SEPSIS MANAGEMENT – CLINICAL UPDATE

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Professor of Medicine and Distinguished Scholar
Cooper Medical School of Rowan University
Director Cooper Research Institute
Senior Critical Care Attending
Cooper University Hospital
Camden NJ USA

Cooper University Hospital

Cooper Medical School of Rowan University

No Potential Financial COI

vs

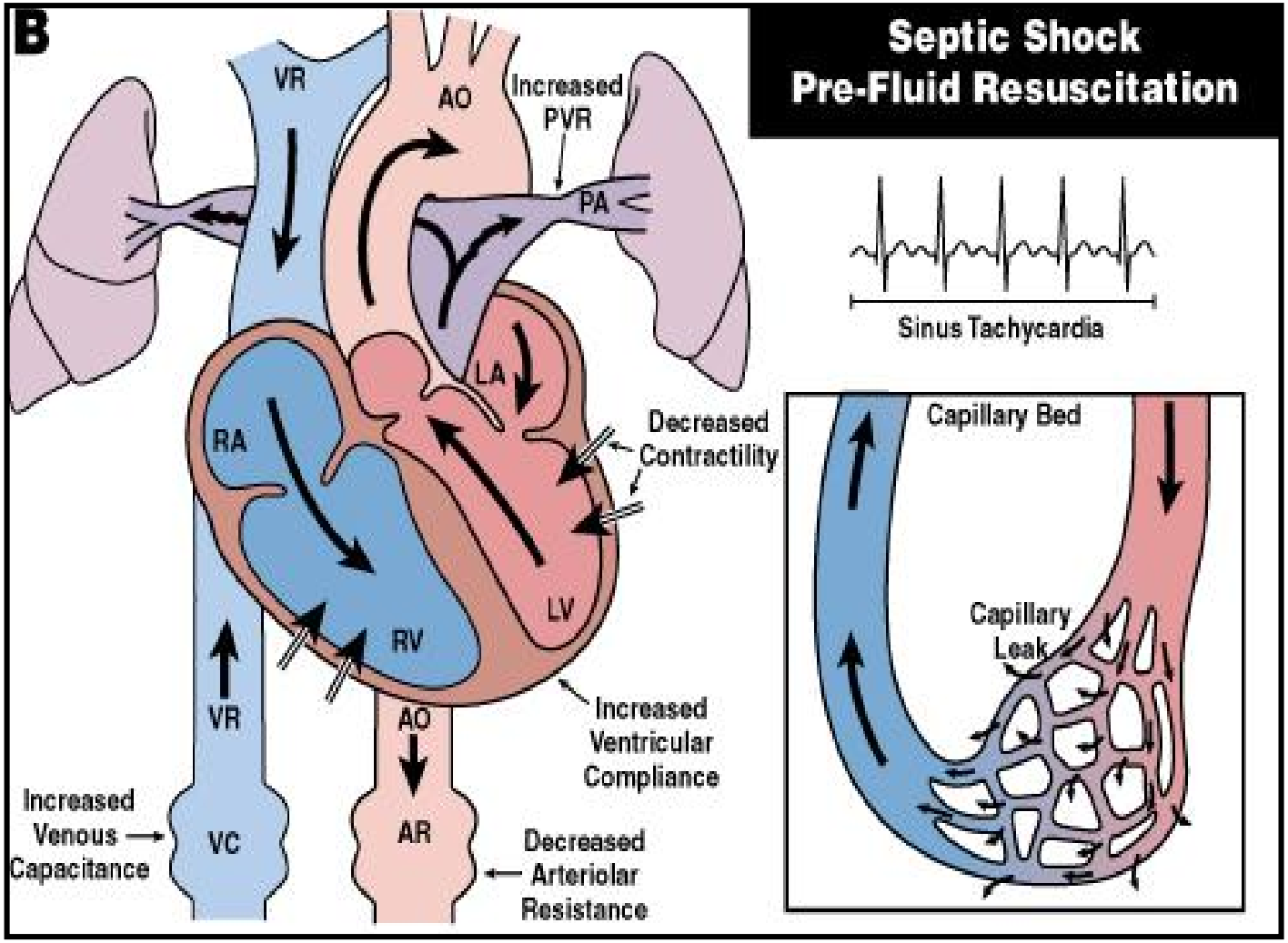
Fluids versus Vasopressors for MAP Target

Surviving Sepsis Campaign

Sepsis Bundles

vs

Fluids versus Vasopressors for MAP Target



Dellinger RP. Cardiovascular management of septic shock. *Crit Care Med* 2003;31:946-955.

