

MULTIPLE ORGAN DYSFUNCTION SYNDROME IN SEPSIS

Imad Khojah, MD MBA CMQ,

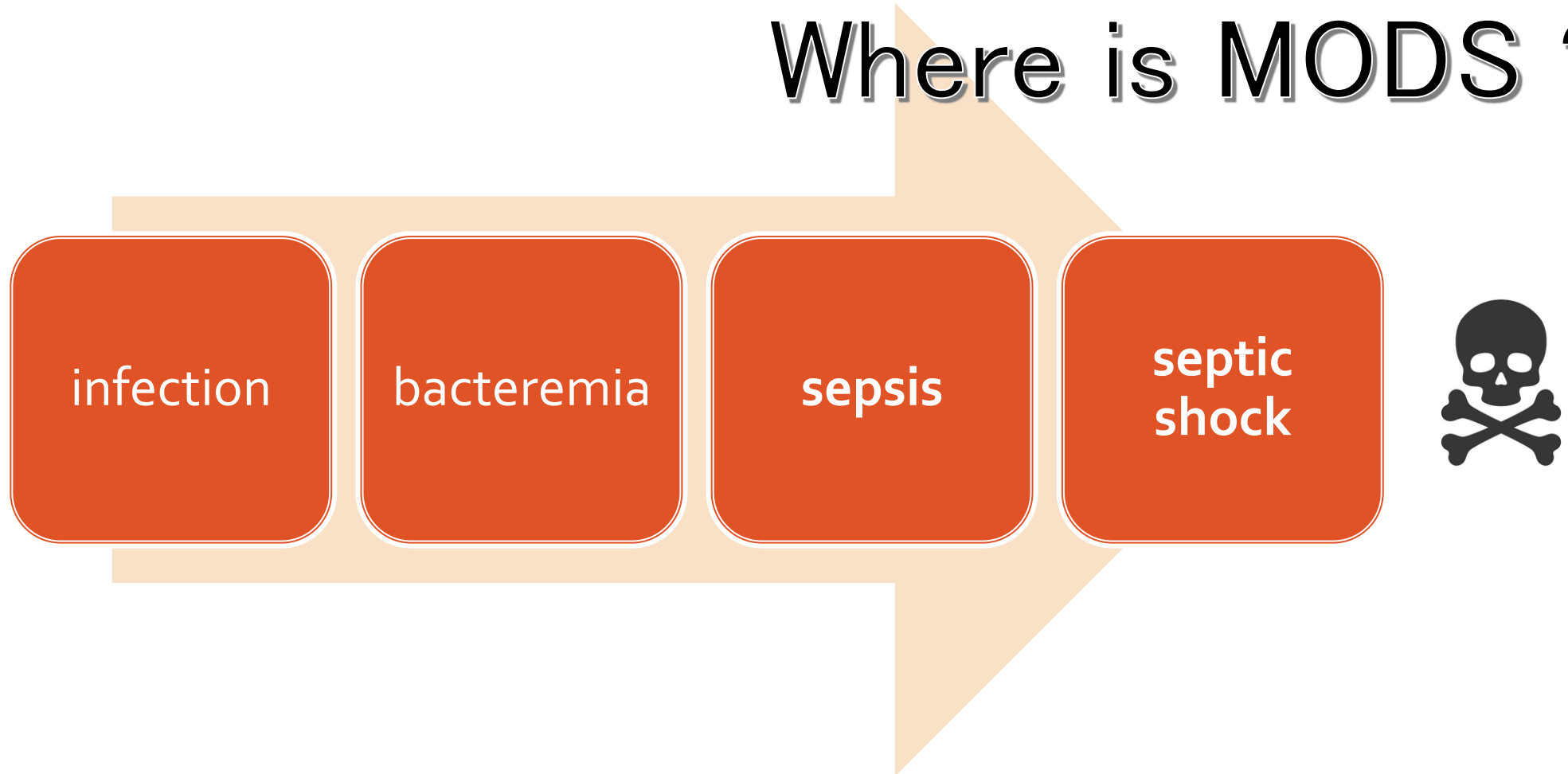
American Board of Emergency Medicine,
American Board of Medical Quality Improvement,
Master of Business Administration,
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Content

- Background review
- Current management
- Future therapy

Sepsis spectrum

Where is MODS ?

