HUMAN SEPSIS LITERATURE REVIEW

CARISSA TONG, BVM&S, MRCVS

ECC RESIDENT

1/14/2021

GOAL FOR TODAY…

- A big picture overview of relevant, major trials surrounding sepsis
- Topics divided based on the major domains of surviving sepsis
- Will not be focusing on critiquing study designs

RECOMMENDED RESOURCES

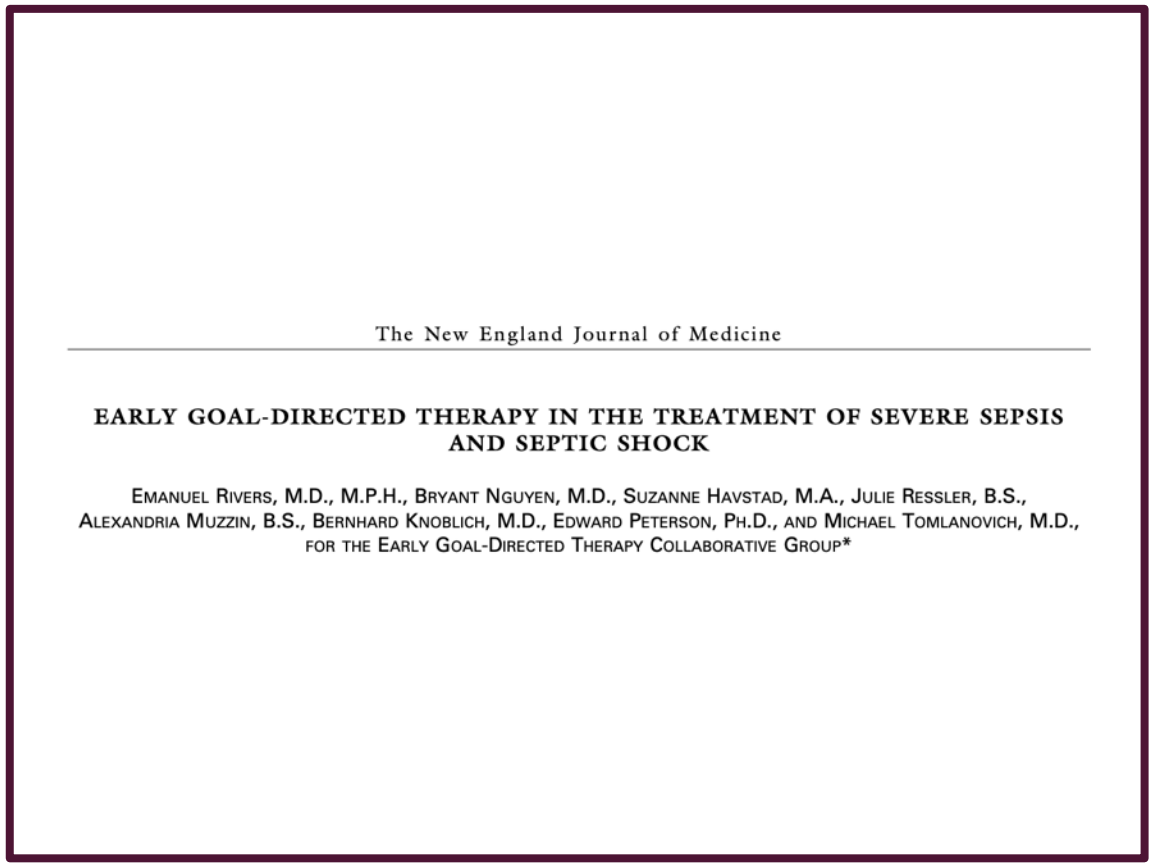
- http://www.thebottomline.org.uk/
- http://www.wikijournalclub.org/
- https://criticalcarereviews.com/index.php/majorstudies/rcts

EARLY GOAL DIRECTED THERAPY

EARLY GOAL DIRECTED THERAPY (EGDT)?

- Involves specific aggressive treatments and intensive monitoring to manage patients with hemodynamic derangements
- Used in patients with myocardial ischemia and in sepsis
- In sepsis, it involves adjustment preload, afterload and contractility to balance DO2
- Targets:
  - Central venous pressure 8-12 mmHg
  - Mean arterial pressure (MAP) >65 mmHg
  - Urine output >0.5 mL/kg/hr
  - Central venous oxygen saturation (SCvO2) > 70%
  - HCT >30%

LANDMARK RIVERS TRIAL (NEJM 2001)



The New England Journal of Medicine

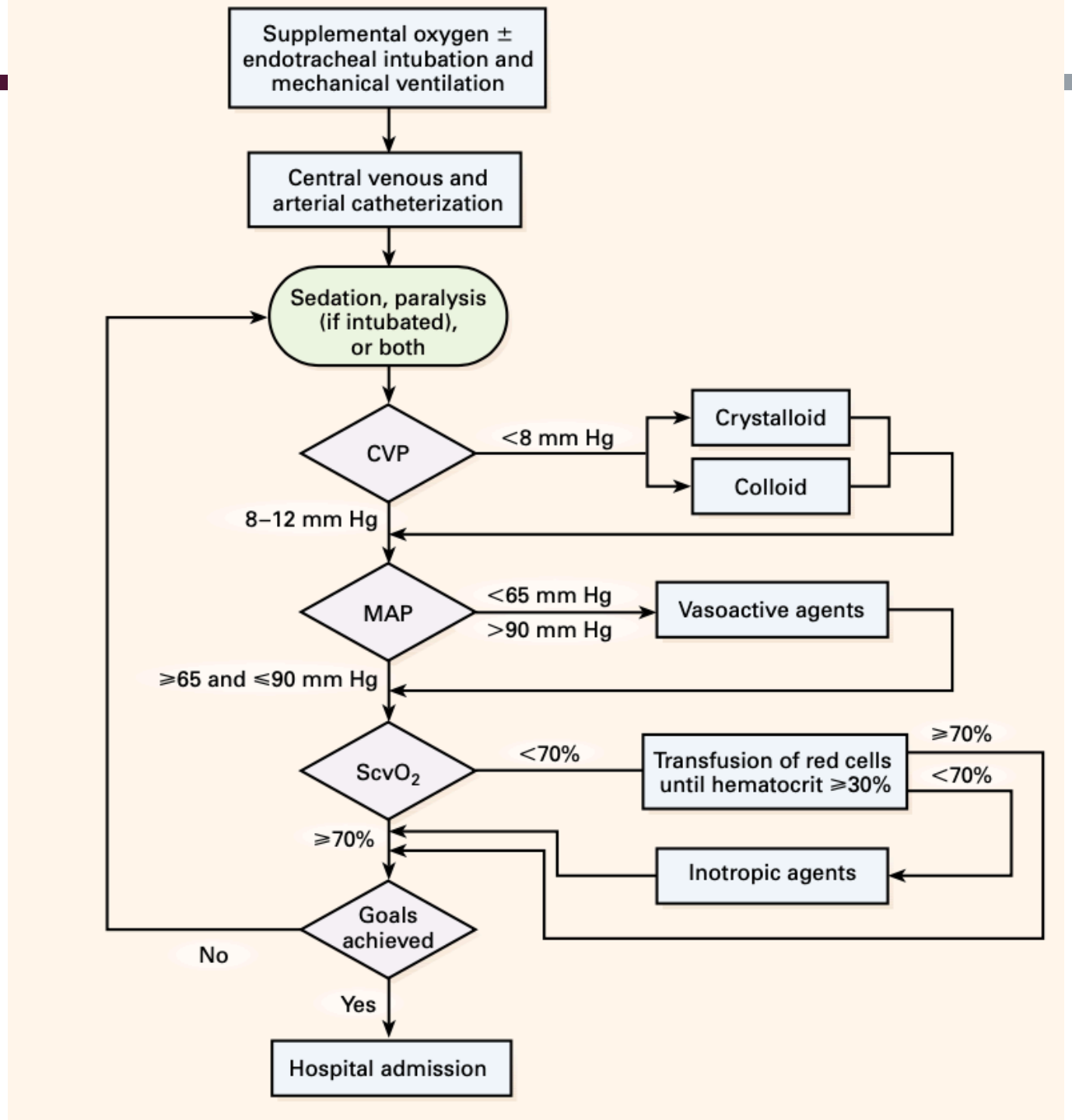
EARLY GOAL-DIRECTED THERAPY IN THE TREATMENT OF SEVERE SEPSIS AND SEPTIC SHOCK

EMANUEL RIVERS, M.D., M.P.H., BRYANT NGUYEN, M.D., SUZANNE HAVSTAD, M.A., JULIE RESSLER, B.S., ALEXANDRIA MUZZIN, B.S., BERNHARD KNOBLICH, M.D., EDWARD PETERSON, PH.D., AND MICHAEL TOMLANOVICH, M.D., FOR THE EARLY GOAL-DIRECTED THERAPY COLLABORATIVE GROUP*

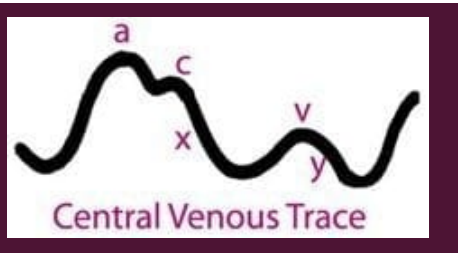
- In adults with severe sepsis or septic shock, does the use of early goal-directed therapy (EGDT) reduce the mortality?
- Single center, non-blinded RCT in the US
- Included those with severe sepsis or septic shock (SBP <90mmHg after 20-30 mL/kg crystalloid bolus over 30 minutes), lactate >4 mmol/L

LANDMARK RIVERS TRIAL (NEJM 2001)

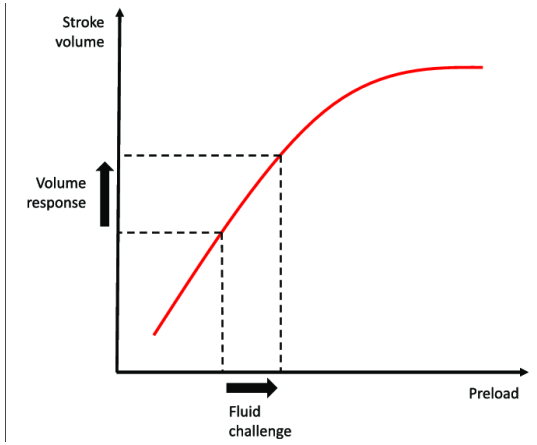
- EGDT was instituted for 6 hours with protocolized tx:
  - Central line: monitor ScvO2 and CVP
  - A-line: monitor IBP
  - +/- intubation and ventilation
  - 500 mL fluid boluses until CVP 8-12 mmHg
  - Vasopressor until MAP 65-90 mmHg
  - If ScvO2 <70% → Transfused until HCT 30%
    - If still <70%, start Dobutamine 2.5-20 mcg/kg/min
- 3 main targets: preload (CVP), perfusion (MAP), and tissue hypoxia (ScvO2)


Supplemental oxygen ± endotracheal intubation and mechanical ventilation
Central venous and arterial catheterization
Sedation, paralysis (if intubated), or both
CVP
<8 mm Hg
Crystalloid
Colloid
8–12 mm Hg
MAP
<65 mm Hg
>90 mm Hg
Vasoactive agents
⩾65 and ⩽90 mm Hg
ScvO2
<70%
Transfusion of red cells until hematocrit ⩾30%
⩾70%
<70%
⩾70%
Inotropic agents
Goals achieved
No
Yes
Hospital admission

CENTRAL VENOUS PRESSURE (CVP)



