What's New in Surgical Critical Care?

Deborah M. Stein, MD, MPH, FACS, FCCM

Objectives

1. Review evidence-based guidelines and new pivotal clinical trials (Process, Arise, Promise) & others

2. Discuss new strategies for assessment of adequacy of resuscitation in shock states

3. Discuss new clinical trials and changes in nutritional support in surgical critical care

Evidence-based guidelines
and
New pivotal clinical trials

Evidence Based Guidelines

Satterfield, et al. Millbank Quarterly. 2009

Evidence Based Guidelines – Surviving Sepsis

Surviving Sepsis Campaign

TABLE 6. Recommendations: Hemodynamic Support and Adjunctive Therapy

G. Fluid Therapy of Severe Sepsis

1. Crystalloids as the initial fluid of choice in the resuscitation of severe sepsis and septic shock (grade 1B).
2. Against the use of hydroxyethyl starches for fluid resuscitation of severe sepsis and septic shock (grade 1B).
3. Albumin in the fluid resuscitation of severe sepsis and septic shock when patients require substantial amounts of crystalloids (grade 2C).
4. Initial fluid challenge in patients with sepsis-induced tissue hypoperfusion with suspicion of hypovolemia to achieve a minimum of 30 mL/kg of crystalloids (a portion of this may be albumin equivalent). More rapid administration and greater amounts of fluid may be needed in some patients (grade 1C).
5. Fluid challenge technique be applied wherein fluid administration is continued as long as there is hemodynamic improvement either based on dynamic (eg, change in pulse pressure, stroke volume variation) or static (eg, arterial pressure, heart rate) variables (UG).

H. Vasopressors

1. Vasopressor therapy initially to target a mean arterial pressure (MAP) of 65 mm Hg (grade 1C).
2. Norepinephrine as the first choice vasopressor (grade 1B).
3. Epinephrine (added to and potentially substituted for norepinephrine) when an additional agent is needed to maintain adequate blood pressure (grade 2B).
4. Vasopressin 0.03 units/minute can be added to norepinephrine (NE) with intent of either raising MAP or decreasing NE dosage (UG).
5. Low dose vasopressin is not recommended as the single initial vasopressor for treatment of sepsis-induced hypotension and vasopressin doses higher than 0.03-0.04 units/minute should be reserved for salvage therapy (failure to achieve adequate MAP with other vasopressor agents) (UG).
6. Dopamine as an alternative vasopressor agent to norepinephrine only in highly selected patients (eg, patients with low risk of tachyarrhythmias and absolute or relative bradycardia) (grade 2C).
7. Phenylephrine is not recommended in the treatment of septic shock except in circumstances where (a) norepinephrine is associated with serious arrhythmias, (b) cardiac output is known to be high and blood pressure persistently low or (c) as salvage therapy when combined inotrope/vasopressor drugs and low dose vasopressin have failed to achieve MAP target (grade 1C).
8. Low-dose dopamine should not be used for renal protection (grade 1A).
9. All patients requiring vasopressors have an arterial catheter placed as soon as practical if resources are available (UG).

I. Inotropic Therapy

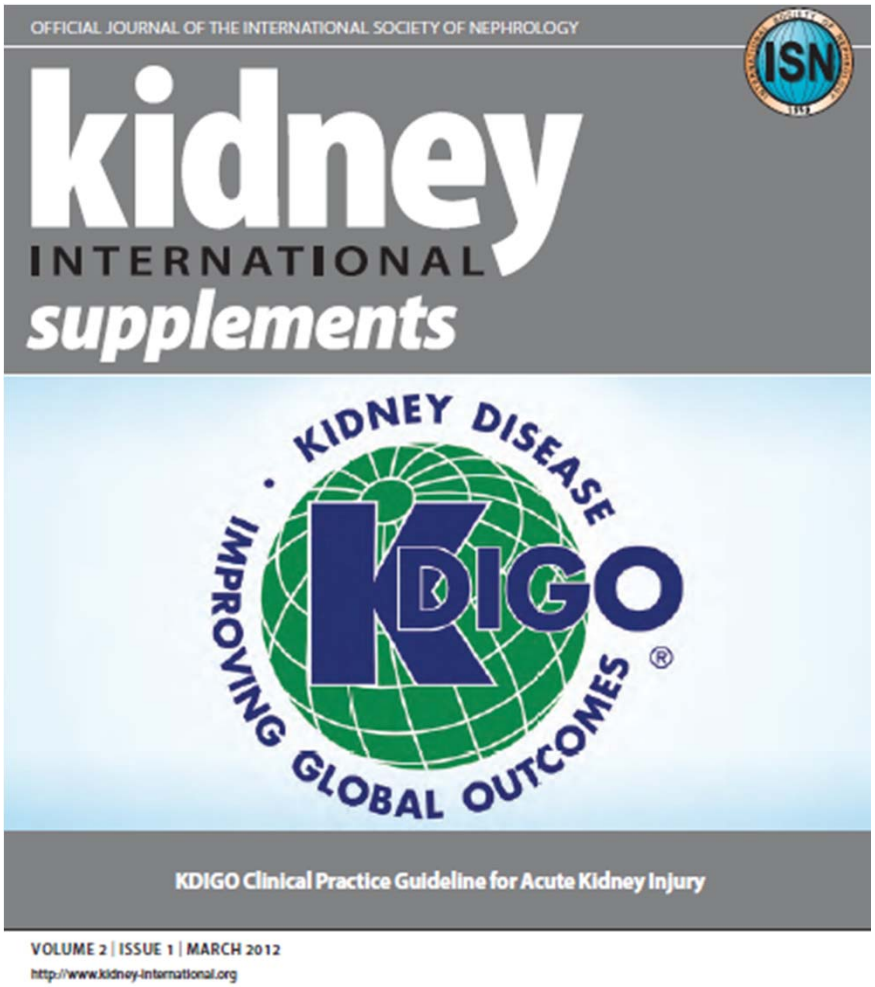
1. A trial of dobutamine infusion up to 20 micrograms/kg/min be administered or added to vasopressor (if in use) in the presence of (a) myocardial dysfunction as suggested by elevated cardiac filling pressures and low cardiac output, or (b) ongoing signs of hypoperfusion, despite achieving adequate intravascular volume and adequate MAP (grade 1C).
2. Not using a strategy to increase cardiac index to predetermined supranormal levels (grade 1B).

J. Corticosteroids

1. Not using intravenous hydrocortisone to treat adult septic shock patients if adequate fluid resuscitation and vasopressor therapy are able to restore hemodynamic stability (see goals for Initial Resuscitation). In case this is not achievable, we suggest intravenous hydrocortisone alone at a dose of 200 mg per day (grade 2C).
2. Not using the ACTH stimulation test to identify adults with septic shock who should receive hydrocortisone (grade 2B).
3. In treated patients hydrocortisone tapered when vasopressors are no longer required (grade 2D).
4. Corticosteroids not be administered for the treatment of sepsis in the absence of shock (grade 1D).
5. When hydrocortisone is given, use continuous flow (grade 2D).

Dellinger RP, et al. Crit Care. 2013

Evidence Based Guidelines – Renal Failure



Kellum JA, et al. Kidney Int Suppl. 2012

Evidence Based Guidelines – Renal Failure

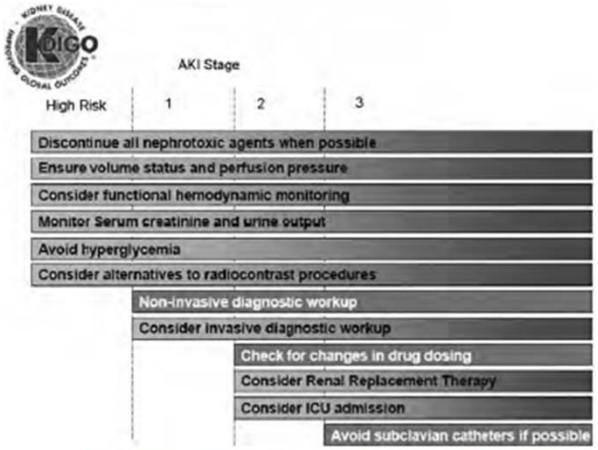


Figure 4 | Stage-based management of AKI. Shading of boxes indicates priority of action—solid shading indicates actions that are equally appropriate at all stages whereas graded shading indicates increasing priority as intensity increases. AKI, acute kidney injury; ICU, intensive-care unit.

5.4.1: We suggest initiating RRT in patients with AKI via an uncuffed nontunneled dialysis catheter, rather than a tunneled catheter. (*2D*)

5.4.2: When choosing a vein for insertion of a dialysis catheter in patients with AKI, consider these preferences (*Not Graded*):
- First choice: right jugular vein;
- Second choice: femoral vein;
- Third choice: left jugular vein;
- Last choice: subclavian vein with preference for the dominant side.

5.4.3: We recommend using ultrasound guidance for dialysis catheter insertion. (*1A*)

5.4.4: We recommend obtaining a chest radiograph promptly after placement and before first use of an internal jugular or subclavian dialysis catheter. (*1B*)

5.4.5: We suggest not using topical antibiotics over the skin insertion site of a nontunneled dialysis catheter in ICU patients with AKI requiring RRT. (*2C*)

5.4.6: We suggest not using antibiotic locks for prevention of catheter-related infections of nontunneled dialysis catheters in AKI requiring RRT. (*2C*)

5.5.1: We suggest to use dialyzers with a biocompatible membrane for IHD and CRRT in patients with AKI. (*2C*)

5.6.1: Use continuous and intermittent RRT as complementary therapies in AKI patients. (*Not Graded*)

5.6.2: We suggest using CRRT, rather than standard intermittent RRT, for hemodynamically unstable patients. (*2B*)

5.6.3: We suggest using CRRT, rather than intermittent RRT, for AKI patients with acute brain injury or other causes of increased intracranial pressure or generalized brain edema. (*2B*)

5.7.1: We suggest using bicarbonate, rather than lactate, as a buffer in dialysate and replacement fluid for RRT in patients with AKI. (*2C*)

5.7.2: We recommend using bicarbonate, rather than lactate, as a buffer in dialysate and replacement fluid for RRT in patients with AKI and circulatory shock. (*1B*)

5.7.3: We suggest using bicarbonate, rather than lactate, as a buffer in dialysate and replacement fluid for RRT in patients with AKI and liver failure and/or lactic acidemia. (*2B*)

5.7.4: We recommend that dialysis fluids and replacement fluids in patients with AKI, at a minimum, comply with American Association of Medical Instrumentation (AAMI) standards regarding contamination with bacteria and endotoxins. (*1B*)

5.8.1: The dose of RRT to be delivered should be prescribed before starting each session of RRT. (*Not Graded*) We recommend frequent assessment of the actual delivered dose in order to adjust the prescription. (*1B*)

5.8.2: Provide RRT to achieve the goals of electrolyte, acid-base, solute, and fluid balance that will meet the patient's needs. (*Not Graded*)

5.8.3: We recommend delivering a Kt/V of 3.9 per week when using intermittent or extended RRT in AKI. (*1A*)

5.8.4: We recommend delivering an effluent volume of 20–25 ml/kg/h for CRRT in AKI (*1A*). This will usually require a higher prescription of effluent volume. (*Not Graded*)

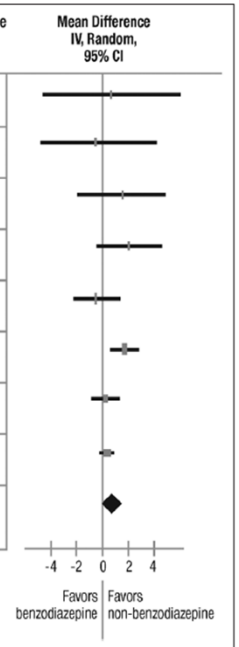
Kellum JA, et al. Kidney Int Suppl. 2012

Evidence Based Guidelines – Pain Agitation Delerium

Clinical Practice Guidelines for the Management of Pain, Agitation, and Delirium in Adult Patients in the Intensive Care Unit

Juliana Barr, MD, FCCM[1]; Gilles L. Fraser, PharmD, FCCM[2]; Kathleen Puntillo, RN, PhD, FAAN, FCCM[3]; E. Wesley Ely, MD, MPH, FACP, FCCM[4]; Céline Gélinas, RN, PhD[5]; Joseph F. Dasta, MSc, FCCM, FCCP[6]; Judy E. Davidson, DNP, RN[7]; John W. Devlin, PharmD, FCCM, FCCP[8]; John P. Kress, MD[9]; Aaron M. Joffe, DO[10]; Douglas B. Coursin, MD[11]; Daniel L. Herr, MD, MS, FCCM[12]; Avery Tung, MD[13]; Bryce R. H. Robinson, MD, FACS[14]; Dorrie K. Fontaine, PhD, RN, FAAN[15]; Michael A. Ramsay, MD[16]; Richard R. Riker, MD, FCCM[17]; Curtis N. Sessler, MD, FCCP, FCCM[18]; Brenda Pun, MSN, RN, ACNP[19]; Yoanna Skrobik, MD, FRCP[20]; Roman Jaeschke, MD[21]

Study or Subgroup	Benzodiazepine Mean	Benzodiazepine SD	Benzodiazepine Total	non-benzodiazepine Mean	non-benzodiazepine SD	non-benzodiazepine Total	Weight	Mean Difference IV, Random, 95% CI
Hall 2001-72+, M/P, SD	9.14	3.99	10	8.46	4.83	4	1.0%	0.68 [-4.66, 6.02]
Hall 2001-24-72, M/P, SD	6.31	5.94	17	6.59	8.34	21	1.4%	-0.28 [-4.83, 4.27]
Pandharipande 2007, L/D, IQR	9	6.66	51	7.5	10.36	52	2.5%	1.50 [-1.86, 4.86]
Carson 2006, L/P, IQR	10.4	7.47	64	8.3	7.4	68	4.2%	2.10 [-0.44, 4.64]
Hall 2001-24, M/P, SD	2.48	1.99	26	2.95	3.9	21	7.8%	-0.47 [-2.31, 1.37]
Riker 2009, M/D, SD, median	7.6	5.35	122	5.9	5.18	244	17.5%	1.70 [0.55, 2.85]
Searle 1997, M/P, SD	3.9	1.7	20	3.7	1.7	21	20.5%	0.20 [-0.84, 1.24]
Huey-Ling 2008, M/P, SD	3.1	1.12	28	2.8	1.13	32	45.1%	0.30 [-0.27, 0.87]
Total (95% CI)			**338**			**463**	**100.0%**	**0.57 [0.03, 1.10]**



Heterogeneity: Tau² = 0.08; Chi² = 8.03, df = 7 ($p = 0.33$), I² = 13%
Test for overall effect Z = 2.08 ($p = 0.04$)

Figure 1. ICU length of stay meta-analysis of high and moderate-quality studies comparing benzodiazepine to nonbenzodiazepine sedation. CI = confidence interval; IQR = interquartile range. L/D = lorazepam vs. dexmedetomidine; L/P = lorazepam vs. propofol; M/P = midazolam vs. propofol; M/D = midazolam vs. dexmedetomidine; SD = standard deviation.

A

- Agitation in critically ill patients may result from inadequately treated pain, anxiety, delirium, and/or ventilator dysynchrony.
- Detection and treatment of pain, agitation, and delirium should be reassessed often in these patients.
- Patients should be awake and able to purposely follow commands in order to participate in their care unless a clinical indication for deeper sedation exists.
- For a comprehensive list of Guideline Statements, Recommendations and GRADES, see back of card.

Assess and Treat	Statements and Recommendations
PAIN	• Pain assessment should be routinely performed in all ICU patients (1B). • Self report is preferred over the use of behavioral pain scales to assess pain in ICU patients who are able to communicate (B). • The BPS and CPOT are the most valid and reliable behavioral pain scales for use in ICU patients who cannot communicate (B). • Vital signs should not be used alone to assess pain, but they may be used adjunctively for pain assessments (2C). • Preemptively treat chest tube removal with either analgesics and/or non-pharmacologic therapy (1C). • Suggest preemptively treating other types of procedural pain with analgesic and/or non-pharmacologic therapy (2C). • Use opioids as first line therapy for treatment of non-neuropathic pain (1C). • Suggest using non-opioid analgesics in conjunction with opioids to reduce opioid requirements and opioid-related side effects (2C). • Use gabapentin or carbamazepine, in addition to intravenous opioids, for treatment of neuropathic pain (1A). • Use thoracic epidural for postoperative analgesia in abdominal aortic surgery patients (1B). • Suggest thoracic epidural analgesia be used for patients with traumatic rib fractures (2B).
AGITATION	• Depth and quality of sedation should be routinely assessed in all ICU patients (1B). • The RASS and SAS are the most valid and reliable scales for assessing quality and depth of sedation in ICU patients (B). • Suggest using objective measures of brain function to adjunctively monitor sedation in patients receiving neuromuscular blocking agents (2B). • Use EEG monitoring either to monitor non-convulsive seizure activity in ICU patients at risk for seizures, or to titrate electrosuppressive medication to achieve burst suppression in ICU patients with elevated intracranial pressure (1A). • Target the lightest possible level of sedation and/or use daily sedative interruption (1B). • Use sedation protocols and checklists to facilitate ICU sedation management (1B). • Suggest using analgesia-first sedation for intubated and mechanically ventilated ICU patients (2B). • Suggest using non-benzodiazepines for sedation (either propofol or dexmedetomidine) rather than benzodiazepines (either midazolam or lorazepam) in mechanically ventilated adult ICU patients (2B).
DELIRIUM	• Delirium assessment should be routinely performed in all ICU patients (1B). • The CAM-ICU and ICDSC delirium monitoring tools are the most valid and reliable scales to assess delirium in ICU patients (A). • Mobilize ICU patients early when feasible to reduce the incidence and duration of delirium, and to improve functional outcomes (1B). • Promote sleep in ICU patients by controlling light and noise, clustering patient care activities, and decreasing stimuli at night (1C). • Avoid using rivastigmine to reduce the duration of delirium in ICU patients (1B). • Suggest avoiding the use of antipsychotics in patients who are at risk for torsades de pointes (2B). • Suggest not using benzodiazepines in ICU patients with delirium unrelated to ETOH/benzodiazepine withdrawal (2B).