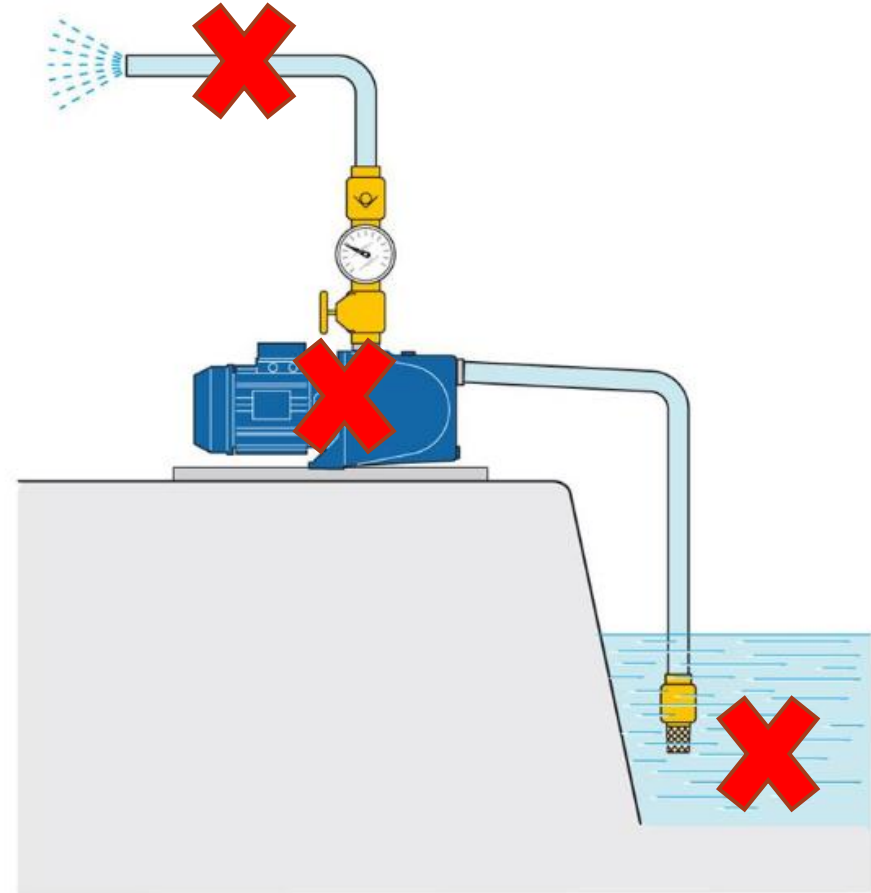


Definitions Old VS. New

	Old (2003)	New (2016)
SIRS	2 out of 4	Removed
Sepsis	Suspected infection + ≥ 2 SIRS	Suspected infection + $2 \geq$ qSOFA
Severe Sepsis	Sepsis + End organ dysfunction	Removed
Septic Shock	Sepsis + Persistent hypotension	Sepsis + Vasopressors to maintain MAP ≥ 65 mmHg Lactate ≥ 2 (despite adequate fluid resuscitation)

Multiple organ dysfunction syndrome

- Types:
 - **Primary:** renal failure due to rhabdomyolysis
 - **Secondary:** ARDS in pancreatitis

