 were randomized to either ATII infusion (N =10) or placebo (N =10) plus standard of care. ATII was started at a dose of 20 ng/kg/min, and titrated for a goal of maintaining a mean arterial pressure (MAP) of 65 mmHg. The infusion (either ATII or placebo) was continued for 6 hours then titrated off. The primary endpoint was the effect of ATII on the standing dose of norepinephrine required to maintain a MAP of 65 mmHg.

Results: ATII resulted in marked reduction in norepinephrine dosing in all patients. The mean hour 1 norepinephrine dose for the placebo cohort was 27.6 ± 29.3 mcg/min versus 7.4 ± 12.4 mcg/min for the ATII cohort (P =0.06). The most common adverse event attributable to ATII was hypertension, which occurred in 20% of patients receiving ATII. 30-day mortality for the ATII cohort and the placebo cohort was similar (50% versus 60%, P =1.00).

Conclusion: Angiotensin II is an effective rescue vasopressor agent in patients with distributive shock requiring multiple vasopressors. The initial dose range of ATII that appears to be appropriate for patients with distributive shock is 2 to 10 ng/kg/min.

POLYMIXIN B HEMOPERFUSION
Endotoxemia

Endotoxin shed from local bacterial infection

Endotoxin translocation from GI Tract

- Every human has 25-30 grams of Endotoxin in their GI tract
- Less than 0.001 grams of Endotoxin is enough to kill a person

Sources of Endotoxin

Endotoxin translocation from GI Tract

- Every human has 25-30 grams of Endotoxin in their GI tract
- Less than 0.001 grams of Endotoxin is enough to kill a person
SEPSIS AND ENDOTOXIN

INTERVENTION

DIRECT HEMOPERFUSION WITH ADSORBENT COLUMN USING POLYMYXIN B IMMOBILIZED FIBER

ANTICOAGULANT
Heparin (3000 U in bolus followed by a continuous infusion of 20 U/kg/h)

BLOOD PUMP
Perfusion rate 80-120 ml/min

Duration: 2 hours

BLOOD TUBE

FEMORAL or IJ VEIN

FEMORAL or IJ VEIN
HEMODYNAMIC EFFECTS OF PMX

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Change in MAP (random) 95% CI</th>
<th>Weight %</th>
<th>Change in MAP (random) 95% CI</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>01 Initial MAP &lt;70</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ono 2004</td>
<td></td>
<td>6.74</td>
<td>25.00 [16.45, 33.55]</td>
<td>D</td>
</tr>
<tr>
<td>Tojimbara 2004</td>
<td></td>
<td>10.26</td>
<td>26.00 [20.98, 31.02]</td>
<td>D</td>
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<tr>
<td>Tsujimoto 2004</td>
<td></td>
<td>6.43</td>
<td>28.40 [19.46, 37.34]</td>
<td>D</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td></td>
<td>23.43</td>
<td>26.25 [22.35, 30.14]</td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity: ( \chi^2 = 0.31, df = 2 ) ( P = 0.85 ), ( I^2 = 0 )%</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Test for overall effect: ( Z = 13.21 ) ( P &lt; 0.000001 )</td>
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<td></td>
<td></td>
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<tr>
<td>02 Initial MAP &gt;=70</td>
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<td></td>
<td></td>
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<tr>
<td>Vincent 2005</td>
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<td>8.68</td>
<td>10.80 [4.33, 17.27]</td>
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<td>Casella 2006</td>
<td></td>
<td>8.48</td>
<td>16.00 [9.34, 22.66]</td>
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<td>Ikeda 2004</td>
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<td>11.49</td>
<td>11.50 [7.58, 15.42]</td>
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<td>Kojica 2006</td>
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<td>5.40</td>
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<td>Nakamura 2004/B</td>
<td></td>
<td>5.89</td>
<td>16.00 [6.34, 25.66]</td>
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<td>Tani 1998</td>
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<td>8.32</td>
<td>15.00 [8.18, 21.82]</td>
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<td>Ueno 2005</td>
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<td>3.86</td>
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<td>Subtotal (95% CI)</td>
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<td>76.57</td>
<td>15.89 [13.45, 18.33]</td>
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<td>Test for heterogeneity: ( \chi^2 = 14.71, df = 8 ) ( P = 0.07 ), ( I^2 = 45.6)%</td>
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<tr>
<td>Total (95% CI)</td>
<td></td>
<td>100.00</td>
<td>18.55 [15.48, 21.62]</td>
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</tr>
<tr>
<td>Test for heterogeneity: ( \chi^2 = 40.10, df = 11 ) ( P &lt; 0.00001 ), ( I^2 = 72.6)%</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Test for overall effect: ( Z = 11.85 ) ( P &lt; 0.000001 )</td>
<td></td>
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<td></td>
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</tbody>
</table>