Surviving Sepsis Campaign

Crit Care Med 2017
Mar,45(3): 486-552

Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016

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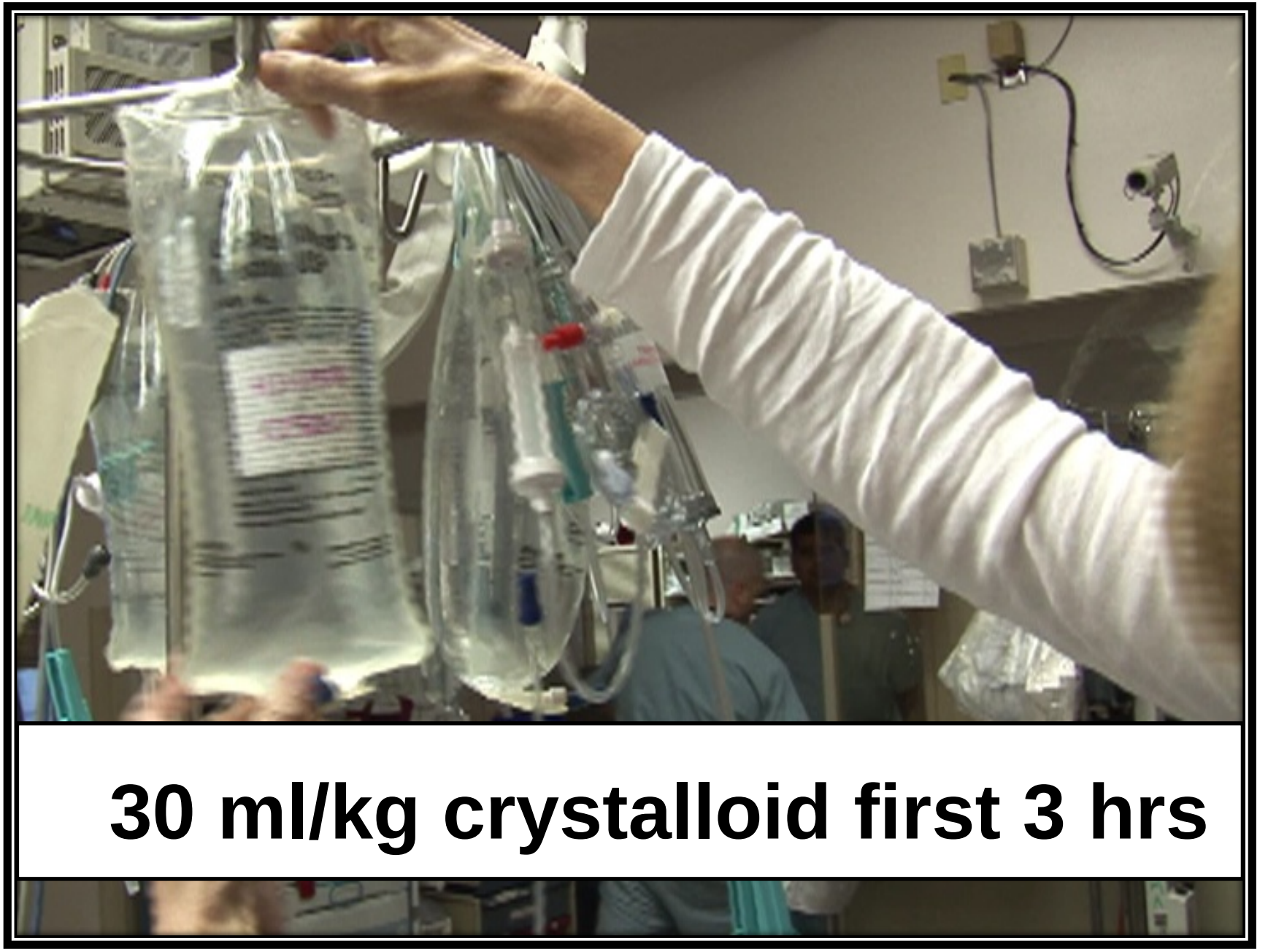


30 ml/kg crystalloid first 3 hrs

SEPSIS BUNDLE PROJECT (SEP)
NATIONAL HOSPITAL INPATIENT QUALITY MEASURES

SEP-1 EARLY MANAGEMENT BUNDLE, SEVERE SEPSIS/SEPTIC SHOCK

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

18.2-21.0 % Mortality

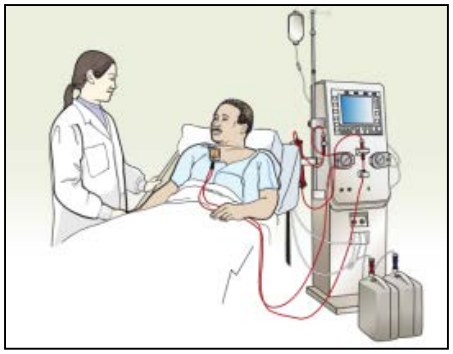
ORIGINAL ARTICLE

Goal-Directed Resuscitation for Patients with Early Septic Shock

The ARISE Investigators and the ANZICS Clinical Trials Group*

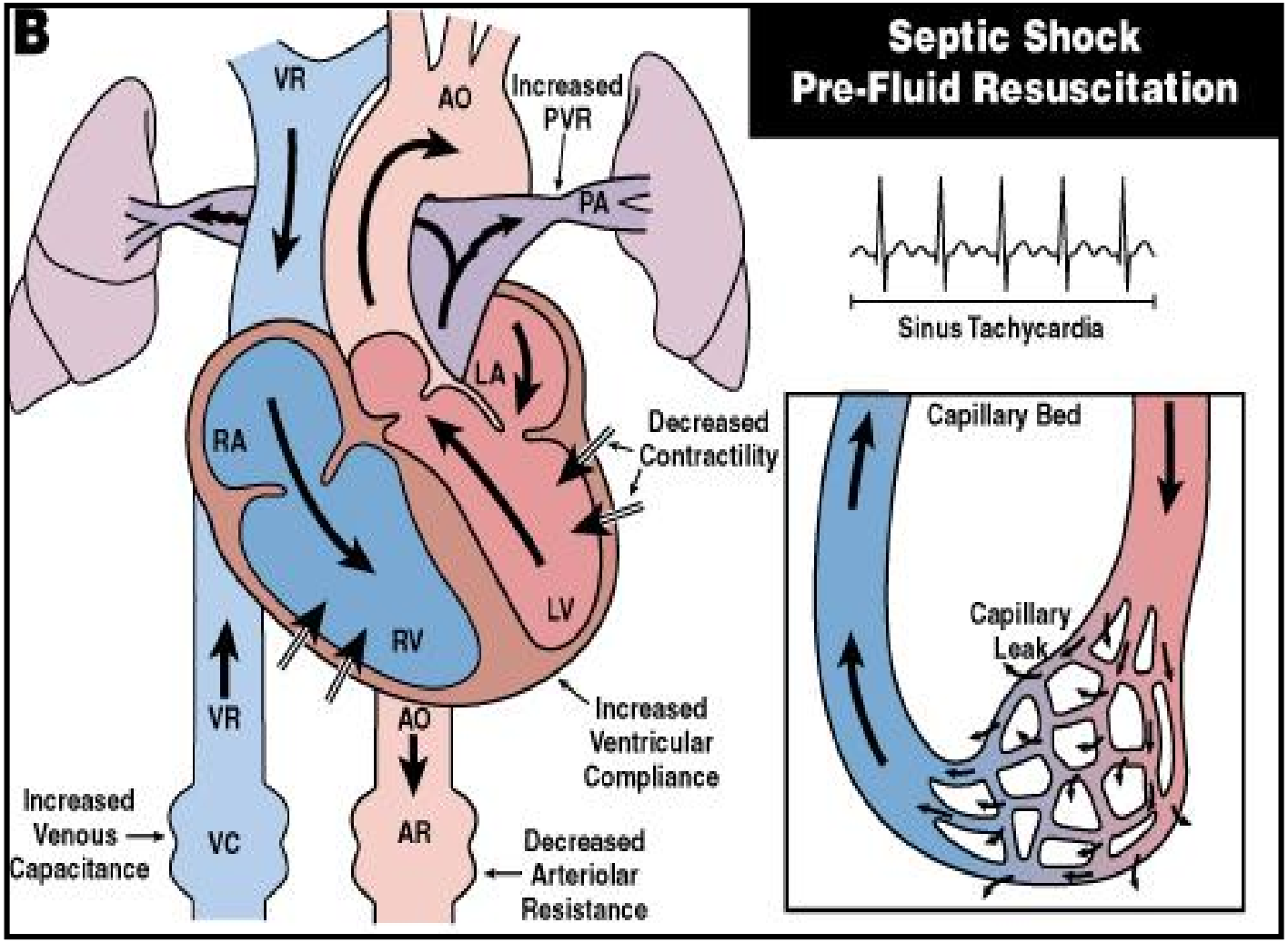
N Engl J Med. 2014 Oct 16;371(16):1496-506.