- Pressure recorded in the right atrium or cranial vena cava at the end of expiration
- Surrogate for the filling pressure of the right side of the heart
- Determined by PRA, intravascular fluid volume, venous capacitance, MSFP, RV and LV function and compliance, pulmonary vascular resistance, intrathoracic and intaabdominal pressures
- Traditionally used to determine fluid responsiveness; a static measure
  - Fluid responsiveness = increase in stroke volume by 10-15% following a fluid bolus
  - Referring to patients who have a "preload reserve"
- Recently shown to be a poor predictor of dynamic fluid responsiveness

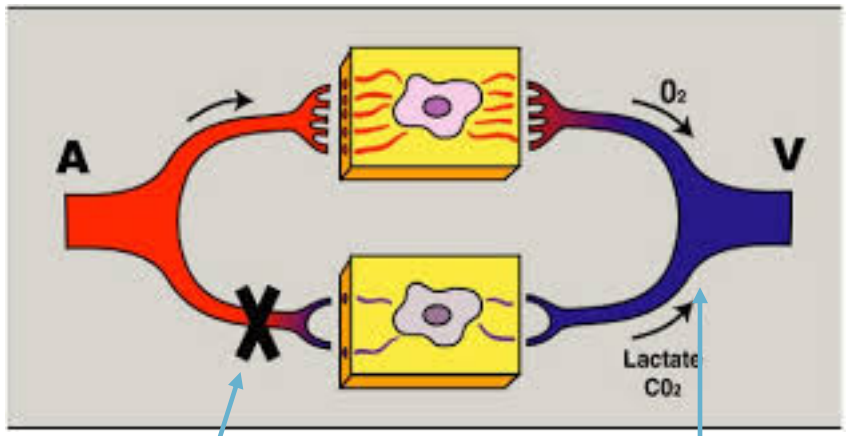


CENTRAL VENOUS OXYGEN SATURATION (SCVO2)

- ScvO2 is a surrogate of SvO2
  - SvO2 = mixed venous Hgb O2 saturation, obtained from pulmonary arterial blood via PA catheter
  - ScvO2 = central venous Hgb O2 saturation, obtained from central line from RA or CrVC
- It represents the balance between DO2 and VO2
- Low SvO2 = venule end of capillaries has low O2 tension and vice versa
- It depends on normal physiology in oxygen supply (macrocirculatory flow), distribution (microcirculatory flow), and processing of O2 (mitochondrial function)
- Shortcomings:
  - Invasiveness
  - Various conditions can cause an "artificial" elevation: sepsis, liver failure, i.e. any disease that alter microcirculation
  - Other less invasiveness measurements (e.g. lactate clearance) is non-inferior to monitoring ScvO2 in sepsis

MICROCIRCULATORY SHUNTING IN SEPSIS

- Sepsis leads to multifactorial microcirculatory failure
  - Physiologic shunting
  - Maldistributed flow,
  - Increased microvascular permeability,
  - Microvascular thrombosis.
- All of which can contribute to a septic patient having normal to high SvO2 despite severe local tissue hypoxia or even dysoxia
- Even though maintaining SvO2 >65-70% is recommended, it does NOT reflect restoration of local tissue oxygenation



Flow impairment

O2 tension maybe the same/high here if there shunting = no O2 uptake

RECOMMEND ADDITIONAL READING….

JOURNAL OF
Veterinary Emergency
AND Critical Care

Clinical Practice Review

Journal of Veterinary Emergency and Critical Care **28**(5) 2018, pp 387–397
doi: 10.1111/vec.12749

Venous oxygen saturation in critical illness

Rebecca A.L. Walton, DVM, DACVECC and Bernie D. Hansen, DVM, MS, DACVECC, DACVIM

LANDMARK RIVERS TRIAL (NEJM 2001)

Results:

- In-hospital mortality better in EDGT compared to control (29.2% vs 44.%)
- 2ry outcome subgroup analyses (severity of sepsis, 28-d and 60-d mortality, cause of in-hospital death) all favored EDGT
- Tertiary data:
  - EGDT group received more fluids in first 6h but no different in 72h
  - More pRBC transfusion in EGDT
  - Earlier inotropic use in EGDT
  - Vasopressor + intubation/ventilation more prevalent in control

LANDMARK RIVERS TRIAL (NEJM 2001)

Various limitations were identified:

- Study population only limited to ED patients
- Single center, non-blinded
- Control group had a lot of co-morbidities and an above-average mortality rate
- CVP unrelated to preload or fluid responsiveness
- No evidence for HCT 30% as transfusion trigger (TRISS)

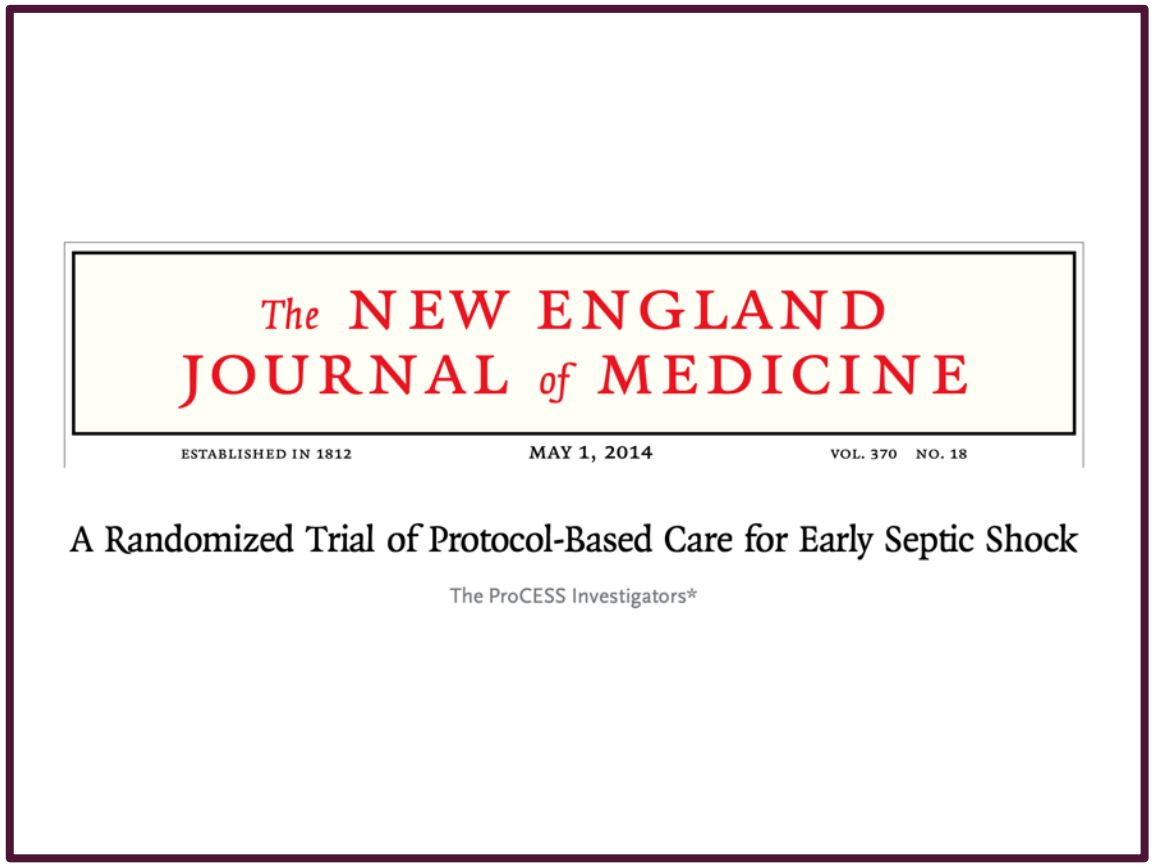
2001 EGDT (Rivers trial)[73]	**Early goal directed therapy** EGDT algorithm† for 6 hours initiated in the ED compared with standard therapy	• 263 severe sepsis • 1 ED	In-hospital mortality	**Benefit** RR 0.58 (0.38 to 0.87)	Required continuous monitoring of $ScvO_2$ Highly influential study, protocols adopted into guidelines
2011 FEAST[141]	**Fluid resuscitation** Three groups: 1. No bolus fluids 2. Bolus 5% albumin 3. Bolus 0.9% saline	• 3141 children with severe febrile illness‡ • Hospitals in Uganda, Kenya, Tanzania	48 hour mortality	**Harm** **Group 2 *v* 1:** RR 1.45 (1.10 to 1.92); **Group 3 *v* 1:** RR 1.44 (1.09 to 1.90)	Similar results at 4 weeks Recruiting hospitals lacked intensive care facilities No subgroup showed benefit from fluid resuscitation
2012 6S Trial[142]	**Type of fluid for resuscitation** 6% hydroxyethyl starch *v* Ringer's acetate (control)	• 804 severe sepsis • 26 Scandinavian ICUs	Death or dialysis dependence at 90 days	**Harm** **Death:** RR 1.17 (1.01 to 1.36) Dialysis: RR 1.35 (1.01 to 1.80)	
2014 ProCESS[143]	**Management of early septic shock** Three groups: 1. Usual care 2. EGDT 3. Protocol based standard therapy§	• 1341 septic shock • 31 North American EDs	60 day mortality	**No differences** **Group 2 *v* 3:** RR 1.15 (0.88-1.51); **Group 3 *v* 1:** RR 1.04 (0.82-1.31)	Severity of illness similar to original EGDT trial
2014 ARISE[144]	**Management of early septic shock** Usual care *v* EGDT	• 1600 septic shock • 51 EDs Australia/New Zealand	90 day mortality	**No differences** AD -0.3% (-4.1% to 3.6%)	
2014 ALBIOS[145]	**Type of fluid for resuscitation** 20% albumin and crystalloid *v* crystalloid (control)	• 1818 severe sepsis • 100 Italian ICUs	28 day mortality	**No differences** RR 1.00 (0.87 to 1.14)	
2014 SEPSISPAM[146]	**Blood pressure target (mm Hg)** MAP 80-85 *v* 65-70 (control)	• 776 septic shock • 29 French ICUs	28 day mortality	**No differences** HR 1.07 (0.84 to 1.38)	Higher MAP group with more atrial fibrillation, less dialysis (in those with chronic hypertension)
2014 TRISS[147]	**Hemoglobin target** Transfusion threshold of 70 *v* 90 g/L	• 1005 septic shock • 32 Scandanavian ICUs	90 day mortality	**No differences** 70 *v* 90 g/L: RR 0.94 (0.78 to 1.09)	No difference in ischemic events
2015 ProMISe[148]	**Management of early septic shock** EGDT *v* Usual care	• 1260 septic shock • 56 English EDs	90 day mortality	**No differences** RR 1.01 (0.85 to 1.20)	EGDT increased costs
2015 SPLIT[149]	**Type of fluid for resuscitation** Buffered crystalloid *v* saline	• Patients requiring crystalloid • 4 New Zealand ICUs	AKI within 90 days	**No differences** RR 1.04 (0.80 to 1.36)	Patients low risk for outcome, modest fluid administration

STUDIES EVALUATING EGDT

3 major trials:

- ProCESS: USA
- ARISE: Australia
- ProMISE: UK

PROCESS (NJEM 2014)



- In adult patients with sepsis, does protocol-based care compared to usual care reduce death within 60 days?
- Multi-center blinded RCT in the US
- Included patients arriving in ED with sepsis (refractory hypotension or lac >4 with 2+ SIRS criteria)
- EGDT group vs protocol-based standard therapy vs usual care
- No difference between groups for 60-d mortality (21% vs 18.2% vs 18.9%)

ARISE (NEJM 2014)