Barr J, et al. Crit Care. 2013

Evidence Based Guidelines - HAI

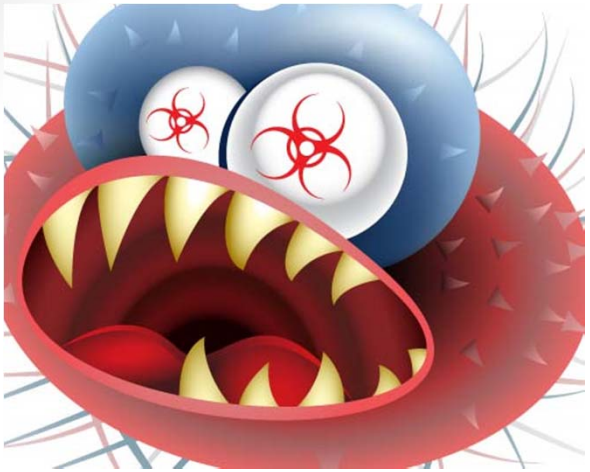
- The most recent estimate produced by the CDC from 2007
  - 1.7 million health care–associated infections per year

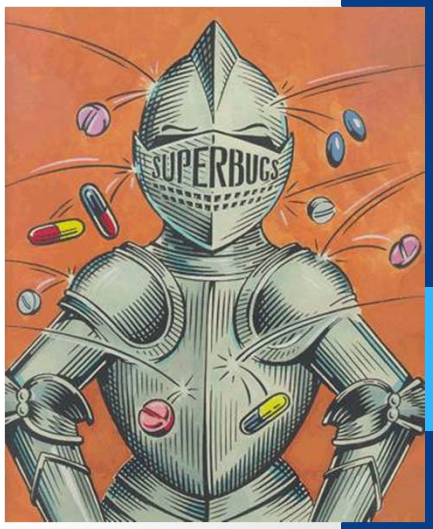
- The estimated deaths associated with HAIs in U.S. hospitals were 98,987
  - 35,967 were for pneumonia
  - 30,665 for bloodstream infections
  - 13,088 for urinary tract infections
  - 8,205 for surgical site infections
  - 11,062 for infections of other sites

- In the US, antibiotic-resistant infections are associated with 23,000 deaths and 2 million illnesses per year
- Estimated excess direct healthcare costs of $20 billion and $35 billion in lost productivity
- Resistant organisms can increase patient-related prescribing costs by $8000 to $30000

Klevens RM, et al. Public Health Rep. 2007
Brusselaers N, et al. Ann Intensive Care. 2011

The bugs are winning….





Evidence Based Guidelines - HAI

- In 2009, the US Department of Health and Human Services (HHS) released a national healthcare-associated infection (HAI) action plan focused on preventing:
  - central line–associated bloodstream infections (CLABSI)
  - catheter-associated urinary tract infections (CAUTI)
  - surgical site infections (SSI)
  - methicillin-resistant *Staphylococcus aureus* (MRSA) bloodstream infections
  - *Clostridium difficile* infection (CDI)

- In 2011, CMS began requiring acute care hospitals to report specific types of HAI data to CMS through the CDC's National Healthcare Safety Network (NHSN) in order to receive their full annual reimbursement updates

Evidence Based Guidelines - HAI

INFECTION CONTROL AND HOSPITAL EPIDEMIOLOGY AUGUST 2014, VOL. 35, NO. 8

SHEA/IDSA PRACTICE RECOMMENDATION: EXECUTIVE SUMMARY

A Compendium of Strategies to Prevent Healthcare-Associated Infections in Acute Care Hospitals: 2014 Updates

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Available online at www.sciencedirect.com

Journal of Hospital Infection

journal homepage: www.elsevierhealth.com/journals/jhin

epic3: National Evidence-Based Guidelines for Preventing Healthcare-Associated Infections in NHS Hospitals in England

H.P. Loveday[a]*, J.A. Wilson[a], R.J. Pratt[a], M. Golsorkhi[a], A. Tingle[a], A. Bak[a], J. Browne[a], J. Prieto[b], M. Wilcox[c]

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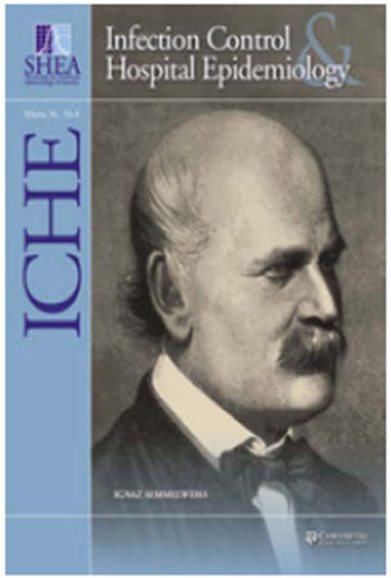


Yokoe DS, et al. Infect Control and Hosp Epidem. 2014
Loveday HP, et al. J Hosp Infect. 2014

Evidence Based Guidelines - SSI

TABLE 2. Selected Risk Factors for and Recommendations to Prevent Surgical Site Infections (SSIs)

Risk factor	Recommendation	Quality of evidence
Intrinsic, patient related (preoperative)		
Unmodifiable		
Age	No formal recommendation. Relationship to increased risk of SSI may be secondary to comorbidities or immunosenescence.[216-218]	NA
History of radiation	No formal recommendation. Prior irradiation at the surgical site increases the risk of SSI, likely due to tissue damage and wound ischemia.[219]	NA
History of SSTIs	No formal recommendation. History of a prior skin infection may be a marker for inherent differences in host immune function.[220]	NA
Modifiable		
Glucose control	Control serum blood glucose levels for all surgical patients, including patients without diabetes.[17] For patients with diabetes mellitus, reduce glycosylated hemoglobin A1c levels to less than 7% before surgery, if possible.[94]	I
Obesity	Increase dosing of prophylactic antimicrobial agent for morbidly obese patients.[76,221]	I
Smoking cessation	Encourage smoking cessation within 30 days of procedure.[17,222-226]	I
Immunosuppressive medications	Avoid immune-suppressive medications in perioperative period, if possible.	III
Hypoalbuminemia	No formal recommendation. Although a noted risk factor,[227] do not delay surgery for use of TPN.	NA
Extrinsic, procedure related (perioperative)		
Preparation of patient		
Hair removal	Do not remove unless hair will interfere with the operation.[17] If hair removal is necessary, remove outside the OR by clipping. Do not use razors.	II
Preoperative infections	Identify and treat infections (eg, urinary tract infection) remote to the surgical site prior to elective surgery.[17] Do not routinely treat colonization or contamination.	II
Operative characteristics		
Surgical scrub (surgical team members' hands and forearms)	Use appropriate antiseptic agent to perform preoperative surgical scrub.[17,228] For most products, scrub the hands and forearms for 2–5 minutes.	II
Skin preparation	Wash and clean skin around incision site. Use a dual agent skin preparation containing alcohol, unless contraindications exist.[17]	I
Antimicrobial prophylaxis	Administer only when indicated.[17]	I
Timing	Administer within 1 hour of incision to maximize tissue concentration[76,a]	I
Blood transfusion	Blood transfusions increase the risk of SSI by decreasing macrophage function. Reduce blood loss and need for blood transfusion to the greatest extent possible.[229-231]	II
Choice of prophylactic agent	Select appropriate agents on the basis of surgical procedure, most common pathogens causing SSIs for a specific procedure, and published recommendations.[76]	I
Duration of prophylaxis	Stop agent within 24 hours after the procedure for all procedures.[76]	II
Surgeon skill/technique	Handle tissue carefully and eradicate dead space.[17]	III
Appropriate gloving	All members of the operative team should double glove and change gloves when perforation is noted.[208]	III
Asepsis	Adhere to standard principles of OR asepsis.[17]	III
Operative time	No formal recommendation in most recent guidelines. Minimize as much as possible without sacrificing surgical technique and aseptic practice.	I
OR characteristics		
Ventilation	Follow American Institute of Architects' recommendations for proper air handling in the OR.[17,232]	III
Traffic	Minimize OR traffic.[17,135,136]	III
Environmental surfaces	Use an EPA-approved hospital disinfectant to clean visibly soiled or contaminated surfaces and equipment.[17]	III
Sterilization of surgical equipment	Sterilize all surgical equipment according to published guidelines.[233] Minimize the use of immediate-use steam sterilization.[17]	II

NOTE. EPA, Environmental Protection Agency; NA, not applicable; OR, operating room; SSTI, skin and soft-tissue infection; TPN, total parenteral nutrition.

[a] Vancomycin and fluoroquinolones can be given 2 hours prior to incision.

Anderson DJ, et al. Infect Control and Hosp Epidem. 2014

- CDC Warns of Growing Threat of Superbugs

- WASHINGTON — Sounding an alarm about the growing threat of superbugs, the Obama administration is proposing a jump in spending to fight antibiotic-resistant germs in hospitals.

- **…the CDC called for every hospital to establish a program to track and improve antibiotic prescribing.**
- **While antibiotics can be life-saving, overuse and misuse of the drugs also spur bacteria to develop resistance.**
- **Health officials said doctors in some hospitals prescribe antibiotics three times as often as others, for similar patients…**

— The Associated Press
March 4th 2014, 6:06 pm

Antibiotic Stewardship

- 30-50% of antibiotic use in hospitals is unnecessary or inappropriate.
- Antibiotic overuse contributes to the growing problems of *Clostridium difficile* infection and antibiotic resistance in healthcare facilities.
- Reducing unnecessary antibiotic use can decrease antibiotic resistance, *Clostridium difficile* infections, and healthcare costs, and improve patient outcomes.

http://www.cdc.gov/getsmart/healthcare/evidence.html

Antibiotic Stewardship

- A systematic review of outcomes related studies for ASPs in an ICU setting was conducted.
- 43 studies were identified between 1996 - 2014.

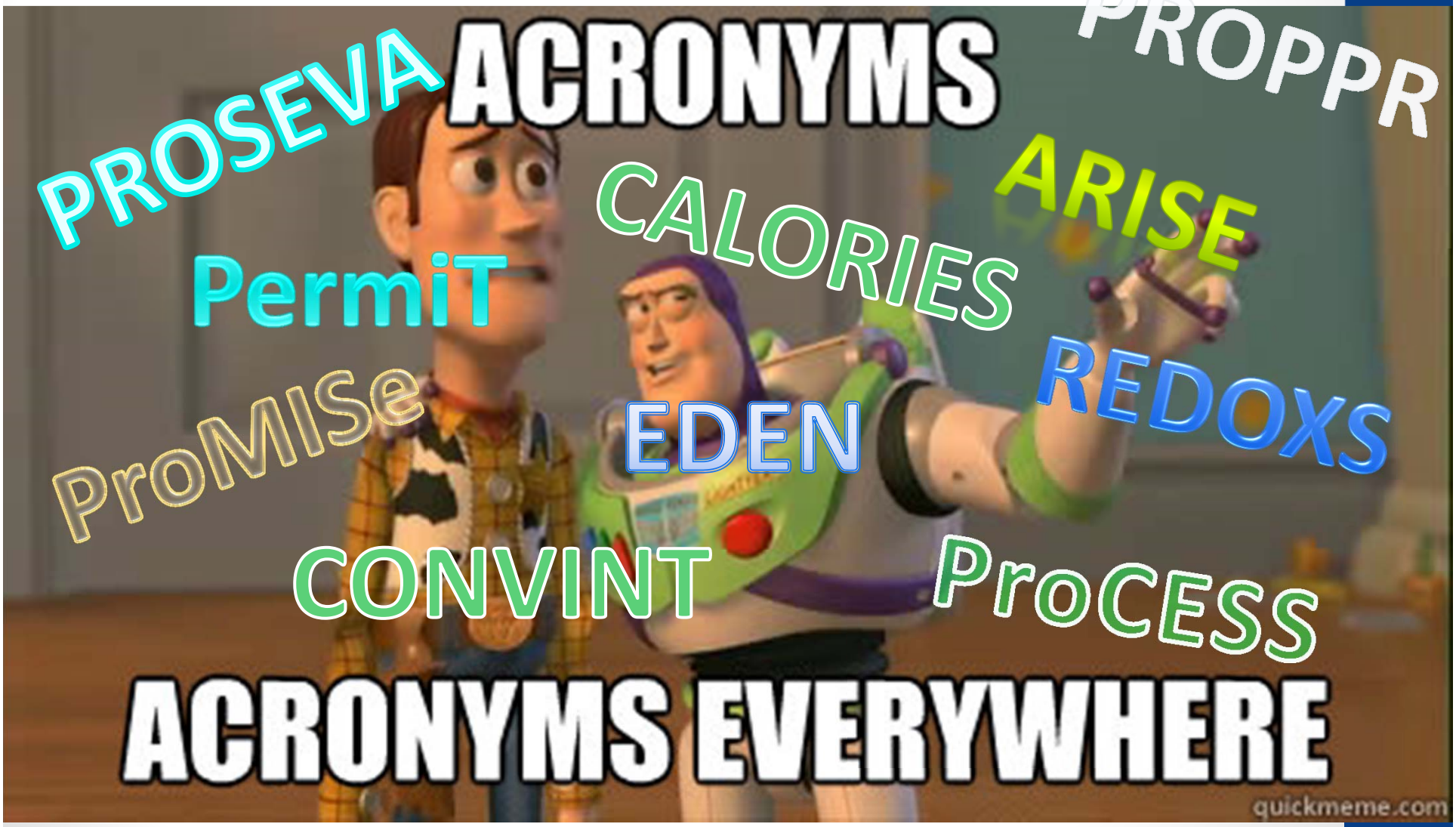
- Of 34 nonprotocolized studies, 29 (85%) were positive with respect to one or more outcome
  - reduced antibiotic use
  - ICU length of stay
  - antibiotic resistance
  - prescribing cost burden.
- Of 9 RCTs, 6 reported positive outcomes
  - reduced antibiotic use
  - ICU length of stay
  - antibiotic resistance

- No study has demonstrated survival benefit of ASP

Zhang YZ and Singh A. World J Crit Care Med. 2015

WHAT IF I TOLD YOU
TO WASH YOUR DAMN HANDS ONCE IN A WHILE?
...emegenerator.net

New Pivotal Clinical Trials



Clinical Trials –Blood Transfusion Ratios PROPPR

Research

Original Investigation

Transfusion of Plasma, Platelets, and Red Blood Cells in a 1:1:1 vs a 1:1:2 Ratio and Mortality in Patients With Severe Trauma
The PROPPR Randomized Clinical Trial

John B. Holcomb, MD; Barbara C. Tilley, PhD; Sarah Baraniuk, PhD; Erin E. Fox, PhD; Charles E. Wade, PhD; Jeanette M. Podbielski, RN; Deborah J. del Junco, PhD; Karen J. Brasel, MD, MPH; Eileen M. Bulger, MD; Rachael A. Callcut, MD, MSPH; Mitchell Jay Cohen, MD; Bryan A. Cotton, MD, MPH; Timothy C. Fabian, MD; Kenji Inaba, MD; Jeffrey D. Kerby, MD, PhD; Peter Muskat, MD; Terence O'Keeffe, MBChB, MSPH; Sandro Rizoli, MD, PhD; Bryce R. H. Robinson, MD; Thomas M. Scalea, MD; Martin A. Schreiber, MS; Deborah M. Stein, MD; Jordan A. Weinberg, MD; Jeannie L. Callum, MD; John R. Hess, MD, MPH; Nena Matijevic, PhD; Christopher N. Miller, MD; Jean-Francois Pittet, MD; David B. Hoyt, MD; Gail D. Pearson, MD, ScD; Brian Leroux, PhD; Gerald van Belle, PhD; for the PROPPR Study Group

- Pragmatic, phase 3, multisite, randomized clinical trial of 680 severely injured patients in 12 level I trauma centers in North America
- Directly from the scene and were predicted to require massive transfusion between 8/2012 and 12/2013.
- Blood product ratios of 1:1:1 (338 patients) vs 1:1:2 (342 patients) during active resuscitation in addition to all local standard-of-care interventions (uncontrolled).

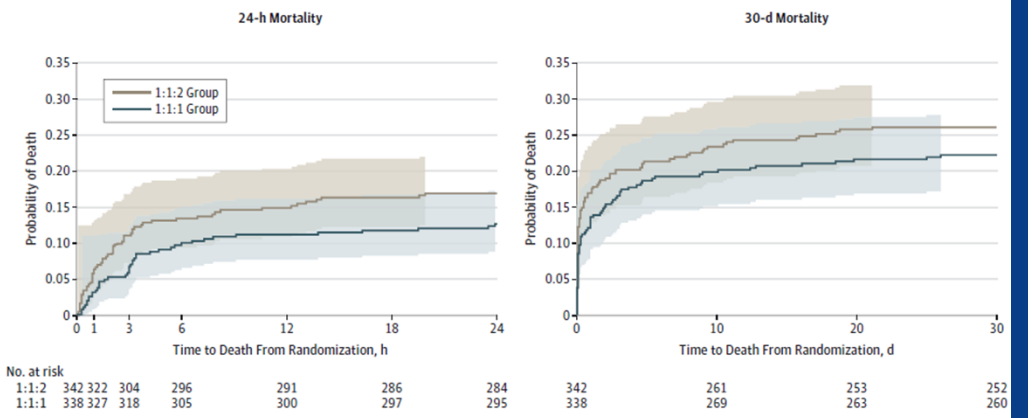
- Primary outcomes were 24-hour and 30-day all-cause mortality.
- Prespecified ancillary outcomes included
  - time to hemostasis
  - blood product volumes transfused
  - complications
  - incidence of surgical procedures
  - functional status.

Holcomb JB, et al. JAMA. 2015

Clinical Trials –Blood Transfusion Ratios PROPPR

- No significant differences were detected in mortality at 24 hours or at 30 days
- Exsanguination, which was the predominant cause of death within the first 24 hours, was significantly decreased in the 1:1:1 group
- More patients in the 1:1:1 group achieved hemostasis than in the 1:1:2 group (86% vs 78%, respectively; *P* = .006).
- Despite the 1:1:1 group receiving more plasma and platelets and similar amounts of red blood cells over the first 24 hours, no differences between the 2 groups were found for the 23 prespecified complications
  - ARDS
  - MOF
  - VTE
  - Sepsis
  - Transfusion related complications

Figure 2. Kaplan-Meier Failure Curves for Mortality at 24 Hours and 30 Days



The colored areas indicate 95% confidence bands, which were calculated using the Hall-Wellner method. The Hall-Wellner bands extend to the last event (death) in each group. For 24-hour mortality, the Cox proportional hazards regression model, adjusted for site as a random effect, produced a hazard ratio (HR) of 0.72 (95% CI, 0.49-1.07). There were no patients lost to follow-up during the first 24 hours from randomization. For 30-day mortality, the Cox proportional hazards regression model, adjusted for site as a random effect, produced an HR of 0.83 (95% CI, 0.61-1.12). Between 24 hours and 30 days, 4 patients were lost to follow-up and were censored when they withdrew consent or were last known to be alive (3 in the 1:1:1 group and 1 in the 1:1:2 group).

