6-10-2015

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

SEPSIS 2015:
YOU SAY YOU WANT A REVOLUTION

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Professor and Chair of Medicine
Cooper Medical School of Rowan University
Medical Director Adult Health Institute
Senior Critical Care Attending
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Cooper University Hospital

Cooper Medical School of Rowan University

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

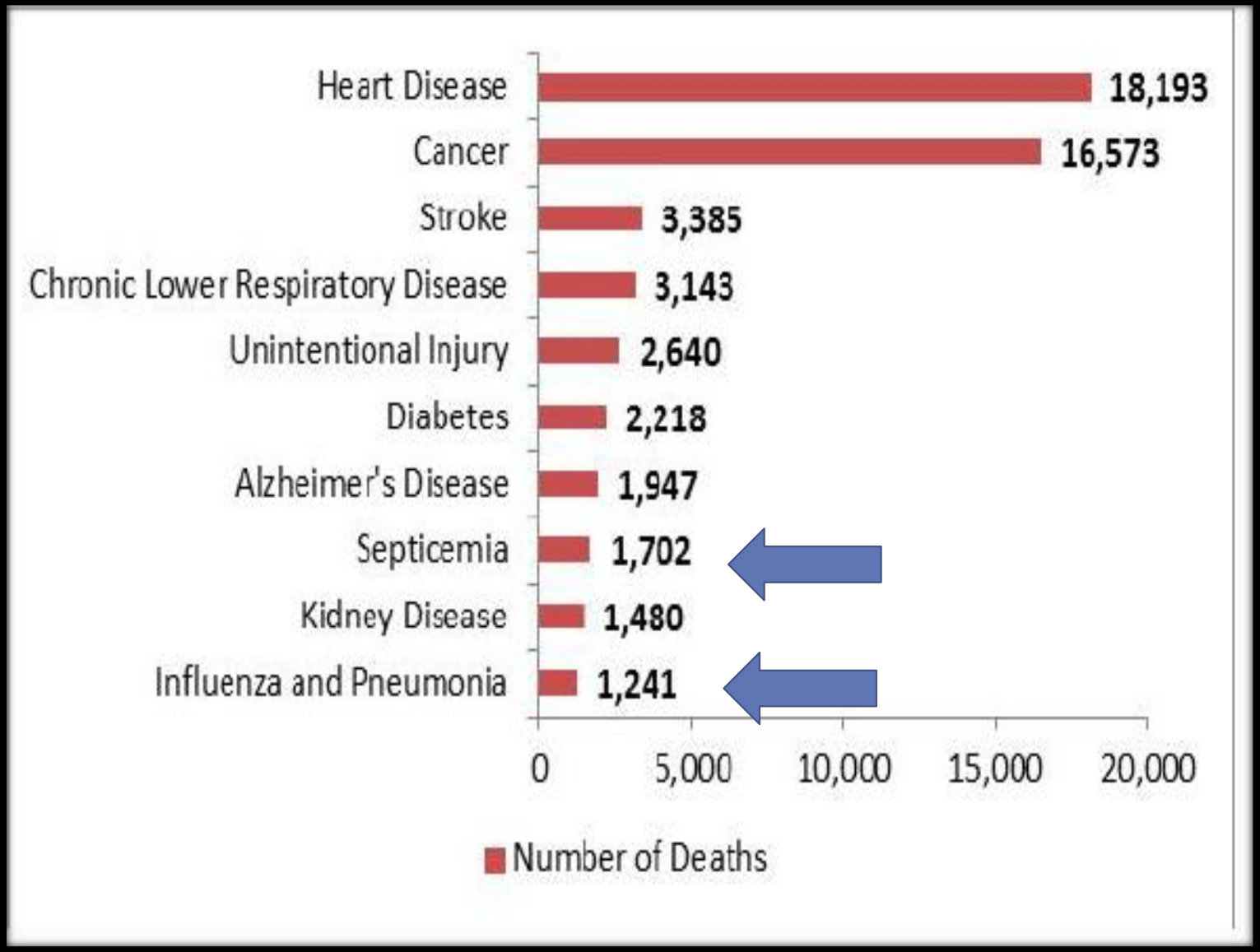
Research : New or Ongoing Clinical Trials

Burden of Severe Sepsis

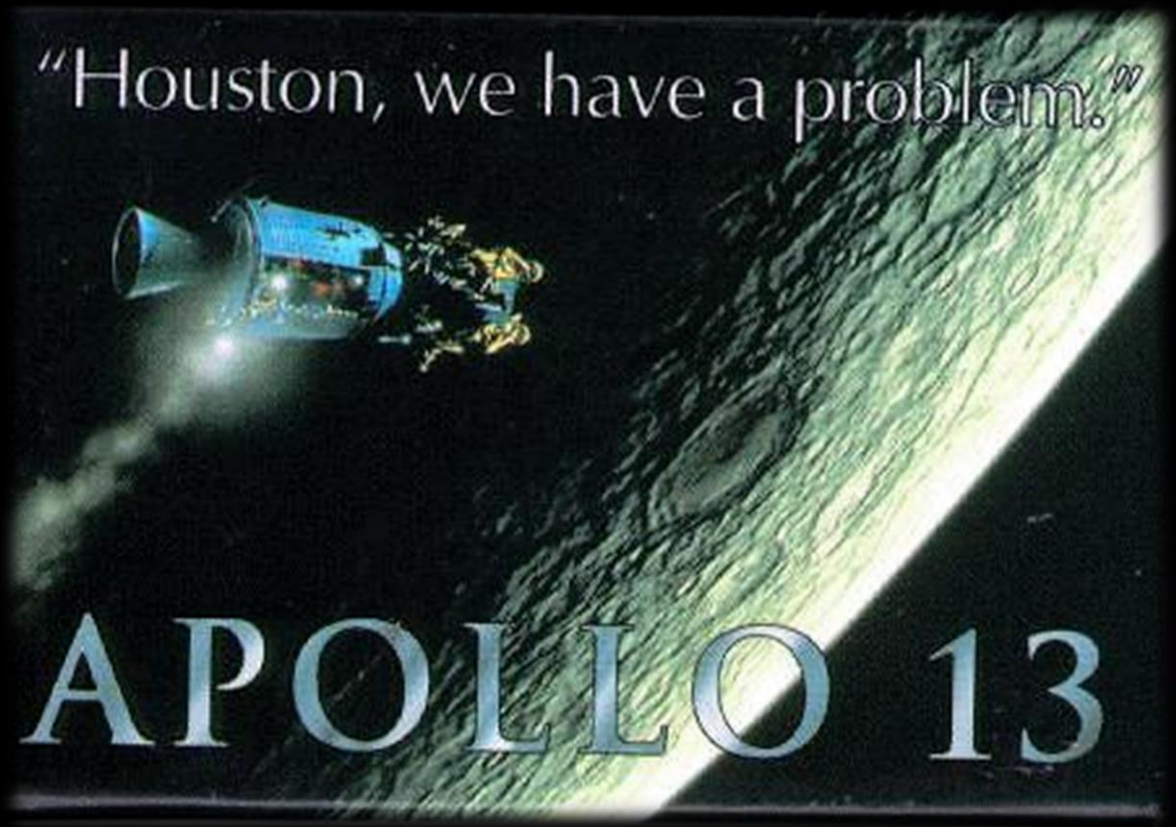
SEVERE SEPSIS

- 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

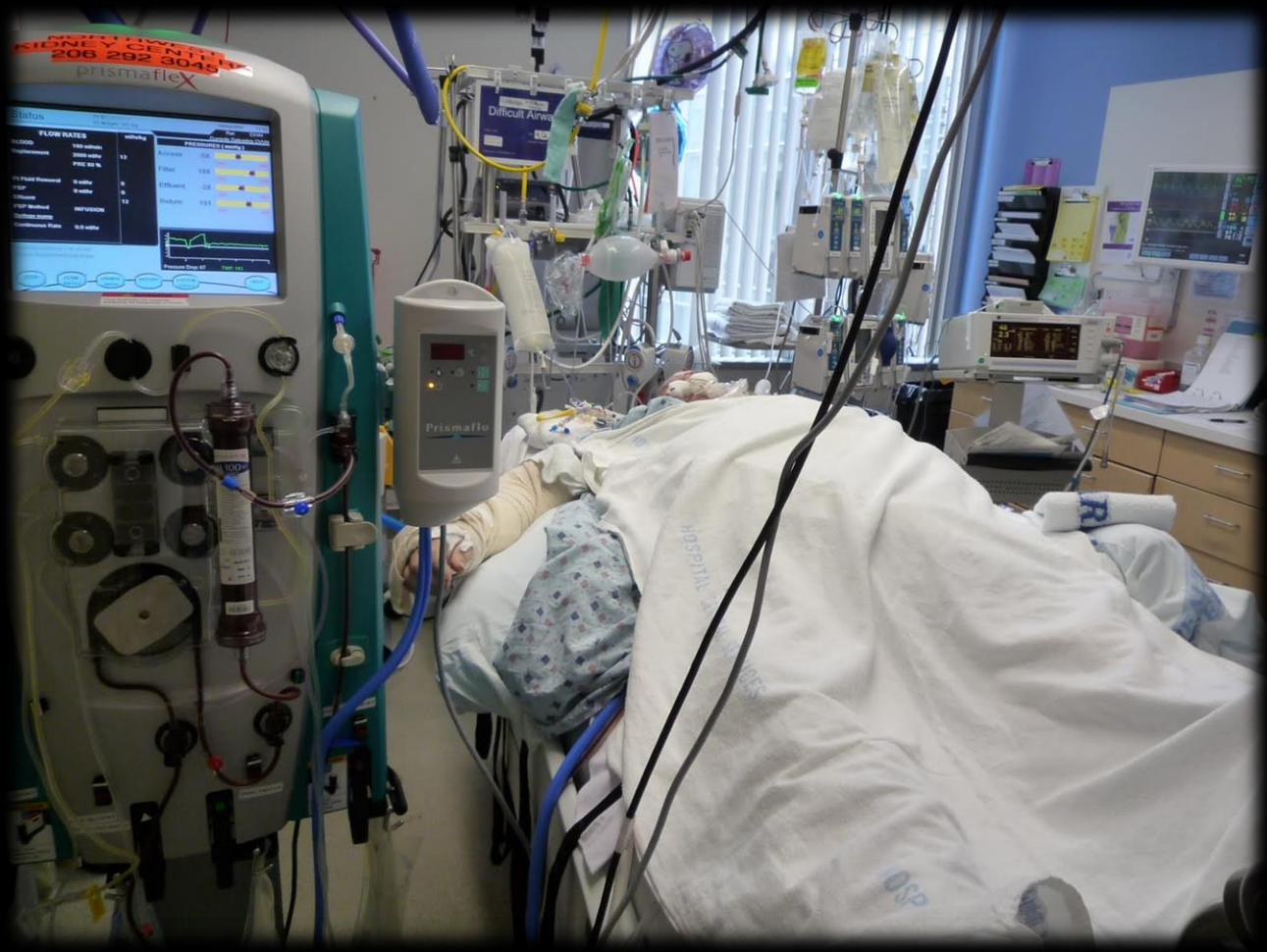
NCHS data brief #62, 2011
US National Lib Med, NIH, 2010
HCUP Statistical Brief #160



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.”




Surviving Sepsis
Campaign

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

R. Phillip Dellinger, Mitchell M. Levy, Andrew Rhodes, Djillali Annane, Herwig Gerlach, Steven M. Opal, Jonathan E. Sevransky, Charles L. Sprung, Ivor S. Douglas, Roman Jaeschke, Tiffany M. Osborn, Mark E. Nunnally, Sean R. Townsend, Konrad Reinhart, Ruth M. Kleinpell, Derek C. Angus, Clifford S. Deutschman, Flavia R. Machado,Gordon D. Rubenfeld, Steven A. Webb, Richard J. Beale, Jean-Louis Vincent, Rui Moreno, and the Surviving Sepsis Campaign Guidelines Committee including the Pediatric Subgroup.

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

<u>Participation and endorsement</u>:

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

GUIDELINES TO BUNDLES

Special Articles

Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock

R. Phillip Dellinger, MD; Jean M. Carlet, MD; Henry Masur, MD; Herwig Gerlach, MD, PhD; Thierry Calandra, MD; Jonathan Cohen, MD; Juan Gea-Banacloche, MD, PhD; Didier Keh, MD; John C. Marshall, MD; Margaret M. Parker, MD; Graham Ramsay, MD; Janice L. Zimmerman, MD; Jean-Louis Vincent, MD, PhD; Mitchell M. 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 Clinical Microbiology and Infectious Diseases, European Society of Intensive Care Medicine, European Respiratory Society, International Sepsis Forum, Society of Critical Care Medicine, Surgical Infection Society.

Objective: In 2003, critical care and infectious disease experts representing 11 international organizations developed management guidelines for severe sepsis and septic shock that would be of practical use for the bedside clinician, under the auspices of the Surviving Sepsis Campaign, an international effort to increase awareness and improve outcome in severe sepsis.

Design: The process included a modified Delphi method, a consensus conference, several subsequent smaller meetings of subgroups and key individuals, teleconferences, and electronic-based discussion among subgroups and among the entire committee.