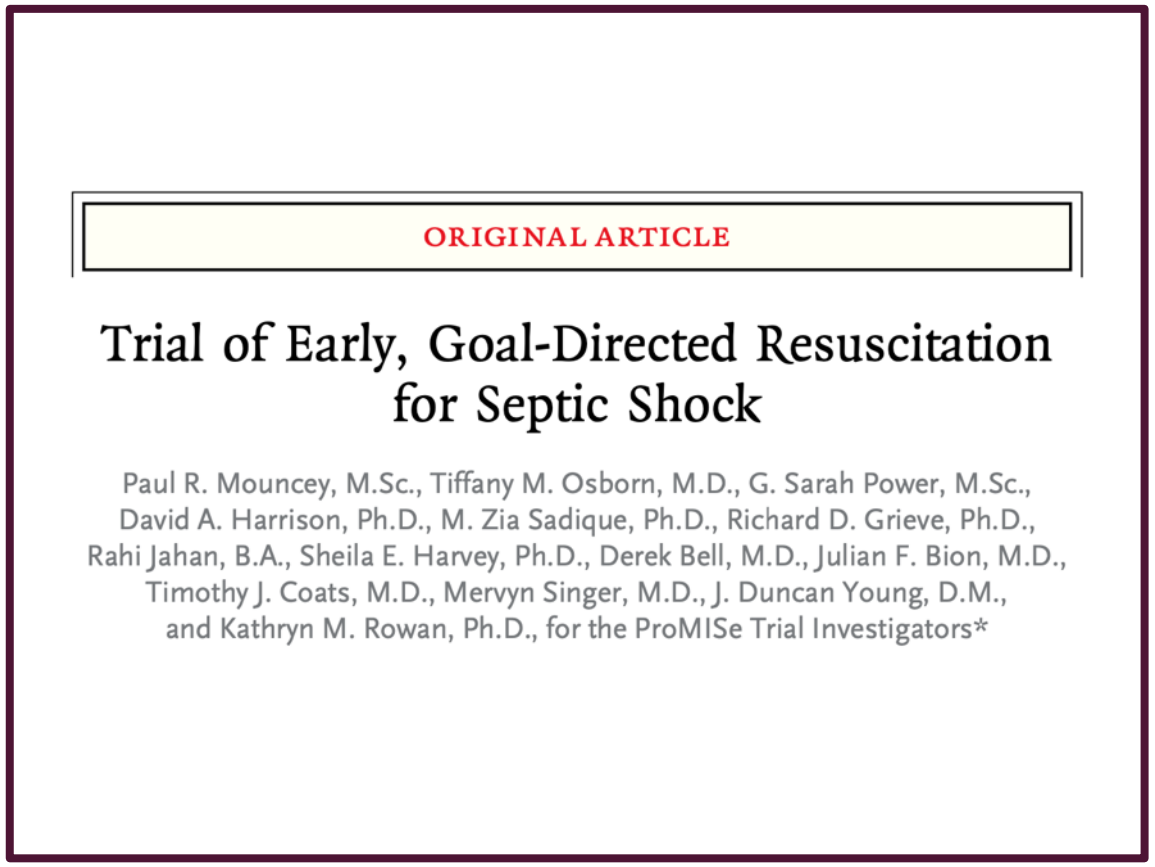
ORIGINAL ARTICLE

Goal-Directed Resuscitation for Patients with Early Septic Shock

The ARISE Investigators and the ANZICS Clinical Trials Group*

- In adult patients with septic shock, does EGDT compared with standard therapy reduce mortality at 90 days?
- Multi-center non-blinded RCT in Australia/NZ/Finland/HK/Ireland
- Included patients arriving in ER with:
  - Suspected/confirmed infection (2+ SIRS criteria)
  - Refractory hypotension (SBP<90 or MAP>65 mmHg after 1L IV challenge w/in 60 mins) or hypoperfusion (Lac ≥4 mmol/L)
  - Received IV ABX prior to randomization
- EDGT (same protocol as Rivers) vs control (usual care)
- No difference at 90d mortality (18.6% vs 18.8%)
  - No difference in LOH, vasopressor infusion, and mechanical ventilation

PROMISE (NEJM 2015)



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*

- In adult patients with septic shock, does EGDT compared with standard therapy reduce mortality at 90 days?
- Multi-center non-blinded RCT in England
  - Essentially the same as ARISE but in England
- No difference in 90d mortality (29.5 vs 29.2%)
  - EGDT had more: central lines, A-lines, vasopressor use, dobutamine use, RBC transfusion
  - No differences b/w IVF admin, resp support and ICU admission
  - Only difference was SOFA score at 6 hours and median length of ICU stay between groups

THE BOTTOM LINE…

- ProCESS (US), ProMISe (UK) and ARISE (Aus/Asia) all found EGDT did not significantly affect survival

ANTIBIOTICS

KUMAR (CCM 2006): ANTIBIOTIC TIMING

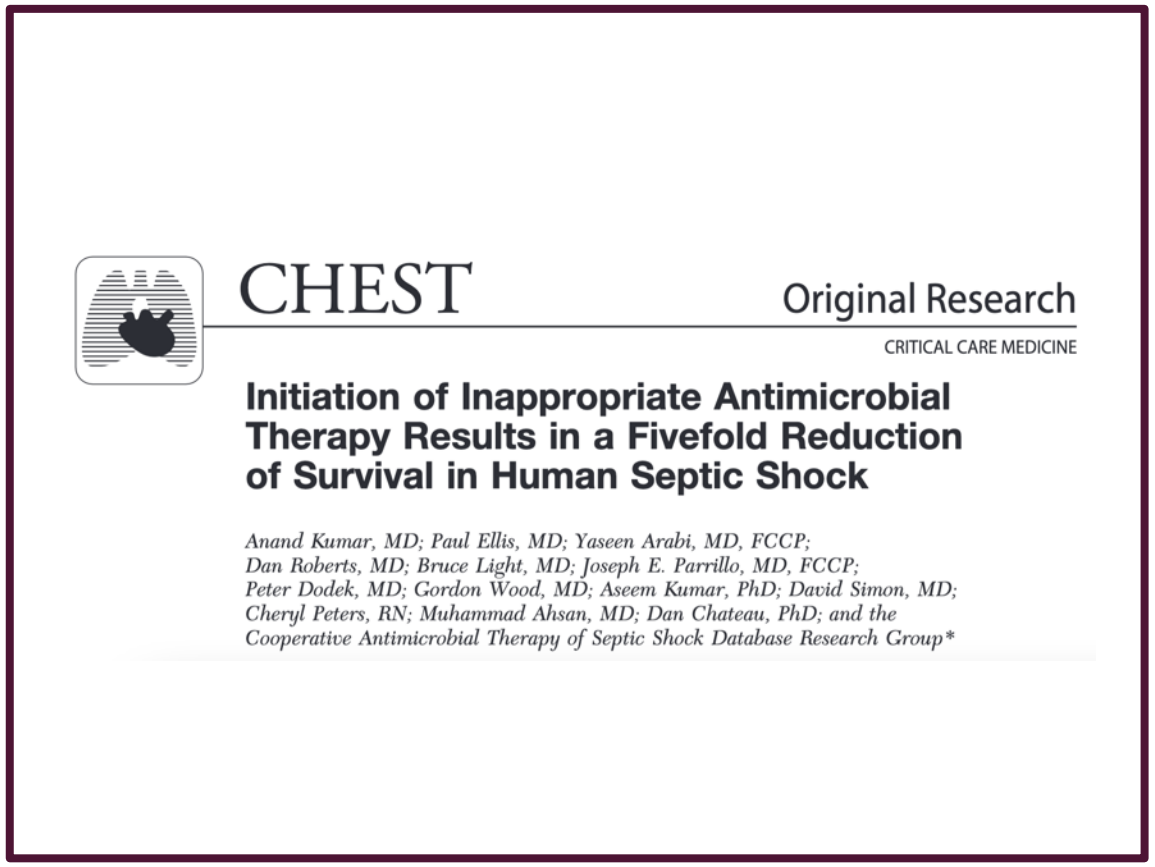
Feature Articles

Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock*

Anand Kumar, MD; Daniel Roberts, MD; Kenneth E. Wood, DO; Bruce Light, MD; Joseph E. Parrillo, MD; Satendra Sharma, MD; Robert Suppes, BSc; Daniel Feinstein, MD; Sergio Zanotti, MD; Leo Taiberg, MD; David Gurka, MD; Aseem Kumar, PhD; Mary Cheang, MSc

- Does a delay in antibiotic administration in patients with septic shock result in an increased mortality?
- Retrospective study of adult septic shock patients from the US + Canada
- Included those fulfilled septic shock guidelines: 2+ SIRS criteria, organ dysfunction, sepsis induced hypotension (MAP<65mmHg) despite adequate IVF
- Decreased survival by 7.6% for every 1-hour delay of initiating ABX
- Only 50% of the patients received effective ABX therapy within the first 6 hours
- Giving ABX effective for isolated or suspected pathogens within the 1st hour of documented hypotension was associated with a survival rate of 79.9%.

KUMAR (CHEST 2009): CHOICE OF ANTIBIOTICS



CHEST Original Research

CRITICAL CARE MEDICINE

Initiation of Inappropriate Antimicrobial Therapy Results in a Fivefold Reduction of Survival in Human Septic Shock

*Anand Kumar, MD; Paul Ellis, MD; Yaseen Arabi, MD, FCCP; Dan Roberts, MD; Bruce Light, MD; Joseph E. Parrillo, MD, FCCP; Peter Dodek, MD; Gordon Wood, MD; Aseem Kumar, PhD; David Simon, MD; Cheryl Peters, RN; Muhammad Ahsan, MD; Dan Chateau, PhD; and the Cooperative Antimicrobial Therapy of Septic Shock Database Research Group**

- In patients with septic shock, what is the relationship between appropriateness of initial empiric antimicrobial therapy and survival?
- Retrospective observational study in Canada, USA, and Saudi Arabia
- Included patients with septic shock (≥ 2 SIRS criteria, suspected/confirmed infection, persistent hypotension needing pressors)
- Inappropriate ABX occurred in 20% of patients and is associated with 5x reduction in survival
  - Effect greatest in those w/ primary blood infections, UTI, or if due to anaerobes or yeast

FLUID THERAPY

FLUID THERAPY

- Traditionally, everyone received 0.9% NaCl
- We have learned that saline is not physiologic:
  - Not a balanced isotonic crystalloid → doesn't contain a buffer or other electrolytes
  - Contains 10% high sodium and 50% higher chloride compared to plasma
  - Acidifying solution
  - Associated with development of AKI
- Shift towards using a balanced crystalloid

ALBUMIN

SAFE (NEJM 2004)

- Does fluid resuscitation with 4% albumin, compared to saline (0.9%NaCl), affect mortality for patients in the ICU?
- There was no difference when 4% albumin is used for fluid resuscitation when compared to 0.9% sodium chloride.
- 4% albumin should be avoided in head injuries

ORIGINAL ARTICLE

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

The SAFE Study Investigators*

ALBIOS (NEJM 2014)