Table 3. Adjudicated Cause of Death by Treatment Group and Period From Randomization

	First 24 Hours			30 Days		
	No. (%)			No. (%)		
	1:1:1 Group (n = 338)	1:1:2 Group (n = 342)	Difference (95% CI),%[a]	1:1:1 Group (n = 335)	1:1:2 Group (n = 341)	Difference (95% CI), %[a]
Total No. of deaths	43	58		75	89	
Cause of death[b]						
Exsanguination	31 (9.2)	50 (14.6)	−5.4 (−10.4 to −0.5)	36 (10.7)	50 (14.7)	−3.9 (−9.1 to 1.2)
Traumatic brain injury	11 (3.3)	12 (3.5)	−0.3 (−3.2 to 2.7)	27 (8.1)	35 (10.3)	−2.2 (−6.7 to 2.2)
Respiratory, pulmonary contusion, or tension pneumothorax	3 (0.9)	1 (0.3)	0.6 (−0.9 to 2.4)	5 (1.5)	2 (0.6)	0.9 (−0.8 to 3.0)
Sepsis	0	0	0 (−1.1 to 1.1)	1 (0.3)	2 (0.6)	−0.3 (−1.9 to 1.2)
Multiple organ failure	0	0	0 (−1.1 to 1.1)	10 (3.0)	8 (2.3)	0.6 (−2.0 to 3.4)
Type of cardiovascular event						
Stroke	0	1 (0.3)	−0.3 (−1.7 to 0.9)	2 (0.6)	1 (0.3)	0.3 (−1.1 to 1.9)
Myocardial infarction	1 (0.3)	1 (0.3)	0 (−1.4 to 1.4)	1 (0.3)	2 (0.6)	−0.3 (−1.9 to 1.2)
Pulmonary embolism	0	1 (0.3)	−0.3 (−1.7 to 0.9)	0	1 (0.3)	−0.3 (−1.7 to 0.9)
Transfusion-related fatality	0	0	0 (−1.1 to 1.1)	1 (0.3)	0	0.3 (−0.8 to 1.7)

[a] Calculated using exact unconditional methods based on the Farrington-Manning score statistic.

[b] A patient may have had more than 1 cause of death.

Holcomb JB, et al. JAMA. 2015

Clinical Trials – Antibiotic Duration

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Trial of Short-Course Antimicrobial Therapy for Intraabdominal Infection

R.G. Sawyer, J.A. Claridge, A.B. Nathens, O.D. Rotstein, T.M. Duane, H.L. Evans, C.H. Cook, P.J. O'Neill, J.E. Mazuski, R. Askari, M.A. Wilson, L.M. Napolitano, N. Namias, P.R. Miller, E.P. Dellinger, C.M. Watson, R. Coimbra, D.L. Dent, S.F. Lowry,* C.S. Cocanour, M.A. West, K.L. Banton, W.G. Cheadle, P.A. Lipsett, C.A. Guidry, and K. Popovsky

- We randomly assigned 518 patients with complicated intraabdominal infection and adequate source control to receive
  - Control Group - antibiotics until 2 days after the resolution of fever, leukocytosis, and ileus, with a maximum of 10 days of therapy
  - Experimental Group - fixed course of antibiotics for 4±1 calendar days.

- The primary outcome was a composite of the following after the index source-control procedure
  - surgical-site infection
  - recurrent intraabdominal infection
  - death within 30 days
- Secondary outcomes included the duration of therapy and rates of subsequent infections.

Sawyer RG, et al. NEJM. 2015

Clinical Trials – Antibiotic Duration

- In patients with intraabdominal infections who had undergone an adequate source control procedure, the outcomes after fixed-duration antibiotic therapy (approximately 4 days) were similar to those after a longer course of antibiotics (approximately 8 days) that extended until after the resolution of physiological abnormalities.

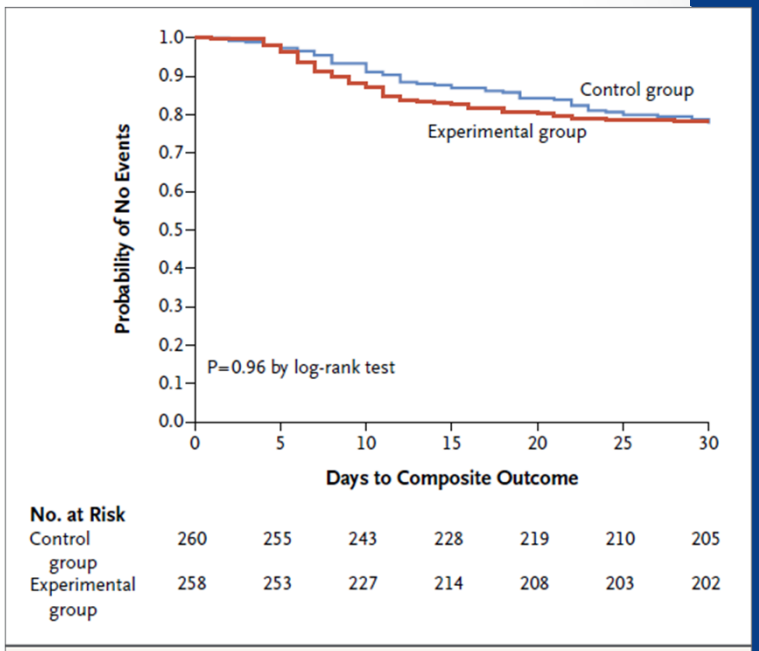


Figure 2. Kaplan–Meier Time-to-Event Curves for the Composite Primary Outcome, According to Treatment Group.
The composite primary outcome was surgical-site infection, recurrent intraabdominal infection, or death.

Sawyer RG, et al. NEJM. 2015

Clinical Trials – EGDT

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*

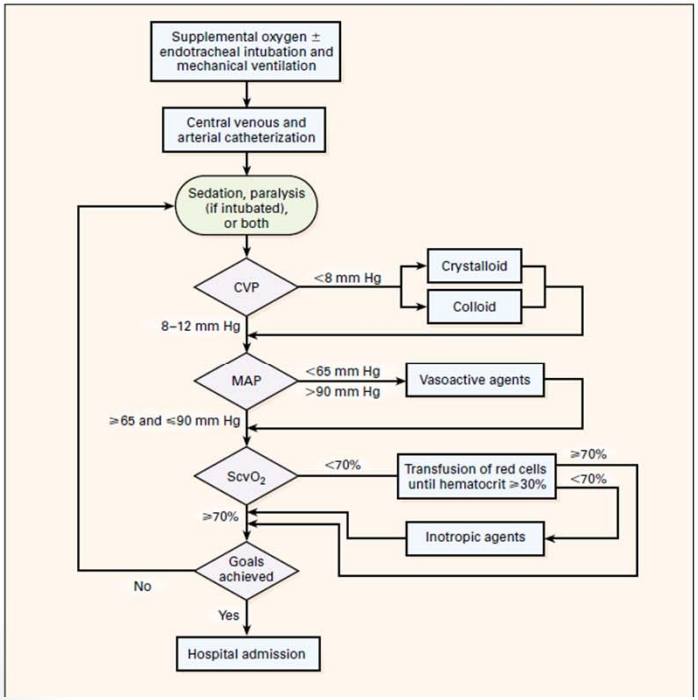


TABLE 3. KAPLAN–MEIER ESTIMATES OF MORTALITY AND CAUSES OF IN-HOSPITAL DEATH.*

VARIABLE	STANDARD THERAPY (N=133)	EARLY GOAL-DIRECTED THERAPY (N=130)	RELATIVE RISK (95% CI)	P VALUE
	no. (%)			
In-hospital mortality†				
All patients	59 (46.5)	38 (30.5)	0.58 (0.38–0.87)	0.009
Patients with severe sepsis	19 (30.0)	9 (14.9)	0.46 (0.21–1.03)	0.06
Patients with septic shock	40 (56.8)	29 (42.3)	0.60 (0.36–0.98)	0.04
Patients with sepsis syndrome	44 (45.4)	35 (35.1)	0.66 (0.42–1.04)	0.07
28-Day mortality†	61 (49.2)	40 (33.3)	0.58 (0.39–0.87)	0.01
60-Day mortality†	70 (56.9)	50 (44.3)	0.67 (0.46–0.96)	0.03
Causes of in-hospital death‡				
Sudden cardiovascular collapse	25/119 (21.0)	12/117 (10.3)	—	0.02
Multiorgan failure	26/119 (21.8)	19/117 (16.2)	—	0.27

*CI denotes confidence interval. Dashes indicate that the relative risk is not applicable.

†Percentages were calculated by the Kaplan–Meier product-limit method.

‡The denominators indicate the numbers of patients in each group who completed the initial six-hour study period.

Rivers E, et al. N Engl J Med 2001

ProCESS

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 MAY 1, 2014 VOL. 370 NO. 18

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

- ***Protocolized Care for Early Septic Shock*** The ProCESS Investigators*

- 31 EDs in the US
- Randomly assigned patients with septic shock to one of three groups for 6 hours of resuscitation:
  - protocol-based EGDT
  - protocol-based standard therapy that did not require the placement of a central venous catheter, administration of inotropes, or blood transfusions
  - usual care
- The primary end point was 60-day in-hospital mortality.

- Enrolled 1341 patients
  - 439 were randomly assigned to protocol-based EGDT
  - 446 to protocol-based standard therapy
  - 456 to usual care

Yealy DM, et al. NEJM. 2014

ProCESS

Figure S1. – Protocol for early goal-directed therapy (EGDT).

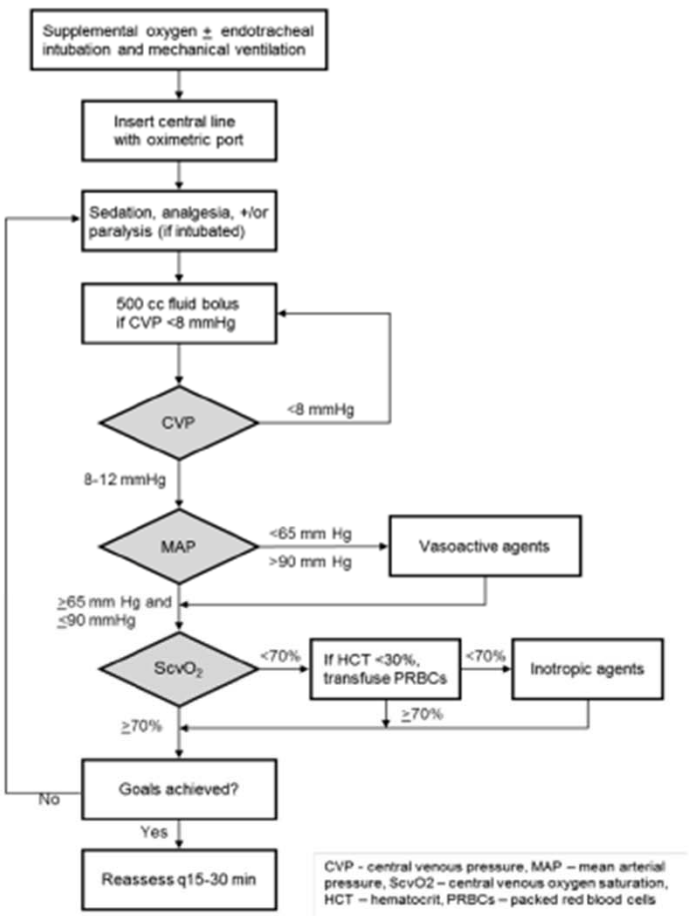
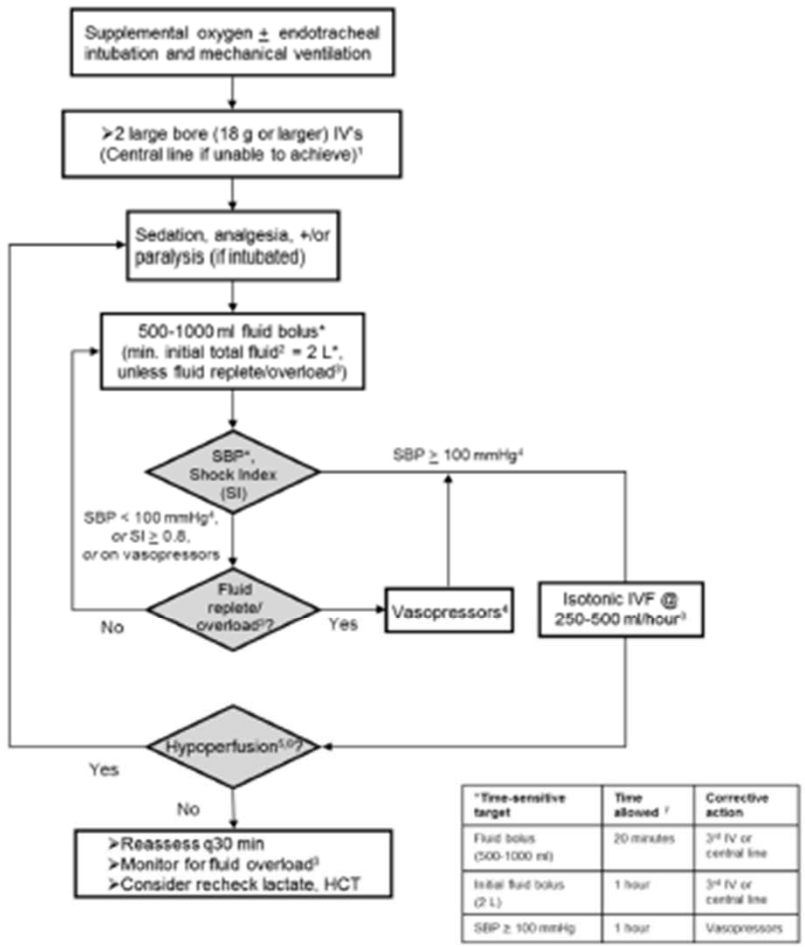


Figure S2. – Protocol for Standard Therapy.

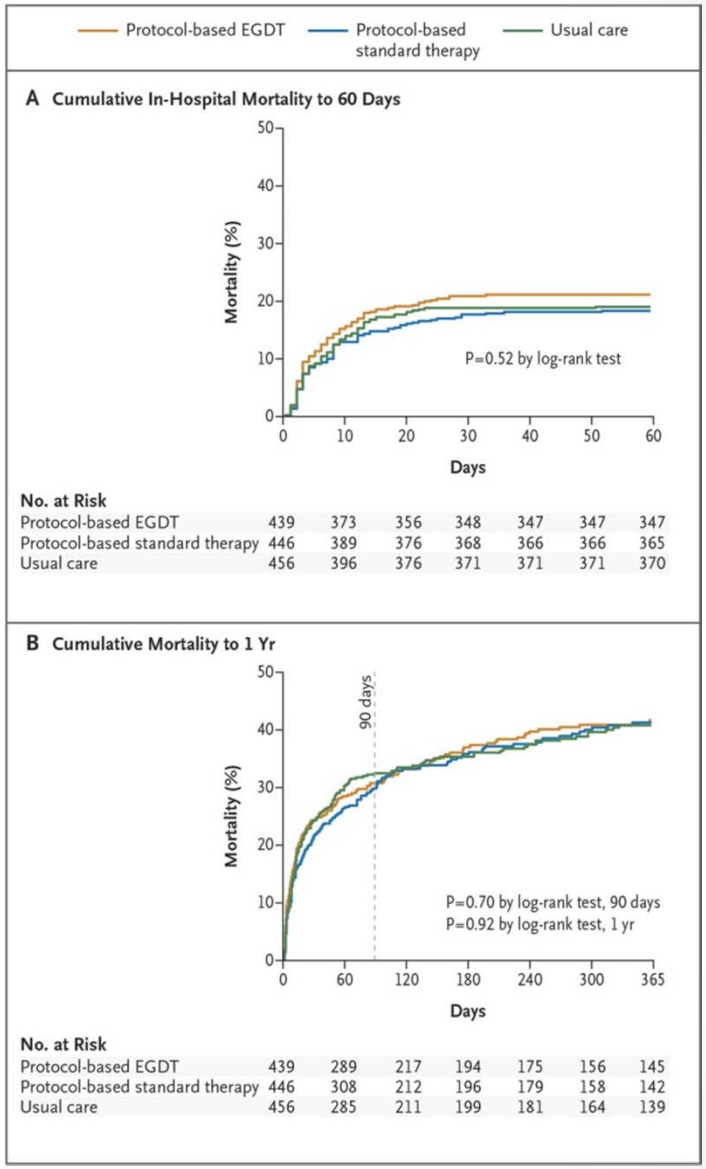


*Time-sensitive target	Time allowed [7]	Corrective action
Fluid bolus (500-1000 ml)	20 minutes	3rd IV or central line
Initial fluid bolus (2 L)	1 hour	3rd IV or central line
SBP ≥ 100 mmHg	1 hour	Vasopressors

Yealy DM, et al. NEJM. 2014

ProCESS

- There were no significant differences in 90-day mortality, 1-year mortality, or the need for organ support



Yealy DM, et al. NEJM. 2014

ARISE

ORIGINAL ARTICLE

Goal-Directed Resuscitation for Patients with Early Septic Shock

The ARISE Investigators and the ANZICS Clinical Trials Group*

- ***Australasian Resuscitation in Sepsis Evaluation***

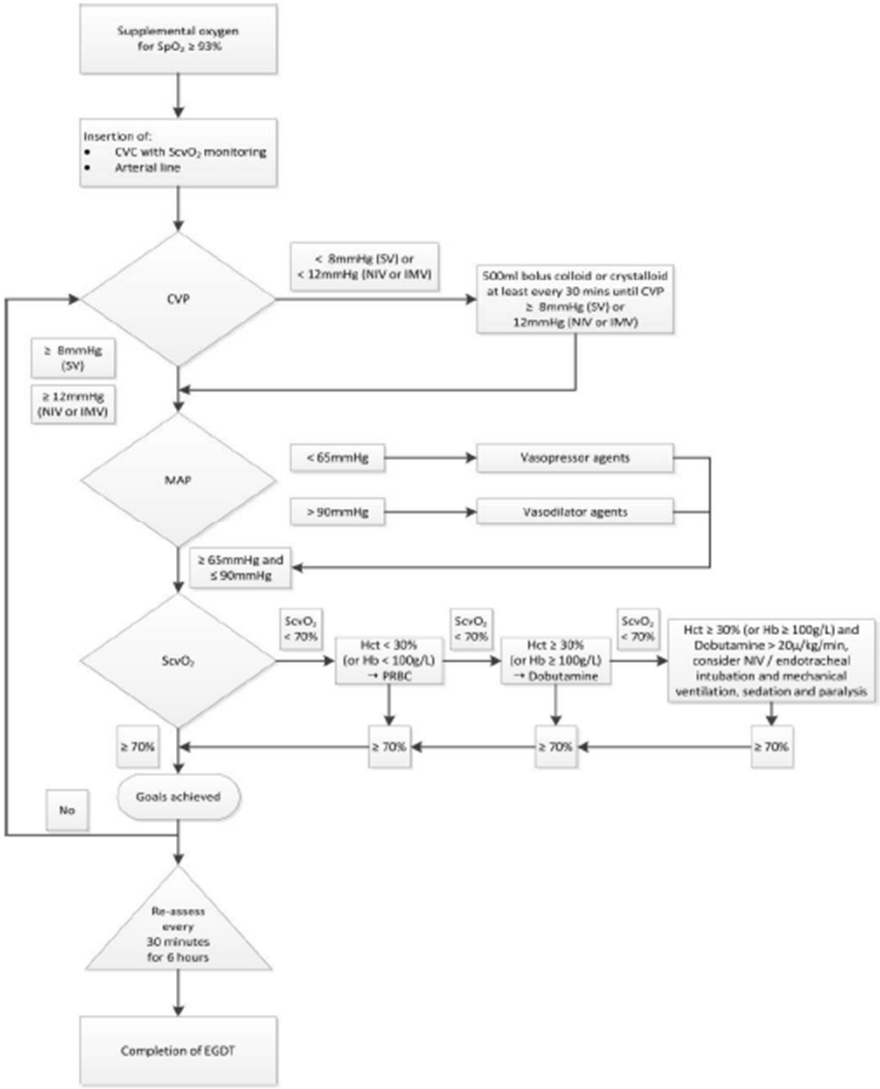
- 51 centers (mostly in Australia or New Zealand)
- Randomly assigned patients presenting to the emergency department with early septic shock to receive either EGDT or usual care.
- The primary outcome was all-cause mortality within 90 days after randomization.