1600 Patients



End Stage Renal Disease on Dialysis

Compensated Congestive Heart failure



Dellinger RP. Cardiovascular management of septic shock. *Crit Care Med* 2003;31:946-955.


NELLCOR
98
64

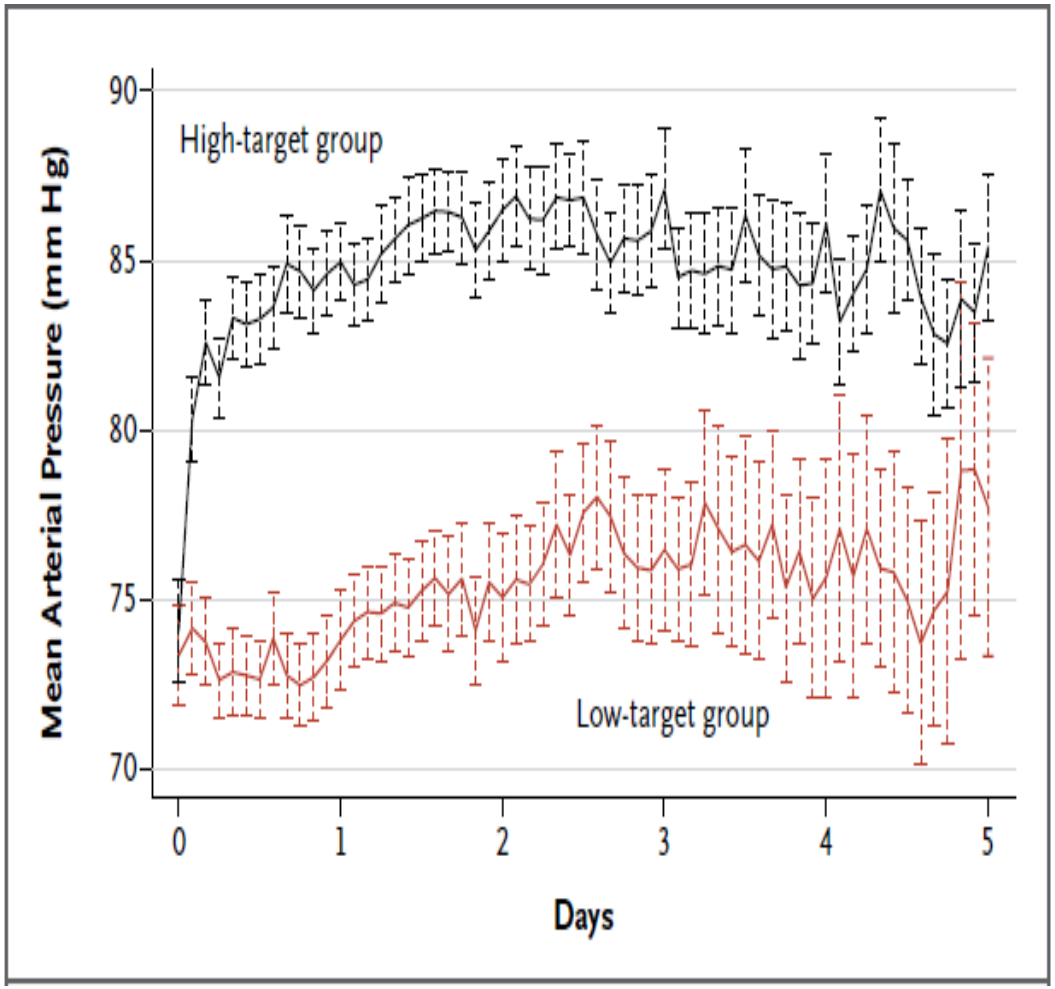
SEPTIC SHOCK

- **Recommend MAP ≥ 65 mm Hg**

Mean Arterial Pressure

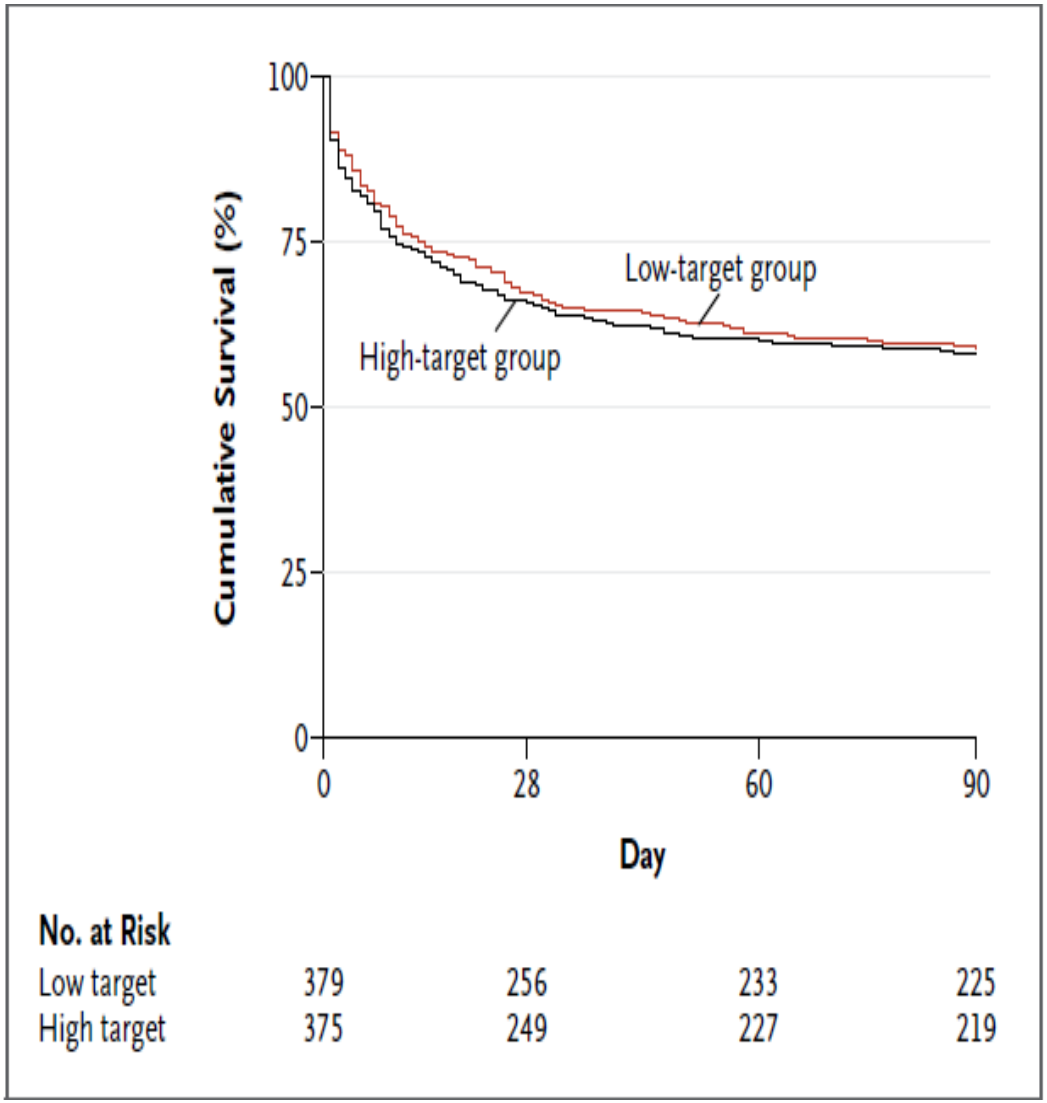
	65 mm Hg	75 mm Hg	85 mm Hg	F/LT
Urinary output (mL)	49 ±18	56 ± 21	43 ±13	.60/.71
Capillary blood flow (mL/min/100 g)	6.0 ± 1.6	5.8 ± 11	5.3 ± 0.9	.59/.55
Red Cell Velocity (au)	0.42 ± 0.06	0.44 ±016	0.42 ± 0.06	.74/.97
$Pico_2$ (mm Hg)	41 ± 2	47 ± 2	46 ± 2	.11/.12
Pa-$Pico_2$ (mm Hg)	13 ± 3	17 ± 3	16 ± 3	.27/.40