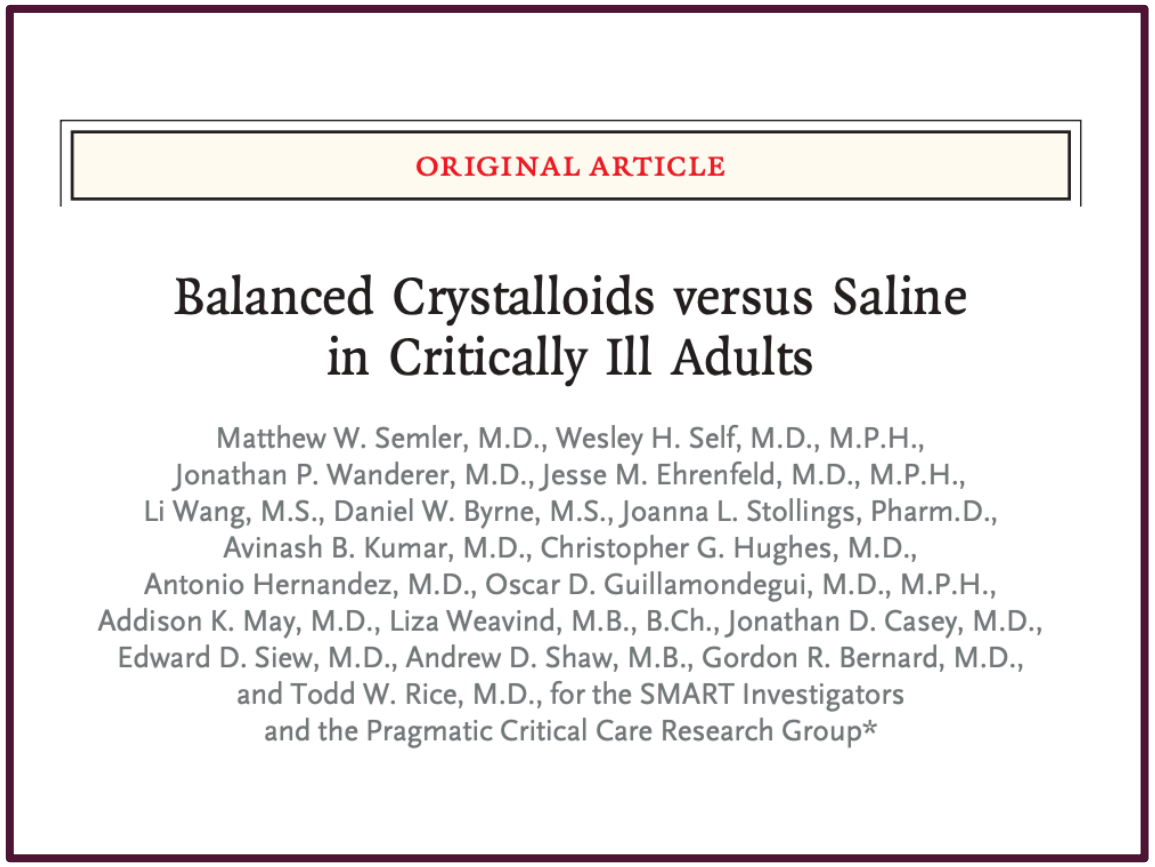
- In adults with severe sepsis or septic shock, does 20% albumin solution with crystalloid fluid compared to crystalloid fluid alone reduce death with 28 days?
- Using albumin in additional to crystalloids to maintain albumin > 30g/L is safe, but doesn't provide survival advantage

ORIGINAL ARTICLE

Albumin Replacement in Patients with Severe Sepsis or Septic Shock

Pietro Caironi, M.D., Gianni Tognoni, M.D., Serge Masson, Ph.D., Roberto Fumagalli, M.D., Antonio Pesenti, M.D., Marilena Romero, Ph.D., Caterina Fanizza, M.Stat., Luisa Caspani, M.D., Stefano Faenza, M.D., Giacomo Grasselli, M.D., Gaetano Iapichino, M.D., Massimo Antonelli, M.D., Vieri Parrini, M.D., Gilberto Fiore, M.D., Roberto Latini, M.D., and Luciano Gattinoni, M.D., for the ALBIOS Study Investigators*

SMART (NEJM 2018)



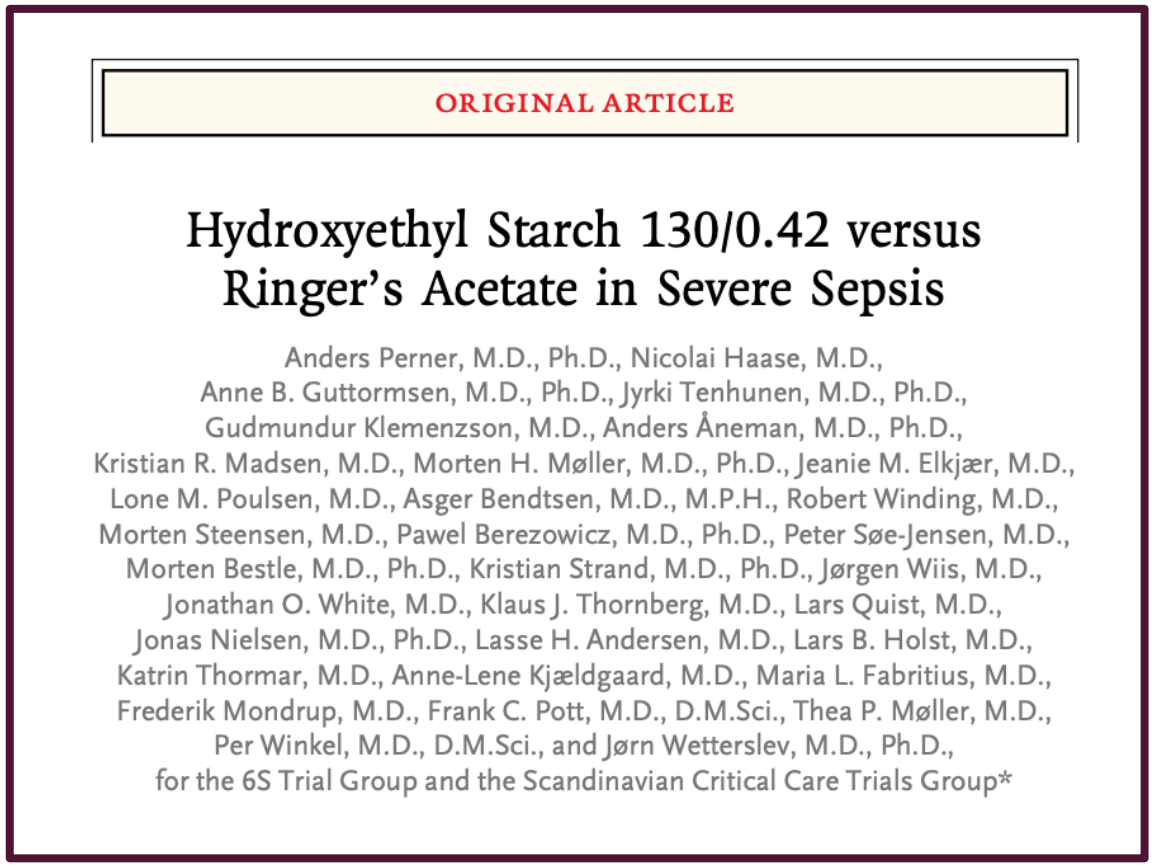
ORIGINAL ARTICLE

Balanced Crystalloids versus Saline in Critically Ill Adults

Matthew W. Semler, M.D., Wesley H. Self, M.D., M.P.H., Jonathan P. Wanderer, M.D., Jesse M. Ehrenfeld, M.D., M.P.H., Li Wang, M.S., Daniel W. Byrne, M.S., Joanna L. Stollings, Pharm.D., Avinash B. Kumar, M.D., Christopher G. Hughes, M.D., Antonio Hernandez, M.D., Oscar D. Guillamondegui, M.D., M.P.H., Addison K. May, M.D., Liza Weavind, M.B., B.Ch., Jonathan D. Casey, M.D., Edward D. Siew, M.D., Andrew D. Shaw, M.B., Gordon R. Bernard, M.D., and Todd W. Rice, M.D., for the SMART Investigators and the Pragmatic Critical Care Research Group*

- In critically ill patients does the administration of balanced crystalloids compared with saline, reduce a 30 day composite outcome of death, new renal replacement therapy or persistent renal dysfunction?
  - Intervention: balanced crystalloid: PLyte-A or LRS
  - Control: normal saline
  - One institution, 5 ICU, rotated types of fluid every calendar month
- Favours administering intravenous balanced crystalloids over saline to decrease a composite outcome of death, new renal replacement therapy or persistent renal dysfunction at 30 days

6S (NEJM 2012)



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 Søe-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*

- In critically ill adults with severe sepsis, does 6% hydroxyethyl starch (6% HES = Tetraspan 6%) compared to Ringer's acetate reduce the incidence of death or end stage kidney failure?
- Patients with severe sepsis who received fluid resuscitation with HES compared with Ringer's acetate had a higher risk of death within 90 days and were more likely to receive renal replacement therapy
  - Caution vs. use of starch-based fluids in severe sepsis
- SSS 3 recommends against HES for intravascular volume replacement

FEAST (NEJM 2011)

ESTABLISHED IN 1812 JUNE 30, 2011 VOL. 364 NO. 26

Mortality after Fluid Bolus in African Children with Severe Infection

Kathryn Maitland, M.B., B.S., Ph.D., Sarah Kiguli, M.B., Ch.B., M.Med., Robert O. Opoka, M.B., Ch.B., M.Med., Charles Engoru, M.B., Ch.B., M.Med., Peter Olupot-Olupot, M.B., Ch.B., Samuel O. Akech, M.B., Ch.B., Richard Nyeko, M.B., Ch.B., M.Med., George Mtove, M.D., Hugh Reyburn, M.B., B.S., Trudie Lang, Ph.D., Bernadette Brent, M.B., B.S., Jennifer A. Evans, M.B., B.S., James K. Tibenderana, M.B., Ch.B., Ph.D., Jane Crawley, M.B., B.S., M.D., Elizabeth C. Russell, M.Sc., Michael Levin, F.Med.Sci., Ph.D., Abdel G. Babiker, Ph.D., and Diana M. Gibb, M.B., Ch.B., M.D., for the FEAST Trial Group*

- Study took place in Africa, in a resource-limited setting
- Pediatric patients with severe febrile illness
- Do fluid boluses with albumin vs saline vs no fluid boluses affect mortality?
- Mortality was worse in the bolus group vs control group at 48h
- However, population had high incidence of co-morbidities (malaria, severe anemia) and was managed with a low transfusion threshold without intensivist
  - Difficult to extrapolate and apply in first world countries

CLASSIC (ICM 2016)

Intensive Care Med (2016) 42:1695–1705
DOI 10.1007/s00134-016-4500-7

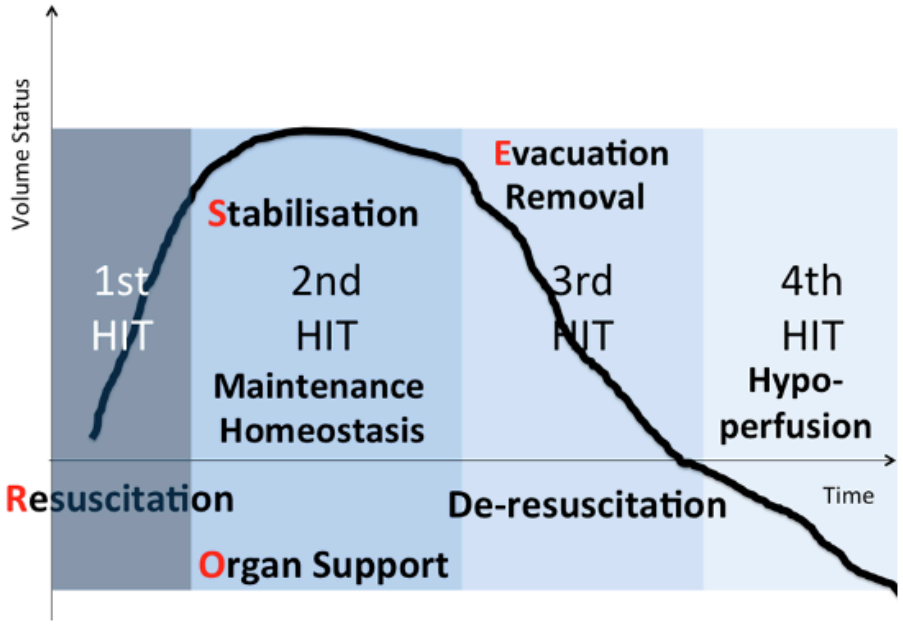
SEVEN-DAY PROFILE PUBLICATION

Restricting volumes of resuscitation fluid in adults with septic shock after initial management: the CLASSIC randomised, parallel-group, multicentre feasibility trial