- Of the 1600 enrolled patients
  - 796 were assigned to the EGDT group
  - 804 to the usual-care group

Peake SL, et al. NEJM. 2014

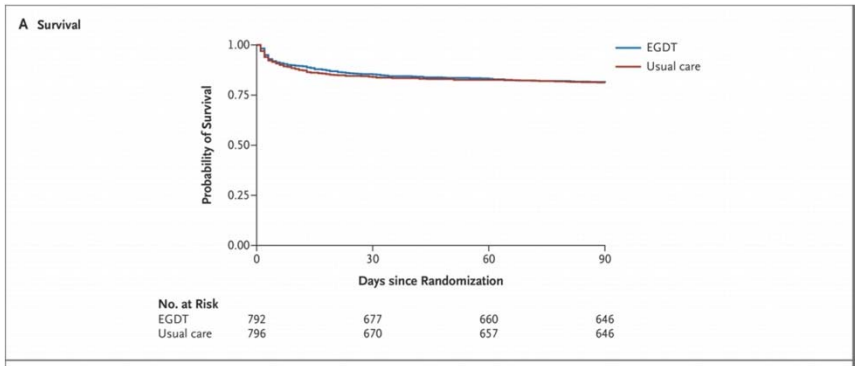
ARISE

Figure S1. Early goal-directed therapy resuscitation algorithm



Peake SL, et al. NEJM. 2014

ARISE



B Subgroup Analyses

Subgroup	EGDT	Usual Care	Odds Ratio (95% CI)	P Value	P Value for Interaction
	no. of events/total no. (%)				
Overall	147/792 (18.6)	150/796 (18.8)			
Country					0.38
Australia	126/677 (18.6)	132/679 (19.4)	0.95 (0.72–1.24)	0.70	
New Zealand	13/67 (19.4)	8/69 (11.6)	1.84 (0.71–4.76)	0.21	
Other	8/48 (16.7)	10/48 (20.8)	0.76 (0.27–2.13)	0.60	
Age					0.15
<65 yr	61/393 (15.5)	50/387 (12.9)	1.24 (0.83–1.85)	0.30	
≥65 yr	86/399 (21.6)	100/409 (24.4)	0.85 (0.61–1.18)	0.33	
APACHE II					0.98
<25	114/720 (15.8)	114/718 (15.9)	1.00 (0.75–1.32)	0.98	
≥25	33/72 (45.8)	36/78 (46.2)	0.99 (0.52–1.88)	0.97	
Invasive mechanical ventilation					0.25
Yes	19/71 (26.8)	23/64 (35.9)	0.65 (0.31–1.36)	0.25	
No	128/721 (17.8)	127/732 (17.3)	1.03 (0.78–1.35)	0.84	
Refractory hypotension					0.50
Yes	90/554 (16.2)	97/557 (17.4)	0.92 (0.67–1.26)	0.60	
No	57/238 (23.9)	53/239 (22.2)	1.11 (0.72–1.69)	0.65	
Hypofusion					0.27
Yes	99/365 (27.1)	93/369 (25.2)	1.10 (0.79–1.54)	0.55	
No	48/427 (11.2)	57/427 (13.3)	0.82 (0.55–1.24)	0.35	
IV fluid volume before randomization					0.41
≥20 ml/kg	106/574 (18.5)	104/572 (18.2)	1.02 (0.76–1.37)	0.90	
<20 ml/kg	28/181 (15.5)	35/181 (19.3)	0.76 (0.44–1.32)	0.33	

0.01 0.1 1.0 10 100

EGDT Better — Usual Care Better

- There was no significant difference in survival time, in-hospital mortality, duration of organ support, or length of hospital stay

Peake SL, et al. NEJM. 2014

ProMISe

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Trial of Early, Goal-Directed Resuscitation for Septic Shock

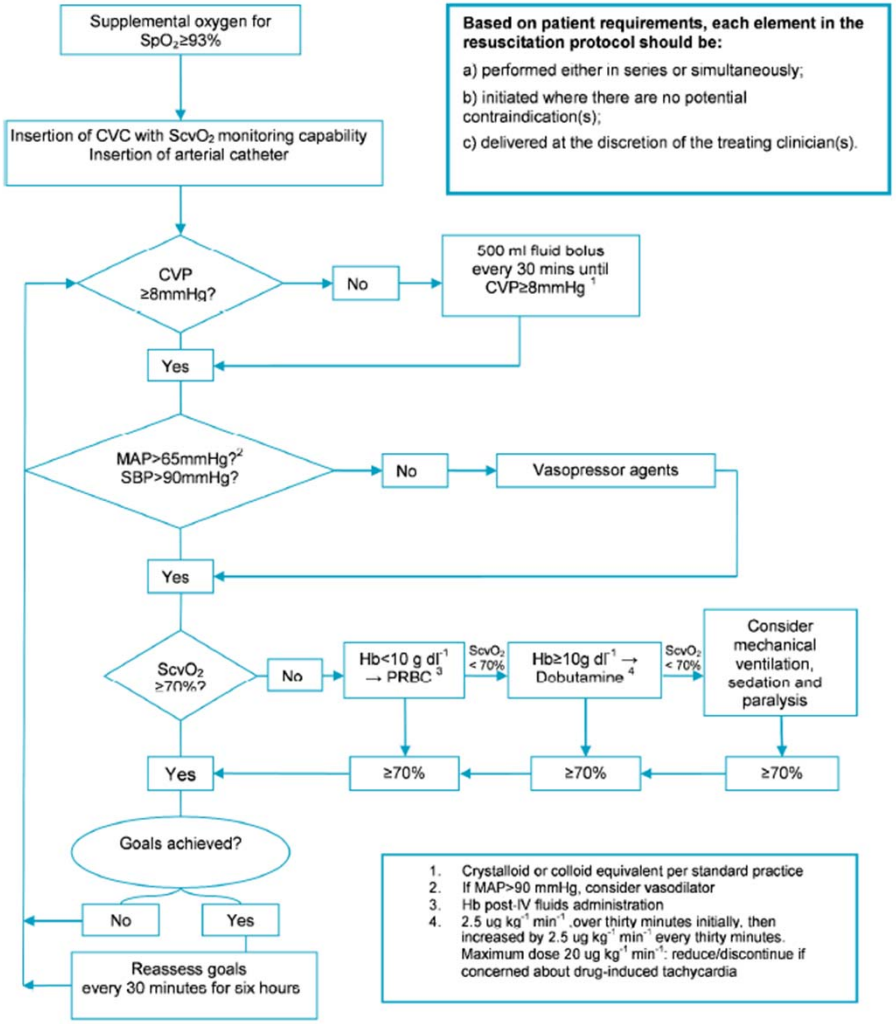
Paul R. Mouncey, M.Sc., Tiffany M. Osborn, M.D., G. Sarah Power, M.Sc., David A. Harrison, Ph.D., M. Zia Sadique, Ph.D., Richard D. Grieve, Ph.D., Rahi Jahan, B.A., Sheila E. Harvey, Ph.D., Derek Bell, M.D., Julian F. Bion, M.D., Timothy J. Coats, M.D., Mervyn Singer, M.D., J. Duncan Young, D.M., and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

- ***Protocolized Management in Sepsis***
- Conducted a pragmatic randomized trial with an integrated cost-effectiveness analysis in 56 hospitals in England
- Patients were randomly assigned to receive either
  - EGDT (a 6-hour resuscitation protocol)
  - usual care.
- The primary clinical outcome was all-cause mortality at 90 days.
- Enrolled 1260 patients
  - 630 assigned to EGDT
  - 630 to usual care

Mouncey PR, et al. NEJM. 2015

ProMISe

Figure S1. Early, Goal-Directed Therapy Resuscitation Protocol.



Adaptation from original EGDT algorithm[25] as follows: arterial catheter recommended, not mandated; option to use SBP as a blood pressure goal, rather than solely MAP; minimum goals set for CVP and MAP, rather than a range.

Mouncey PR, et al. NEJM. 2015

ProMISe

- In patients with septic shock who were identified early and received intravenous antibiotics and adequate fluid resuscitation, hemodynamic management according to a strict EGDT protocol did not lead to an improvement in outcome.
- Increased treatment intensity in the EGDT group was indicated by
  - increased use of intravenous fluids, vasoactive drugs, and red-cell transfusions
  - significantly worse organ-failure scores, more days receiving advanced cardiovascular support, and longer stays in the intensive care unit
- There were no significant differences in any other secondary outcomes, including health-related quality of life, or in rates of serious adverse events.
- On average, EGDT increased costs, and the probability that it was cost-effective was below 20%.

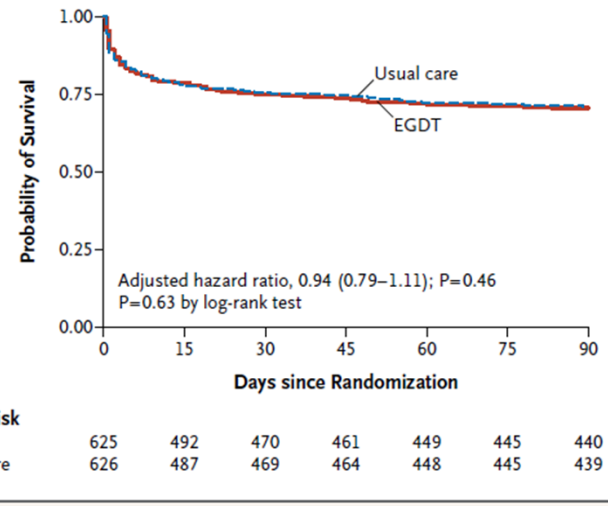
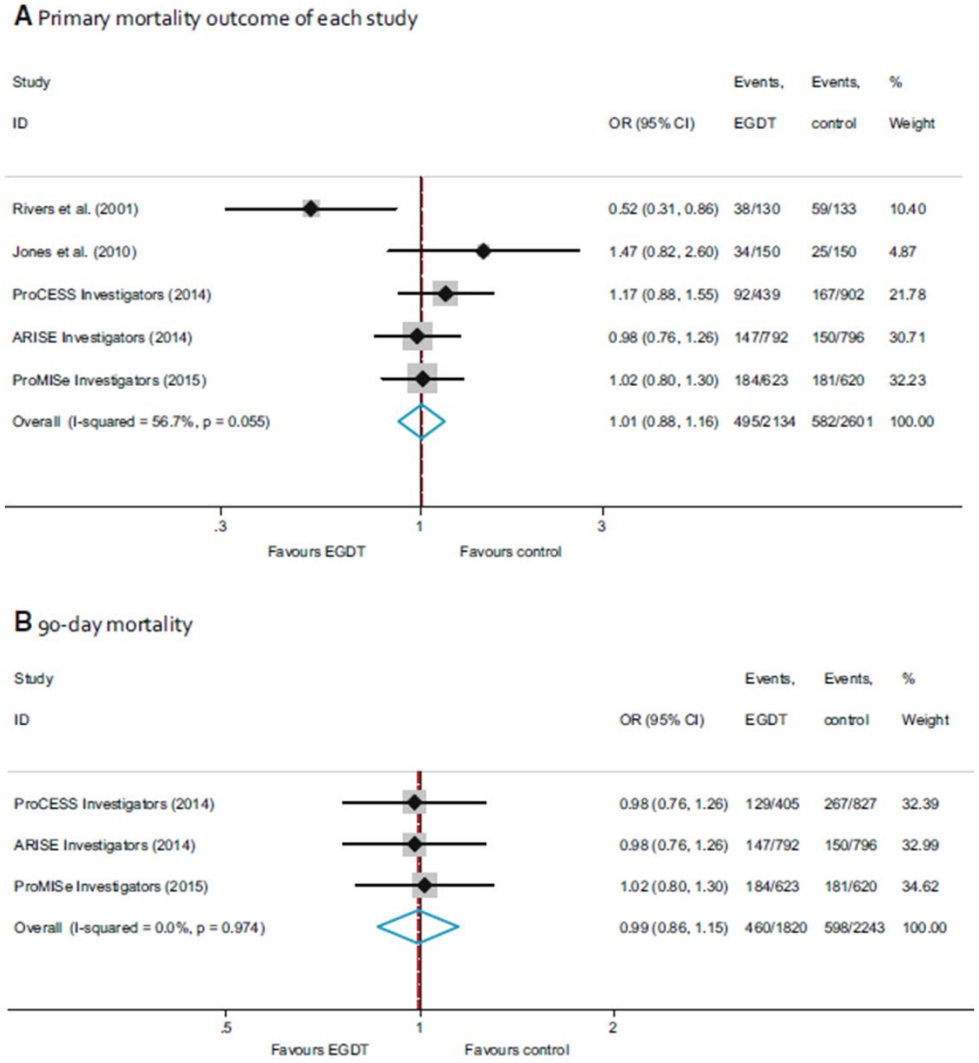


Figure 2. Kaplan–Meier Survival Estimates.
Shown is the probability of survival for patients with severe sepsis receiving early, goal-directed therapy (EGDT) and those receiving usual care at 90 days.

Mouncey PR, et al. NEJM. 2015

Hmmmm….

EGDT



Angus DC, et al. Intensive Care Med. 2015

EGDT

Table 2 Patient characteristics and primary mortality outcome of the included studies

Author	No. of patients		APACHE II score		Hypotension (%)		Lactate (mmol/L)		Primary mortality (%)	
	EGDT	Control	EGDT	Control	EGDT	Control	EGDT	Control	EGDT	Control
Primary objective										
Rivers et al. [1]	130	133	21.4 ± 6.9	20.4 ± 7.4	54.6	51.1	7.7 ± 4.7	6.9 ± 4.5	29.2[f]	44.4[f]
Jones et al. [19]	150	150	NA[b]	NA[b]	82.0	80.1	4.2 ± 3.1	3.9 ± 3.1	22.7	16.7
ProCESS Investigators [8][a]	439	902	20.8 ± 8.1	20.7 ± 7.4	55.6	53.5	4.8 ± 3.1	4.9 ± 3.4	21.0	18.5
ARISE Investigators [10]	796	804	15.4 ± 6.5	15.8 ± 6.5	70.0	69.8	4.4 ± 3.3	4.2 ± 2.8	18.6	18.8
ProMISe Investigators [12]	630	630	18.7 ± 7.1	18.0 ± 7.1	54.1	55.6	5.2 ± 3.5	5.1 ± 3.5	29.5	29.2
Secondary objective										
Wang et al. [21]	16	17	28 ± 7	27 ± 6	100	100	NA	NA	25.0	41.2
De Oliviera et al. [20]	51	51	NA[c]	NA[c]	94.1	92.2	1.1 (0.7–2.5)[e]	1.2 (0.8–2.3)[e]	11.8	39.2
EGDT Collaborative [22]	163	151	23.5 ± 5.7	21.8 ± 6.5	NA	NA	NA	NA	25.2	42.4
Tian et al. [23]	19	43	20.9 ± 8.6	17.6 ± 5.7[d]	100	100	NA	NA	63.2	36.4[d]
Yu et al. [24]	23	25	17.9 ± 3.8	18.2 ± 6.0	100	100	NA	3.4 ± 1.3	28.0	20.0
Lu et al. [25]	40	42	27.6 ± 8.9	28.9 ± 10.1	100	100	7.3 ± 3.1	7.5 ± 3.8	17.5	16.7