Methods: We used a modified Delphi methodology for grading recommendations, built on a 2001 publication sponsored by the International Sepsis Forum. We undertook a systematic review of the literature graded along five levels to create recommendation grades from A to E, with A being the highest grade. Pediatric considerations were provided to contrast adult and pediatric management.

Results: Key recommendations, listed by category and not by hierarchy, include early goal-directed resuscitation of the septic patient during the first 6 hrs after recognition; appropriate diagnostic studies to ascertain causative organisms before starting antibiotics; early administration of broad-spectrum antibiotic therapy; reassessment of antibiotic therapy with microbiology and clinical data to narrow coverage, when appropriate; a usual 7–10 days of antibiotic therapy guided by clinical response; source control with attention to the method that balances risks and benefits; equivalence of crystalloid and colloid resuscitation; aggressive fluid challenge to restore mean circulating filling pressure; vasopressor preference for norepinephrine and dopamine; cautious use of vasopressin pending further studies; avoiding low-dose dopamine administration for renal protection; consideration of dobutamine inotropic therapy in some clinical situations; avoidance of supranormal oxygen delivery as a goal of therapy; stress-dose steroid therapy for septic shock; use of recombinant activated protein C in patients with severe sepsis and high risk for death; with resolution of tissue hypoperfusion and in the absence of coronary artery disease or acute hemorrhage, targeting a hemoglobin of 7–9 g/dL; appropriate use of fresh frozen plasma and platelets; a low tidal volume and limitation of inspiratory plateau pressure strategy for acute lung injury and acute respiratory distress syndrome; application of a minimal amount of positive end-expiratory pressure in acute lung injury/acute respiratory distress syndrome; a semirecumbent bed position unless contraindicated; protocols for weaning and sedation/analgesia, using either intermittent bolus sedation or continuous infusion sedation with daily interruptions/lightening; avoidance of neuromuscular blockers, if at all possible; maintenance of blood glucose <150 mg/dL after initial stabilization; equivalence of continuous veno-veno hemofiltration and intermittent hemodialysis; lack of utility of bicarbonate use for pH ≥ 7.15; use of deep vein thrombosis/stress ulcer prophylaxis; and consideration of limitation of support where appropriate. Pediatric considerations included a more likely need for intubation due to low functional residual capacity; more difficult intravenous access; fluid resuscitation based on weight with 40–60 mL/kg or higher needed; decreased cardiac output and increased systemic vascular resistance as the most common hemodynamic profile; greater use of physical examination therapeutic end points; unsettled issue of high-dose steroids for therapy of septic shock; and greater risk of hypoglycemia with aggressive glucose control.

Conclusion: Evidence-based recommendations can be made regarding many aspects of the acute management of sepsis and septic shock that are hoped to translate into improved outcomes for the critically ill patient. The impact of these guidelines will be formally tested and guidelines updated annually and even more rapidly as some important new knowledge becomes available. (Crit Care Med 2004; 32:858–873)

Key Words: sepsis; severe sepsis; septic shock; sepsis syndrome; infection; guidelines; evidence-based medicine; Surviving Sepsis Campaign

DOI: 10.1097/01.CCM.0000117317.18092.E4

Severe Sepsis Bundles:

Sepsis Resuscitation Bundle

(To be accomplished as soon as possible and scored over first 6 hours):

1. Serum lactate measured.
2. Blood cultures obtained prior to antibiotic administration.
3. From the time of presentation, broad-spectrum antibiotics administered within 3 hours for ED admissions and 1 hour for non-ED ICU admissions.
4. In the event of hypotension and/or lactate > 4 mmol/L (36 mg/dl):
   a) Deliver an initial minimum of 20 ml/kg of crystalloid (or colloid equivalent*).
   b) Apply vasopressors for hypotension not responding to initial fluid resuscitation to maintain mean arterial pressure (MAP) ≥ 65 mm Hg.
5. In the event of persistent hypotension despite fluid resuscitation (septic shock) and/or lactate > 4 mmol/L (36 mg/dl):
   a) Achieve central venous pressure (CVP) of ≥ 8 mm Hg.
   b) Achieve central venous oxygen saturation ($ScvO_2$) of ≥ 70%.**

Sepsis Management Bundle

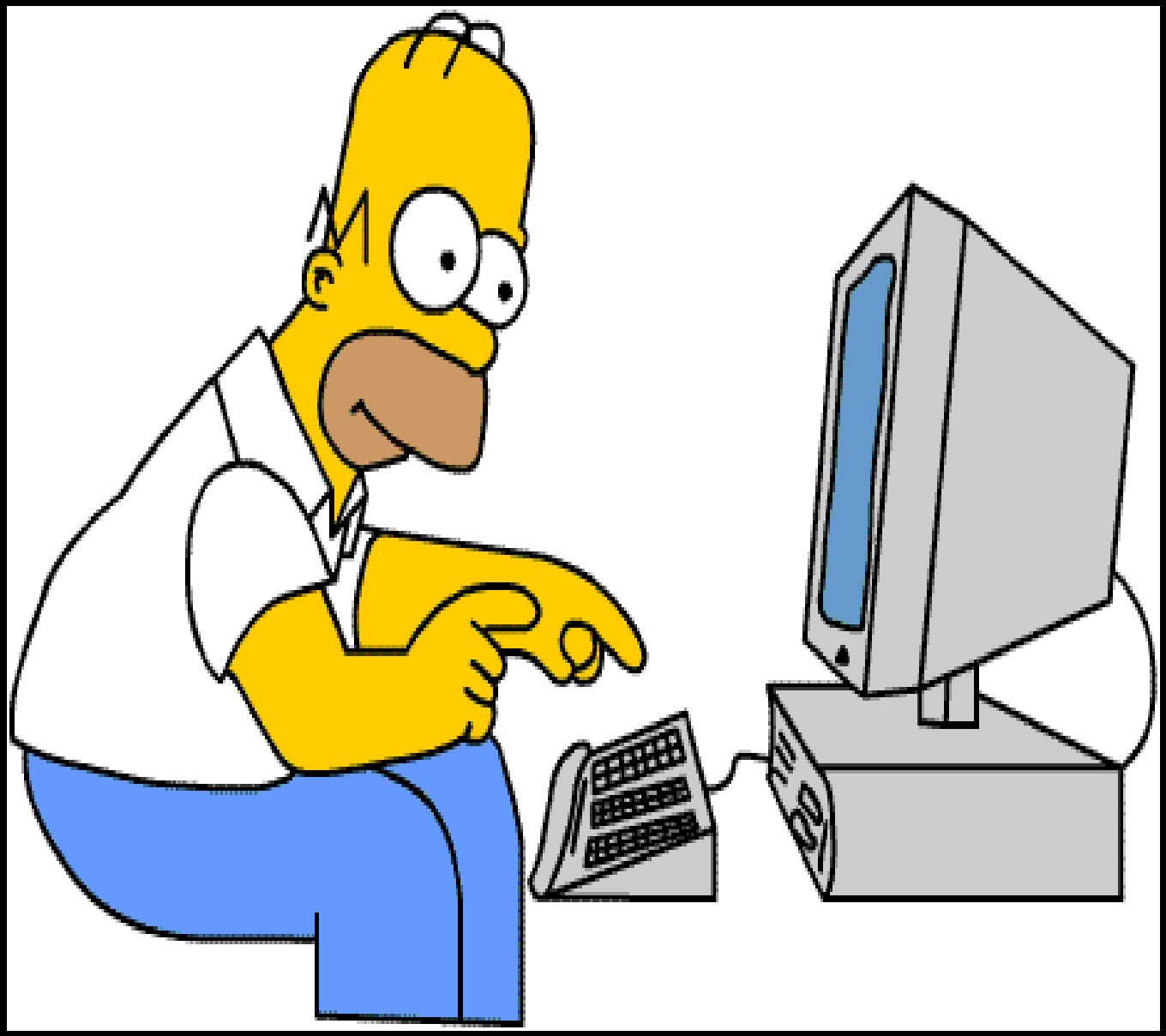
(To be accomplished as soon as possible and scored over first 24 hours):

1. Low-dose steroids* administered for septic shock in accordance with a standardized ICU policy.
2. Drotrecogin alfa (activated) administered in accordance with a standardized ICU policy.
3. Glucose control maintained ≥ lower limit of normal, but < 150 mg/dl (8.3 mmol/L).
4. Inspiratory plateau pressures maintained < 30 cm H_2O for mechanically ventilated patients.

**See the individual chart measurement tool for an equivalency chart.*

***Achieving a mixed venous oxygen saturation (SvO_2) of 65% is an acceptable alternative.*

CONVERTING GOALS TO MEASURABLE INDICATORS



Surviving Sepsis Campaign

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 ($ScvO_2$) > 70% or mixed venous oxygen saturation ($ScvO_2$) > 65%

Implement the 6-hour bundle. Available at: http://ssc.sccm.org/6hr_bundles.

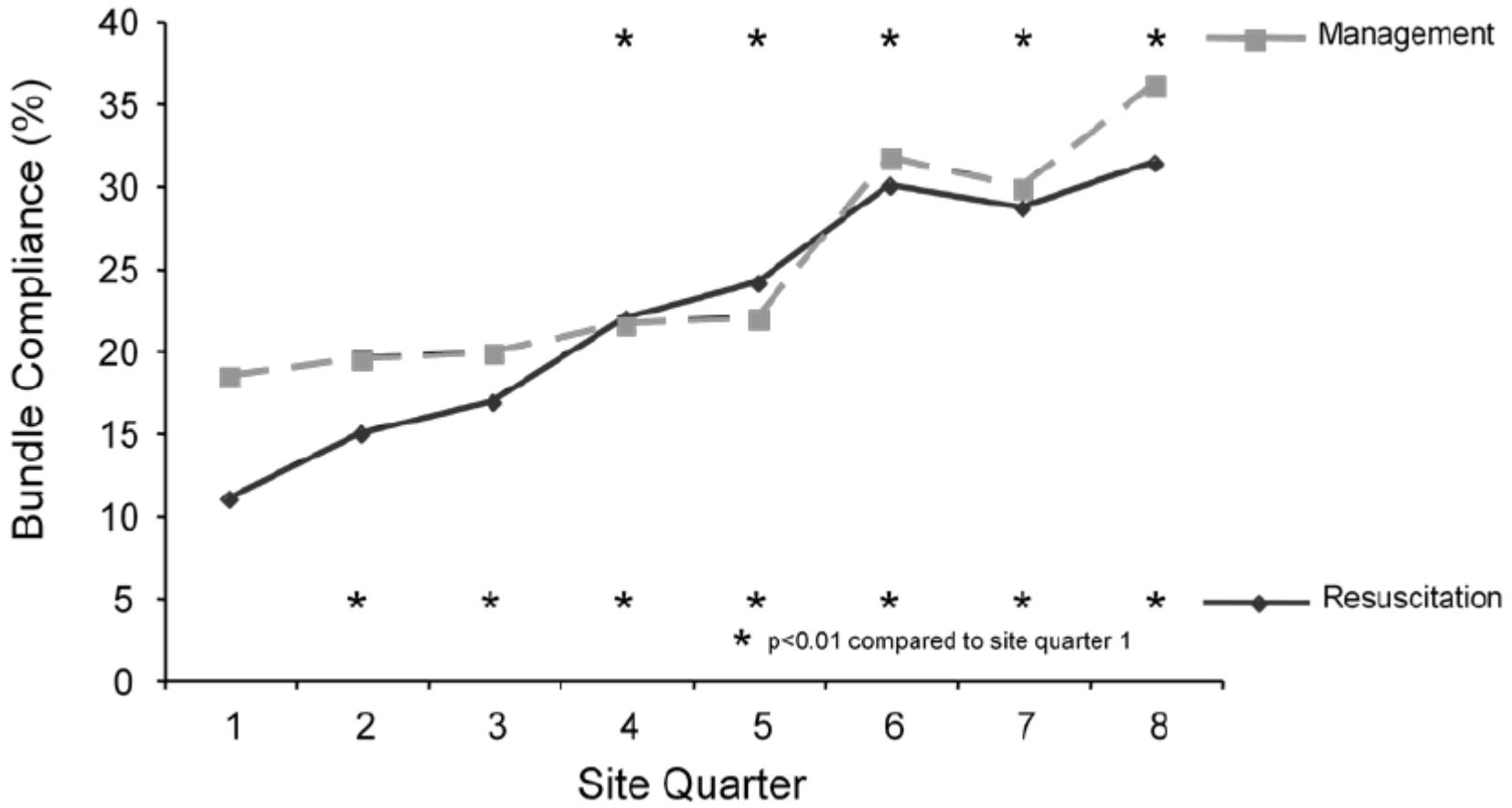
Severe Sepsis Management Bundle

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 H20 for mechanically ventilated patients.