Peter B. Hjortrup[1], Nicolai Haase[1], Helle Bundgaard[2], Simon L. Thomsen[3], Robert Winding[4], Ville Pettilä[5], Anne Aaen[6], David Lodahl[7], Rasmus E. Berthelsen[8], Henrik Christensen[9], Martin B. Madsen[1], Per Winkel[10], Jørn Wetterslev[10], Anders Perner[1,11*], The CLASSIC Trial Group, The Scandinavian Critical Care Trials Group

- In ICU patients with septic shock who have had initial fluid resuscitation, what are the effects and feasibility of a protocol restricting further resuscitation fluid as opposed to standard care?
- Fluid restriction group: Allowed 250-500 mL crystalloid bolus during ICU stay for severe hypotension
  - Lactate >4, MAP <50 despite norepi CRI, mottling score >2, oliguria of >0.1 mL/kg/hr in the last hour
- Control group: Standard care – clinician's choice
- In both group: Targeted MAP >65 mmHg, used norepi as 1st line, free choice crystalloid, colloids banned, monitored fluid bolus effects for 30 mins after, other concomitant tx for sepsis can be used (based on 2012 guidelines)
- Results:
  - Less fluids used in first 5h and overall ICU stay length shorter in restricted group
  - No difference in total fluid inputs and cumulative balance in first 5 days in ICU

ROSE CONCEPT OF FLUID THERAPY



- Restrictive fluid therapy should be practiced once resuscitation is accomplished

Malbrain *et al. Ann. Intensive Care (2018) 8:66*
https://doi.org/10.1186/s13613-018-0402-x

Annals of Intensive Care

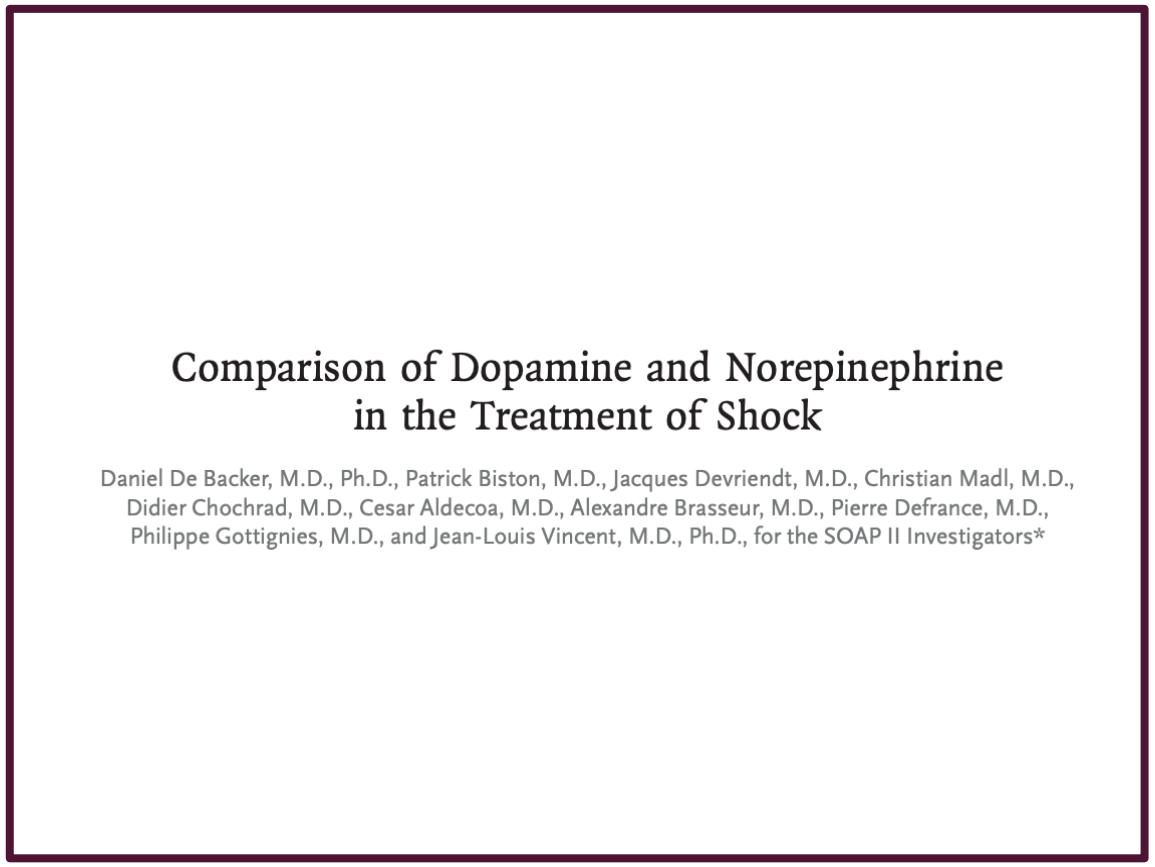
REVIEW Open Access

Principles of fluid management and stewardship in septic shock: it is time to consider the four D's and the four phases of fluid therapy

Manu L. N. G. Malbrain[1,2*], Niels Van Regenmortel[3], Bernd Saugel[4], Brecht De Tavernier[3], Pieter-Jan Van Gaal[3], Olivier Joannes-Boyau[5], Jean-Louis Teboul[6], Todd W. Rice[7], Monty Mythen[8] and Xavier Monnet[6]

VASOPRESSOR USE

SOAP II (NEJM 2010)

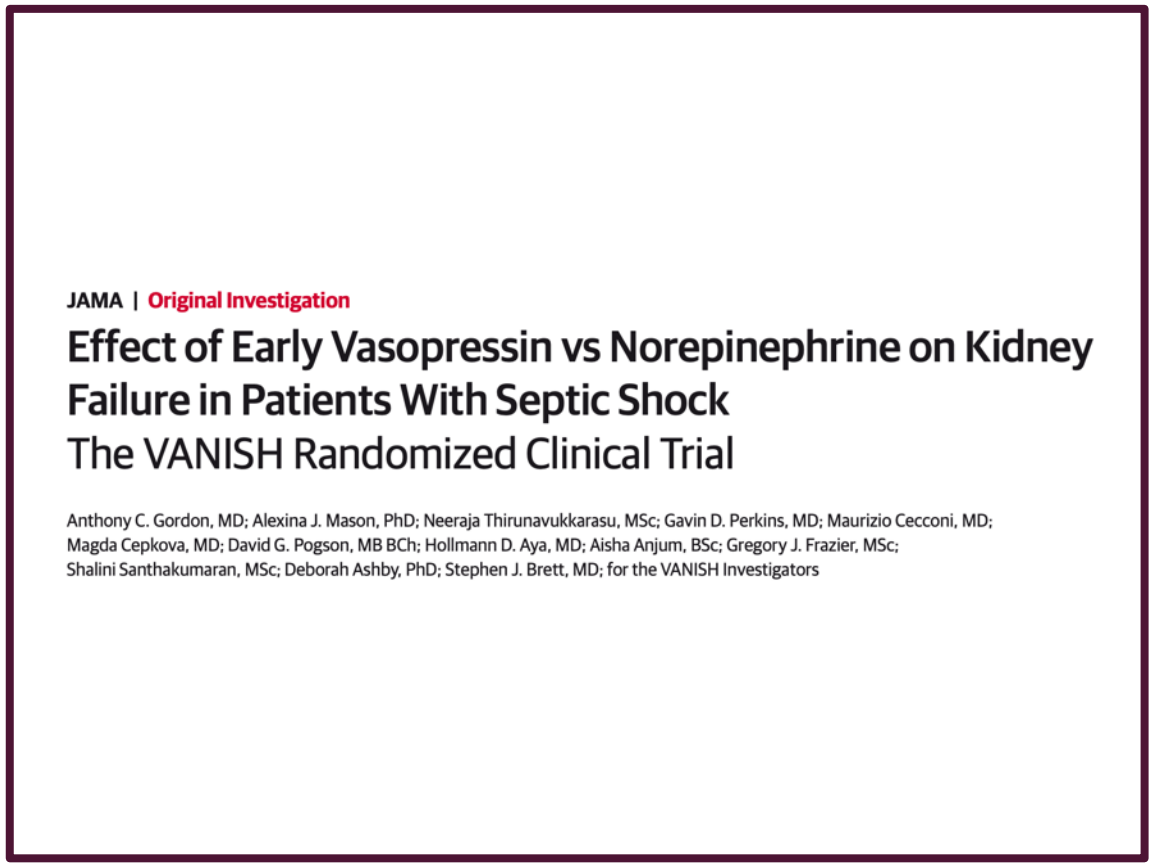


Comparison of Dopamine and Norepinephrine in the Treatment of Shock

Daniel De Backer, M.D., Ph.D., Patrick Biston, M.D., Jacques Devriendt, M.D., Christian Madl, M.D., Didier Chochrad, M.D., Cesar Aldecoa, M.D., Alexandre Brasseur, M.D., Pierre Defrance, M.D., Philippe Gottignies, M.D., and Jean-Louis Vincent, M.D., Ph.D., for the SOAP II Investigators*

- SOAP stands for The Sepsis Occurrence in Acutely Ill Patients
- Among patients with shock, how does dopamine compare to norepinephrine in decreasing mortality?
  - SOAP I had showed that dopamine was an independent predictor of increased mortality in shock
  - Shock defined as MAP < 70 or SBP < 100 despite adequate fluid, signs of tissue hypoperfusion
- In the treatment of shock, norepinephrine and dopamine compare similarly with respect to 28-day mortality, but dopamine is associated with an increased risk of arrhythmias.