Adapted from Table 4, page 2731, from LeDoux, Astiz ME, Carpati CM, Rackow ED. Effects of perfusion pressure on tissue perfusion in septic shock. *Crit Care Med* 2000; 28:2729-2732



Asfar P, et al. N Engl J Med. 2014 Apr 24;370(17):1583-93.

776 Patients

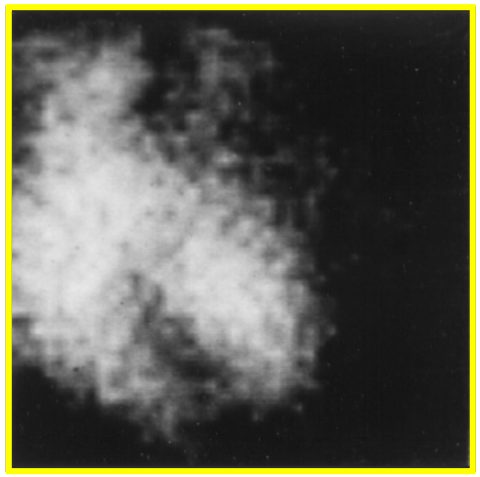


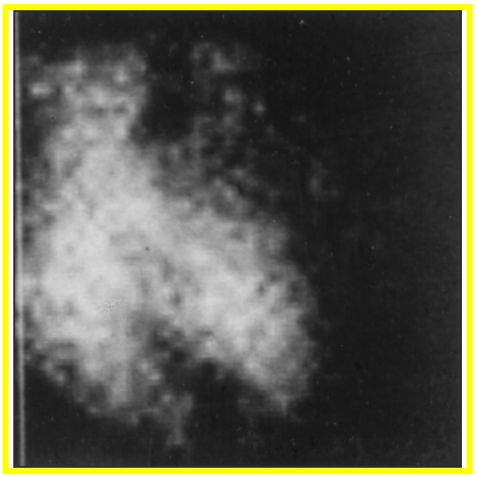
Asfar P, et al. N Engl J Med. 2014 Apr 24;370(17):1583-93.

CHOICE OF VASOPRESSOR

During Septic Shock

End Diastole

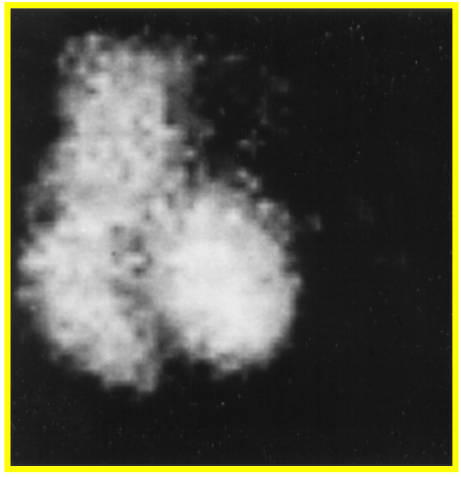


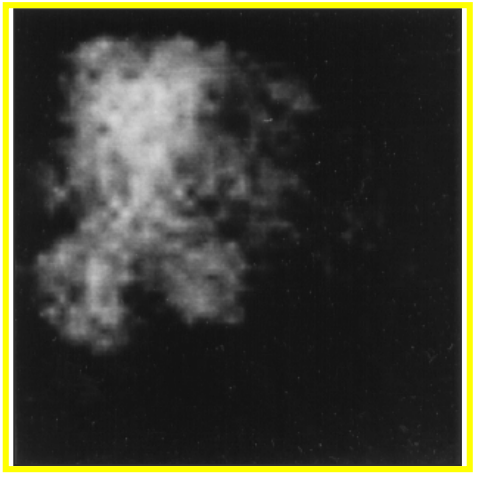


End Systole

10 Days Post Shock

End Diastole





End Systole

VASOPRESSORS IN SEPTIC SHOCK

First Line

Norepinephrine

Second Line

Epinephrine

Low Dose Vasopressin

(.01-.03 units/min**)**

Niche Drugs

Dopamine
(sinus bradycardia)