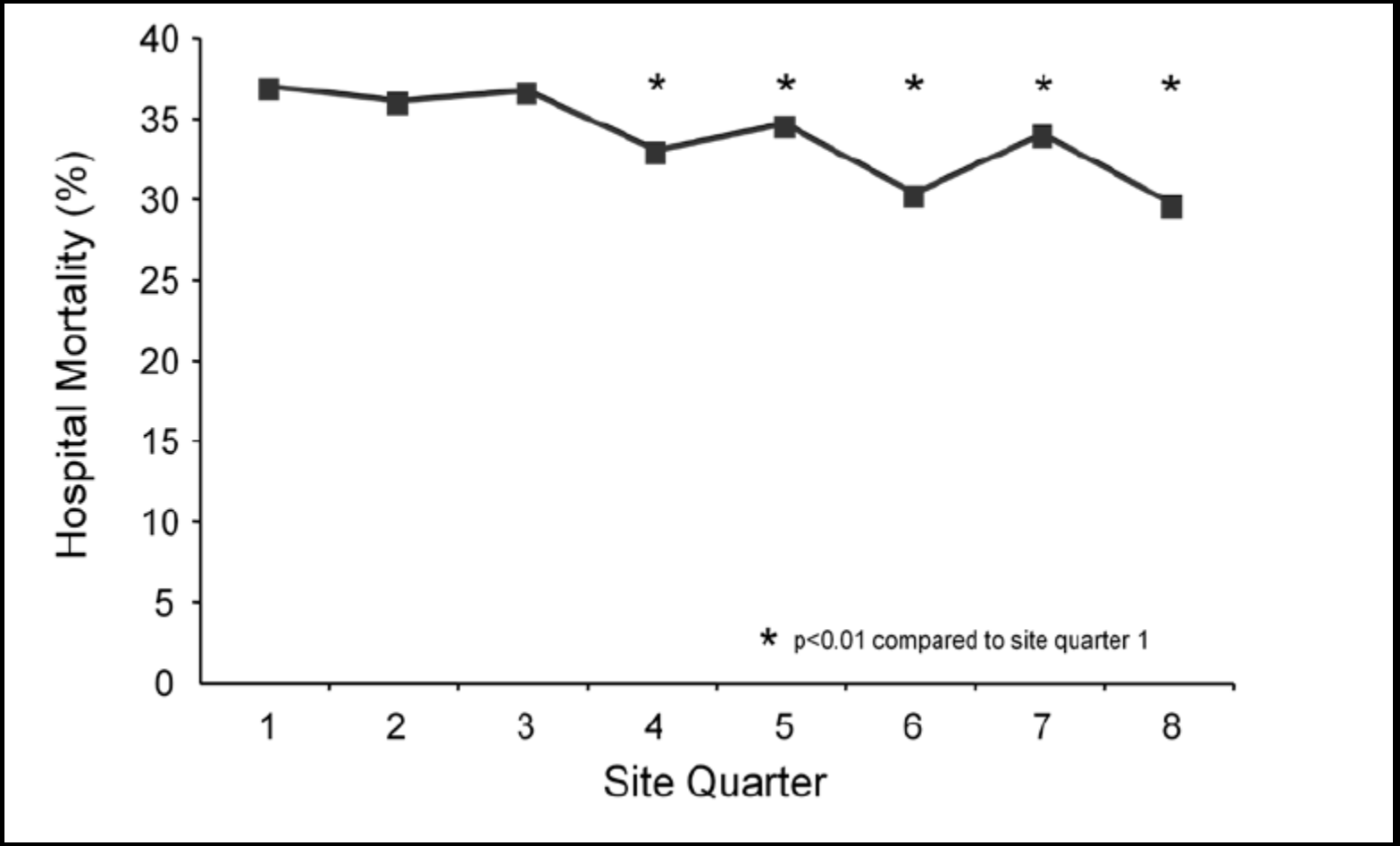
Implement the 24-hour bundle. Available at: http://ssc.sccm.org/24hr_bundles.

CHANGE IN COMPLIANCE OVER TIME

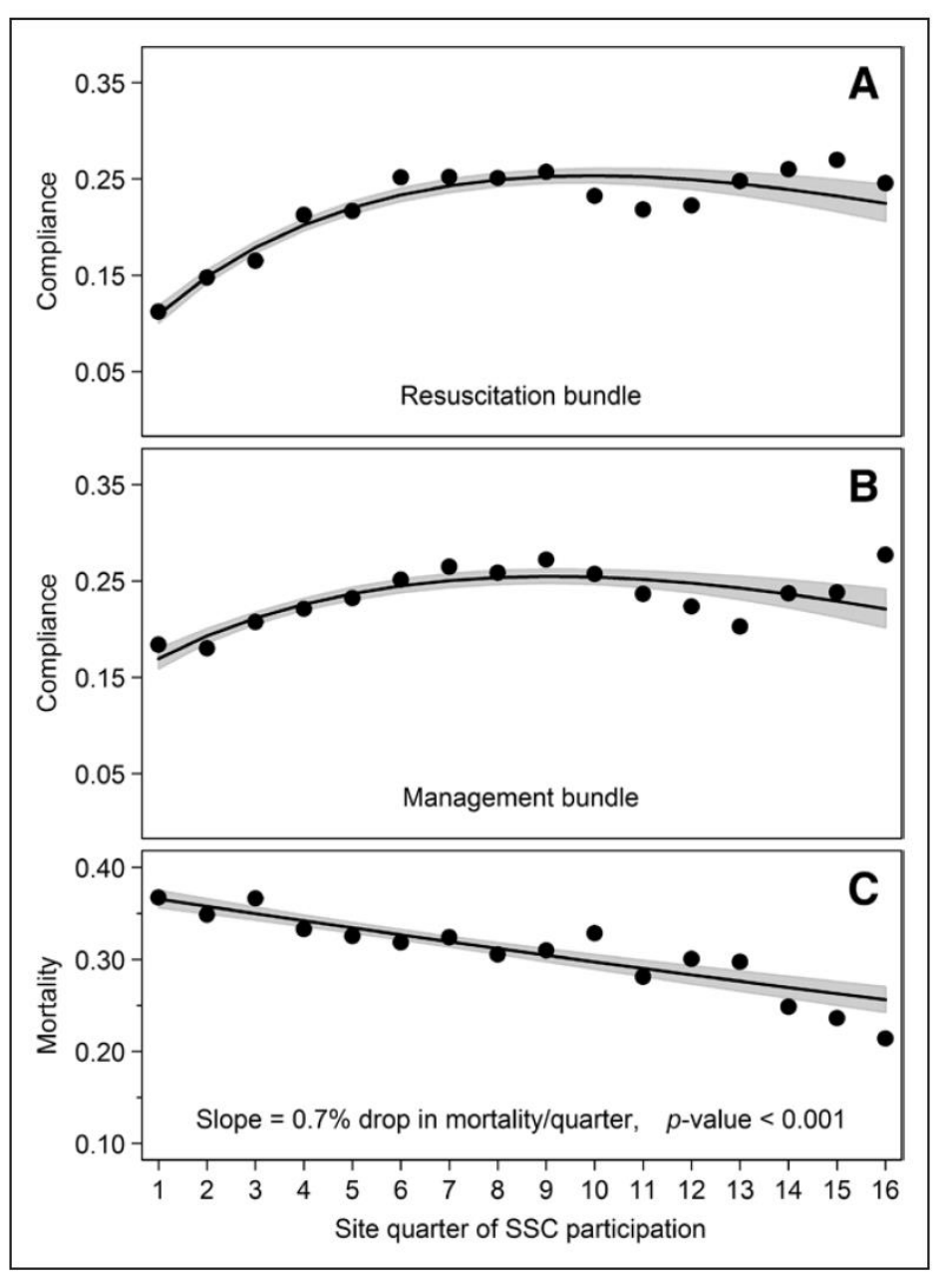


Levy MM, Dellinger, RP, Townsend SA et al.
CCM 38(2):367-374, February 2010.

CHANGE IN MORTALITY OVER TIME

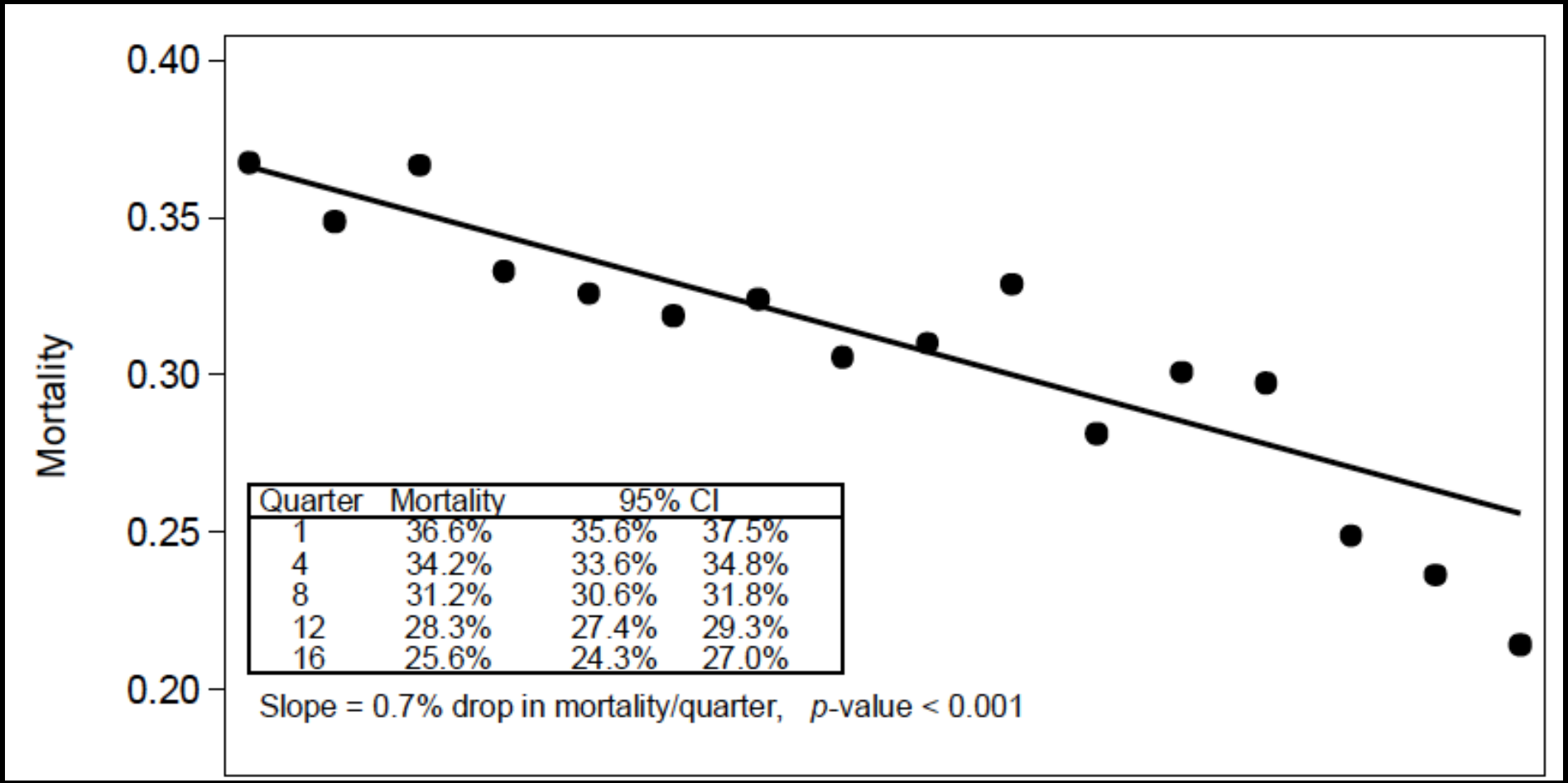


Levy MM, Dellinger, RP, Townsend SA et al.
CCM 38(2):367-374, February 2010.