VANISH (JAMA 2016)



JAMA | Original Investigation

Effect of Early Vasopressin vs Norepinephrine on Kidney Failure in Patients With Septic Shock

The VANISH Randomized Clinical Trial

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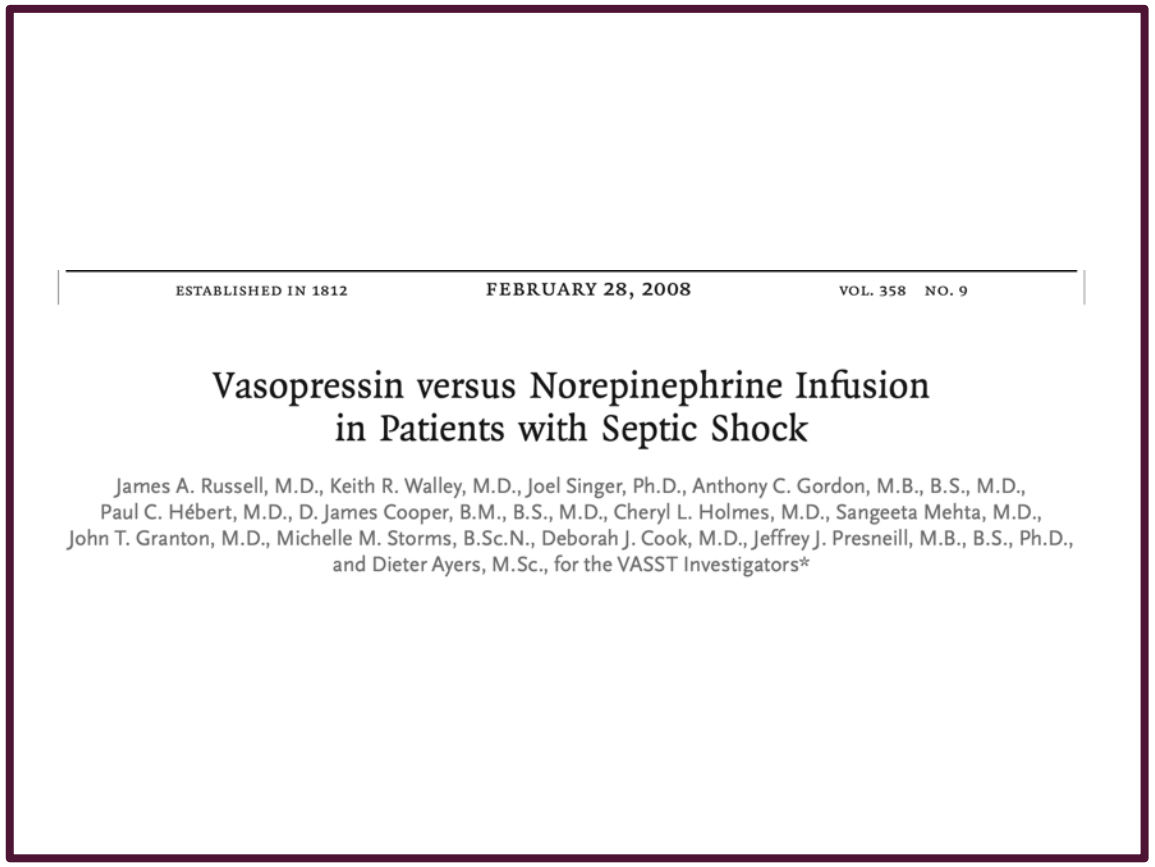
- Does early vasopressin use reduce the risk of kidney failure in patients with septic shock compared with norepinephrine?
  - Open-labelled vasopressor permitted for up to 6h prior to enrollment
  - Study drug 1 was vasopressin titrated up to 0.06 U/min and norepi titrated up to 12 mcg/min to maintain MAP 65-75
  - Study drug 2 (Hydrocortisone or placebo) given once they reached max dose of drug 1
- Early vasopressin maintains blood pressure and reduces the requirement for norepinephrine and renal replacement therapy.
- Vasopressin didn't reduce the number of renal replacement free days or mortality rate, and there was no clinical interaction with corticosteroids

VASST (NEJM 2008)



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Vasopressin versus Norepinephrine Infusion in Patients with Septic Shock

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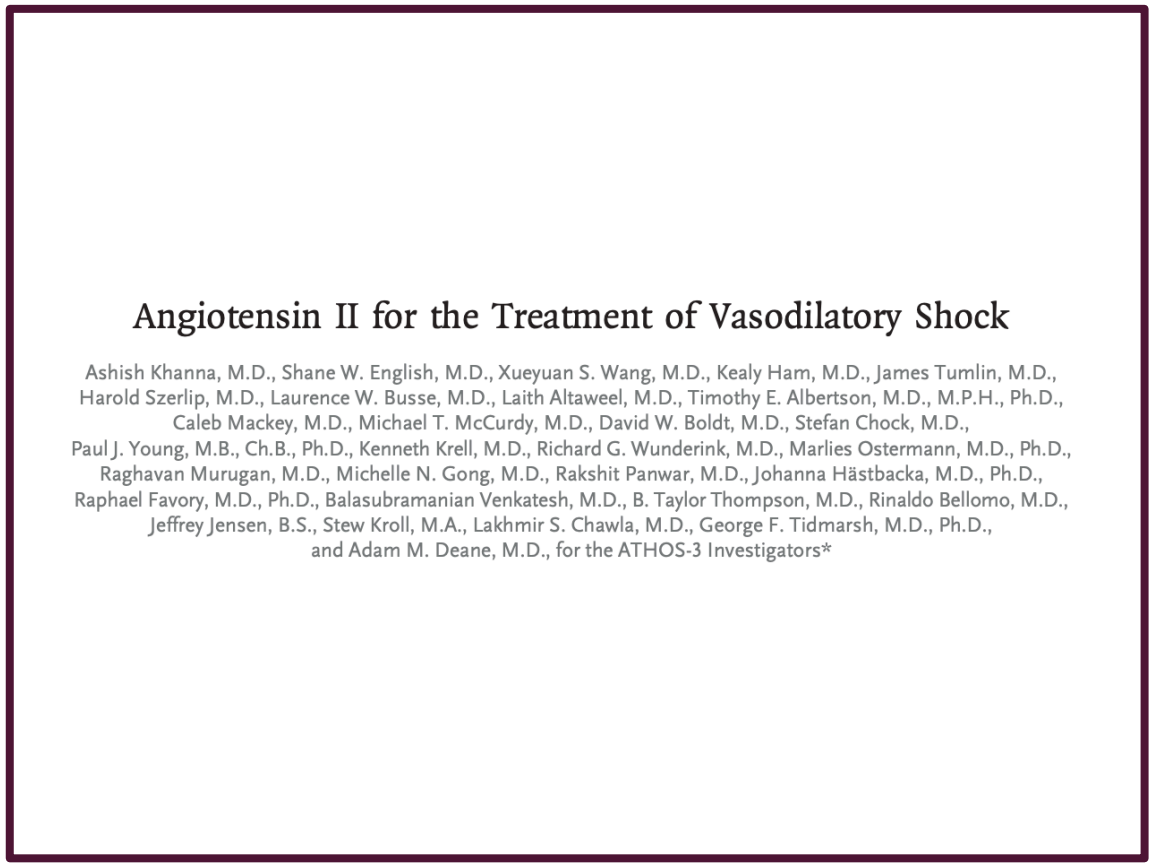
- In adult patients with septic shock, does the addition of vasopressin infusion (0.01-0.03u/min) to a norepinephrine infusion compared to a norepinephrine infusion alone decrease mortality rate at 28 days?
- Study drug was vasopressin and control was norepi
  - Target MAP 65-75 mmHg
- No difference in mortality, MAP, need for RRT between the two groups
- Did not investigate vasopressor-refractory septic shock

ATHOS-3 (NEJM 2017)



Angiotensin II for the Treatment of Vasodilatory Shock

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- In patients with refractory vasodilatory shock does the addition of angiotensin II improve blood pressure compared with standard vasopressor therapy?
  - Included patients who required norepi > 0.2mcg/kg/min for 6-48h to maintain MAP 55-70 mmHg
  - ATII: 20 ng/kg/min, dose adjusted in first 3h to incr MAP to 75 mmHg
- Angiotensin II increases blood pressure in patients that didn't respond to conventional vasopressors
- Numerically patients were less likely to have adverse events and die compared with the control group

BLOOD PRESSURE TARGETS

- 2 major trials evaluating a higher versus lower BP targets
- **SEPSISPAM (NEJM 2014):** High versus low Blood-Pressure Target in Patients with Septic Shock
  - For the majority of patients in septic shock a target MAP of 65-70 is a good starting point.
  - In those with chronic hypertension, should target a higher MAP
- **OVATION pilot trial:** Higher versus lower blood pressure targets for vasopressor therapy in shock: a multicenter pilot randomized controlled trial.
  - Lower 60-65 vs higher 75-80 mmHg MAP target
  - Risk of cardiac arrhythmias and hospital mortality were not different between the 2 groups

HOW DID THESE RESULTS IMPACT SSC?

- Instituted hour 1 bundle:
- Measure lactate. Remeasure if >2 mmol/L
- Obtain blood culture prior to administration of antibiotics
- Administer broad-spectrum antibiotics w/in an hour of recognizing sepsis/septic shock
- Begin rapid infusion of 30 mL/kg crystalloid for hypotension OR lactate $\geq$ 4 mmol/L
- Apply vasopressors if patient is hypotensive during or after fluid resuscitation to maintain MAP $\geq$ 65 mmHg
- Norepi is the first line vasopressor

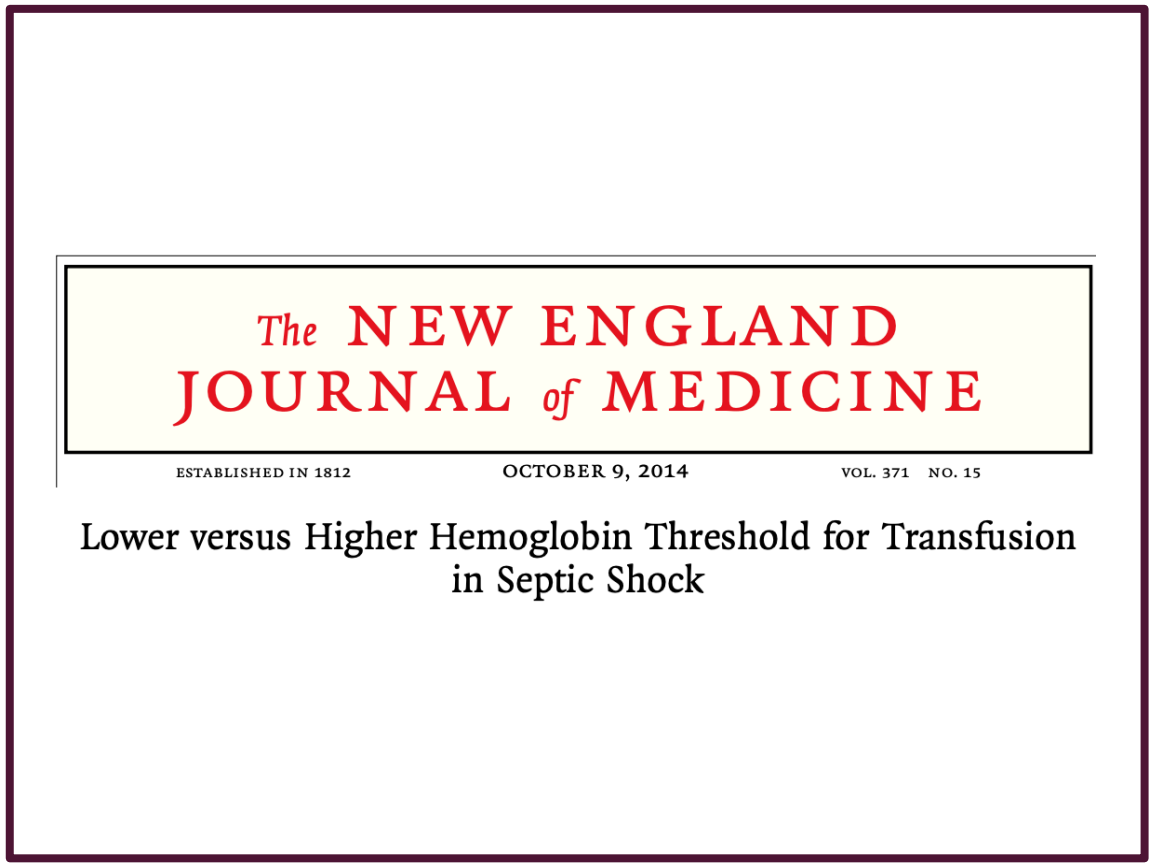
CORTICOSTEROIDS USE IN SEPSIS

USE OF CORTICOSTEROIDS

- Various trials evaluating the use of hydrocortisone for treatment of CIRCI
- Covered by TBW's board review recently
- The list of relevant literature to this topic includes:
  - Annae trial (NEJM 2002)
  - CORTICUS (NEJM 2008)
  - HYPRESS (NEJM 2016)
  - ADRENAL (NEJM 2018)
  - APROCCHSS (NEJM 2018)