Phenylephrine
(high cardiac output or serious tachyarrhythmias and salvage)

The NEW ENGLAND JOURNAL of MEDICINE

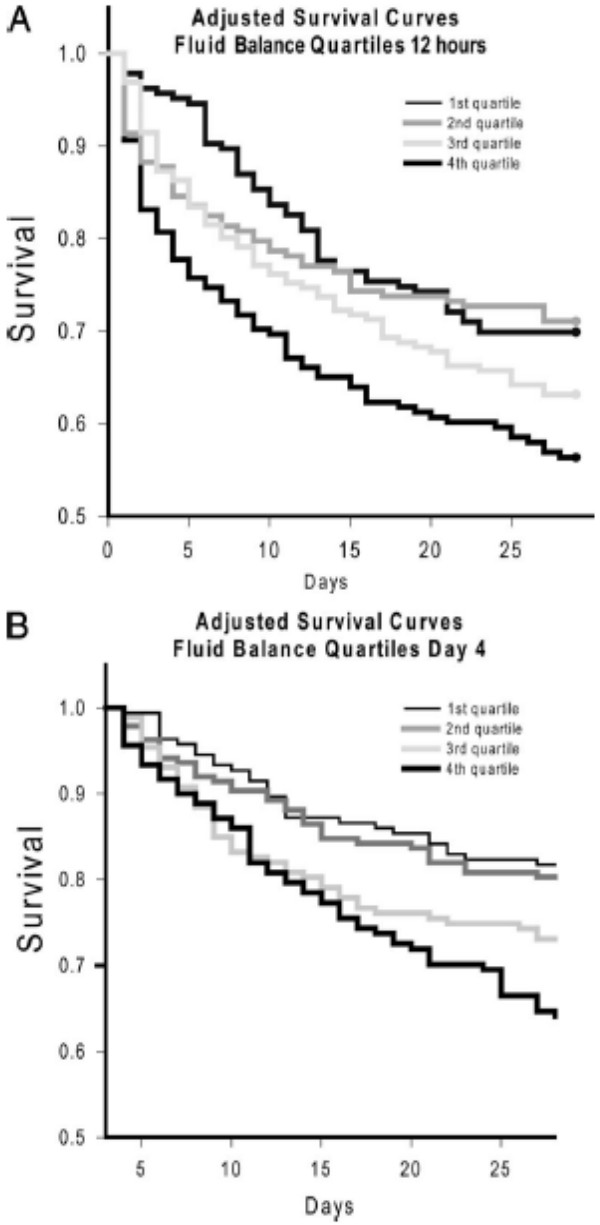
ESTABLISHED IN 1812 AUGUST 3, 2017 VOL. 377 NO. 5

Angiotensin II for the Treatment of Vasodilatory Shock

Ashish Khanna, M.D., Shane W. English, M.D., Xueyuan S. Wang, M.D., Kealy Ham, M.D., James Tumlin, M.D., Harold Szerlip, M.D., Laurence W. Busse, M.D., Laith Altaweel, M.D., Timothy E. Albertson, M.D., M.P.H., Ph.D., Caleb Mackey, M.D., Michael T. McCurdy, M.D., David W. Boldt, M.D., Stefan Chock, M.D., Paul J. Young, M.B., Ch.B., Ph.D., Kenneth Krell, M.D., Richard G. Wunderink, M.D., Marlies Ostermann, M.D., Ph.D., Raghavan Murugan, M.D., Michelle N. Gong, M.D., Rakshit Panwar, M.D., Johanna Hästbacka, M.D., Ph.D., Raphael Favory, M.D., Ph.D., Balasubramanian Venkatesh, M.D., B. Taylor Thompson, M.D., Rinaldo Bellomo, M.D., Jeffrey Jensen, B.S., Stew Kroll, M.A., Lakhmir S. Chawla, M.D., George F. Tidmarsh, M.D., Ph.D., and Adam M. Deane, M.D., for the ATHOS-3 Investigators*

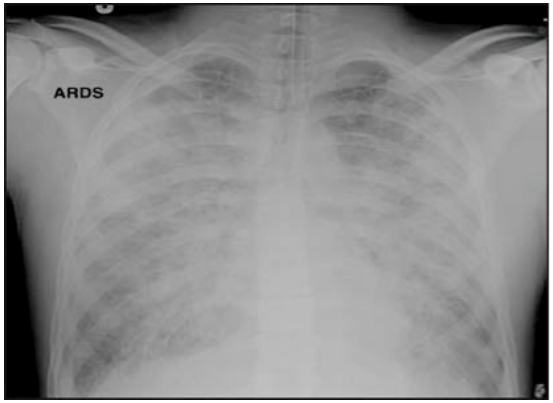
Controversy

- How much fluid after the initial bolus?