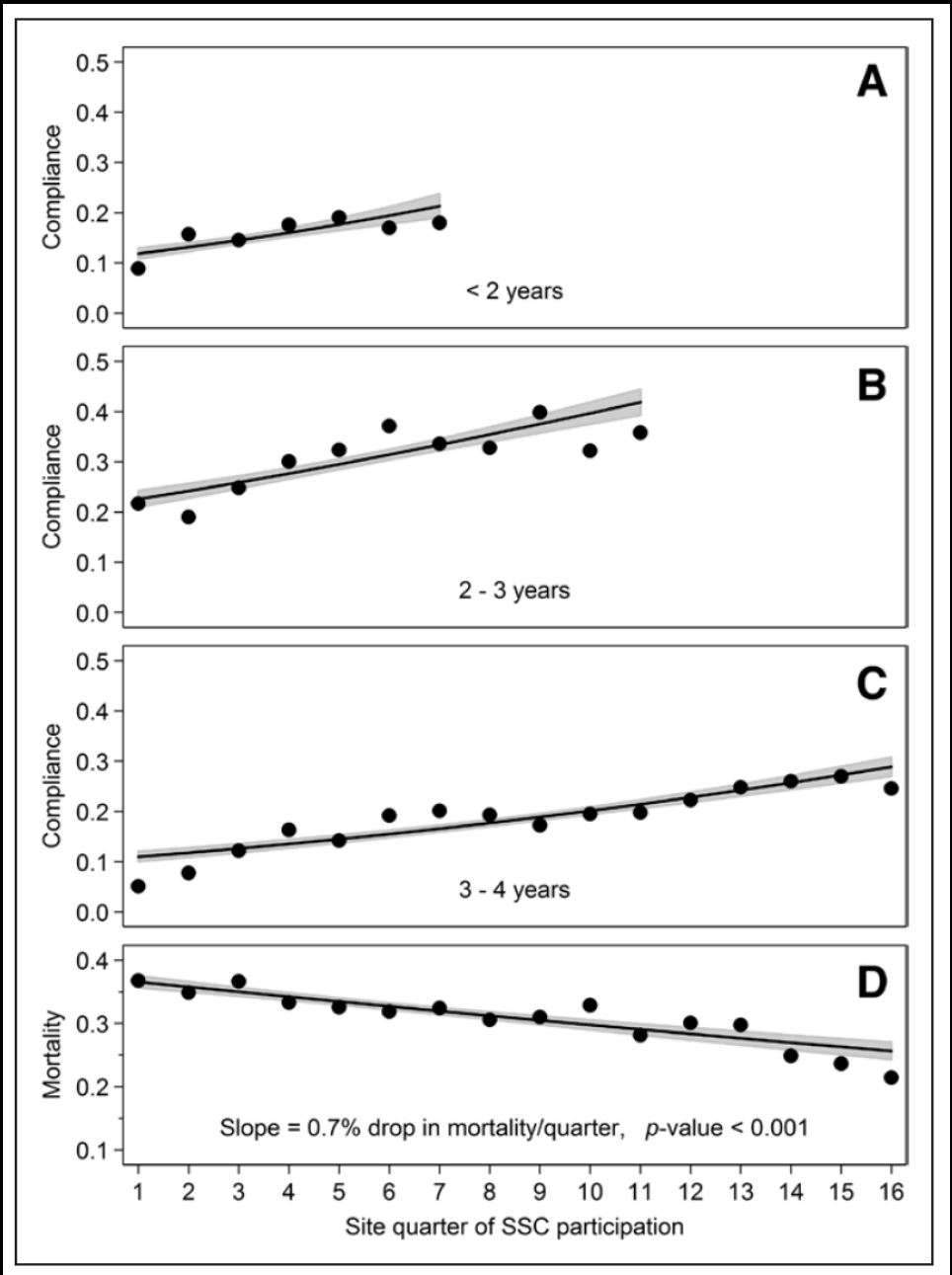
Levy, et al. Crit Care Med. 2015 Jan;43(1):3-12.

SSC MORTALITY



Levy, et al. Crit Care Med. 2015 Jan;43(1):3-12.

WHY?



Levy, et al. Crit Care Med. 2015 Jan;43(1):3-12.

INITIAL RESUSCITATION OF SEPSIS INDUCED TISSUE HYPOPERFUSION

Recommend

Insertion central venous catheter

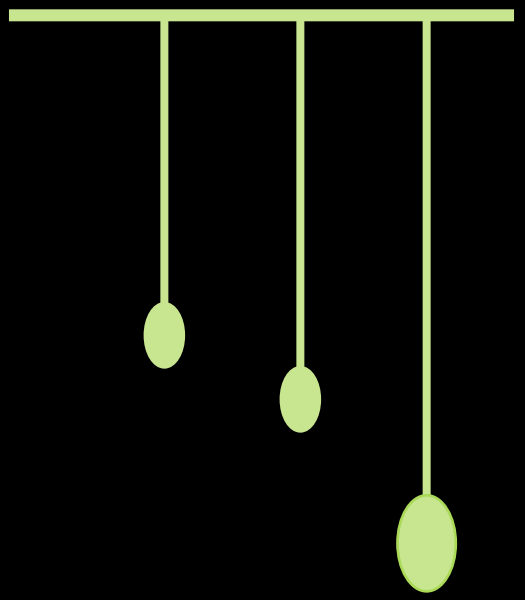
Recommended goals :

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

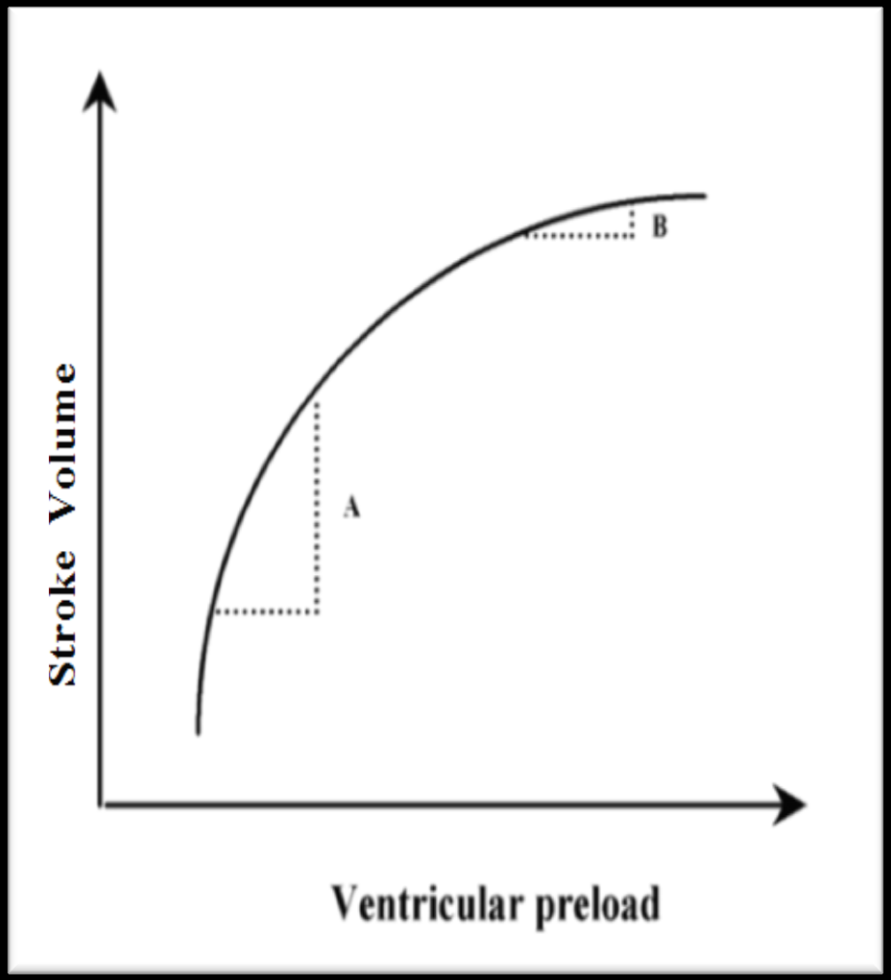
Grade 1C

STARLING PRINCIPLE RELATES TO VOLUME

The Starling principle relates to the fact that the more a myocardial fibril is stretched the greater the contraction.



EXPECTED RESULT OF VOLUME EXPANSION



CENTRAL VENOUS PRESSURE POORLY PREDICTS CARDIAC PRELOAD AND VOLUME STATUS

Michard F, et al. Chest 2002; 121:2000–2008.

Kumar A, et al. Crit Care Med 2004; 32:691–699.

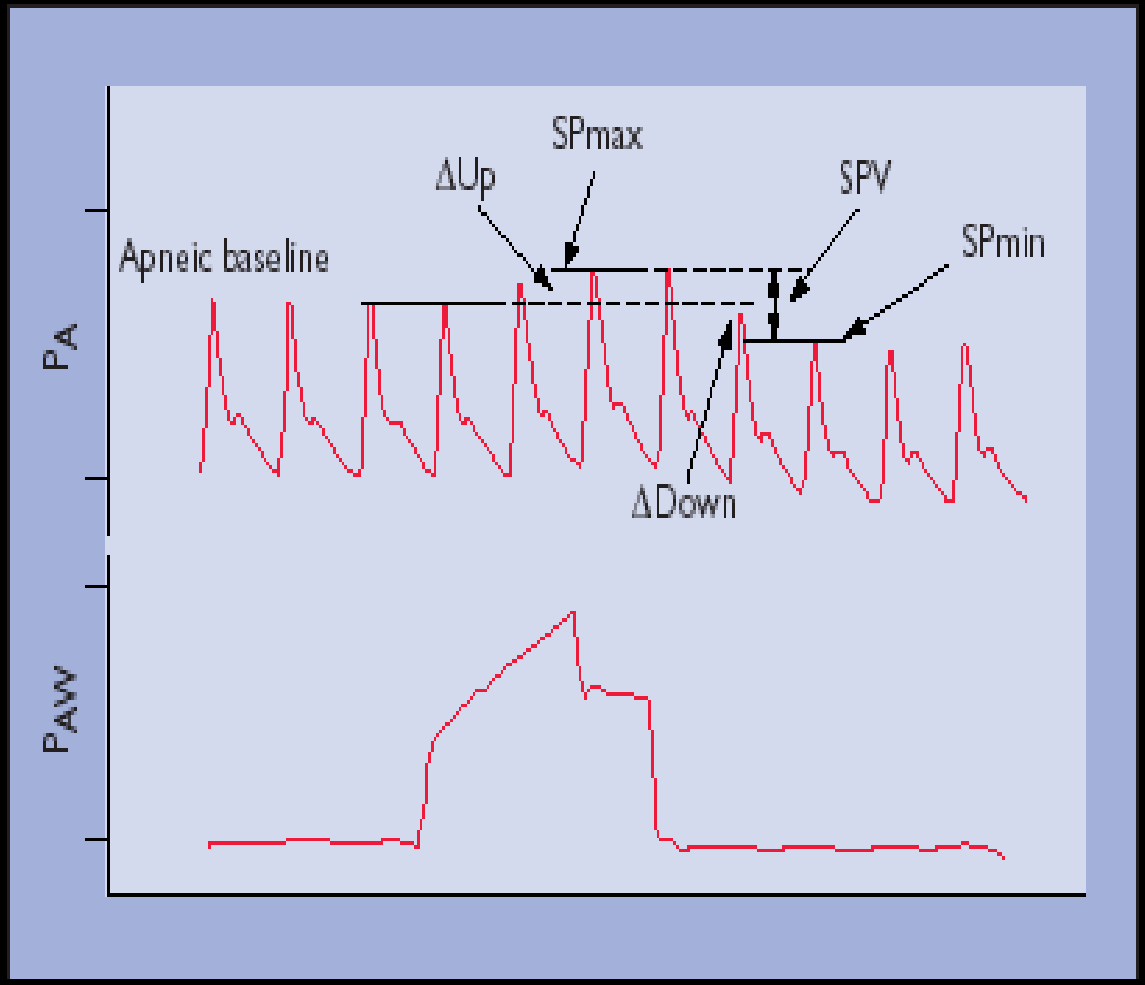
Shippy CR, et al. Crit Care Med 1984; 12:107–112.

INTRAVASCULAR VOLUME STATUS AND PERFUSION PARAMETERS

- Limitation of pressure measurement to predict fluid responsiveness

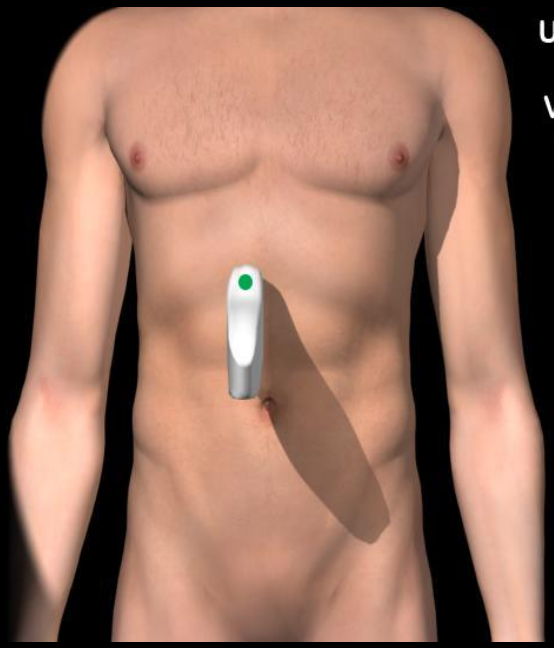
- There are alternatives to CVP for judging fluid responsiveness that are in general more reliable