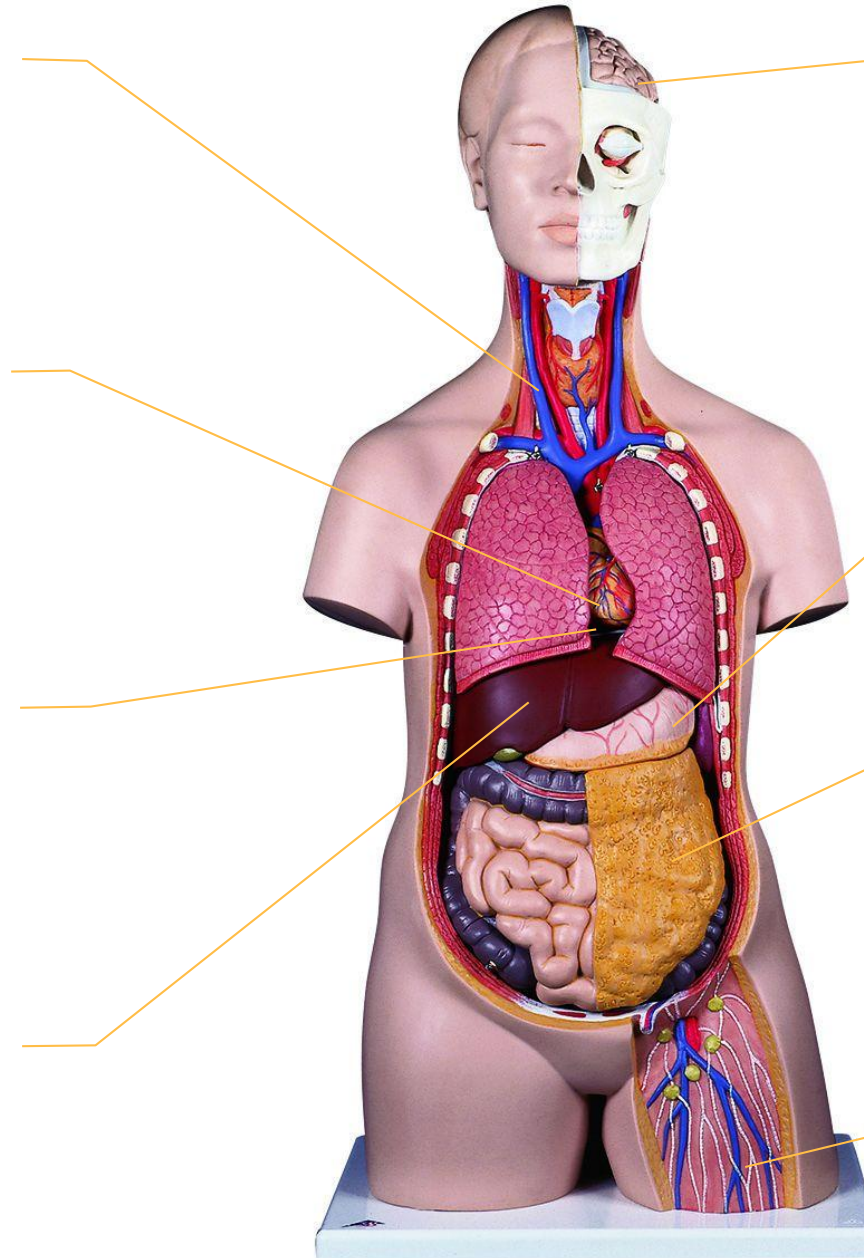


Hematologic: aPTT >125% of normal, platelets < 50-80,000. DIC

Cardiovascular:
Decreased ejection fraction, pressor needs, **SBP<100**

Pulmonary: Hypoxia, hypercarbia, ARDS requiring PEEP >10 cm H₂O and FIO₂ < 0.5.
RR>22