Angus DC, et al. Intensive Care Med. 2015

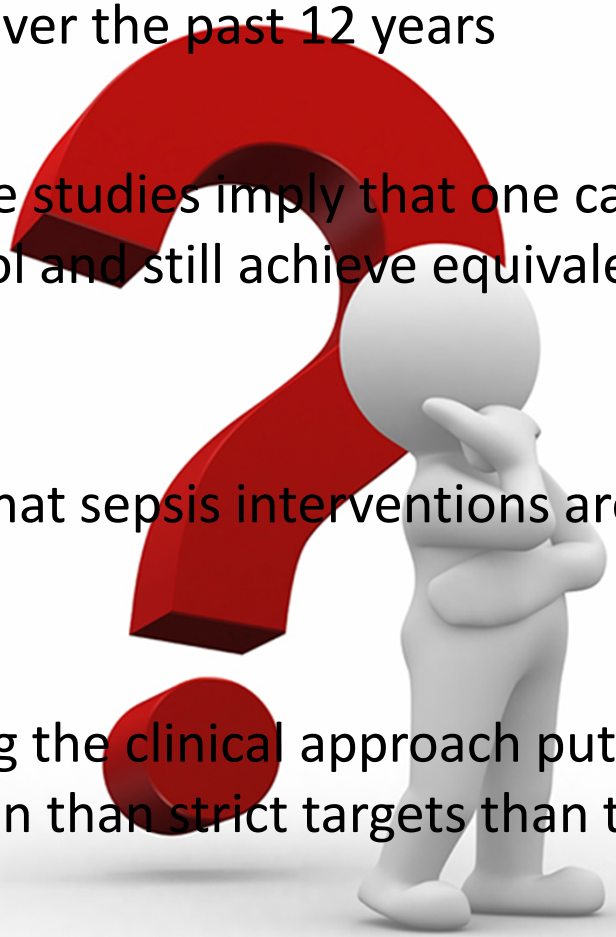
EGDT

Author	Fluids (ml)		Vasopressor (%)		Dobutamine (%)		Blood transfusion (%)		Time to first antimicrobial (min), median (IQR)	
	EGDT	Control	EGDT	Control	EGDT	Control	EGDT	Control	EGDT	Control
Primary objective										
Rivers et al. [1]	4981 ± 2984	3499 ± 2438	27.4	30.3	13.7	0.8	64.1	18.5	NA	NA
Jones et al. [19]	4300 ± 2210	4500 ± 2360	75.3	72.0	5.3	3.3	3.3	7.3	115 (66–170)	115 (62–180)
ProCESS Investigators [8]	2805 ± 1957	2783 ± 1880	54.9	48.1	5.7	1.0	14.4	7.9	NA	NA
ARISE Investigators [10]	1964 ± 1415	1713 ± 1401	66.6	57.8	15.4	2.6	13.6	7.0	70 (38–114)	67 (39–110)
ProMISe Investigators [12]	2226 ± 1443	2022 ± 1271	53.3	46.6	18.1	3.8	8.8	3.8	NA[b]	NA[b]
Secondary objective										
Wang et al. [21]	4895 ± 210	2340 95	100	100	NA	NA	NA	NA	NA	NA
De Oliviera et al. [20].	NA[a]	NA[a]	49.0	56.9	29.4	7.8	45.1	15.7	NA	NA
EGDT Collaborative [22]	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Tian et al. [23]	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Yu et al. [24]	3300 ± 1210	3600 ± 1360	80.0	72.0	4.0	8.0	20.0	16.0	NA	NA
Lu et al. [25]	2809 ± 795	3608 ± 715	87.5	76.2	NA	NA	NA	NA	NA	NA

Angus DC, et al. Intensive Care Med. 2015

Bottom Line

- Lots has changed over the past 12 years
- The results of these studies imply that one can stray from the strict EGDT protocol and still achieve equivalent results in sepsis care
- It does not mean that sepsis interventions are neither early nor goal-directed
- The rules governing the clinical approach put more emphasis on clinician intuition than strict targets than those promoted by EGDT



EGDT

Author	Fluids (ml)		Vasopressor (%)		Dobutamine (%)		Blood transfusion (%)		Time to first antimicrobial (min), median (IQR)	
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EGDT Collaborative [22]	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
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Yu et al. [24]	3300 ± 1210	3600 ± 1360	80.0	72.0	4.0	8.0	20.0	16.0	NA	NA
Lu et al. [25]	2809 ± 795	3608 ± 715	87.5	76.2	NA	NA	NA	NA	NA	NA

Angus DC, et al. Intensive Care Med. 2015

Evidence Based Guidelines - Sepsis

Empiric Antibiotic Treatment Reduces Mortality in Severe Sepsis and Septic Shock From the First Hour: Results From a Guideline-Based Performance Improvement Program*

Ricard Ferrer, MD, PhD[1]; Ignacio Martin-Loeches, MD, PhD[2]; Gary Phillips, MAS[3]; Tiffany M. Osborn, MD, MPH[4]; Sean Townsend, MD[5]; R. Phillip Dellinger, MD, FCCP, FCCM[6]; Antonio Artigas, MD, PhD[2]; Christa Schorr, RN, MSN[6]; Mitchell M. Levy, MD, FCCP, FCCM[7]

- Retrospective analysis of large dataset collected for the surviving sepsis campaign
- Over 28,000 patients

- Demonstrated that delay in 1st antibiotic administration was associated with increased in-hospital mortality

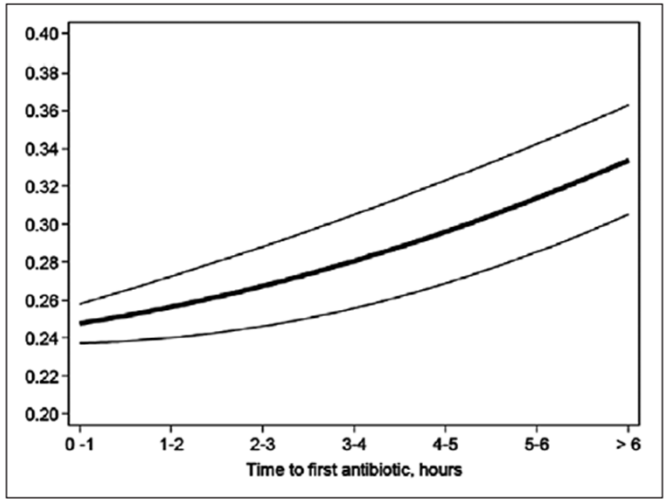


Figure 2. Predicted hospital mortality and the associated 95% CIs for time to first antibiotic administration. The results are adjusted by the sepsis severity score (SSS), ICU admission source (emergency department [ED], ward, vs ICU), and geographic region (Europe, United States, and South America). Probability of hospital mortality is based on the subject having the following specific characteristics: the patient is from the United States, admission source is the ED, and the SSS is 52 (median of all observations).

Ferrer R, et al. Critical Care Med. 2014

Strategies for assessment of adequacy of resuscitation

End Points of Resuscitation

- A confession…

End Points of Resuscitation

- MAP
- CVP
- Pulse pressure variation
- Cardiac output
- Lactate
- Base deficit
- ScvO2
- SvO2
- Urine output

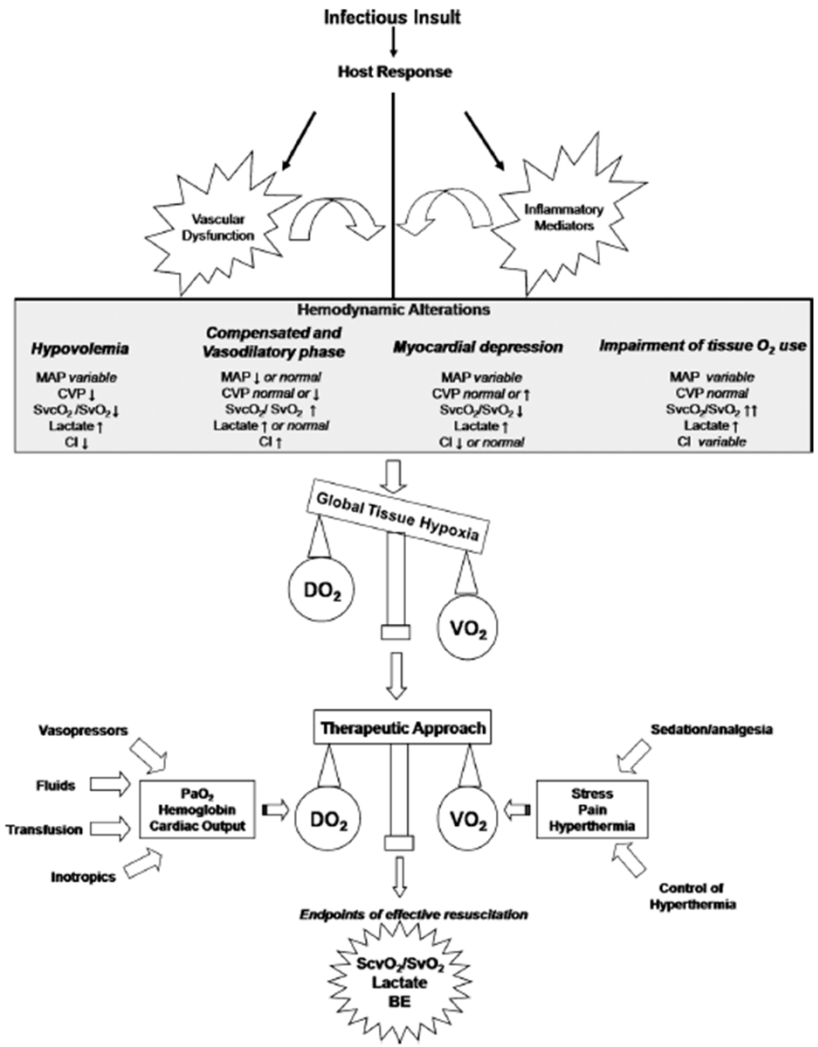
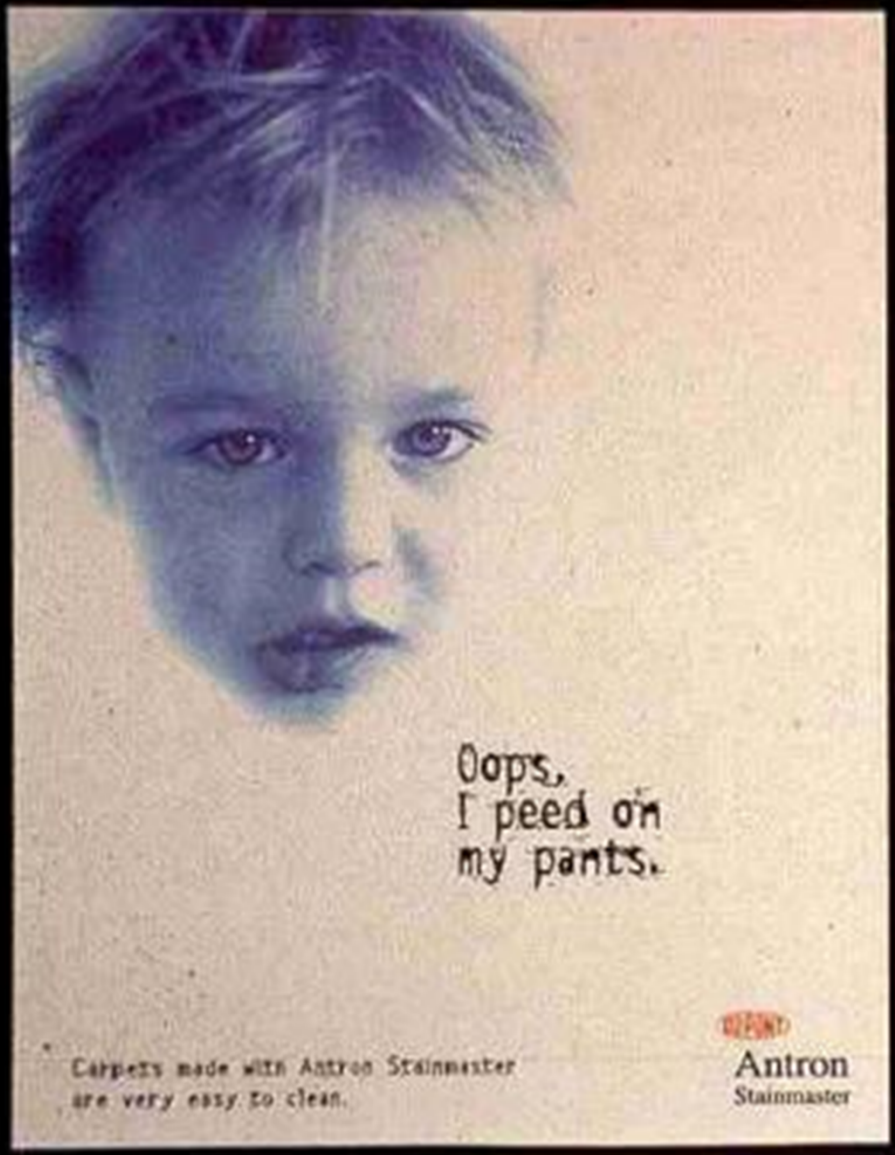
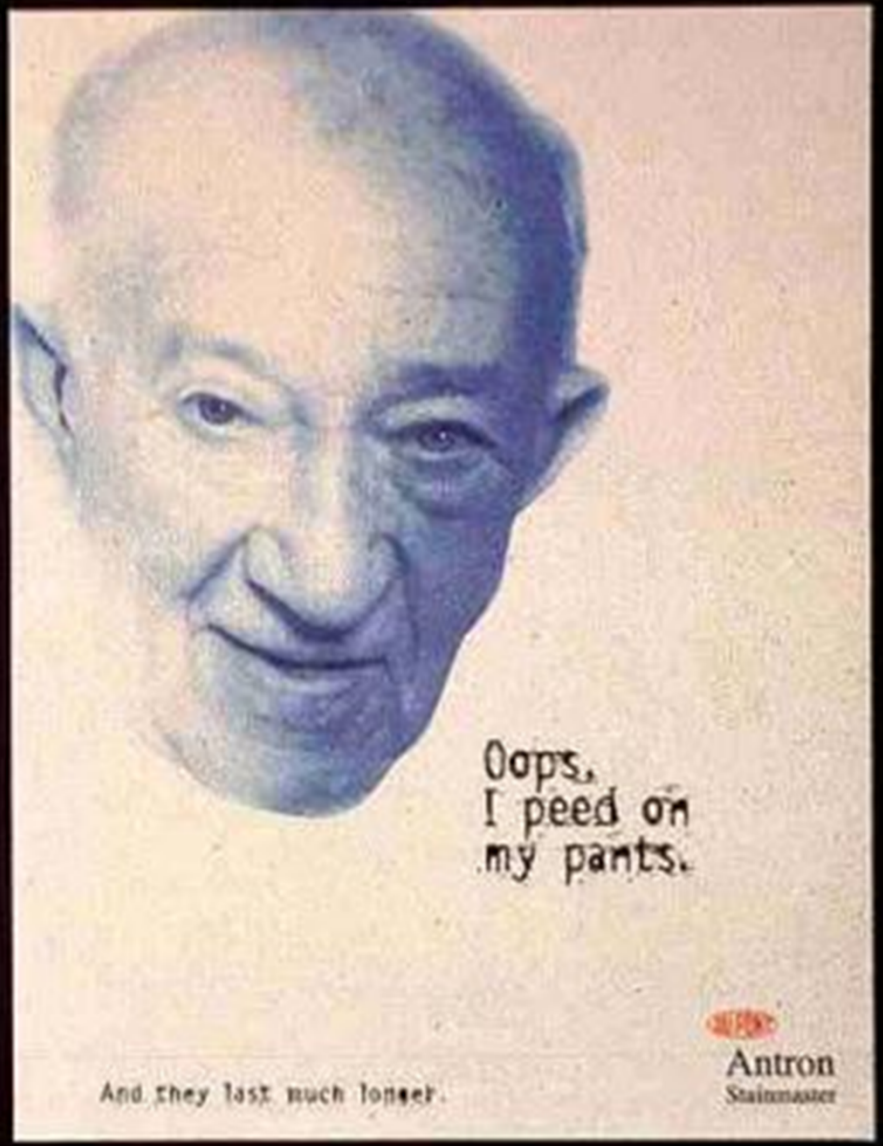


FIG. 1. **Different hemodynamic profiles during sepsis and therapeutic approach.** BE–base excess; CI–cardiac index; CVP–central venous pressure; DO_2–oxygen delivery; MAP–mean arterial pressure; $ScvO_2/SvO_2$–venous oxygen saturation; VO_2–oxygen consumption (adapted from Rivers et al. [10, 11] with permission).

da Silva Ramos FJ and Pontes Azevedo LC. Shock. 2010



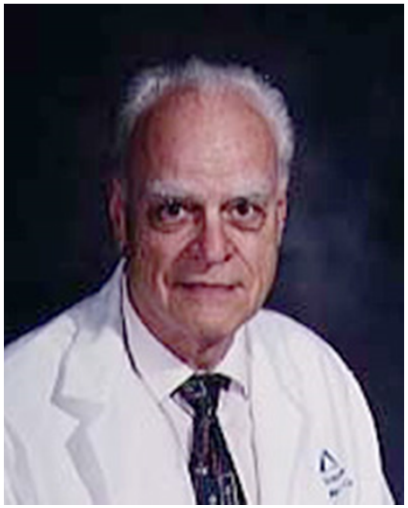


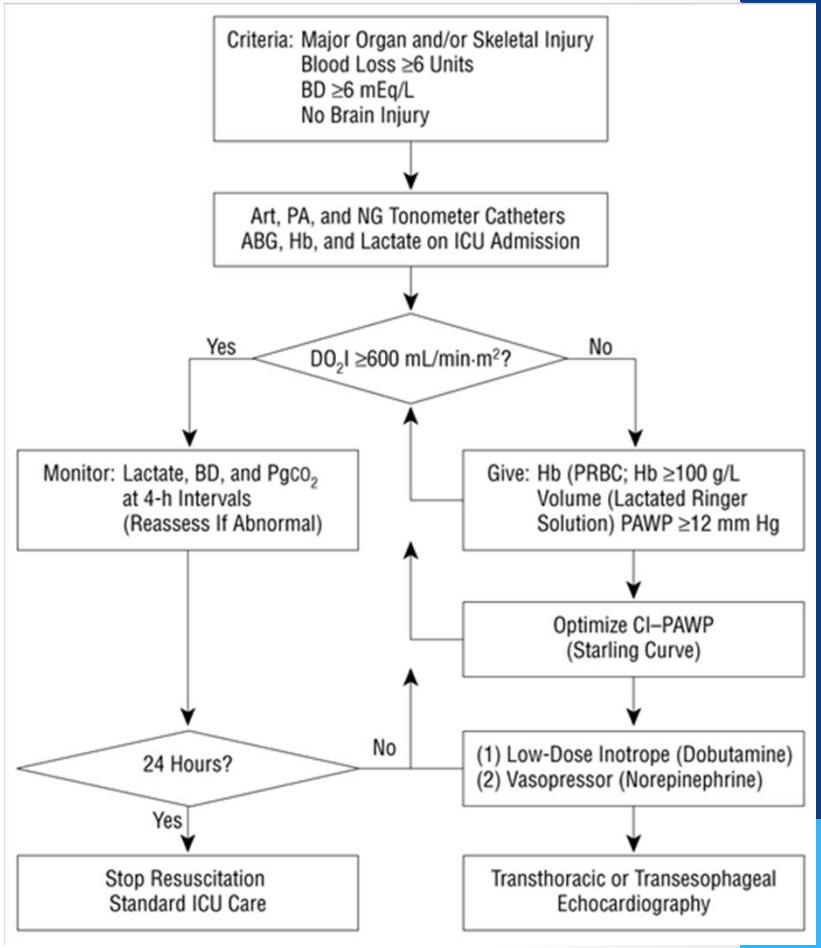
Consecutive pages

Back in the day…

"Supranormal" Resuscitation

- Shoemaker's landmark studies that "supranormal resuscitation" resulted in improved survival in high-risk surgical patients
  - DO2 >600
  - VO2 >170
  - CI >4.5





Shoemaker WC, et al. Chest. 1988
McKinely BA, et al. JAMASurg. 2000

“Supranormal” Resuscitation

- Subsequent studies have failed to demonstrate benefit and many have demonstrated harm

The New England
Journal of Medicine

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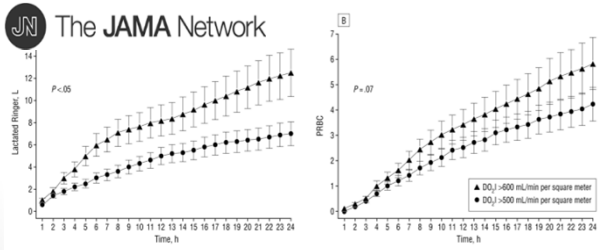
Volume 333 OCTOBER 19, 1995 Number 16

A TRIAL OF GOAL-ORIENTED HEMODYNAMIC THERAPY IN CRITICALLY ILL PATIENTS

LUCIANO GATTINONI, M.D., LUCA BRAZZI, M.D., PAOLO PELOSI, M.D., ROBERTO LATINI, M.D., GIANNI TOGNONI, M.D., ANTONIO PESENTI, M.D., AND ROBERTO FUMAGALLI, M.D., FOR THE SvO_2 COLLABORATIVE GROUP*



From: **Supranormal Trauma Resuscitation Causes More Cases of Abdominal Compartment Syndrome.** Balogh Z, et al. Arch Surg. 2003;138(6):637-643.