ARTERIAL SYSTOLIC PRESSURE VARIATION

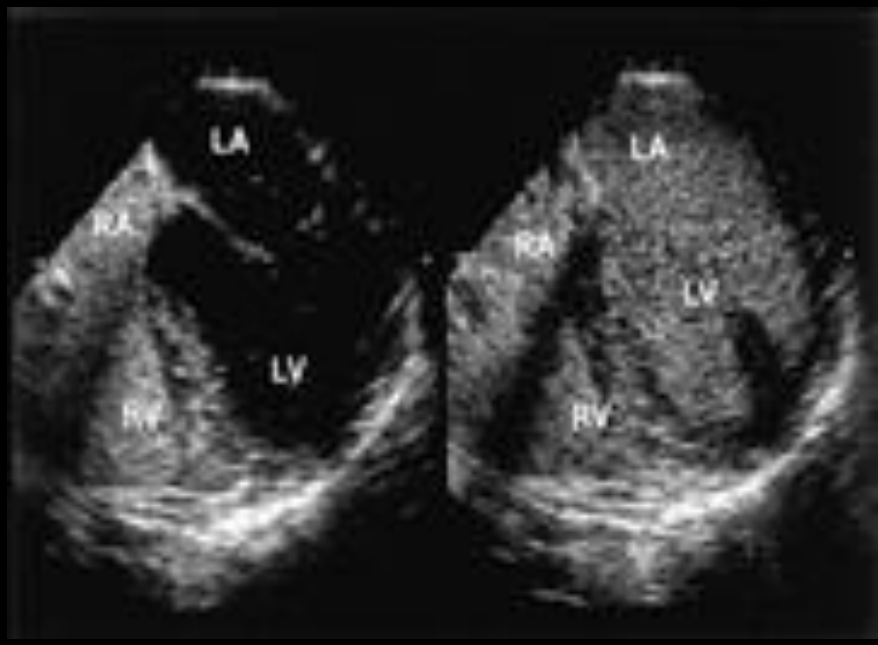


Parry-Jones, et al. *Int J Respir Crit Care Med* 2003;2:67

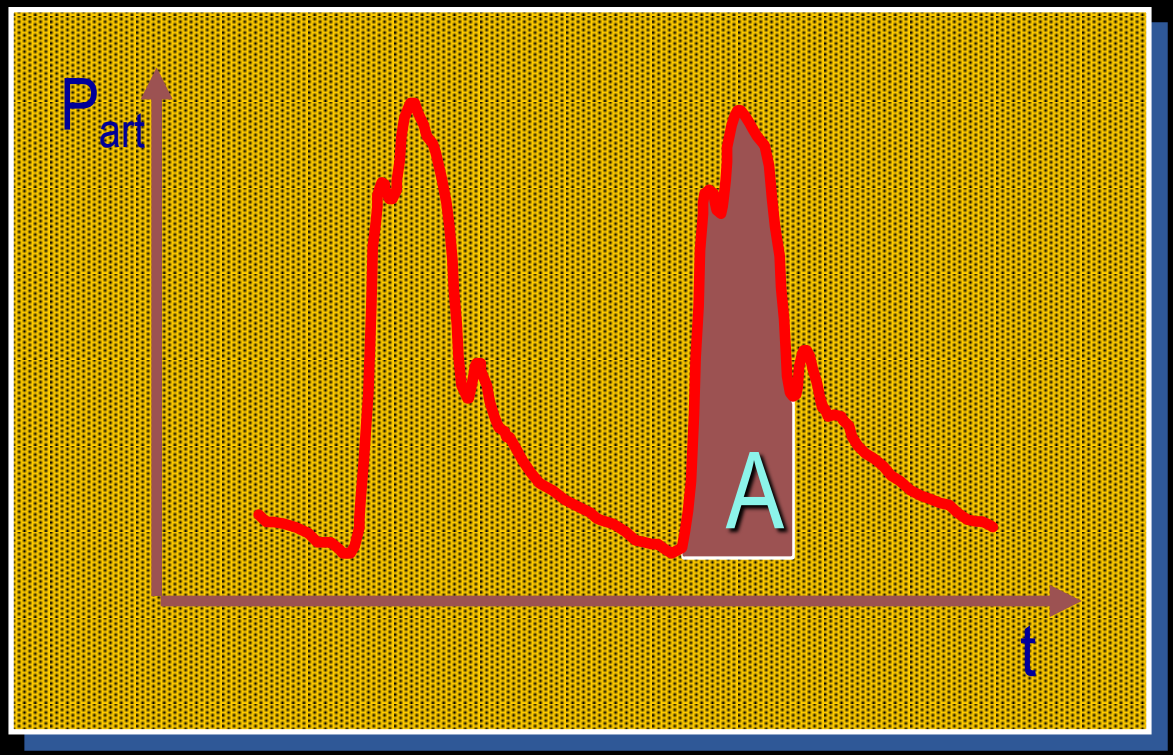
EFFECT ON CARDIAC FILLING



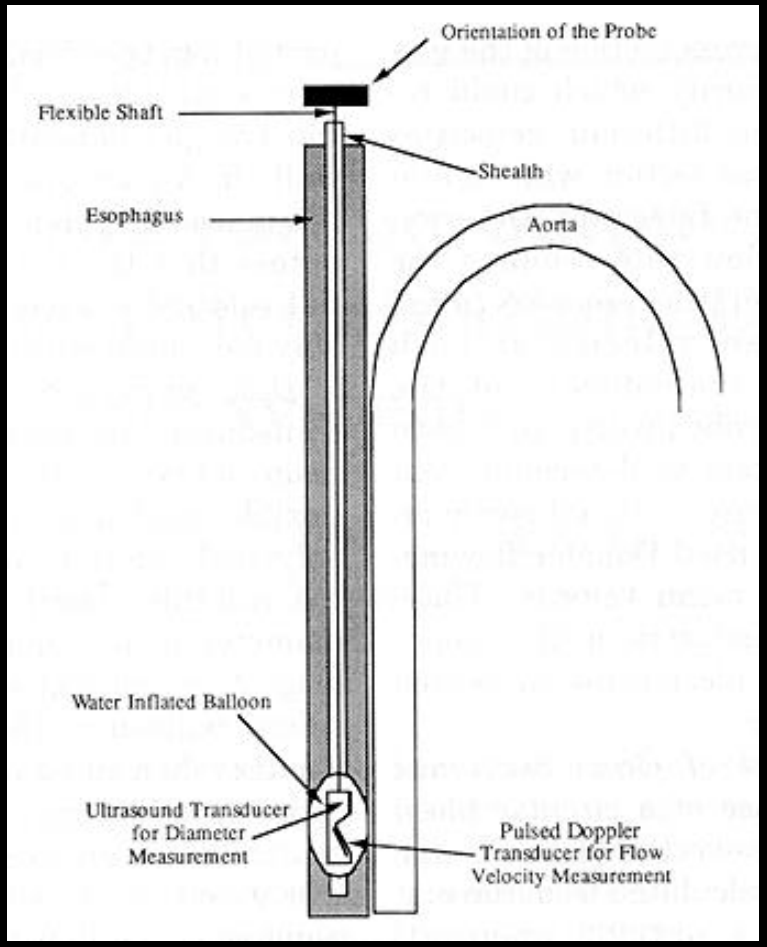
Ultrasound
Inferior
Vena Cava
Long Axis



EFFECT ON STROKE VOLUME



EFFECT ON STROKE VOLUME



Surviving Sepsis Campaign Bundles 2012

To be accomplished as soon as possible and scored over first 3 hrs:	To be accomplished as soon as possible and scored over first 6 hrs:
✓ Serum lactate measured. ✓ Blood cultures obtained prior to antibiotics administered. ✓ Administer broad-spectrum antibiotics. ✓ For hypotension and/or lactate > 4 mmol/L: ✓ Deliver an initial minimum of 30 ml/kg of crystalloid	✓ Apply vasopressors for hypotension not responding to initial fluid resuscitation to maintain MAP ≥ 65 mm Hg. ✓ In the event of persistent arterial hypotension despite volume resuscitation (septic shock) or initial lactate >4 mmol/L (36mg/dL): ✓ Measure CVP* ✓ Measure $ScvO_2$* ✓ Remeasure lactate if initial lactate is elevated*

Dellinger RP, Levy ML, Rhodes A et al. Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock 2012. Critical Care Medicine 2013; 41:580-637

The BEATLES

You say you want a revolution

Revolution

NATIONAL QUALITY FORUM
2012 NQF: SEPSIS 0500

TO BE COMPLETED WITHIN 3 HOURS OF TIME OF PRESENTATION :

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 ≥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.

ORIGINAL ARTICLE

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

The ProCESS Investigators*

N Engl J Med. 2014 May 1;370(18):1683-93.

Over 1500 Patients

ORIGINAL ARTICLE

Goal-Directed Resuscitation for Patients with Early Septic Shock

The ARISE Investigators and the ANZICS Clinical Trials Group*

N Engl J Med. 2014 Oct 16;371(16):1496-506.

1600 Patients

EARLY GOAL DIRECTED THERAPY (EGDT)

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
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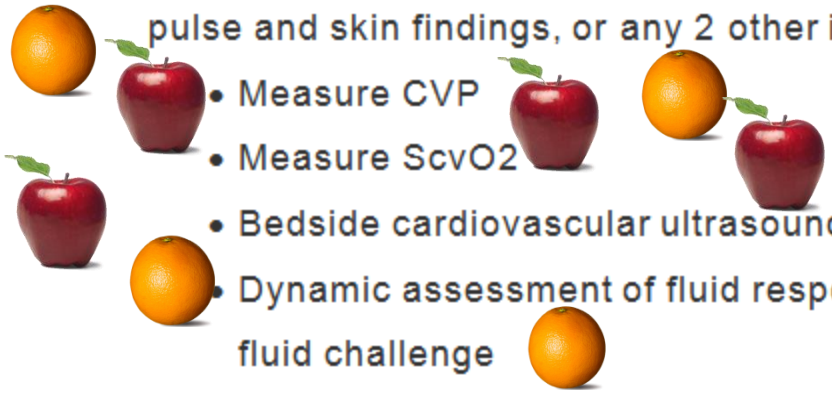


- Measure CVP
- Measure ScvO2
- Bedside cardiovascular ultrasound
- Dynamic assessment of fluid responsiveness with passive leg raise or fluid challenge

G. Re-measure lactate if initial lactate is elevated

Mandated Measurement SEP-1
Fall 2015

The BEATLES

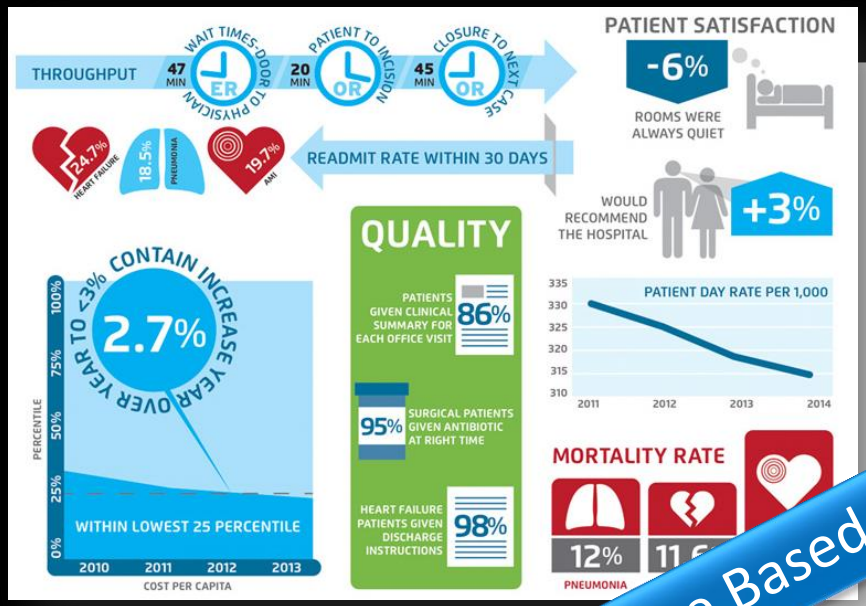
You say you got a real solution
Well, you know
We'd all love to see the plan

Revolution

The BEATLES

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

Revolution



Value Based Purchasing

The BEATLES

You tell me it’s (for) the institution

Revolution

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

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1600 Patients

	ProCESS	ARISE
Enrollment	<2 hours from detection of shock	2.8 hours (median) from presentation to ED
Antibiotics	75% received prior to enrollment	70 minutes (median) from presentation to ED
Fluids	>2 liters prior ot enrollment	2515ml (mean) prior to enrollment

- 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
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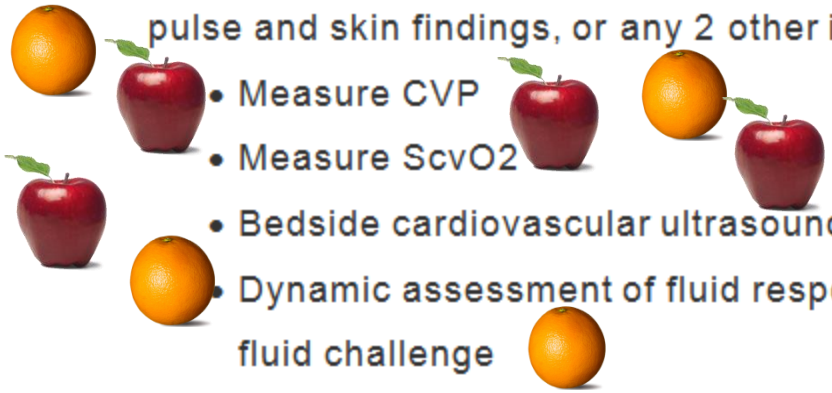


- Measure CVP
- Measure ScvO2
- Bedside cardiovascular ultrasound
- Dynamic assessment of fluid responsiveness with passive leg raise or fluid challenge

G. Re-measure lactate if initial lactate is elevated

IMPORTANCE OF REASSESSMENT

CMS SEP-1

- Sepsis is a big problem
- Logic of indicators is good
- Benchmarked performance