Hepatic: elevated Bilirubin, liver function test > 2x normal



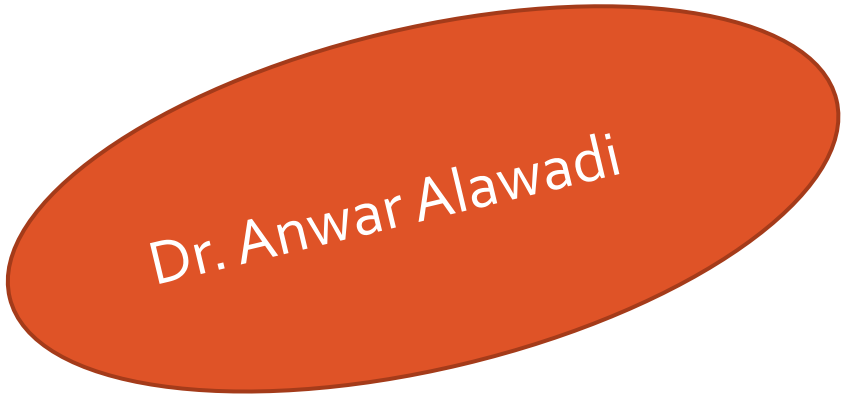
CNS: Confusion
GCS<14, coma

GI: Stress ulceration / food intolerance

Renal: Oliguria (< 500 mL/day) or increasing creatinine (2-3 mg/dL), Dialysis

Peripheral nervous system: Neuropathies

How to diagnose sepsis?



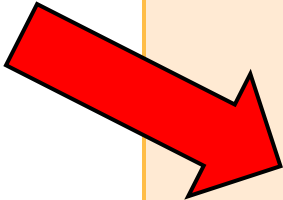
Dr. Anwar Alawadi

MANAGEMENT

Bundle management

Surviving Sepsis
Campaign®

1 hours bundle

- 
- Measure Lactate Level
 - Obtain blood culture
 - Administer broad spectrum antibiotic
 - **Administer 30ml/kg IVF**
 - **Administer Vasopressors to maintain MAP >65mm Hg**

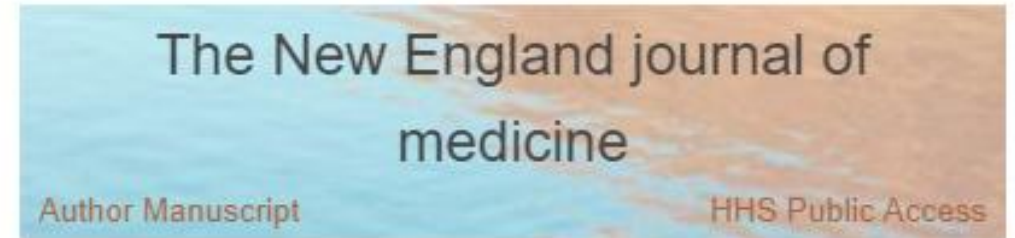
6 hours bundle

- Re-assess Volume Status by either repeated focused exam or two of the following:
 - CVP
 - ScvO₂
 - Bedside ultrasound
 - PaO₂/PaO₂ ratio
- Re-initiate vasopressors if initial was elevated

Dr.Ahmad Wazzan

Does it work?

- New York required hospitals use protocols in 2013
- Patients with sepsis at 149 hospitals in New York state (N = 49 331) 2014-2016
- Multicenter retrospective cohort study
- bundle management is associated with mortality reduction (early Abx)



Time to Treatment and Mortality during Mandated Emergency Care for Sepsis

Christopher W. Seymour, M.D., Foster Gesten, M.D., [...], and Mitchell M. Levy, M.D.

Time to Treatment and Mortality during Mandated Emergency Care for Sepsis
[N Engl J Med. 2017 Jun 8; 376\(23\): 2235-2244.](#) Author manuscript.

What guide my fluid management? (ProCESS trial)

- EGDT vs. protocol-based vs. usual care
- 1341 pt, 31 US centers, RCT



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

The ProCESS Investigators*

- Conclusion?