TRANSFUSION IN SEPSIS

TRISS



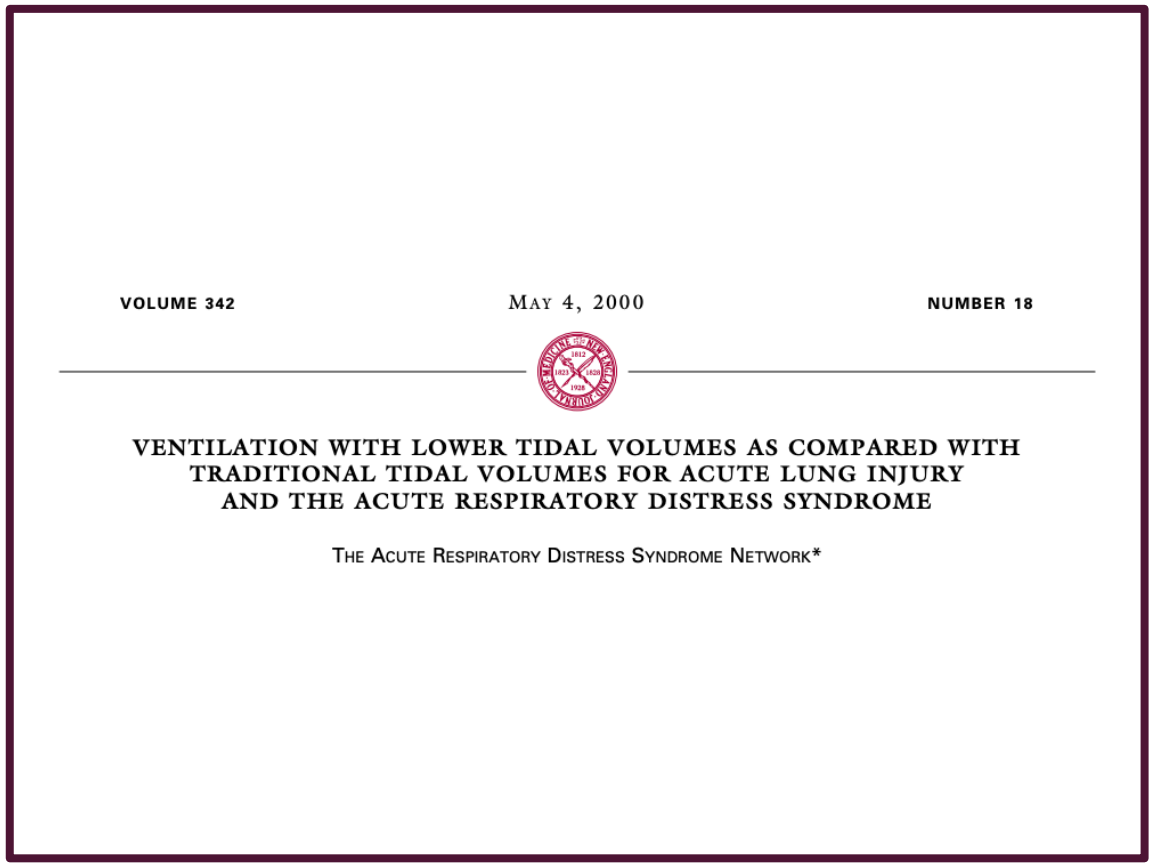
- In patients with septic shock, how does a restrictive transfusion strategy compare with a liberal transfusion strategy in terms of 90-day mortality?
- ICU patients with septic shock to a restrictive (Hgb ≤7) vs liberal (Hgb ≤ 9) transfusion strategy in Europe
- No difference in primary outcome (death by 90 days)- similar mortality and rate of ischemia events

MECHANICAL VENTILATION

MECHANICAL VENTILATION

- Over 50% of patients with severe sepsis or septic shock will develop ARDS
- 2002 human review found that sepsis accounted for 8.8% of acute respiratory failure and is associated with high mortality
- Majority of literature evaluating ventilatory strategy in ALI/ARDS, not specified to septic patients

ARDSNET TRIAL: ARMA (NEJM 2000)



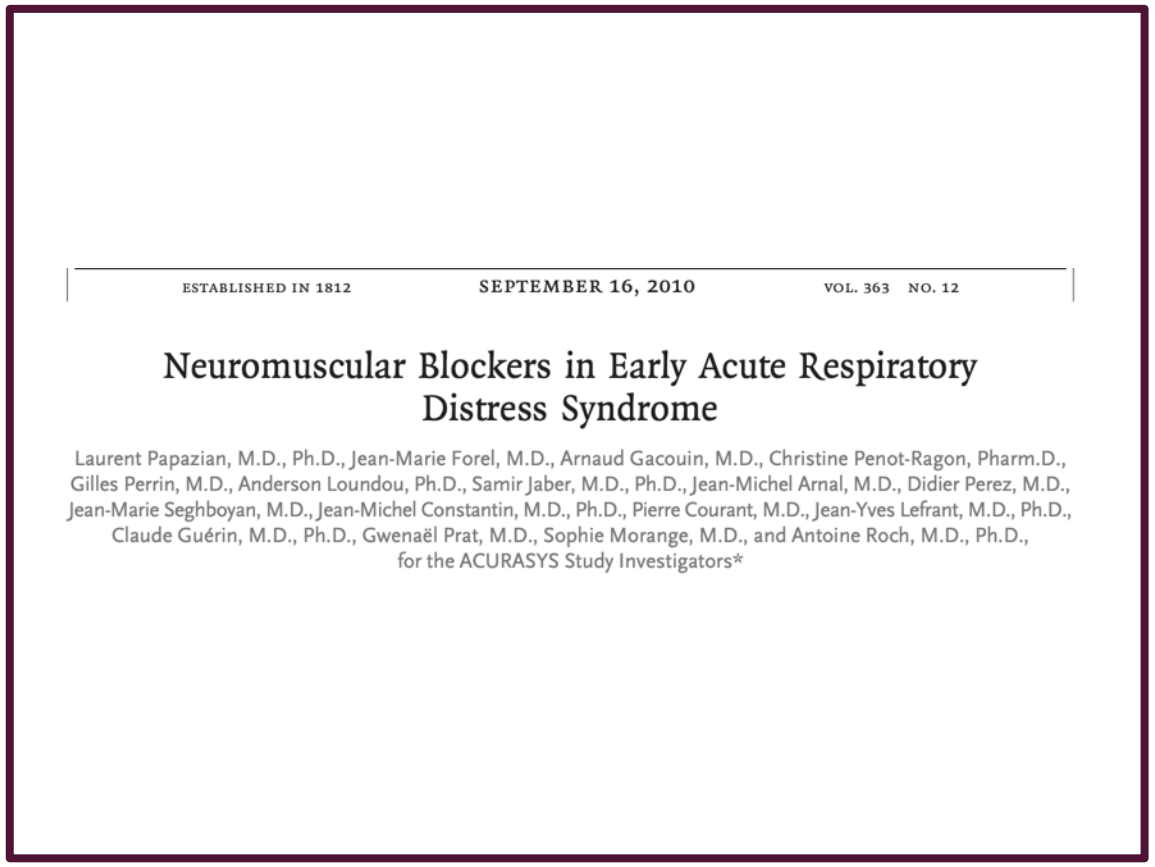
VOLUME 342 MAY 4, 2000 NUMBER 18

VENTILATION WITH LOWER TIDAL VOLUMES AS COMPARED WITH TRADITIONAL TIDAL VOLUMES FOR ACUTE LUNG INJURY AND THE ACUTE RESPIRATORY DISTRESS SYNDROME

THE ACUTE RESPIRATORY DISTRESS SYNDROME NETWORK*

- In patients with Acute Lung Injury (ALI) or Acute Respiratory Distress Syndrome (ARDS), does ventilation with lower tidal volumes compared with traditional higher tidal volumes reduce death or ventilator-free days?
  - Criteria: PF < 300 with bilateral pulmonary infiltrates, no clinical evidence of LA hypertension, PCWP $\leq$ 18 mmHg
  - Volume assist-control ventilation modes
- Low VT (6 mL/kg, Pplt <30) versus higher VT (12 mL/kg, Pplat <50)
- Adult patients with acute lung injury or acute respiratory distress syndrome should be ventilated with tidal volumes of 6 ml/kg, limiting plateau pressures to 30 cm water.

ACURASYS (NEJM 2010)



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Neuromuscular Blockers in Early Acute Respiratory Distress Syndrome

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- In patients with moderate-severe ARDS does the early use of a neuromuscular blocking agent (cisatricurium x 48 hours) improve mortality?
  - Mod-severe ARDS: mechanically ventilated with ETT, PF $\leq$ 150 with PEEP $\geq$ 5, VT 6-8 mL/kg, bilateral pulmonary infiltrates and absence of clinical evidence of LA hypertension
- Significant improvement in mortality for patients with severe ARDS who were treated with early NMB

OTHER VENTILATION RELATED TRIALS

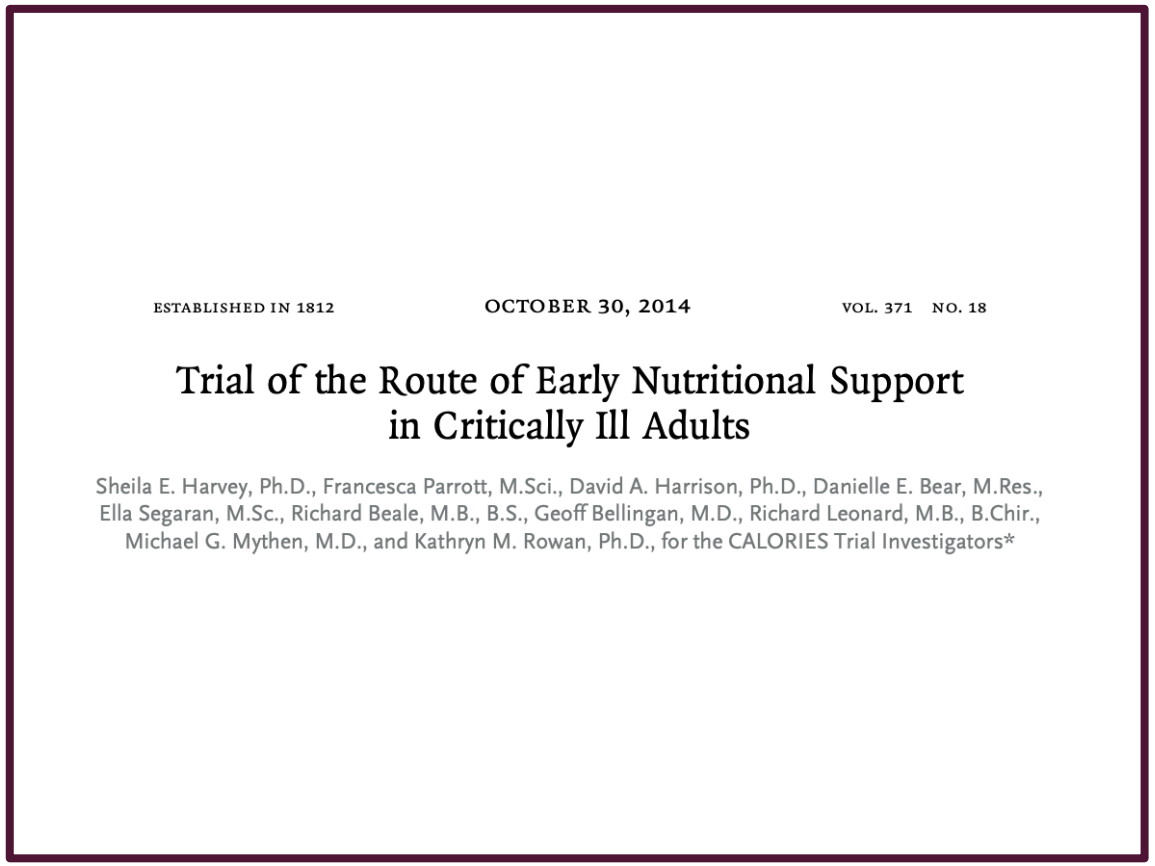
- **PROSEVA** (NEJM 2013): Evaluating prone positioning in ARDS → Proning helps!
  - Not really applicable to vet med since we almost always ventilate in sternal recumbency
- **OSCAR** and **OSCILLATE** trials (NEJM 2013): Evaluating high-frequency oscillation in ARDS → Harmful, don't use
- **BALTI-1** and **BALTI-2** (Lancet 2012): Evaluated IV beta-2 agonists in ARDS → Poorly tolerated, can worsen outcome