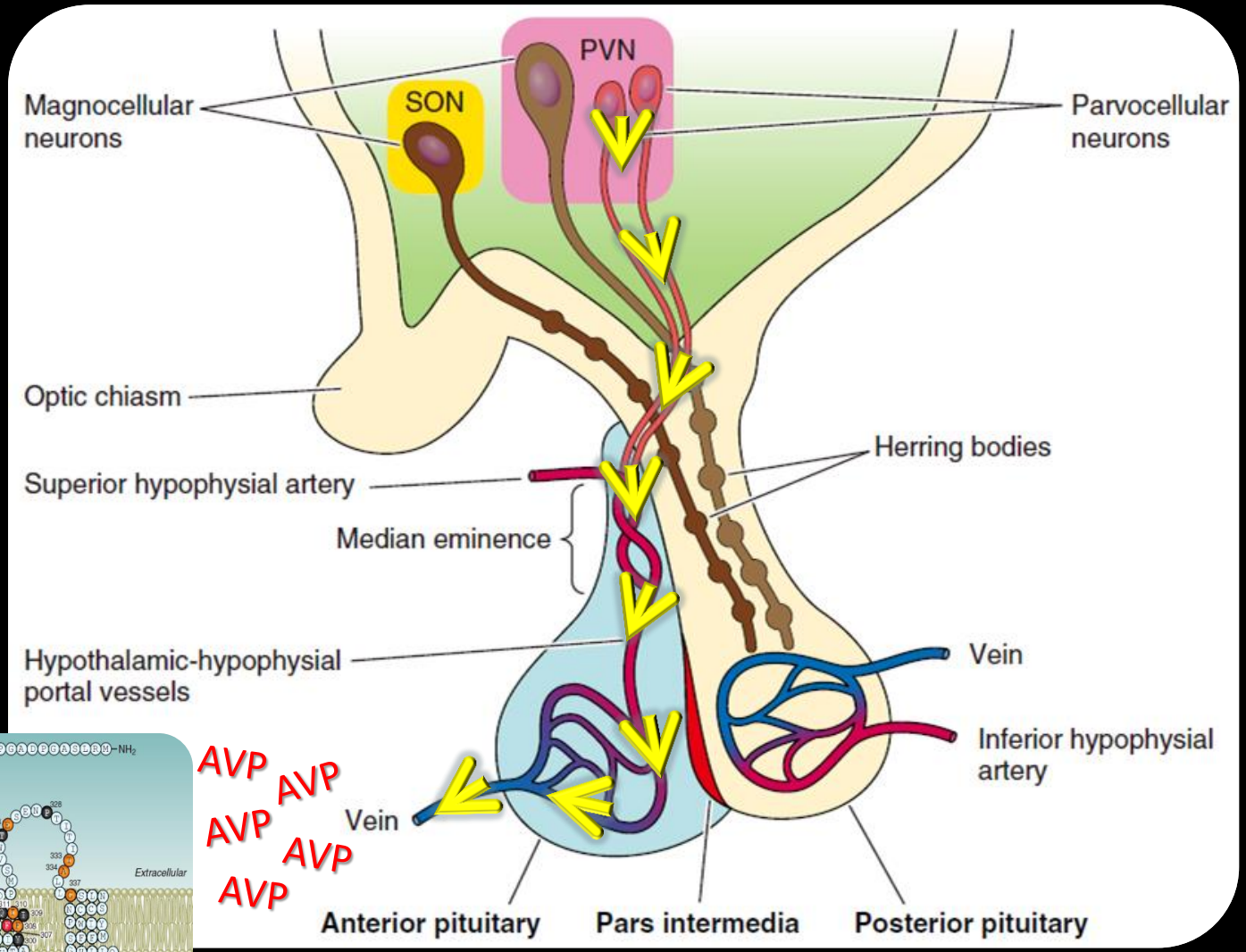
The BEATLES

Don’t you know it’s gonna be
alright, alright, alright

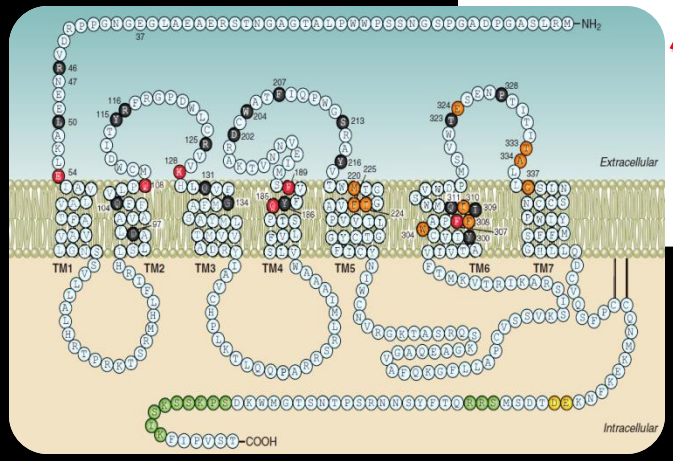
Revolution

Research / New or Ongoing Clinical Trials

SELEPRESSIN



V1A Receptor



Koshimizu, et al. Physiol Rev. 2012 Oct;92(4):1813-64.

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, PhD[1,2]; Perenlei Enkhbaatar, MD, PhD[1]; Régent Laporte, DVM, MSc, PhD[3]; Halina Wiśniewska, MS[3]; Lillian D. Traber, RN[1]†; ChiiDean Lin, PhD[4]; Juanjuan Fan, PhD[4]; Hal K. Hawkins, MD, PhD[5]; Robert A. Cox, PhD[5]; Kazimierz Wiśniewski, PhD[3]; Claudio D. Schteingart, PhD[3]; Donald W. Landry, MD, PhD[6]; Pierre J.-M. Rivière, PhD[3]; Daniel L. Traber, PhD, FCCM[1]†

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 vasopressor 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 V_2 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 V_2 receptor agonist arginine vasopressin because of its lack of agonist activity at the vasopressin V_2 receptor. (*Crit Care Med* 2014; 42:e525–e533)

***See also p. 1747.**

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†Deceased.

Drs. Marc O. Maybauer, Dirk M. Maybauer, Enkhbaatar, and Laporte contributed equally to this work.

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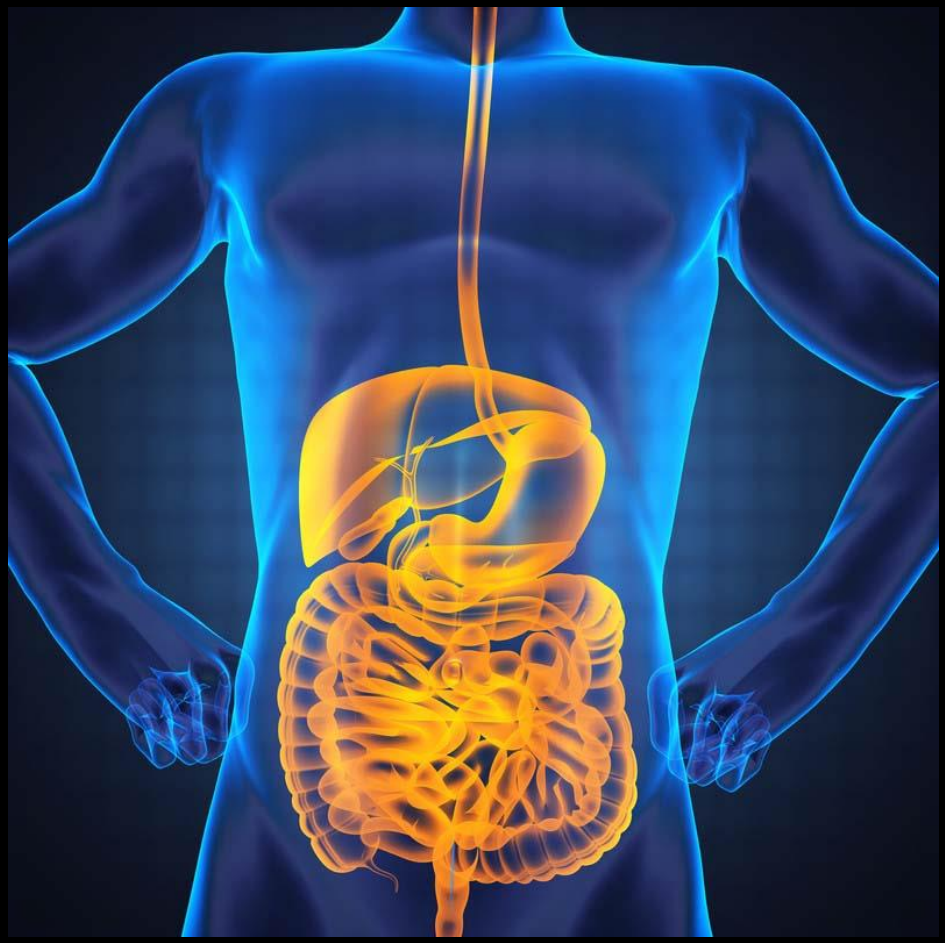
Drs. Marc O. Maybauer, Dirk M. Maybauer, Enkhbaatar, Traber, Hawkins, Cox, and Traber are/were employees of the University of Texas Medical Branch at Galveston, which was contracted by the Ferring Research Institute to conduct the study reported here. Drs. Lin and Fan are employees of Forestat Consulting 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 are/were employees of the Ferring Research Institute. Dr. Lin consulted for Ferring Research Institute. Drs. Landry and Traber were consultants for

LB1148



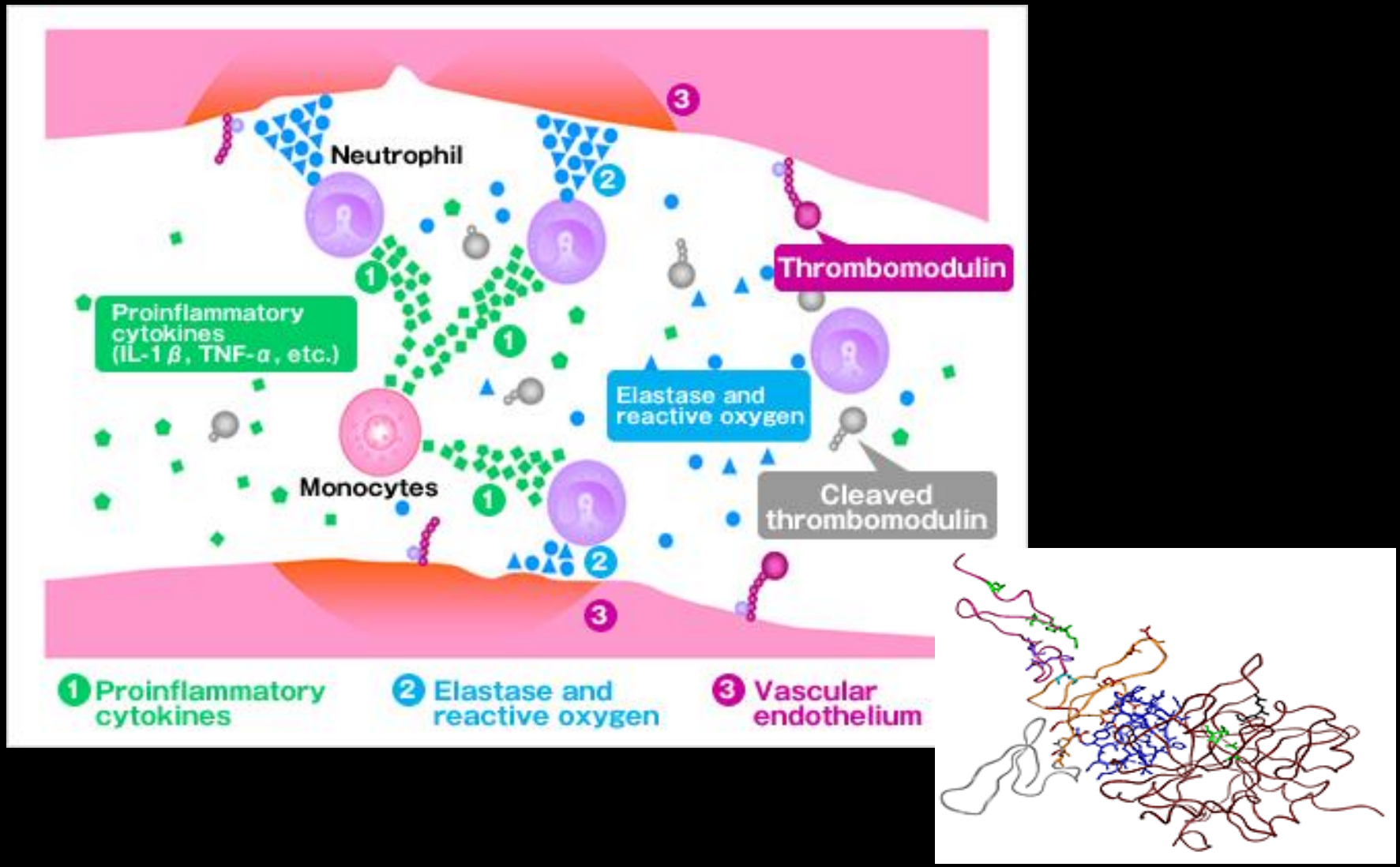
Gut Integrity in Shock

"SSAIL" TRIAL (TREATMENT OF SEPTIC SHOCK BY INHIBITING AUTODIGESTION AND PRESERVING GUT INTEGRITY WITH ENTERIC LB1148)