ARISE trial ProMISE trial

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Goal-Directed Resuscitation for Patients with Early Septic Shock

The ARISE Investigators and the ANZICS Clinical Trials Group*

ABSTRACT

N ENGL J MED 371;16 NEJM.ORG **OCTOBER 16, 2014**

1600 pt from 51 center in Australia and New Zealand RCT

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Trial of Early, Goal-Directed Resuscitation for Septic Shock

Paul R. Mouncey, M.Sc., Tiffany M. Osborn, M.D., G. Sarah Power, M.Sc., David A. Harrison, Ph.D., M. Zia Sadique, Ph.D., Richard D. Grieve, Ph.D., Rahi Jahan, B.A., Sheila E. Harvey, Ph.D., Derek Bell, M.D., Julian F. Bion, M.D., Timothy J. Coats, M.D., Mervyn Singer, M.D., J. Duncan Young, D.M., and Kathryn M. Rowan, Ph.D., for the ProMISe Trial Investigators*

ABSTRACT

N ENGL J MED 372;14 NEJM.ORG **APRIL 2, 2015**

1260 pt from 56 center in England RCT

**Which IV fluid to use in
sepsis?**

Balanced salt solutions vs NS

- 149 pt retrospective chart review
- BS associated with a lower odds of mortality

American Journal of Emergency Medicine 36 (2018) 625–629

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ELSEVIER

Original Contribution

Choice of resuscitative fluids and mortality in emergency department patients with sepsis

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Mortality

ABSTRACT

Objective: Balanced resuscitative fluids (BF) have been associated with decreased incidence of hyperchloremic metabolic acidosis in sepsis. We hypothesized that higher proportions of BF during resuscitation would thus be associated with improved mortality in Emergency Department (ED) patients with sepsis.

Methods: This was a retrospective chart review of adult ED patients who presented with sepsis to a large, urban teaching hospital over one year. The choice of resuscitation fluid in the first 2 days of hospitalization was defined as either normal saline (NS) or balanced fluids (BF; Lactated Ringer's or Isolyte). The primary study outcome was in-hospital mortality, which was analyzed with multivariable logistic regression based on the proportion of BF received during the initial ED resuscitation.

Results: Of 149 patients screened, 33 were excluded, leaving 115 for analysis, of whom 18 died (16% overall mor-

Crystalloid vs albumin (SAFE) trial

- meta-analysis of 15 RCT
- no difference in mortality



OPEN ACCESS

Citation: Jiang L, Jiang S, Zhang Y (2014) Albumin versus Other Fluids for Resuscitation in Patients with Trauma. PLoS ONE 9(12): e111466. doi:10.1371/journal.pone.0111466

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THE NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Comparison of Albumin and Saline for Fluid Resuscitation in the Intensive Care Unit

The SAFE Study Investigators*

ABSTRACT

Fluid Resuscitation in Sepsis: A

, Yuefeng Ma*
Department of Emergency Medicine & Institute of Emergency

Crystalloid versus hydroxyethyl starch (HES) (6S) trial

- Conclusion?
- HES associated with higher mortality

THE NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Hydroxyethyl Starch 130/0.42 versus Ringer's Acetate in Severe Sepsis

Anders Perner, M.D., Ph.D., Nicolai Haase, M.D., Anne B. Guttormsen, M.D., Ph.D., Jyrki Tenhunen, M.D., Ph.D., Gudmundur Klemenzson, M.D., Anders Åneman, M.D., Ph.D., Kristian R. Madsen, M.D., Morten H. Møller, M.D., Ph.D., Jeanie M. Elkjær, M.D., Lone M. Poulsen, M.D., Asger Bendtsen, M.D., M.P.H., Robert Winding, M.D., Morten Steensen, M.D., Pawel Berezowicz, M.D., Ph.D., Peter Søb-Jensen, M.D., Morten Bestle, M.D., Ph.D., Kristian Strand, M.D., Ph.D., Jørgen Wiis, M.D., Jonathan O. White, M.D., Klaus J. Thornberg, M.D., Lars Quist, M.D., Jonas Nielsen, M.D., Ph.D., Lasse H. Andersen, M.D., Lars B. Holst, M.D., Katrin Thormar, M.D., Anne-Lene Kjældgaard, M.D., Maria L. Fabritius, M.D., Frederik Mondrup, M.D., Frank C. Pott, M.D., D.M.Sci., Thea P. Møller, M.D., Per Winkel, M.D., D.M.Sci., and Jørn Wetterslev, M.D., Ph.D., for the 6S Trial Group and the Scandinavian Critical Care Trials Group*

ABSTRACT

BACKGROUND

Hydroxyethyl starch (HES) is widely used for fluid resuscitation in intensive care units (ICUs), but its safety and efficacy have not been established in patients with severe sepsis.