The Journal of TRAUMA® Injury, Infection, and Critical Care

Normal versus Supranormal Oxygen Delivery Goals in Shock Resuscitation: The Response Is the Same

Bruce A. McKinley, PhD, Rosemary A. Kozar, MD, PhD, Christine S. Cocanour, MD, Alicia Valdivia, RN, R. Matthew Sailors, PhD, Drue N. Ware, MD, and Frederick A. Moore, MD

Background: Shock resuscitation is integral to early management of severely injured patients. Our standardized shock resuscitation protocol, developed in 1997 and implemented as a computerized intensive care unit (ICU) bedside decision support tool in 2000, used oxygen delivery index (Do_2I) ≥ 600 mL/min/m² as the intervention endpoint. In a recent publication, Shoemaker et al. refuted positive outcome effect of early supranormal Do_2 (i.e., Do_2I ≥ 600) resuscitation. In response to and because of ongoing concern for excessive volume loading, we decreased our Do_2I endpoint from 600 to 500. Our hypothesis was that by decreasing the Do_2I endpoint, less crystalloid would be administered. We compare resuscitation responses to the protocol with goals of Do_2I ≥ 600 versus 500 in two patient cohorts.

Methods: A standardized protocol was used to direct bedside decisions for resuscitation of patients with major injury (Injury Severity Score > 15), blood loss (≥ 6 units of packed red blood cells), metabolic stress (base deficit ≥ 6 mEq/L), and no severe brain injury. The protocol logic is to attain and maintain Do_2I ≥ a specified goal for the first 24 ICU hours using primarily blood and volume loading. Two cohorts were compared: Do_2I ≥ 500 (18 patients admitted February–August 2001) versus Do_2I ≥ 600 (18 patients admitted during 2000 age and gender matched with the Do_2I ≥ 500 group). Data were analyzed using analysis of variance, χ^2, and t tests ($p < 0.05$).

Results: Both groups had similar demographics (age 30 ± 3 years; 78% men; Injury Severity Score 27 ± 3), hemodynamics, and severity of shock at start of resuscitation in the ICU. Resuscitation response was Do_2I increase to ≥ 600 for both cohorts within ~12 hours. Throughout the 24-hour ICU process, the Do_2I ≥ 500 cohort received less lactated Ringer's volume than the Do_2I ≥ 600 cohort (total of 8 ± 1 vs. 12 ± 2 L; $p < 0.05$) and tended to receive less blood transfusion (total of 3 ± 1 vs. 5 ± 1 units of packed red blood cells).

Conclusion: Shock resuscitation using Do_2I ≥ 500 was indistinguishable from Do_2I ≥ 600 mL/min/m². Less volume loading was required to attain and maintain Do_2I ≥ 500 than 600 using computerized protocol technology to standardize resuscitation during the first 24 ICU hours.

Key Words: Shock, Resuscitation, Oxygen delivery index, Hemodynamics, Supranormal performance, trauma hemorrhage.

J Trauma. 2002;53:825–832.

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Endpoints of Resuscitation of Critically Injured Patients: Normal or Supranormal?

A Prospective Randomized Trial

George C. Velmahos, MD, PhD,* Demetrios Demetriades, MD, PhD,* William C. Shoemaker, MD,* Linda S. Chan, PhD,† Raymond Tatevossian, BS,* Charles C.J. Wo, BS,* Pantelis Vassiliu, MD,* Edward E. Cornwell III, MD,* James A. Murray, MD,* Bradley Roth, MD,* Howard Belzberg, MD,* Juan A. Asensio, MD,* and Thomas V. Berne, MD*

*From the *Department of Surgery, Division of Trauma and Critical Care, and the †Department of Biostatistics and Outcomes Research, University of Southern California, and the Los Angeles County+USC Medical Center, Los Angeles, California*

"Supranormal" Resuscitation

- In this study, attempts at early optimization did not improve the outcome of the examined subgroup of severely injured patients.

- Severely injured patients who can achieve optimal hemodynamic values are more likely to survive than those who cannot, *regardless of the resuscitation technique*.

Table 2. OUTCOME PARAMETERS

	Optimal Group (n = 40)	Control Group (n = 35)	*P*
Death	15% (6)	11% (4)	.742
Organ failure	38% (15)	57% (20)	.108
Sepsis	40% (16)	51% (18)	.359
All complications	62% (24)	71% (25)	.468
ICU days	15 ± 23	15 ± 12	.908
Hospital days	25 ± 24	27 ± 21	.722

ICU, intensive care unit.
Results are given as mean ± standard deviations for continuous variables and proportions of outcome for categorical variables.

Table 4. OUTCOMES BETWEEN PATIENTS WHO ACHIEVED AND DID NOT ACHIEVE OPTIMAL VALUES

	With Optimal Values (n = 42)	Without Optimal Values (n = 33)	*P*
Death	0% (0)	30% (10)	.0001
Organ failure	29% (12)	70% (23)	.0005
Sepsis	31% (13)	64% (21)	.006
All complications	60% (25)	76% (25)	.217
ICU days	10 ± 11	21 ± 24	.017
Hospital days	22 ± 17	31 ± 28	.105

ICU, intensive care unit.
Results are given as mean ± standard deviations for continuous variables or as proportions of outcomes for categorical variables.

Velmahos GC, et al. Ann Surg. 2000

Fluid Management

NIH-PA Author Manuscript

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NIH-P

NIH Public Access
Author Manuscript
J Trauma Acute Care Surg. Author manuscript; available in PMC 2014 May 01.

Published in final edited form as:
J Trauma Acute Care Surg. 2013 May ; 74(5): 1215–1222. doi:10.1097/TA.0b013e3182826e13.

Aggressive Early Crystalloid Resuscitation adversely affects Outcomes in Adult Blunt Trauma Patients: An Analysis of the Glue Grant Database

George Kasotakis, MD, Antonis Sideris, MD, Yuchiao Yang, PhD, Marc de Moya, MD, Hasan Alam, MD, David R King, MD, Ronald Tompkins, MD, ScD, George Velmahos, MD, MsEd, PhD, and The Inflammation and Host Response to Injury Investigators

Abstract

Background—Evidence suggests that aggressive crystalloid resuscitation is associated with significant morbidity in various clinical settings. We wanted to assess whether aggressive early crystalloid resuscitation adversely affects outcomes in adult blunt trauma patients.

Methods—Data were derived from the Glue Grant database. Our primary outcome measure was all-cause in-hospital mortality. Secondary outcomes included days on mechanical ventilation; intensive care unit (ICU) and hospital length of stay (LOS); inflammatory - (acute lung injury and respiratory distress syndrome [ALI/ARDS], multiple organ failure [MOF]) and resuscitation-related morbidity (abdominal and extremity compartment syndromes, acute renal failure) and nosocomial infections (ventilator associated pneumonia [VAP], bloodstream [BSI], urinary tract [UTI] and surgical site infections [SSI]).

Results—In our sample of 1,754 patients, in-hospital mortality was not affected, but ventilator days ($p<0.001$), as well as ICU ($p=0.009$) and hospital ($p=0.002$) LOS correlated strongly with the amount of crystalloids infused in the first 24 hours post-injury. Amount of crystalloid resuscitation was also associated with development of ARDS ($p<0.001$), MOF ($p<0.001$), bloodstream ($p=0.001$) and SSI ($p<0.001$), as well as abdominal ($p<0.001$) and extremity compartment syndromes ($p=0.028$) in a dose-dependent fashion, when age, Glasgow Coma Scale (GCS) severity of injury and acute physiologic derangement, comorbidities, and colloid & blood product transfusions were controlled for.

Conclusion—Crystalloid resuscitation is associated with a substantial increase in morbidity, as well as ICU and hospital LOS in adult blunt trauma patients.

Level of Evidence—2b

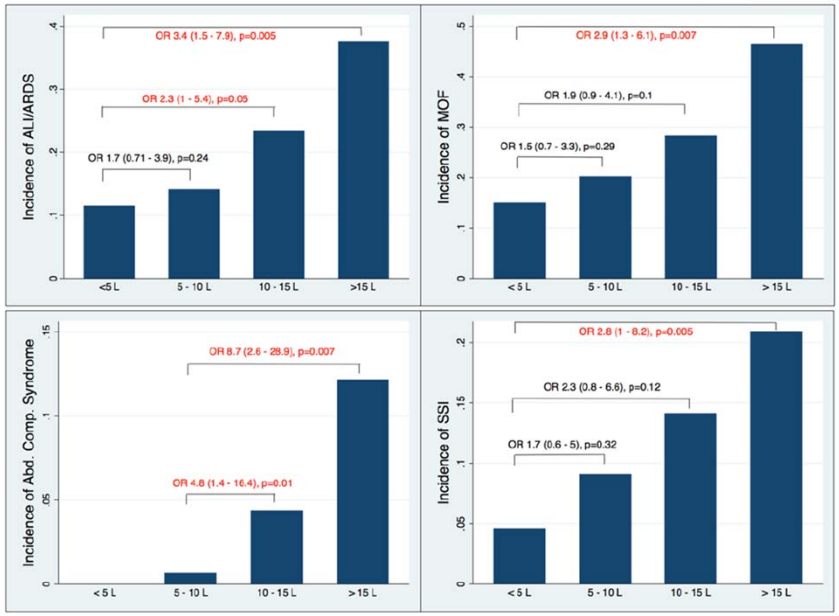


Figure 2.
Adjusted Odds Rations for the development of ALI or ARDS, MOF, abdominal compartment syndrome and SSI across the four 24h crystalloid resuscitations volume groups.

Kasotakis, et al. J Trauma Acute Care Surg. 2013

Fluid Management

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Comparison of Two Fluid-Management Strategies in Acute Lung Injury

The National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network*

ABSTRACT

- Fluid-conservative/CVC
  - fluids were restricted and diuretics administered to maintain a CVP <4 mmHg
- Fluid-conservative/PAC
  - fluids were restricted and diuretics administered to maintain a PAOP <8 mmHg
- Fluid-liberal/CVC
  - fluids were used to maintain a CVP between 10-14 mmHg
- Fluid-liberal/PAC
  - fluids were used to maintain a PAOP between 14-18 mmHg.

The National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network
N Engl J Med. 2006

Fluid Management

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Comparison of Two Fluid-Management Strategies in Acute Lung Injury

The National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network*

ABSTRACT

Table 3. Main Outcome Variables.*

Outcome	Conservative Strategy	Liberal Strategy	P Value
Death at 60 days (%)	25.5	28.4	0.30
Ventilator-free days from day 1 to day 28†	14.6±0.5	12.1±0.5	<0.001
ICU-free days†			
Days 1 to 7	0.9±0.1	0.6±0.1	<0.001
Days 1 to 28	13.4±0.4	11.2±0.4	<0.001
Organ-failure–free days†‡			
Days 1 to 7			
Cardiovascular failure	3.9±0.1	4.2±0.1	0.04
CNS failure	3.4±0.2	2.9±0.2	0.02
Renal failure	5.5±0.1	5.6±0.1	0.45
Hepatic failure	5.7±0.1	5.5±0.1	0.12
Coagulation abnormalities	5.6±0.1	5.4±0.1	0.23
Days 1 to 28			
Cardiovascular failure	19.0±0.5	19.1±0.4	0.85
CNS failure	18.8±0.5	17.2±0.5	0.03
Renal failure	21.5±0.5	21.2±0.5	0.59
Hepatic failure	22.0±0.4	21.2±0.5	0.18
Coagulation abnormalities	22.0±0.4	21.5±0.4	0.37
Dialysis to day 60			
Patients (%)	10	14	0.06
Days	11.0±1.7	10.9±1.4	0.96

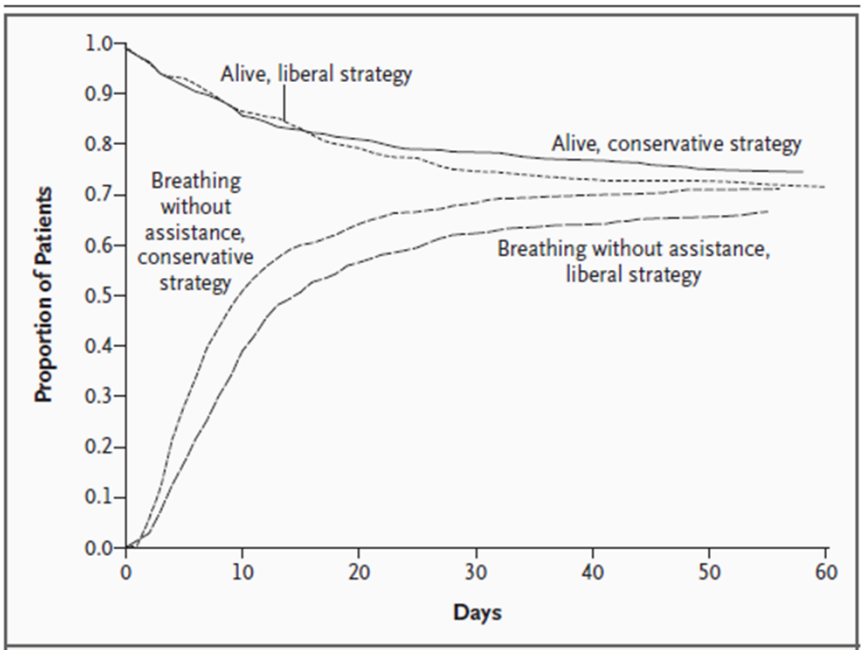
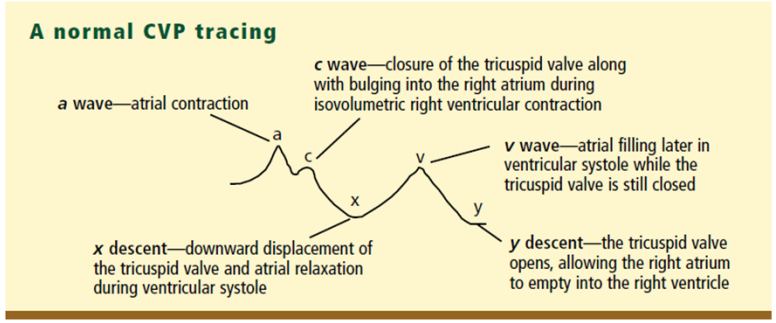


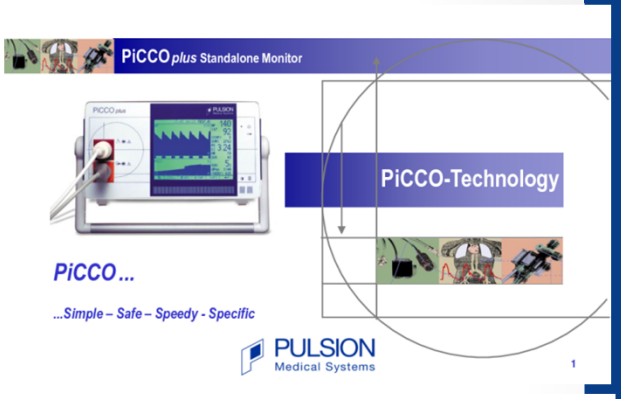
Figure 3. Probability of Survival to Hospital Discharge and of Breathing without Assistance during the First 60 Days after Randomization.