Cruz D. et al. Critical Care 2007; 11:R47
### Table 1. Baseline Characteristics of the Treatment Groups

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Polymyxin B Hemoperfusion (n = 34)</th>
<th>Conventional Therapy (n = 30)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>61 (57-66)</td>
<td>67 (61-72)</td>
<td>.09</td>
</tr>
<tr>
<td>Male sex, No. (%)</td>
<td>24 (71)</td>
<td>18 (60)</td>
<td>.53</td>
</tr>
<tr>
<td>APACHE II score</td>
<td>21 (19-23)</td>
<td>20 (18-23)</td>
<td>.86</td>
</tr>
<tr>
<td>SOFA score</td>
<td>11 (10-12)</td>
<td>9 (8-11)</td>
<td>.07</td>
</tr>
<tr>
<td>Mean arterial pressure, mm Hg</td>
<td>76 (72-80)</td>
<td>74 (70-78)</td>
<td>.40</td>
</tr>
<tr>
<td>Noradrenaline, µg/kg/min</td>
<td>0.27 (0.17-0.36)</td>
<td>0.24 (0.13-0.36)</td>
<td>.70</td>
</tr>
<tr>
<td>Dopamine, µg/kg/min</td>
<td>3.4 (1.7-4.4)</td>
<td>4.6 (2.9-5.6)</td>
<td>.13</td>
</tr>
<tr>
<td>Inotropic score</td>
<td>29.9 (20.4-39.4)</td>
<td>28.6 (16.6-40.7)</td>
<td>.85</td>
</tr>
<tr>
<td>Vasopressor dependency index, mm Hg²</td>
<td>4.3 (2.7-5.9)</td>
<td>4.1 (2.3-6.0)</td>
<td>.87</td>
</tr>
<tr>
<td>White blood cell count, 1000/µL</td>
<td>13.7 (11.4-16.0)</td>
<td>11.4 (9.0-13.8)</td>
<td>.12</td>
</tr>
<tr>
<td>(\text{Paco}_2/\text{Fi}_2)</td>
<td>235 (206-265)</td>
<td>217 (188-247)</td>
<td>.53</td>
</tr>
<tr>
<td>Diuresis, mL/h</td>
<td>66 (50-90)</td>
<td>87 (59-116)</td>
<td>.22</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>2.3 (1.7-2.9)</td>
<td>1.7 (1.3-2.2)</td>
<td>.18</td>
</tr>
<tr>
<td>Renal replacement therapy, No. (%)</td>
<td>13 (38)</td>
<td>6 (20)</td>
<td>.17</td>
</tr>
</tbody>
</table>

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; \(\text{Paco}_2\), fraction of inspired oxygen; SOFA, Sequential Organ Failure Assessment.

SI conversion: To convert creatinine to µmol/L, multiply by 88.4.

Patients in the polymyxin B hemoperfusion group were treated with 2 sessions of direct hemoperfusion with polymyxin B in addition to standard conventional therapy. Range of APACHE II score was 0 to 71, with lower scores indicating better organ function. Range of SOFA score was 0 to 24, with lower scores indicating better organ function. See "Methods" section for formulas for inotropic score and vasopressor dependency index.
Figure 3. Estimation of Survival Rate According to Treatment Group

Patients in the polymyxin B hemoperfusion group were treated with 2 sessions of direct hemoperfusion with polymyxin B in addition to standard conventional therapy.
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