METHODS

In this multicenter, parallel-group, blinded trial, we randomly assigned patients with severe sepsis to fluid resuscitation in the ICU with either 6% HES 130/0.42 (Tetraspan) or Ringer's acetate at a dose of up to 33 ml per kilogram of ideal body weight per day. The primary outcome measure was either death or end-stage kidney failure (dependence on dialysis) at 90 days after randomization.

RESULTS

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Perner at the Department of Intensive Care 4131, Rigshospitalet, Blegdamsvej 9, DK-2100 Copenhagen, Denmark, or at anders.perner@rh.regionh.dk.

*Members of the Scandinavian Starch for Severe Sepsis/Septic Shock (6S) trial group are listed in the Supplementary Appendix, available at NEJM.org.

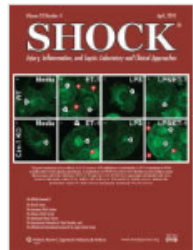
This article was published on June 27, 2012, and updated on July 12, 2012, at NEJM.org.

PATIENTS WHO FAIL INITIAL THERAPY

Vasopressors 1st agent

Drug	heart rate	contractility	Arterial constriction
Dobutamine	+	+++	-
Dopamine	++	++	++
Epinephrine	+++	+++	+
Norepinephrine	++	++	+++
Phenylephrine	NA	NA	+++

Dopamine Vs Norepinephrine



Shock

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Copyright: (C)2010 The Shock Society

Publication Type: [Clinical Aspects]

DOI: 10.1097/SHK.0b013e3181c6ba6f

ISSN: 1073-2322

Accession: 00024382-201004000-00006

Keywords: Dopamine, norepinephrine, septic shock, vasopressor therapy, arrhythmia, safety

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[Clinical Aspects]

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EFFICACY AND SAFETY OF DOPAMINE VERSUS NOREPINEPHRINE IN THE MANAGEMENT OF SEPTIC SHOCK

Patel, Gourang P.; Grahe, Jaime Simon; Sperry, Mathew; Singla, Sunit; Elpern, Ellen; Lateef, Omar; Balk, Robert A.

- 252 pt in RCT
- DA and NE were equally effective (28-day mortality).
- But! more arrhythmias with DA .



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Critical Care Medicine

Issue: Volume 40(3), March 2012, p 725-730

Copyright: (C) 2012 by the Society of Critical Care Medicine and Lippincott Williams & Wilkins

Publication Type: [Feature Articles]

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Accession: 00003246-201203000-00003

Keywords: adrenergic agents, adverse effects, mortality, outcome, vasopressor

[Feature Articles]

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Dopamine versus norepinephrine in the treatment of septic shock: A meta-analysis*

De Backer, Daniel MD, PhD; Aldecoa, Cesar MD; Njimi, Hassane MSc, PhD; Vincent, Jean-Louis MD, PhD, FCCM

- Meta analysis
- 2769 pt
- In septic shock, DA has greater mortality and a higher incidence of arrhythmic event.