NUTRITION IN SEPSIS

NUTRITION SUPPORT IN SEPSIS

- Septic patient commonly develop a negative energy balance
- In most, oral nutritional intake is inadequate, impractical or impossible in septic patients
- Early, enteral nutrition is recommended
- Hypercaloric feeding (>10% of calculated or measured energy target) associated with complication and poor outcome
  - Insulin resistance and hyperglycemia, hepatic steatosis, prolonged organ support (e.g. mechanical ventilation), and increased mortality
- Moved to relative hypocaloric, trophic or trickle feeding methods to prevent negative effects of starvation to the gut
  - Mucosal atrophy, reduced absorption of nutrients, and bacterial translocation

ROUTE OF DELIVERY



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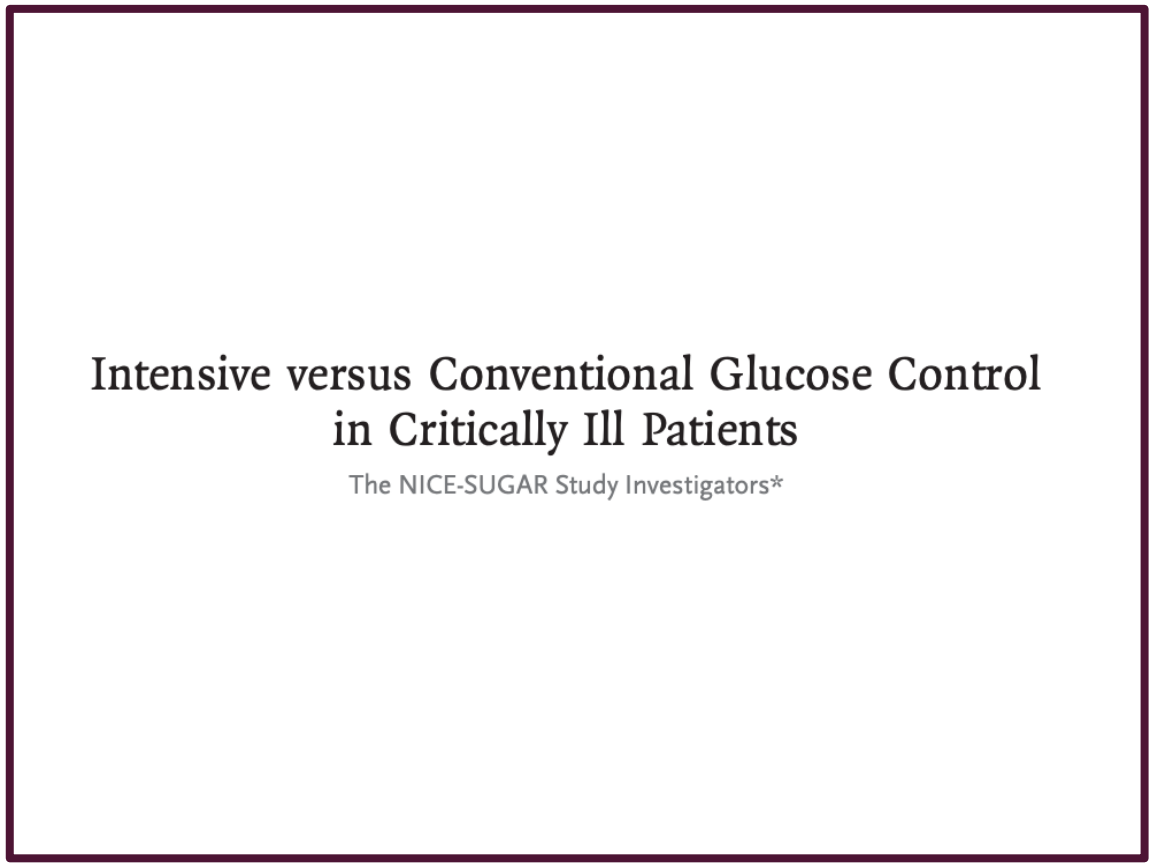
Trial of the Route of Early Nutritional Support in Critically Ill Adults

Sheila E. Harvey, Ph.D., Francesca Parrott, M.Sci., David A. Harrison, Ph.D., Danielle E. Bear, M.Res., Ella Segaran, M.Sc., Richard Beale, M.B., B.S., Geoff Bellingan, M.D., Richard Leonard, M.B., B.Chir., Michael G. Mythen, M.D., and Kathryn M. Rowan, Ph.D., for the CALORIES Trial Investigators*

CALORIES (NEJM 2014)

- Compared paternal vs enteral nutrition in critically ill patients
- Nutrition was delivered within 36 h after admission and continued for up to 5 days
- Early parenteral nutrition is neither more harmful nor more beneficial than through the enteral route.
- Enteral feeding does increase episodes of vomiting and hypoglycemia but with no evidence of harm or nosocomial infection.

GLYCEMIC CONTROL


Intensive versus Conventional Glucose Control in Critically Ill Patients

The NICE-SUGAR Study Investigators*

NICE-SUGAR (NEJM 2009)

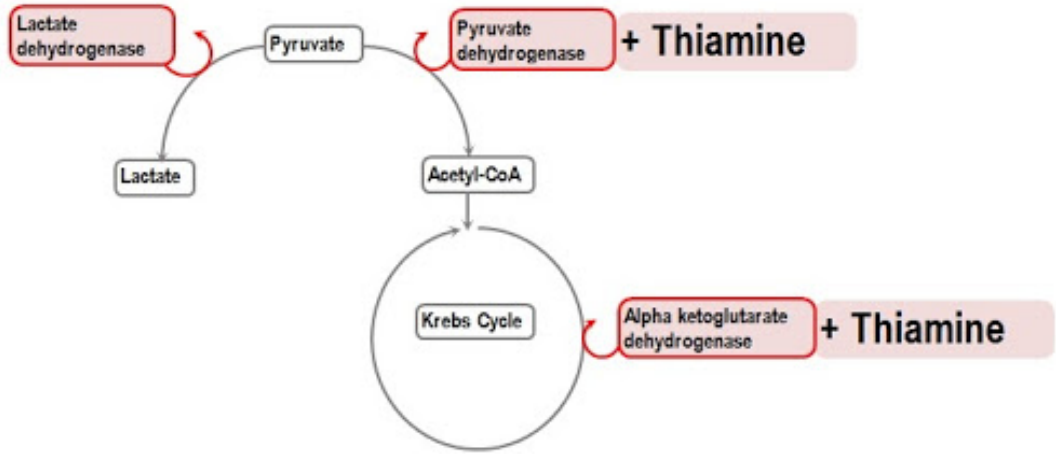
- In critically ill adults that are expected to be in Intensive Care for 3 days or more, does intensively controlled blood glucose (81-108 mg/dL) compared to conventionally controlled blood glucose (<180mg/dL) reduce mortality at 90 days?
- Better survival associated with conventional BG target of < 180 mg/dL

OTHER TREATMENTS…

METABOLIC RESUSCITATION: HAT THERAPY

- Vitamin C
  - Anti-inflammatory
  - Antioxidant: Prevents vascular endothelial damage and maintain microvascular integrity
  - Cofactor for catecholamine synthesis
- Thiamine
  - Thiamine deficiency reported in 20% of critically ill septic patients (Donnino 2010)
  - Thiamine supplementation reported to improve lactate clearance (Woolum 2018)
- Hydrocortisone to treat CIRCI

THIAMINE AND LACTATE CLEARANCE



- Thiamine is converted to active thiamine pyrophosphate = essential coenzyme for CHO metabolism
- Thiamine normally stored in skeletal muscle
- Thiamine pyrophosphate is a coenzyme in the pyruvate dehydrogenase complex → accelerates pyruvate conversion to Acetyl-CoA
- In thiamine deficiency, this pathway is limited for lactate clearance

MARIK (CHEST 2017)

- Does intravenous vitamin C, hydrocortisone and thiamine in addition to standard treatment, improve mortality in ICU patients with severe sepsis or septic shock, compared with standard treatment alone?
- Single center retrospective study in the US
- Included severe sepsis or septic shock with PCT >2 ng/mL
- Intervention group received vitamin C (1.5g IV x 4d or until discharge) + hydrocortisone (50 mg IV 7 days or until discharge, tapered over 3 days) + thiamine (200 mg x 4d or until discharge)
- Primary outcome: in-hospital mortality significantly lower in intervention group (8.5% vs 40.4%)
- Low quality of evidence
  - Small sample size = incr risk of bias
  - Lack of concurrent comparator group
  - Single center

SUBSEQUENT STUDIES…

- VITAMINS (JAMA 2020): No difference except HAT therapy improved SOFA score
- HYVCTTSSS (CHEST 2020): No difference but HAT therapy was associated with hypernatremia
- ORANGES (CHEST 2020): HAT therapy reduced time to resolution of shock (suspect steroid effects)
- ATESS (ICM 2020): No difference between groups

Bottom line: None of the above trials were able to reproduce the results from the Marik trial

ACTIVATED PROTEIN C (APC)

- APC theorized to help balance out the pro-inflammatory and the procoagulant state in sepsis
- **PROWESS (NEJM 2001)** evaluated APC in severe sepsis and showed a survival benefit
  - However, it was very controversial
    - Had early termination
    - Adjusted inclusion/exclusion criteria mid-protocol
    - The company altered Drotrecogin Alfa (DrotAA) manufacturing mid-study
- **PROWESS-SHOCK trial (NEJM 2012)**: DrotAA in Adults with Septic Shock List of authors.
  - Performed as a follow up to PROWESS
  - It did not reduce mortality compared to placebo in septic shock
  - It was subsequently withdrew from the market → no longer available

G-CSF AND GM-CSF

- Granulocyte colony stimulating factor (G-CSF) proposed to stimulate production of neutrophils and modulate the function and activity of developing and mature neutrophils
- Granulocyte-macrophage CSF (GM-CSF) may induce proliferation and differentiation of granulocytes + macrophages
- One study in 2008 evaluated the use of G-CSF (Stephens, CCM 2008) did not improve outcomes of patients with septic shock
- A meta-analysis performed in 2011(Bo, CC 2011) also did not find a difference in 28-d and in-hospital mortality

THANK YOU!

ANY QUESTIONS?