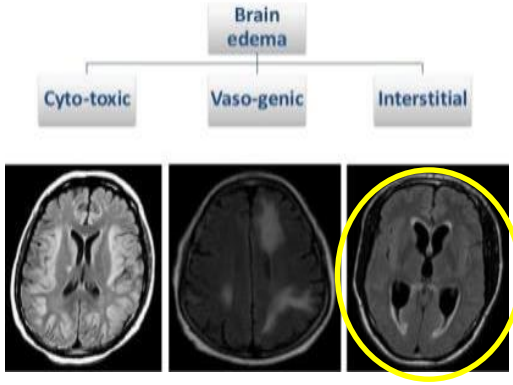


Boyd et al. Crit Care Med 2011;39:259-265

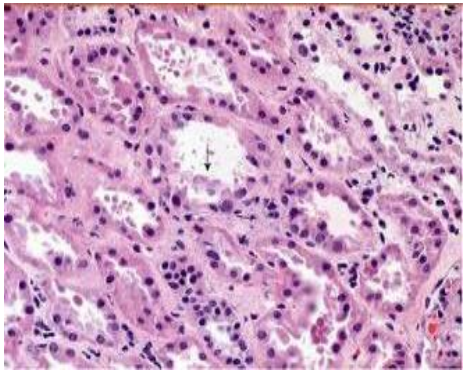
Interstitial Edema



Lungs



Brain



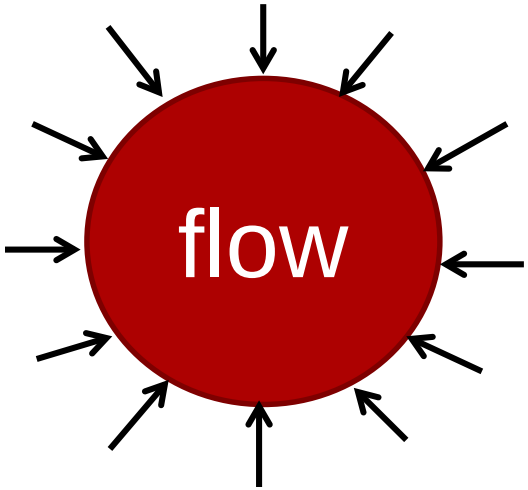
Kidney

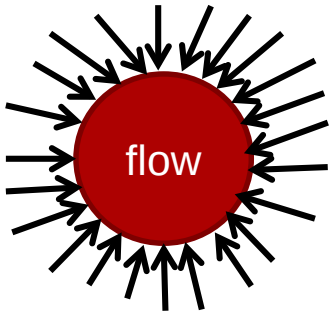
De-resuscitation


24 HOUR HELP LINE 1-866-697-8243
REF CAR-505
System One
U.272
2.5.
L/hr
250.
L/hr
(0.00)
ml/hr
(000)
200.
ml/min
STAGE
TriMedx

Arterial Pressure = Flow x Resistance

Arterial Pressure Drives Tissue Perfusion and is Determined by Cardiac Output and Systemic Systemic Vascular Resistance





Assume continued leak and MAP target 70 mm Hg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ARTICLE IN PRESS

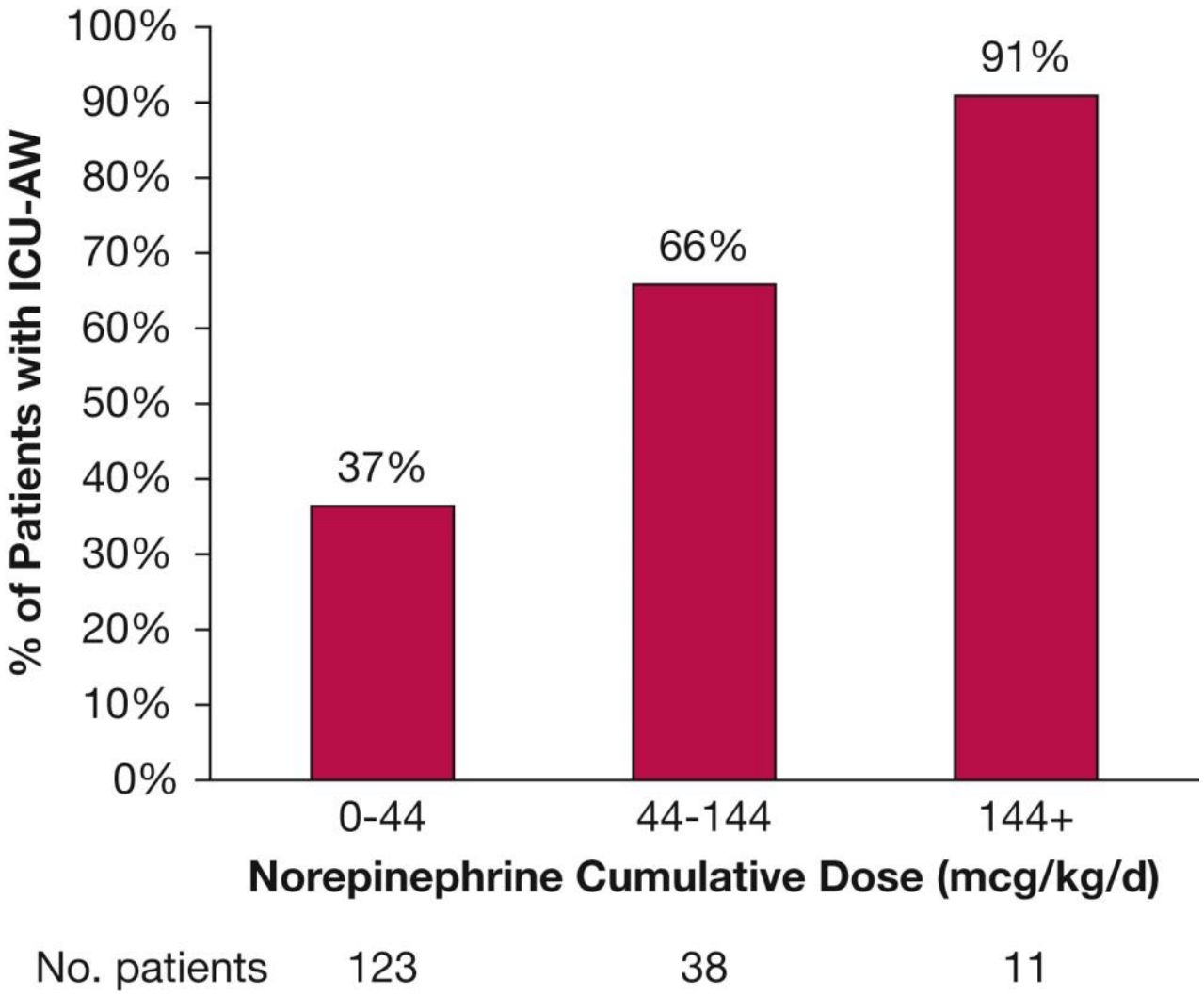
[Original Research]

CHEST

Impact of Vasoactive Medications on ICU-Acquired Weakness in Mechanically Ventilated Patients