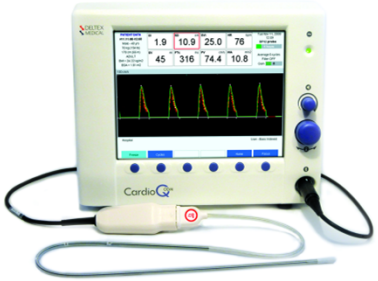
The National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network
N Engl J Med. 2006

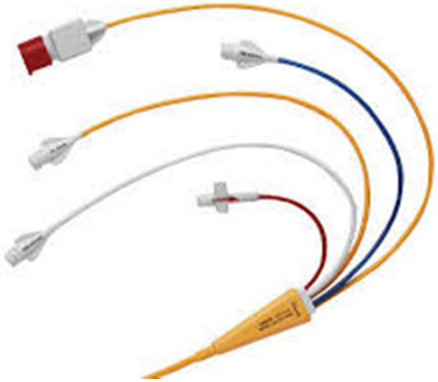
Euvolemia…

Assessing Adequacy of Resuscitation









Assessing Adequacy of Resuscitation

ORIGINAL ARTICLE

A, B, C, D, echo: Limited transthoracic is a useful tool to guide therapy for the trauma bay—A pilot s

Paula Ferrada, MD, Poornima Vanguri, MD, Rahul J. Anand, MD, Jame
Michel Aboutanos, MD, Ajai Malhotra, MD, *and* Rao Ivatur

Review Article

AAST 2011 PLENARY PAPER

Focused rapid echocardiographic evaluation versus vascular cather-based assessment of cardiac output and function in critically ill trauma patients

Sarah B. Murthi, MD, John R. Hess, MD, MPH, Aaron Hess, BA, Lynn G. Stansbury, MD, MPH, *and* Thomas M. Scalea, MD, *Baltimore, Maryland*

Crit Ultrasound J (2011) 3:123–129
DOI 10.1007/s13089-011-0083-2

ORIGINAL ARTICLE

EGLS: Echo-guided life support

An algorithmic approach to undifferentiated shock

Jean-François Lanctôt · Maxime Valois · Yanick Beaulieu

Received: 2 June 2011 / Accepted: 1 November 2011 / Published online: 17 November 2011
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ORIGINAL ARTICLE

Transthoracic Focused Rapid Echocardiographic Examination: Real-Time Evaluation of Fluid Status in Critically Ill Trauma Patients

Paula Ferrada, MD, Sarah Murthi, MD, Rahul J. Anand, MD, Grant V. Bochicchio, MD, and Thomas Scalea, MD

nformation and services, is
at:
14/6/e667.full.html

Mailhot,[1] David Riley,[3] and Diku Mandavia[1]

ICU DIRECTOR

TECHNOLOGY AT THE BEDSIDE

An Evidence-Based Approach for Integrating Bedside Ultrasound Into Routine Practice in the Assessment of Undifferentiated Shock

Jonathan Elmer, MD,[1] and Vicki E. Noble, MD[2]

The Journal of TRAUMA® *Injury, Infection, and Critical Care*

Accuracy of Cardiac Function and Volume Status Estimates Using the Bedside Echocardiographic Assessment in Trauma/Critical Care

Mark Gunst, MD, Vafa Ghaemmaghami, MD, Jason Sperry, MD, Melissa Robinson, MD, Terence O'Keeffe, MD, Randall Friese, MD, and Heidi Frankel, MD

Pershad J, et al. Pediatrics. 2004
Gunst M, et al. J Trauma. 2008
Elmer and Noble. ICU Director. 2010
Lanctot J-F, et al. Crit Ultrasound J. 2011
Murthi SB, et al. J Trauma. 2012
Seif D, et al. Crit Care Res Prac. 2012
Ferrada P, et al. J Trauma. 2013

Assessing Adequacy of Resuscitation

CARDIAC FUNCTION	LV S: CI L/min/m^2, SVi ml/m^2, EF % LV D: Impaired filling (Grade 1-4), Elevated LAP (> 15 mmHg) RV: Visual assessment (normal, mild, moderate, severe dysfunction)
VOLUME STATUS	Static: LV internal dimension, Visual assessment LV/RV, IVC diameter Dynamic: IVC diameter change %, Stroke volume variation %
AFTERLOAD	LV: Systemic Vascular Resistance (calculated from CO and MAP) RV: Pulmonary Systolic Artery Pressure
ANATOMY	Effusion, Valvular dysfunction

Figure 1. Measurements of FREE. *Left column*, Categories of the examination. IVC, inferior vena cava; LAP, left atrial pressure; LV, left ventricle; LV D, left ventricular diastolic function; LV S, left ventricle systolic function; MAP, mean arterial blood pressure; RV, right ventricle; SVi, stroke volume index.

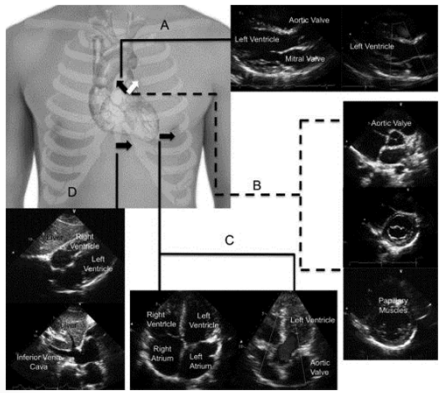
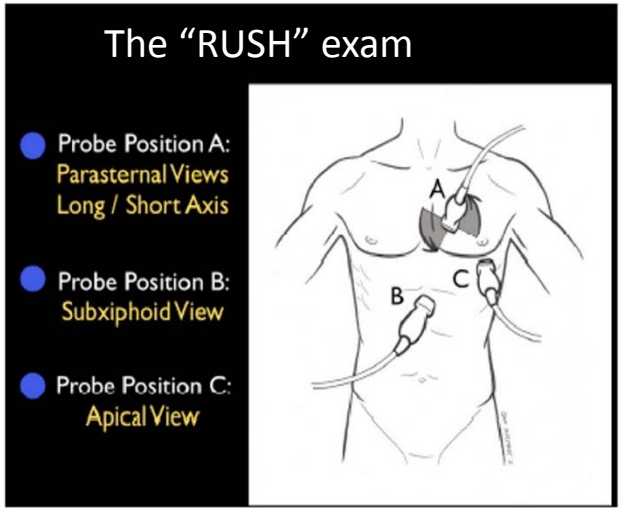


Table 1 The BEAT Examination

	Assessment	View(s)	Measurement
Beat	Cardiac index	PSL	SV
Effusion	Pericardial effusion	PSL	None
Area	Subjective cardiac function	PSS (LV), A4C (RV)	None
Tank	Volume status	PSL, subcostal	IVC diameter

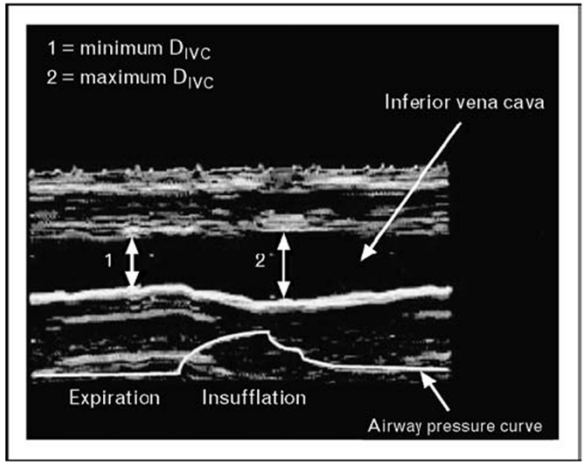
PSL indicates parasternal long axis; PSS, parasternal short axis; A4C, apical 4 chamber; IVC, inferior vena cava; LV, left ventricle; RV, right ventricle; SV, stroke volume.

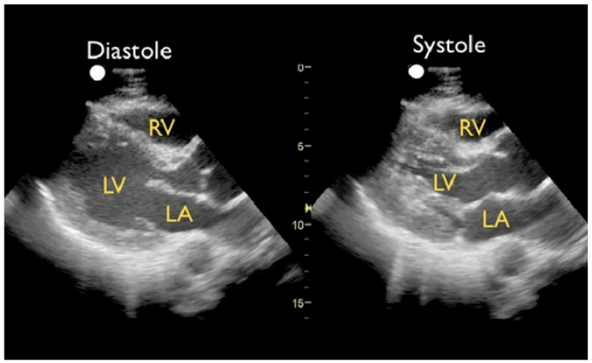


Seif D, et al. Crit Care Res Prac. 2012
Gunst M, et al. J Trauma. 2008
Murthi SB, et al. J Trauma. 2012

Assessing Adequacy of Resuscitation

Figure 1 Transthoracic view of the respiratory variation in inferior vena cava diameter





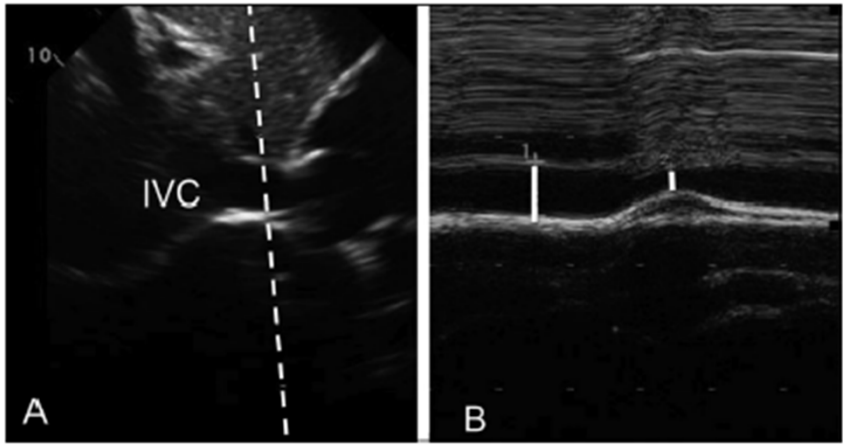


Figure 2. The fourth view of the FREE, SA view, with M mode demonstrating collapsibility of the IVC.

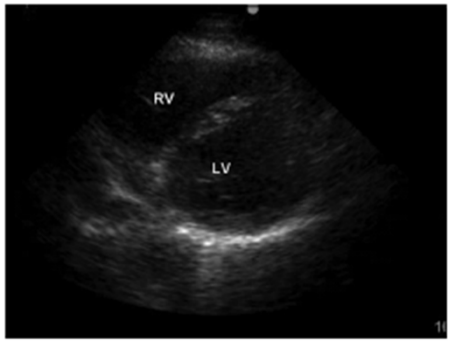


Fig. 3. *Parasternal short axis view. LV, left ventricle; RV, right ventricle. LV global systolic function is assessed here in the BEAT.*

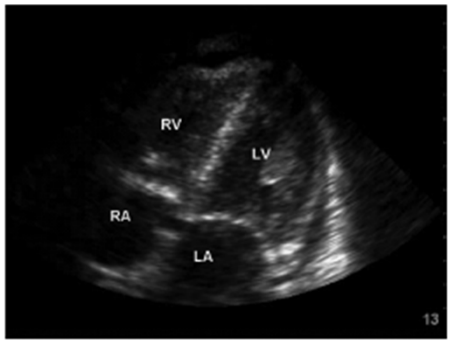


Fig. 4. *Apical 4 chamber view. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle. RV systolic and diastolic function (as may be depressed with a blunt cardiac injury or massive pulmonary embolus) is assessed here in the BEAT.*

Gunst M, et al. J Trauma. 2008
Elmer and Noble. ICU Director. 2010
Seif D, et al. Crit Care Res Prac. 2012
Murthi SB, et al. J Trauma. 2012
Ferrada P, et al. J Trauma. 2011

New clinical trials and changes in nutritional support

Nutritional Support

- Gastric vs. jejunal feeding
- Low energy vs. full nutrition
- TPN vs. enteral feeding
- Timing of TPN
- Supplements

Gastric vs. Jejunal Feeding

- RCT
- 181 mechanically ventilated patients with elevated gastric residual volumes within 72 hours of ICU admission

A multicenter, randomized controlled trial comparing early nasojejunal with nasogastric nutrition in critical illness*

Andrew R. Davies, MBBS; Siouxzy S. Morrison, MPH; Michael J. Bailey, PhD; Rinaldo Bellomo, MD; David J. Cooper, MD; Gordon S. Doig, PhD; Simon R. Finfer, FCICM; Daren K. Heyland, MD; for the ENTERIC Study Investigators and the ANZICS Clinical Trials Group

Objective: Current guidelines recommend enteral nutrition in critically ill adults; however, poor gastric motility often prevents nutritional targets being met. We hypothesized that early nasojejunal nutrition would improve the delivery of enteral nutrition.

Design: Prospective, randomized, controlled trial.

Setting: Seventeen multidisciplinary, closed, medical/surgical, intensive care units in Australia.

Patients: One hundred and eighty-one mechanically ventilated adults who had elevated gastric residual volumes within 72 hrs of intensive care unit admission.

Interventions: Patients were randomly assigned to receive early nasojejunal nutrition delivered via a spontaneously migrating frictional nasojejunal tube, or to continued nasogastric nutrition.

Measurements and Main Results: The primary outcome was the proportion of the standardized estimated energy requirement that was delivered as enteral nutrition. Secondary outcomes included incidence of ventilator-associated pneumonia, gastrointestinal hemorrhage, and in-hospital mortality rate. There were 92 patients assigned to early nasojejunal nutrition and 89 to continued nasogastric nutrition. Baseline characteristics were similar. Nasojejunal tube placement into the small bowel was confirmed in 79 (87%) early nasojejunal nutrition patients after a median of 15 (interquartile range 7–32) hrs. The proportion of targeted energy delivered from enteral nutrition was 72% for the early nasojejunal nutrition and 71% for the nasogastric nutrition group (mean difference 1%, 95% confidence interval –3% to 5%, p = .66). Rates of ventilator-associated pneumonia (20% vs. 21%, p = .94), vomiting, witnessed aspiration, diarrhea, and mortality were similar. Minor, but not major, gastrointestinal hemorrhage was more common in the early nasojejunal nutrition group (12 [13%] vs. 3 [3%], p = .02).

Conclusions: In mechanically ventilated patients with mildly elevated gastric residual volumes and already receiving nasogastric nutrition, early nasojejunal nutrition did not increase energy delivery and did not appear to reduce the frequency of pneumonia. The rate of minor gastrointestinal hemorrhage was increased. Routine placement of a nasojejunal tube in such patients is not recommended. (Crit Care Med 2012; 40: 2342–2348)

Key Words: critically ill; critical illness; enteral nutrition; nasojejunal; nutrition; randomized controlled trial

Davies AR, et al. Crit Care Med. 2012

Gastric vs. Jejunal Feeding

- Primary outcome was proportion of standardized estimated energy requirements that was delivered

- Secondary outcomes included:
  - VAP
  - GI bleed
  - In-hospital mortality

Table 1. Characteristics of patients in each group

Characteristic	Nasogastric Nutrition (n = 89)	Early Nasojejunal Nutrition (n = 91)
Age, yrs (mean, SD)	54 (18)	51 (19)
Men (n, %)	71 (80%)	62 (68%)
Height, cm (mean, SD)	173 (10)	172 (10)
Weight, kg (mean, SD)	84 (19)	84 (25)
Body mass index, kg/m^2 (mean, SD)	29 (6)	28 (8)
Nonoperative admission to ICU (n, %)	52 (58%)	59 (65%)
Elective admission to ICU (n, %)	7 (8%)	7 (8%)
ICU readmission (n, %)	0 (0%)	4 (4%)
Acute Physiology and Chronic Health Evaluation II score (mean, SD)	20 (8)	20 (7)
Receiving vasopressors at enrolment (n, %)	67 (75%)	74 (81%)
Serum albumin at enrolment, mmol/L (mean, SD)	27 (6)	27 (7)
Receiving nutrition via nasogastric tube at enrolment (n, %)	84 (94%)	84 (92%)
Predicted energy requirements, kilocalories/day (mean, SD)	2224 (356)	2222 (409)
Diagnosis (n, %)		
Multitrauma	34 (38%)	32 (35%)
Traumatic brain injury	24 (27%)	21 (24%)
Other than brain injury	10 (11%)	11 (12%)
Sepsis/respiratory	28 (31%)	26 (29%)
Cardiovascular	14 (16%)	19 (21%)
Neurological	9 (10%)	8 (9%)
Gastrointestinal	4 (4%)	6 (7%)
Hospital admission to enrolment, days (median, interquartile range)	2 (2–3)	2 (2–3)
ICU admission to enrolment, hrs (mean, SD)	43 (17)	42 (15)

ICU, intensive care unit.

Davies AR, et al. Crit Care Med. 2012

Gastric vs. Jejunal Feeding

Table 2. Energy delivery from enteral nutrition

Variable	Nasogastric Nutrition (n = 89)	Early Nasojejunal Nutrition (n = 91)	*p*
Proportion of estimated energy requirements delivered by enteral nutrition for study period (mean, SD)	71% (19%)	72% (21%)	.66
Proportion of estimated energy requirements delivered by enteral nutrition over first 10 days (mean, SD)	71% (19%)	72% (21%)	.76
Daily energy delivered, kilocalories (mean, SD)	1444 (485)	1497 (521)	.49

Table 3. Other outcomes

Variable	Nasogastric Nutrition (n = 89)	Early Nasojejunal Nutrition (n = 91)	*p*
Ventilator-associated pneumonia by blinded adjudication panel (n, %)	19 (21%)	18 (20%)	.94
Accidental withdrawal of enteral tube (n, %)	18 (20%)	23 (25%)	.42
Vomiting (n, %)	27 (30%)	30 (33%)	.70
Witnessed aspiration (n, %)	4 (4%)	5 (5%)	.76
Abdominal distension (n, %)	18 (20%)	16 (18%)	.65
Diarrhea (n, %)	27 (30%)	26 (29%)	.79
Minor gastrointestinal hemorrhage (n, %)	3 (3%)	12 (13%)	.02
Major gastrointestinal hemorrhage (n, %)	2 (2%)	2 (2%)	.98
Duration of mechanical ventilation, days (median, IQR)	8 (5–14)	8 (6–12)	.84
Duration of intensive care unit stay, days (median, IQR)	11 (7–16)	10 (7–15)	.85
Duration of hospitalization, days (median, IQR)	24 (15–32)	20 (11–33)	.57
Hospital mortality (n, %)	12 (13%)	13 (14%)	.88

IQR, interquartile range.

- No difference in energy delivery
- Slight increase in minor GI bleed in NJ group
- No difference in rate of other secondary end points

Davies AR, et al. Crit Care Med. 2012

Gastric vs. Jejunal Feeding

- Systematic review and meta-analysis
- Relevant randomized controlled trials that compared small bowel to gastric feeding in patients with severe TBI were identified

- The primary outcome was risk of pneumonia
- Secondary outcomes included:
  - VAP
  - Mortality
  - ICU LOS
  - Hospital LOS
  - duration of mechanical ventilation
  - total number of complications
  - Aspiration
  - Diarrhea
  - Distention
  - Glasgow Coma Scale score
  - Injury Severity Score
  - Acute Physiology and Chronic Health Evaluation II score.