2nd agent

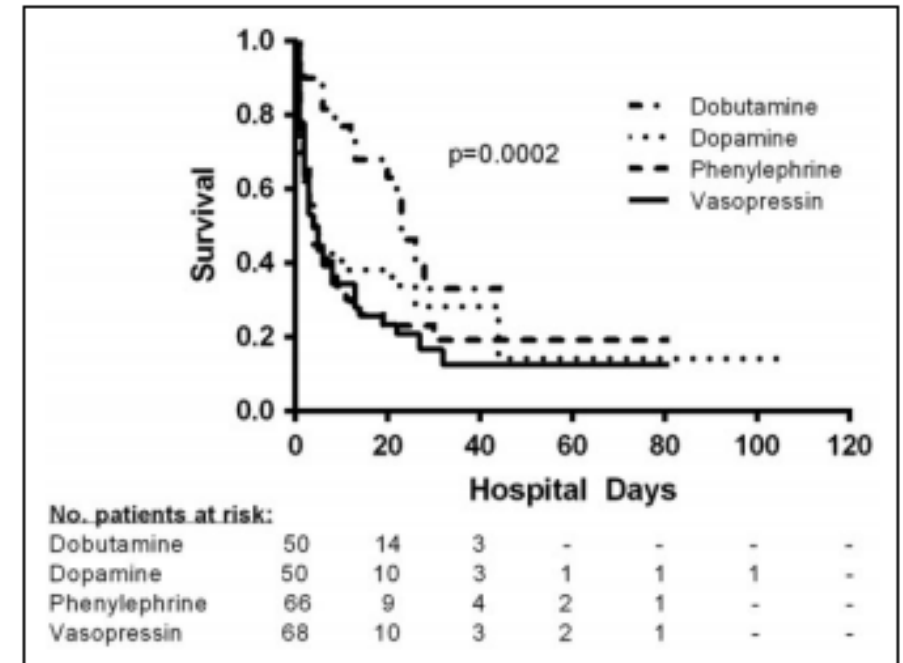
- Distributive shock vs. low cardiac output
- Goal: to identify vasoactive agent in septic shock who are refractory to NE
- 234 pt RCT
- Dobutamine is associated with decreased mortality

Original Research

Comparative Effectiveness of Second Vasoactive Agents in Septic Shock Refractory to Norepinephrine

H. Bryant Nguyen, MD, MS^{1,2,3}, Samantha Lu, MD⁴,
Isabella Possagnoli, MD², and Phillip Stokes, MD⁴

Journal of Intensive Care Medicine
2017, Vol. 32(7) 441-459
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DOI: 10.1177/0885066616647941
journals.sagepub.com/home/jic
SAGE



Target MAP (high vs low)

- 776 pt , Multicenter RCT
- (65-70 vs 80-85)
- No 28D mortality benefit to targeting a higher MAP
- atrial fibrillation



- Pilot RCT
- among patients aged 75 years or older, a higher MAP target was associated with increased hospital mortality (60 versus 13 percent)

Intensive Care Med (2016) 42:542–550
DOI 10.1007/s00134-016-4237-3

ORIGINAL



Higher versus lower blood pressure targets for vasopressor therapy in shock: a multicentre pilot randomized controlled trial

François Lamontagne^{1,2,3*}, Maureen O. Meade^{4,5}, Paul C. Hébert⁶, Pierre Asfar⁷, François Lauzier^{8,9,25}, Andrew J.E. Seely^{10,11}, Andrew G. Day¹², Sangeeta Mehta¹³, John Muscedere¹⁴, Sean M. Bagshaw¹⁵, Niall D. Ferguson¹³, Deborah J. Cook^{4,5}, Salmaan Kanji¹¹, Alexis F. Turgeon^{9,25}, Margaret S. Herridge¹³, Sanjay Subramanian¹⁶, Jacques Lacroix¹⁷, Neill K.J. Adhikari^{13,18}, Damon C. Scales^{13,18}, Alison Fox-Robichaud⁴, Yoanna Skrobik¹⁹, Richard P. Whitlock^{20,21}, Robert S. Green²², Karen K.Y. Koo²³, Teddie Tanguay²⁴, Sheldon Magder¹⁹, Daren K. Heyland¹² and for the Canadian Critical Care Trials Group.