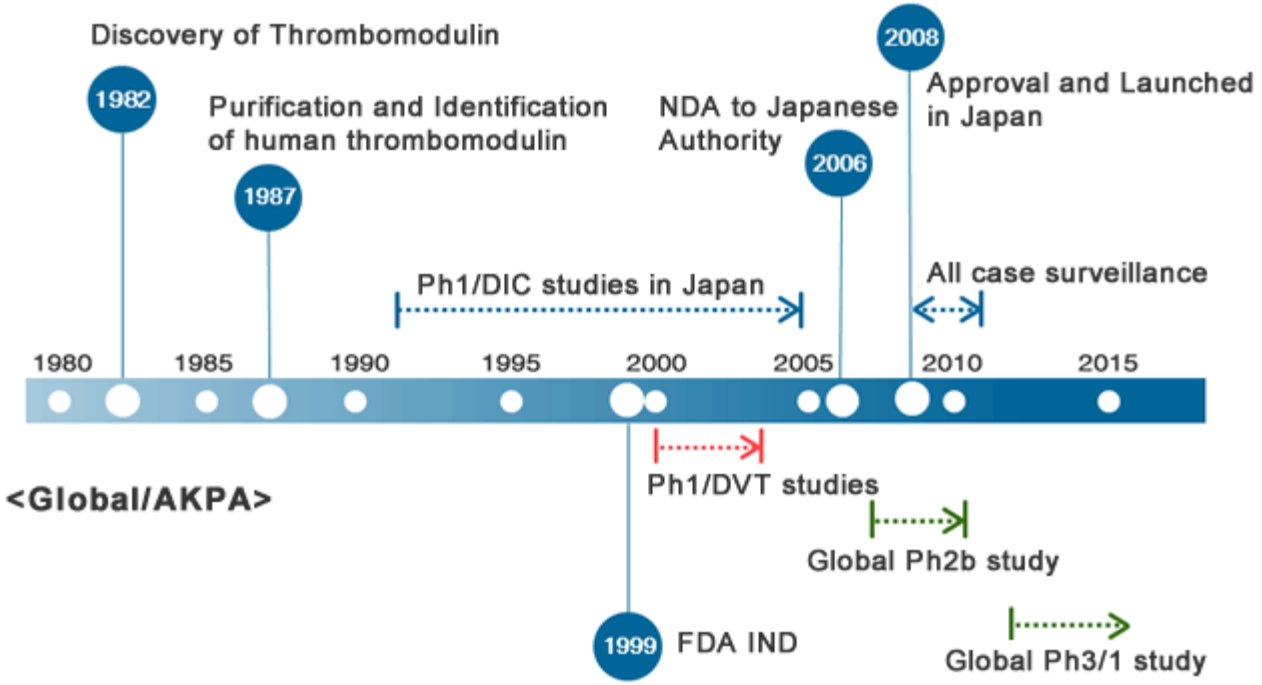
- LB1148 – broad-spectrum serine protease inhibitor delivered enterally to gut

- Inhibit the intraluminal pancreatic proteolytic enzymes (proteases) that leak due to loss of gut integrity

SOLUBLE THROMBOMODULIN


Neutrophil
Thrombomodulin
Proinflammatory cytokines (IL-1β, TNF-α, etc.)
Elastase and reactive oxygen
Monocytes
Cleaved thrombomodulin
1 Proinflammatory cytokines
2 Elastase and reactive oxygen
3 Vascular endothelium

History of ART-123 Development



ANGIOTENSIN II

Chawla et al. Critical Care 2014, 18:534
http://ccforum.com/content/18/5/534

CRITICAL CARE

RESEARCH Open Access

Intravenous angiotensin II for the treatment of high-output shock (ATHOS trial): a pilot study

Lakhmir S Chawla[1,3*], Laurence Busse[2], Ermira Brasha-Mitchell[3], Danielle Davison[3], Jacqueline Honiq[3], Ziyad Alotaibi[4] and Michael G Seneff[3]

Abstract

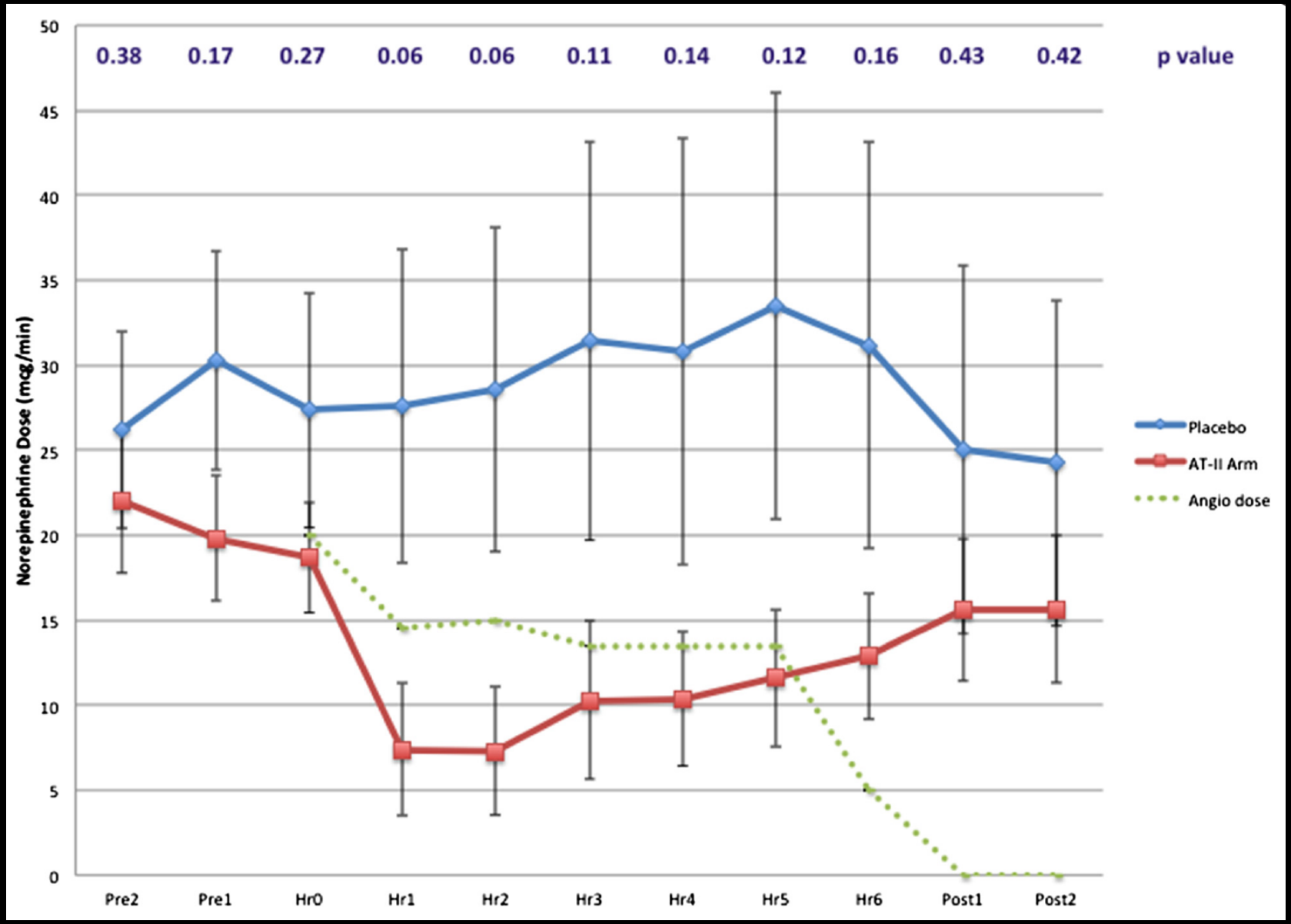
Introduction: Patients with distributive shock who require high dose vasopressors have a high mortality. Angiotensin II (ATII) may prove useful in patients who remain hypotensive despite catecholamine and vasopressin therapy. The appropriate dose of parenteral angiotensin II for shock is unknown.

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.

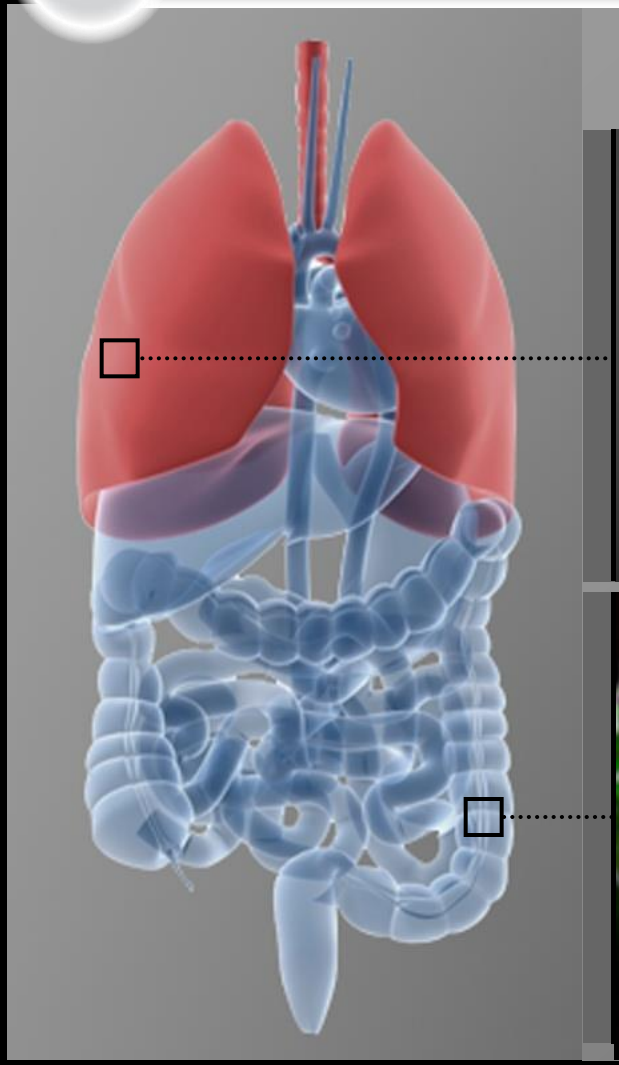
Trial registration: Clinicaltrials.gov NCT01393782. Registered 12 July 2011.



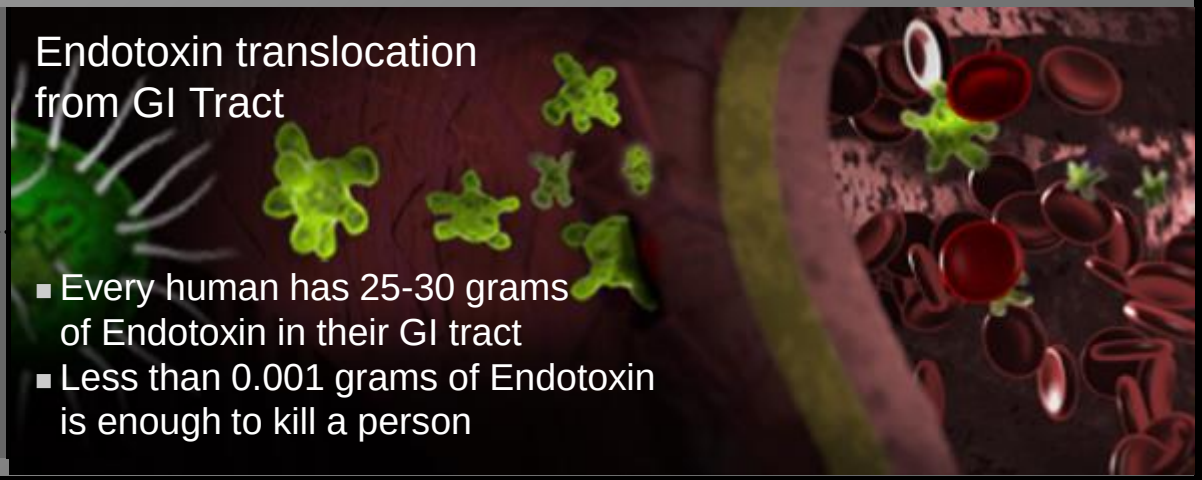
Chawla, et al. Crit Care. 2014 Oct 6;18(5):534.