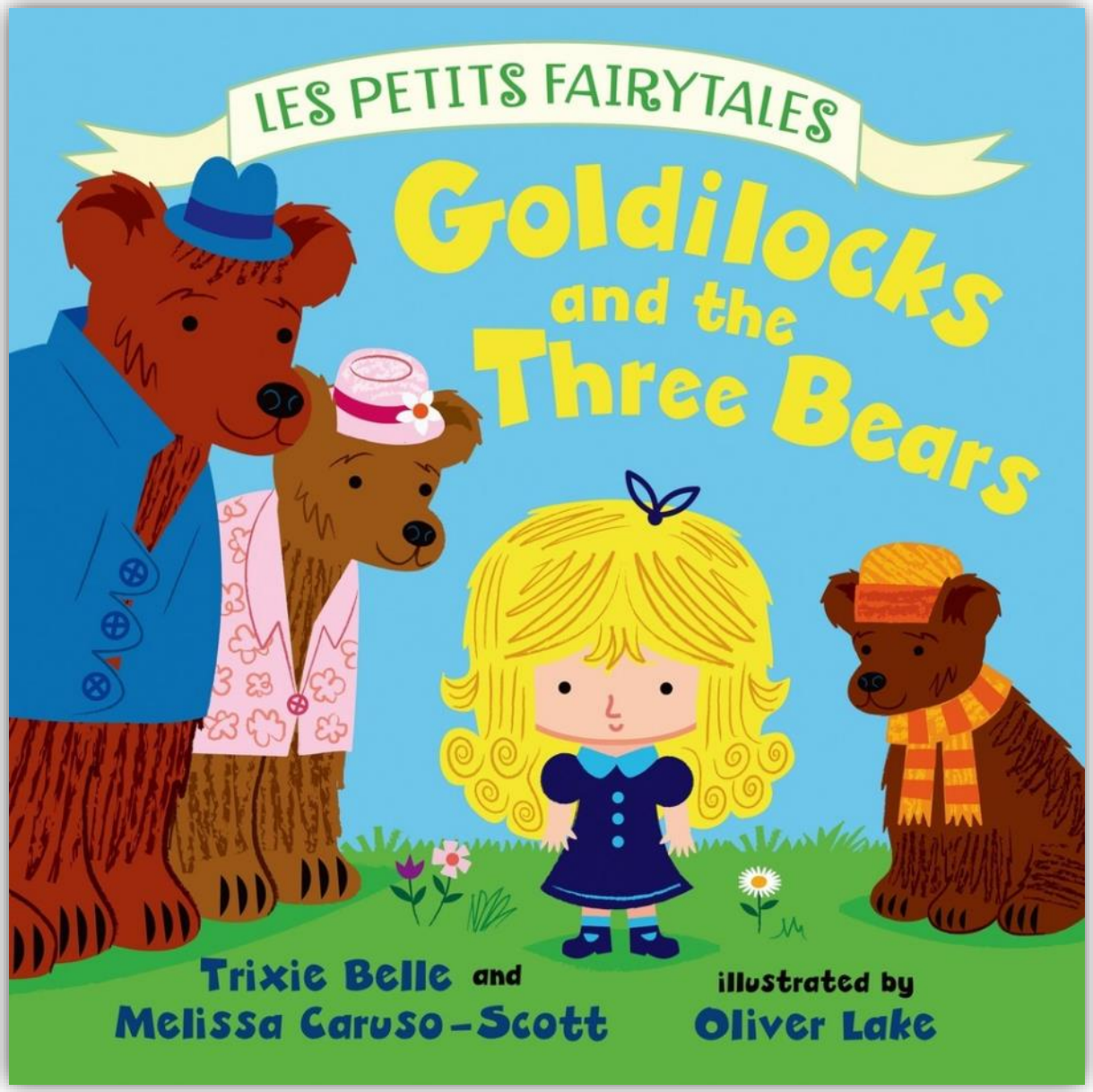
Krysta S. Wolfe, MD; Bhakti K. Patel, MD; Erica L. MacKenzie, MD; Shewit P. Giovanni, MD; Anne S. Pohlman, MSN; Matthew M. Churpek, MD, MPH, PhD; Jesse B. Hall, MD; and John P. Kress, MD

Wolfe, KS. et al. Chest 2018



Wolfe, KS. et al. Chest 2018

Correct balance of fluids and vasopressors is the goal


LES PETITS FAIRYTALES
Goldilocks and the Three Bears
Trixie Belle and Melissa Caruso-Scott
illustrated by Oliver Lake

Goldilocks

Not enough

Too Much

Just Right

Correct balance of fluids and vasopressors is the goal

We just aren't sure what it is for any given patient.

Crystalloid Liberal or Vasopressors Early Resuscitation of Sepsis Trial
CLOVERS Trial

National Heart Lung Blood Institute

Prevention and Early Treatment of Acute Lung Injury Network
PETAL Network

1600 20th Street, NW • Washington, D.C. 20009 • 202/588-1000 • www.citizen.org

August 28, 2018

Jerry Menikoff, M.D., J.D.
Director
Office for Human Research Protections
U.S. Department of Health and Human Services
1101 Wootton Parkway, Suite 200
Rockville, MD 20852

Re: **Project Title: Crystalloid Liberal or Vasopressors Early Resuscitation in Sepsis Trial**
Sponsor: National Heart, Lung, and Blood Institute (NHLBI), National Institutes of Health
Principal Investigator: David A. Schoenfeld, Ph.D., Massachusetts General Hospital, Clinical Coordination Center for the NHLBI-funded Clinical Trials Network for the Prevention and Early Treatment of Acute Lung Injury (PETAL Network)
ClinicalTrials.gov Identifier: NCT03434028

Dear Dr. Menikoff:

Public Citizen, a consumer advocacy organization with more than 500,000 members and supporters nationwide, hereby requests that the Office for Human Research Protections (OHRP) immediately direct NHLBI to terminate enrollment in the Crystalloid Liberal or Vasopressors Early Resuscitation in Sepsis trial (CLOVERS) and launch a compliance oversight investigation of the trial and its review and approval by the responsible institutional review board(s) (IRBs).

https://www.citizen.org/sites/default/files/2446.pdf

Surviving Sepsis Campaign

Sepsis Bundles

GUIDELINES TO BUNDLES - 2004

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

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Severe Sepsis Bundles:

6 hour

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%.**

24 hour

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.*

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SURVIVING SEPSIS CAMPAIGN: INTERNATIONAL GUIDELINES FOR MANAGEMENT OF SEVERE SEPSIS AND SEPTIC SHOCK 2012