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Corticosteroid Therapy



Dr. Srinath Kumar

Table 2 General management of the critically ill patient with sepsis and septic shock

Mechanical ventilation	Target tidal volumes of 6 mL/kg ideal bodyweight. If sepsis-related acute respiratory distress syndrome (ARDS) target tidal volumes of 6 mL/kg ideal bodyweight and plateau airway pressure of 30 cm H ₂ O. In intensive care units (ICU) experienced in the practice, ventilate patients with severe ARDS in the prone position for 16 h each day. Extracorporeal membrane oxygenation (ECMO) may reduce mortality in patients with very severe ARDS, such patients should be referred to an ECMO retrieval service.
Venous thromboembolism prophylaxis	Pharmacologic prophylaxis using unfractionated heparin or low-molecular-weight heparin is recommended in the absence of contraindications to the use of these agents. Non-pharmacological prophylaxis recommendations include; anti-embolism stockings and consideration of passive and early mobilisation, where appropriate.
Nutrition	Early initiation of enteral feeding using trophic/hypocaloric or full enteral feeding is recommended in patients who can tolerate enteral feeding. Early feeding should be commenced within 48 h and feeding goals met ideally within 72 h of admission to the ICU. If enteral feeding is not fully established within a week, parenteral supplementation should be considered.
Glucose control	Blood glucose should be managed using a protocolised approach with commencement after two consecutive levels are >10 mmol/L. The target of blood glucose level is 6–10 mmol/L. Measurement should be conducted every 1–2 h until values and insulin infusion rates stabilise, then every 4 h thereafter in patients receiving insulin infusions.
Sedation and analgesia	Continuous or intermittent sedation should be minimised in mechanically ventilated patients. Common approaches include implementation of nurse-directed protocols, administration of intermittent sedation, and daily sedation interruption. Short-acting sedatives including propofol and dexmedetomidine may result in improved outcomes. Other pain, agitation and delirium guidelines provide additional detail on implementation of sedation management for mechanically ventilated patients with sepsis and septic shock.
Positioning and early mobilisation	Elevate bed head between 30 and 45° for mechanically ventilated patients. Regular pressure area care as per unit specific guidelines. Active and early mobilisation should commence as soon as the patient is stable enough to participate. While, to date, no studies have found improvements in short- and long-term mortality active early mobilisation may improve mobility status and muscle strength, with several larger multicentre trials underway.
Agreement on treatment goals	Sepsis is common in elderly patients and in patients with serious underlying medical conditions and unlimited interventions will not be appropriate for all patients. Limitations to treatment may include both withholding and withdrawing life sustaining treatments when these will no longer produce an outcome acceptable to the individual patient. Agreement on treatment goals should whenever possible be informed by the patient's pre-stated wishes either to family or close friends or in legal documents such as advance directives or living wills.

Thompson K, Venkatesh B, Finfer S. Sepsis and septic shock: current approaches to management. Intern Med J. 2019 Feb;49(2):160-170. doi: 10.1111/imj.14199.PubMed PMID: 30754087.

Investigational vs Ineffective

- Beta-blockade
- Vitamin C, thiamine, and hydrocortisone combination
- Anticoagulants
- Naloxone
- Pentoxifylline
- Statins
- Inhibition of TLR-4 (Eritoran)
- IVIG
- Cytokine and endotoxin inactivation or removal
- Interferon-gamma
- GM-CSF, sargramostim, molgramostim
- IL-7, IL-15, or anti-PDL1
- Hemofiltration

- The Toll-like receptor (TLR)-4 antagonist, TAK 242 (Resatorvid)
- The human anti-endotoxin monoclonal antibody, HA-1A
- The human anti-Enterobacteriaceae common antigen (ECA) monoclonal antibody
- Alkaline phosphatase
- Granulocyte colony-stimulating factor (filgrastim, G-CSF)
- Anti-tumor necrosis factor monoclonal antibody
- Tumor necrosis factor receptor antagonist
- Interleukin-1 receptor antagonist
- Antithrombin (formerly known as antithrombin III)
- Recombinant human tissue factor pathway inhibitor (tifacogin)
- Ibuprofen
- N-acetylcysteine
- Nitric oxide inhibitors
- The bradykinin antagonist, deltibant
- Growth hormone
- Intravenous selenium supplementation
- Talactoferrin – restores the barrier properties of the gastrointestinal mucosa
- Calcitriol
- Levosimendan
- Hypothermia
- Hyperoxia
- Hypertonic saline
- Hemoperfusion through a membranous polymyxin B fiber column (PBFC)

THANK YOU