POLYMYXIN B HEMOPERFUSION

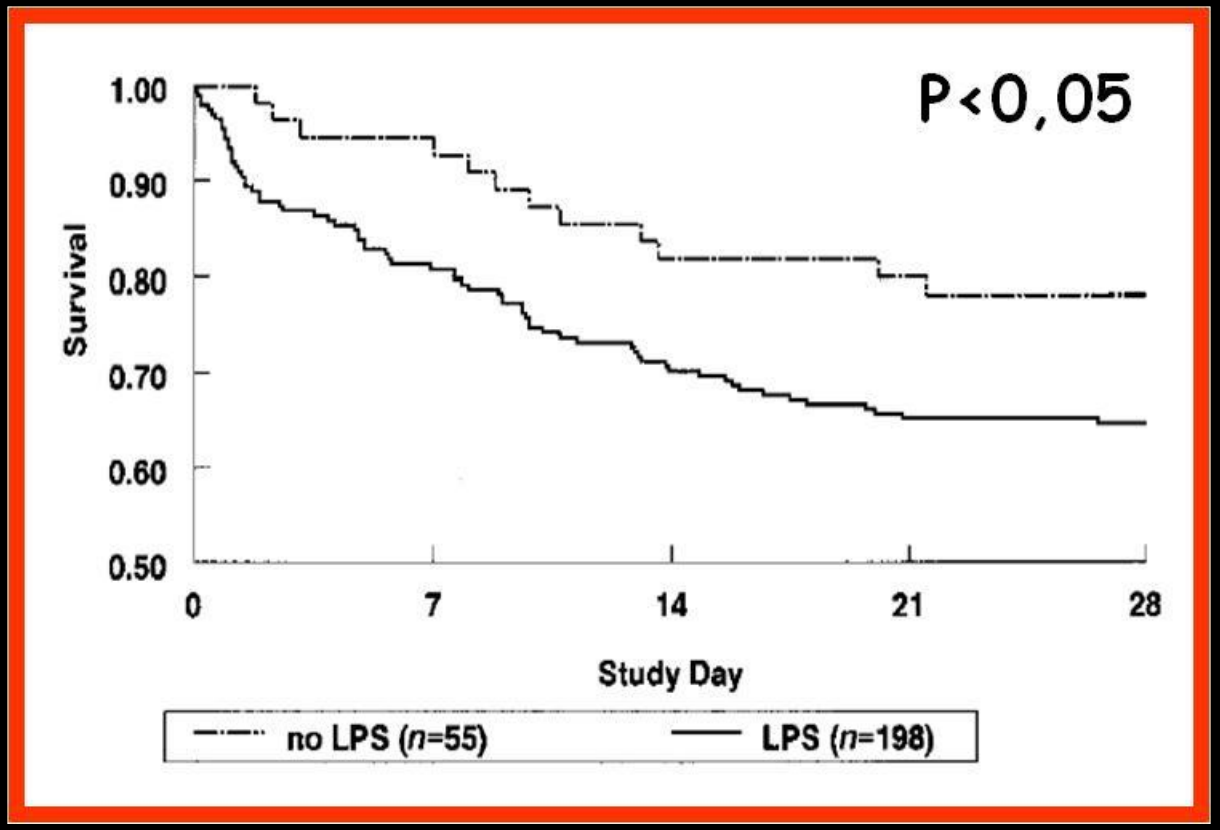
SOURCES OF ENDOTOXIN



Endotoxemia



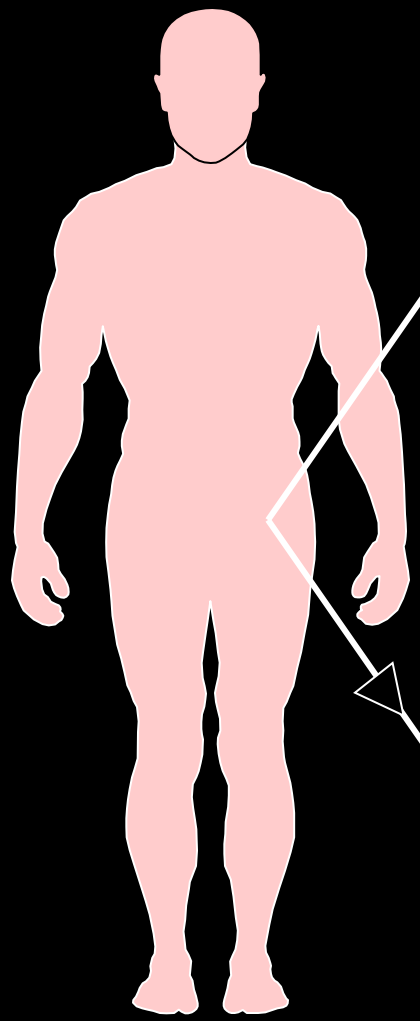
SEPSIS AND ENDOTOXIN



Opal SM, et al. Infect Dis, 1999

INTERVENTION

DIRECT HEMOPERFUSION WITH ADSORBENT COLUMN USING POLYMYXIN B IMMOBILIZED FIBER



Duration: 2 hours

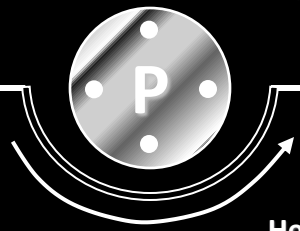
BLOOD TUBE

FEMORAL or IJ VEIN

FEMORAL or IJ VEIN

BLOOD PUMP

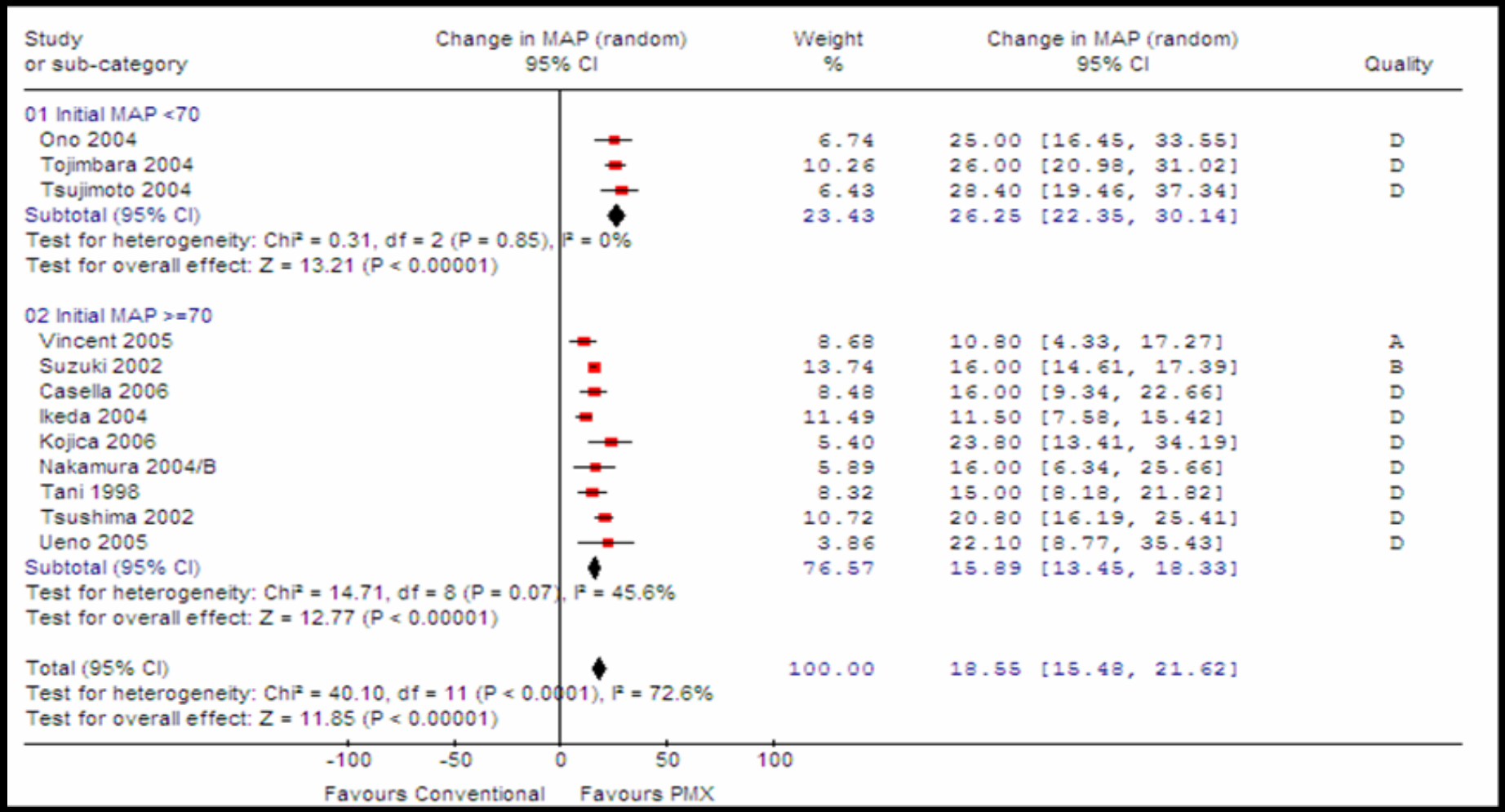
Perfusion rate 80-120 ml/min



ANTICOAGULANT

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

HEMODYNAMIC EFFECTS OF PMX



Cruz D. et al. Critical Care 2007; 11:R47

EUPHRATES
A CLINICAL TRIAL IN ADULTS WITH SEPTIC SHOCK AND ENDOTOXEMIA

Table 1. Baseline Characteristics of the Treatment Groups[a]

Characteristics	Mean (95% Confidence Interval) Polymyxin B Hemoperfusion (n = 34)	Conventional Therapy (n = 30)	*P* Value
Age, y	61 (57-66)	67 (61-72)	.09
Male sex, No. (%)	24 (71)	18 (60)	.53
APACHE II score	21 (19-23)	20 (18-23)	.86
SOFA score	11 (10-12)	9 (8-11)	.07
Mean arterial pressure, mm Hg	76 (72-80)	74 (70-78)	.40
Noradrenaline, µg/kg/min	0.27 (0.17-0.36)	0.24 (0.13-0.36)	.70
Dopamine, µg/kg/min	3.1 (1.7-4.4)	4.6 (3.0-6.2)	.13
Inotropic score	29.9 (20.4-39.4)	28.6 (16.6-40.7)	.85
Vasopressor dependency index, mm Hg^{-1}	4.3 (2.7-5.9)	4.1 (2.3-6.0)	.87
White blood cell count, 1000/µL	13.7 (11.4-16.0)	11.4 (9.0-13.8)	.12
Pao_2/Fio_2	235 (206-265)	217 (188-247)	.53
Diuresis, mL/h	66 (50-90)	87 (59-116)	.22
Creatinine, mg/dL	2.3 (1.7-2.9)	1.7 (1.3-2.2)	.18
Renal replacement therapy, No. (%)	13 (38)	6 (20)	.17

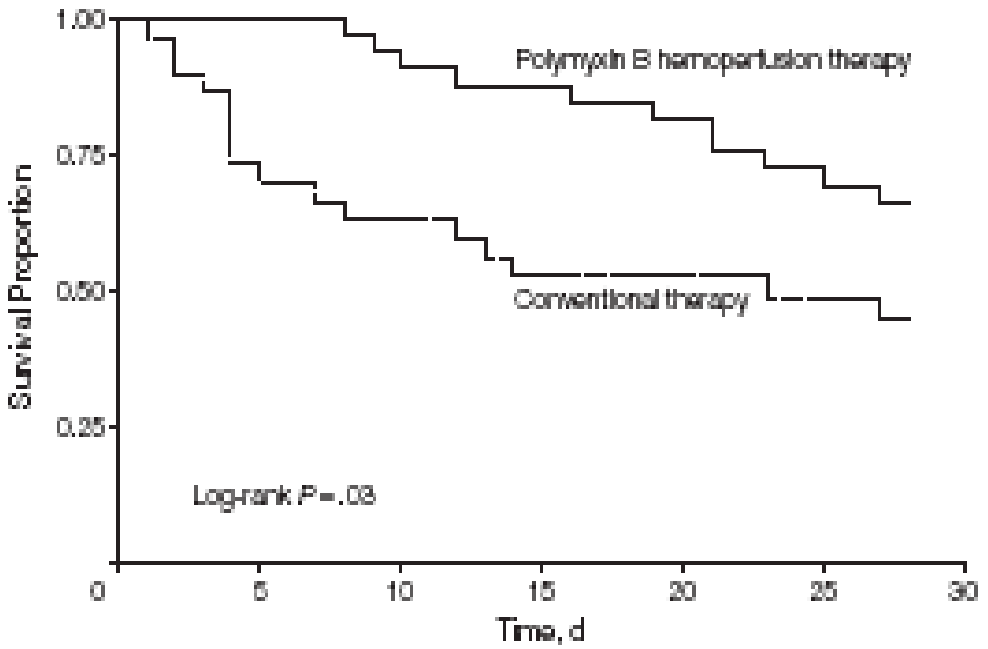
Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; Fio_2, fraction of inspired oxygen; SOFA, Sequential Organ Failure Assessment.

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

[a]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.

JAMA. 2009;301(23):2445-2452

Figure 3. Estimation of Survival Rate According to Treatment Group



No. at risk							
Polymyxin B hemoperfusion therapy	34	34	32	30	27	22	18
Conventional therapy	30	22	19	15	15	12	11

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

JAMA. 2009;301(23):2445-2452


EUPHRATES
A CLINICAL TRIAL IN ADULTS WITH
SEPTIC SHOCK AND ENDOTOXEMIA

ENDOTOXIN ACTIVITY ASSAY
EAA™

EUPHRATES
A CLINICAL TRIAL IN ADULTS WITH SEPTIC SHOCK AND ENDOTOXEMIA

The only FDA cleared test for detection of Endotoxin

Thank You