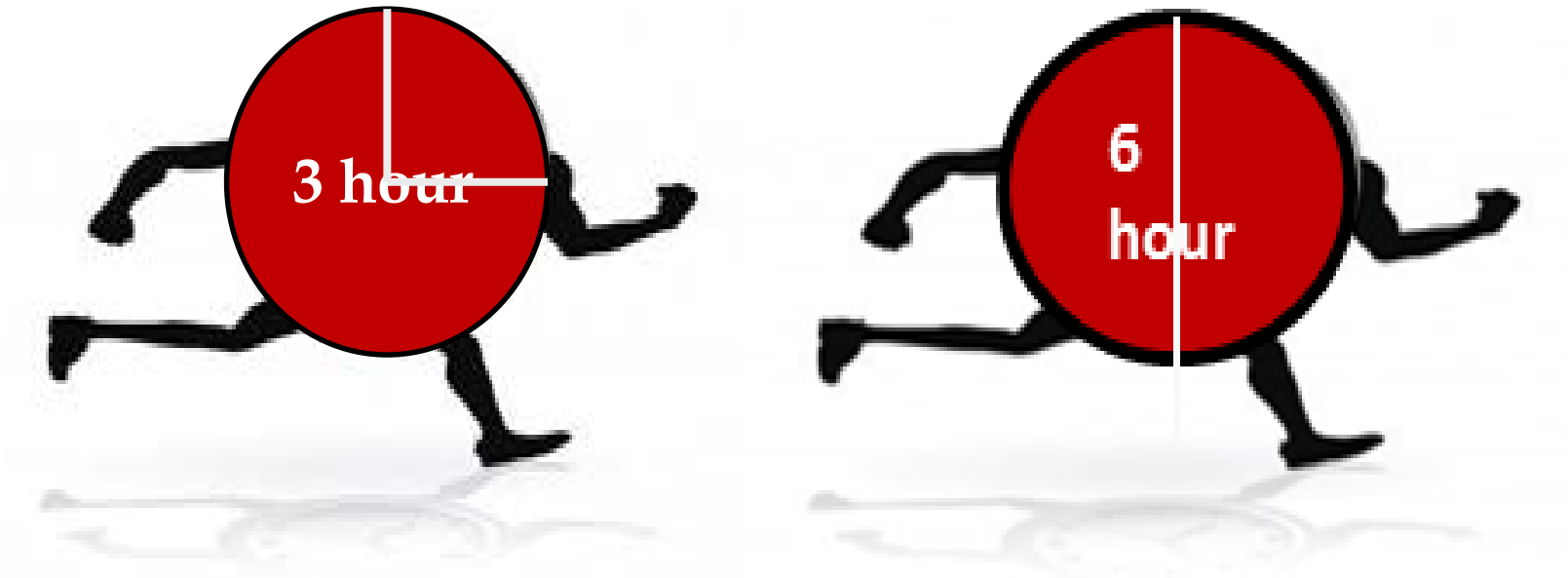
R. Phillip Dellinger, Mitchell M. Levy, Andrew Rhodes, Djillali Annane, Herwig Gerlach, Steven M. Opal, Jonathan E. Sevransky, Charles L. Sprung, Ivor S. Douglas, Roman Jaeschke, Tiffany M. Osborn, Mark E. Nunnally, Sean R. Townsend, Konrad Reinhart, Ruth M. Kleinpell, Derek C. Angus, Clifford S. Deutschman, 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

Surviving Sepsis Campaign

2012 Surviving Sepsis Campaign Guidelines

Two Clocks



2012 SEPSIS BUNDLES

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

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

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

1600 Patients

SEPSIS BUNDLE PROJECT (SEP)
NATIONAL HOSPITAL INPATIENT QUALITY MEASURES

SEP-1 EARLY MANAGEMENT BUNDLE, SEVERE SEPSIS/SEPTIC SHOCK

SEPTIC SHOCK
Reassessment after 30 ml kg fluid Rx

6 hr.

Persistent Hypotension
OR Lactate > 4

- Reassessment after 30 ml/kg crystalloid

Shock Assessment

Physical Exam (ALL)

- Vital Signs (T, HR, RR, BP)
- Cardiopulmonary exam
- Capillary refill evaluation
- Peripheral Pulse evaluation
- Skin evaluation

OR

Hemodynamics (2 of 4)

- CVP
- SVO2
- Bedside cardiovascular ultrasound
- Passive leg raise / fluid challenge

Sepsis Bundles

Surviving Sepsis Campaign

BUNDLES

TO BE COMPLETED WITHIN 3 HOURS:

1) Measure lactate level.
2) Obtain blood cultures prior to administration of antibiotics.
3) Administer broad spectrum antibiotics.
4) Administer 30 ml/kg crystalloid for hypotension or lactate ≥4mmol/L.

"Time of presentation" is defined as the time of triage in the emergency department or, if presenting from another care venue, from the earliest chart annotation consistent with all elements of severe sepsis or septic shock ascertained through chart review.

TO BE COMPLETED WITHIN 6 HOURS:

5) Apply vasopressors (for hypotension that does not respond to initial fluid resuscitation) to maintain a mean arterial pressure (MAP) ≥65 mm Hg.
6) 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 according to Table 1.
7. Re-measure lactate if initial lactate elevated.

http://www.sccm.org/SiteCollectionDocuments/SSCBundleCard_Web.pdf Accessed 9/15/2016

Surviving Sepsis Campaign

Three Clocks

Hour-1 Bundle

- The objective of the "hour-1" bundle is to *begin* resuscitation and management immediately.
- Although some of the resuscitation measures may require more than an hour to complete, the focus is to *begin* treatment immediately.

Hour-1 Bundle- 5 Key Elements

1. Measure lactate level. (To be remeasured if initial lactate is >2 mmol/L).
2. Obtain blood cultures prior to administration of antibiotics.
3. Administer broad-spectrum antibiotics.
4. Begin rapid administration of 30ml/kg crystalloid fluids for hypotension or lactate ≥4 mmol/L.
5. Apply vasopressors if the patient is hypotensive during or after fluid resuscitation to maintain mean arterial pressure (MAP) ≥65 mm Hg.

Levy MM, Evans LE, Rhodes A. *Crit Care Med.* 2018; 46(6):997-1000.

Surviving Sepsis Campaign

Three Clocks

SCCM News

SCCM and ACEP Release Joint Statement About the Surviving Sepsis Campaign Hour-1 Bundle

The Society of Critical Care Medicine (SCCM) and the American College of Emergency Physicians (ACEP) acknowledge concerns expressed about the recently released Surviving Sepsis Campaign (SSC) hour-1 bundle and the appropriateness of implementation in the United States. Both organizations understand the importance of prompt and optimal sepsis diagnosis and treatment. SCCM and ACEP, along with other involved international experts, are organizing a meeting as soon as possible to carefully review the recommendations and provide guidance on bundle implementation and care of potentially septic patients who present to U.S. emergency departments. SCCM recommends that hospitals not implement the hour-1 bundle in its present form in the United States at this time.

Critical Connections. News Edition. September 13, 2018.


THE
BOTTOM
LINE

TO SAVE LIVES.....

Early identification

Early antibiotics

Early **appropriate** fluid resuscitation

THANK YOU