JNS CLINICAL ARTICLE

Comparisons between small intestinal and gastric feeding in severe traumatic brain injury: a systematic review and meta-analysis of randomized controlled trials

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Wang D, et al. J Neurosurg. 2015

Gastric vs. Jejunal Feeding

- Five randomized controlled trials with 325 participants
- Compared with gastric feeding, small bowel feeding was associated with a significant reduction in the incidence of pneumonitis and ventilator-associated pneumonia
- Small intestinal feeding was also associated with a decrease in the total number of complications

Study or Subgroup	Small Intestinal Events	Small Intestinal Total	Gastric Events	Gastric Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Grahm 1989	2	17	3	15	2.5%	0.59 [0.11, 3.06]	1989
Kortbeek 1999	10	37	18	43	16.6%	0.65 [0.34, 1.22]	1999
Taylor 1999	18	41	26	41	38.7%	0.69 [0.46, 1.05]	1999
Minard 2000	6	12	7	15	11.0%	1.07 [0.49, 2.34]	2000
Acosta-Escribano 2010	16	50	31	54	31.2%	0.56 [0.35, 0.89]	2010
Total (95% CI)		**157**		**168**	**100.0%**	**0.67 [0.52, 0.87]**	
Total events	52		85				

Heterogeneity: Tau² = 0.00; Chi² = 2.06, df = 4 (P = 0.73); I² = 0%
Test for overall effect: Z = 3.04 (P = 0.002)

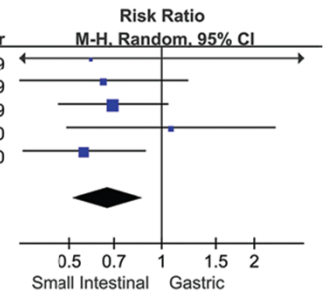


FIG. 5. Pneumonia. Five studies reported the incidence of overall pneumonia. Shown is a forest plot comparing small bowel feeding and gastric feeding with respect to pneumonia outcome. Results are shown by using a random-effects model with RR and 95% CIs. M-H = Mantel-Haenszel (method). Figure is available in color online only.

TABLE 3. Clinical outcomes: dichotomous data

Outcome	No. of Patients	No. of Trials	Small Bowel Group (n/N)	Gastric Group (n/N)	RR (95% CI)	p Value	I² (%)	p Value for Heterogeneity
VAP	189	2	21 of 87	45 of 97	0.52 (0.34–0.81)	0.0003	0	0.38
Mortality	293	4	13 of 140	22 of 153	0.81 (0.44–1.49)	0.49	0	0.64
Total complications	186	2	22 of 91	52 of 95	0.43 (0.20–0.93)	0.03	68	0.08
Aspiration	131	2	0 of 62	4 of 69	0.23 (0.03–1.90)	0.17	0	0.95
Diarrhea	131	2	15 of 62	16 of 69	1.05 (0.29–3.86)	0.94	78	0.03
Distention	131	2	5 of 62	10 of 69	0.71 (0.32–1.58)	0.41	0	0.39

TABLE 4. Clinical outcomes: continuous data

Outcome	No. of Patients	No. of Trials	WMD (95% CI)	p Value	I² (%)	p Value for Heterogeneity
Length of ICU stay	211	3	2.25 (−6.74 to 11.24)	0.62	86	0.007
Length of hospital stay	211	3	2.66 (−8.80 to 14.12)	0.65	59	0.12
Duration of MV	211	3	1.03 (−5.06 to 7.12)	0.74	80	0.02
GCS score	293	4	0.00 (−0.82 to 0.82)	1	0	1
ISS	189	3	2.61 (−1.46 to 6.68)	0.21	0	0.7
APACHE II score	266	3	−1.38 (−3.19, 0.43)	0.13	22	0.26

Wang D, et al. J Neurosurg. 2015

Low Energy vs. Full Nutrition

ONLINE FIRST

Initial Trophic vs Full Enteral Feeding in Patients With Acute Lung Injury

The EDEN Randomized Trial

- RCT, open label
- 1000 adults with ALI requiring mechanical ventilation
- Main outcome measure was ventilator-free days to day 28

Rice TW, et al. JAMA. 2012

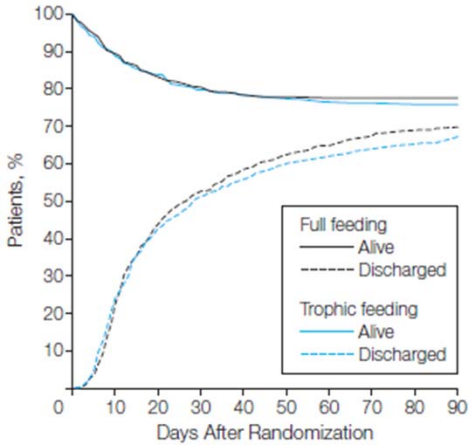
Low Energy vs. Full Nutrition

Table 2. Clinical Outcomes

Outcome	Trophic Feeding (n = 508)	Full Feeding (n = 492)	*P* Value
Ventilator-free days, No. (95% CI)	14.9 (13.9-15.8)	15.0 (14.1-15.9)	.89
Failure-free days, No. (95% CI)			
Cardiovascular	19.1 (18.2-20.0)	18.9 (18.1-19.8)	.75
Renal	20.0 (19.0-20/9)	19.4 (18.4-20.5)	.43
Hepatic	22.0 (21.2-22.9)	22.6 (21.8-23.5)	.37
Coagulation	22.3 (21.4-23.1)	23.1 (22.3-23.9)	.16
ICU-free days, No. (95% CI)	14.4 (13.5-15.3)	14.7 (13.8-15.6)	.67
60-d mortality, No. (%) [95% CI]	118 (23.2) [19.6-26.9]	109 (22.2) [18.5-25.8]	.77
Development of infections, No. (%) [95% CI]			
VAP	37 (7.3) [5.0-9.5]	33 (6.7) [4.5-8.9]	.72
Clostridium difficile colitis	15 (3.0) [1.5-4.4]	13 (2.6) [1.2-4.1]	.77
Bacteremia, No. (%)	59 (11.6) [8.8-14.4]	46 (9.3) [6.8-11.9]	.24

Abbreviations: ICU, intensive care unit; VAP, ventilator-associated pneumonia.

Figure 3. Survival and Hospital Discharge



Percentages were calculated daily; the denominator at all times represents all patients in each group with the exception of 1 patient in the full-feeding group who was lost to follow-up and censored in these plots at day 36. The solid lines represent the proportion of patients surviving at each time; dashed lines represent the proportion of patients discharged from the hospital at each time. The areas above the solid lines represent the proportion of patients who have died in each group at each time; the areas below the dashed lines represent the proportion of patients alive and discharged from the hospital at each time. Areas between the solid and dashed lines represent the proportion of patients alive but still hospitalized in each group at each time.

- Similar baseline characteristics
- Trophic feeding <u>did not increase</u> the number of vent-free days or reduce 60-day mortality

Rice TW, et al. JAMA. 2012

Low Energy vs. Full Nutrition

- We assessed whether delivery of 100% of the energy target from days 4 to 8 in the ICU with EN plus supplemental parenteral nutrition (SPN) could optimize clinical outcome

- RCT in two centers in Switzerland
- Enrolled patients on day 3 of admission to the ICU
  - who had received less than 60% of their energy target from EN
  - were expected to stay for longer than 5 days
  - expected and to survive for longer than 7 days

Heidegger AP, et al. Lancet 2013

Low Energy vs. Full Nutrition

- 153 patients to SPN and 152 to EN
- Mean energy delivery between 103% of energy target for SPN group vs. 77% for the EN group
- 27% in the SPN group had a nosocomial infection vs. 38% in the EN group (p=0.03)
- The SPN group had a lower mean number of nosocomial infections per patient

- "Individually optimized energy supplementation with SPN starting 4 days after ICU admission <u>could reduce nosocomial infections</u> and should be considered as a strategy to improve clinical outcome in patients in the ICU for whom EN is insufficient"

Heidegger AP, et al. Lancet 2013

Low Energy vs. Full Nutrition

Tian et al. Critical Care (2015) 19:180
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RESEARCH Open Access

Effect of initial calorie intake via enteral nutrition in critical illness: a meta-analysis of randomised controlled trials

Feng Tian[1†], Xinying Wang[1†], Xuejin Gao[2], Xiao Wan[1], Chao Wu[1], Li Zhang[1], Ning Li[1*] and Jieshou Li[1]

- Meta-analysis
- 8 RCT studies
- 1895 patients

Table 1 Characteristics of the enrolled studies

Study	No. randomized		Characteristics of patients	BMI (SD)		Mean APACHE II score (SD)	
	LE	HE		LE	HE	LE	HE
Arabi *et al.* [21]	120	120	>18 years old ICU >48 hours	28.5 (7.4)	28.5 (8.4)	25.2 (7.5)	25.3 (8.2)
Braunschweig *et al.* [22]	38	40	>18 years old Medical or surgical ICU ALI <24 hours	30.1 (8.9)	29.8 (9.3)	27.7 (7.9)	23.4 (9.3)
Charles *et al.* [23]	41	42	>18 years old Artificial nutrition >48 hours ICU >48 hours	32.9 (2.0)	28.1 (0.9)	16.6 (0.9)	17.3 (0.8)
Desachy *et al.* [24]	50	50	>18 years old Medical or surgical ICU Mechanical ventilation >72 hours	27 (5)	25 (3)	40 (11)[1]	42 (17)[1]
Peake *et al.* [25]	55	57	≥18 years old Enteral nutrition ≥2 days Mechanical ventilation	26.2 (6.4)	27.8 (7.9)	22 (8.9)	23 (9.1)
Rice *et al.* [26]	98	102	ICU admission Mechanical ventilation >72 hours	29.2 (10.2)	28.2 (9.4)	26.9 (8.1)	26.9 (6.6)
Rice *et al.* [27]	508	492	ICU admission ALI <48 hours Mechanical ventilation >72 hours	29.9 (7.8)	30.4 (8.2)	92 (28)[2]	90 (27)[2]
Taylor *et al.* [28]	41	41	Head injury necessitating mechanical ventilation Glasgow Coma Scale >3	N/A	N/A	14[3]	14[3]

[1]Mean APACHE III score. [2]Mean Simplified Acute Physiology Score II. [3]Standard deviation was not reported. ALI, acute lung injury; APACHE, Acute Physiology And Chronic Health Evaluation; BMI, body mass index; HE, high-energy; LE, low-energy; N/A, not available; SD, standard deviation.

Table 2 Nutritional targets and interventions

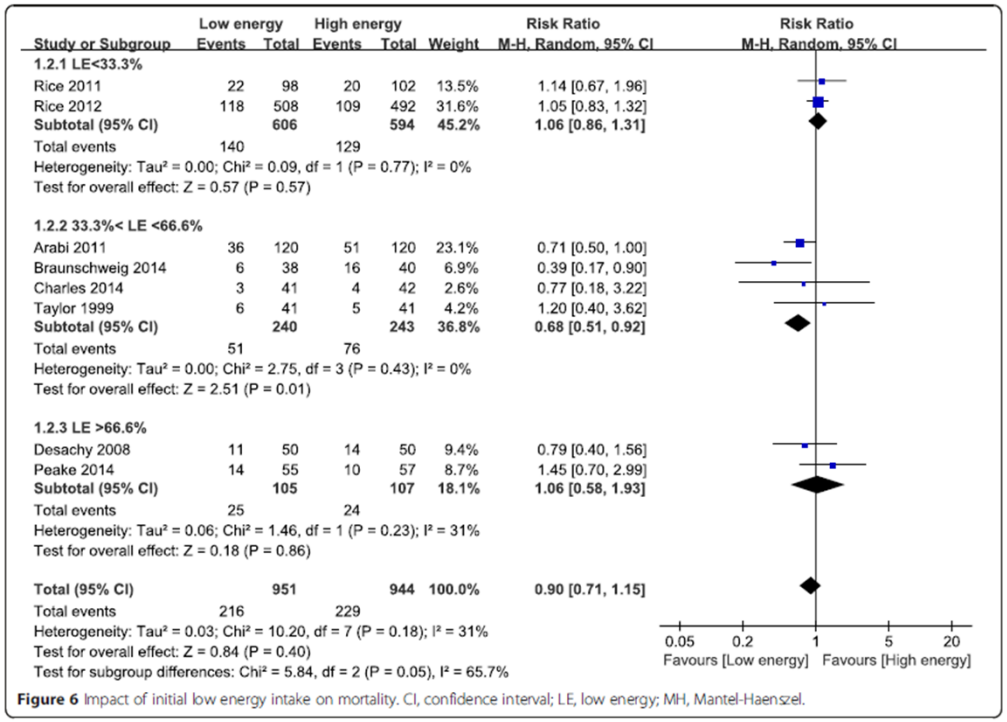
Study	Duration of study (days)	Daily target calorie supply (Kcal/kg)		Mean daily percentage of caloric goal (%)		Mean daily protein intake (g/kg)	
		LE	HE	LE	HE	LE	HE
Arabi *et al.* [21]	7	N/A[1]	N/A[1]	59.0	71.4	65.2%[2]	63.7%[2]
Braunschweig *et al.* [22]	20	25-30	25-30	55.4	84.7	0.68	0.95
Charles *et al.* [23]	10-12	25-30	25-30	40.5	73	1.1	1.1
Desachy *et al.* [24]	5	25	25	76	95	N/A	N/A
Peake *et al.* [25]	10	25-30	25-30	72	102	1.05	1.02
Rice *et al.* [26]	7	25-30	25-30	15	74.8	0.17	0.85
Rice *et al.* [27]	6	25-30	25-30	25	80	N/A	N/A
Taylor *et al.* [28]	7	35	35	36.8	59.2	0.57	1.03

[1]The caloric requirement was estimated using the Harris-Benedict equation and adjusted for stress factors. [2]The percentage of protein requirement was calculated on the basis of patient condition and underlying diseases. HE, high-energy; LE, low-energy; N/A, not available.

Tian F, et al. Crit Care. 2015

Low Energy vs. Full Nutrition

- 3 groups
- High-energy intake does <u>not improve outcomes and may increase complications</u> in critically ill patients who are not malnourished
- Initial moderate nutrient intake compared to high energy may <u>reduce mortality</u>



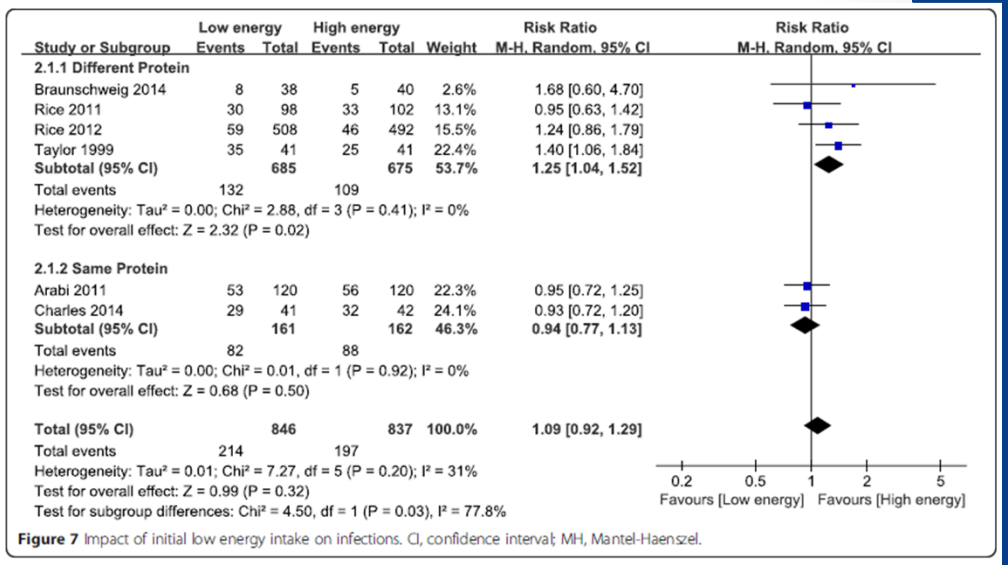
Study or Subgroup	Low energy Events	Low energy Total	High energy Events	High energy Total	Weight	Risk Ratio M-H, Random, 95% CI
1.2.1 LE<33.3%						
Rice 2011	22	98	20	102	13.5%	1.14 [0.67, 1.96]
Rice 2012	118	508	109	492	31.6%	1.05 [0.83, 1.32]
Subtotal (95% CI)		**606**		**594**	**45.2%**	**1.06 [0.86, 1.31]**
Total events	140		129			
Heterogeneity: Tau² = 0.00; Chi² = 0.09, df = 1 (P = 0.77); I² = 0%						
Test for overall effect: Z = 0.57 (P = 0.57)						
1.2.2 33.3%< LE <66.6%						
Arabi 2011	36	120	51	120	23.1%	0.71 [0.50, 1.00]
Braunschweig 2014	6	38	16	40	6.9%	0.39 [0.17, 0.90]
Charles 2014	3	41	4	42	2.6%	0.77 [0.18, 3.22]
Taylor 1999	6	41	5	41	4.2%	1.20 [0.40, 3.62]
Subtotal (95% CI)		**240**		**243**	**36.8%**	**0.68 [0.51, 0.92]**
Total events	51		76			
Heterogeneity: Tau² = 0.00; Chi² = 2.75, df = 3 (P = 0.43); I² = 0%						
Test for overall effect: Z = 2.51 (P = 0.01)						
1.2.3 LE >66.6%						
Desachy 2008	11	50	14	50	9.4%	0.79 [0.40, 1.56]
Peake 2014	14	55	10	57	8.7%	1.45 [0.70, 2.99]
Subtotal (95% CI)		**105**		**107**	**18.1%**	**1.06 [0.58, 1.93]**
Total events	25		24			
Heterogeneity: Tau² = 0.06; Chi² = 1.46, df = 1 (P = 0.23); I² = 31%						
Test for overall effect: Z = 0.18 (P = 0.86)						
Total (95% CI)		**951**		**944**	**100.0%**	**0.90 [0.71, 1.15]**
Total events	216		229			
Heterogeneity: Tau² = 0.03; Chi² = 10.20, df = 7 (P = 0.18); I² = 31%						
Test for overall effect: Z = 0.84 (P = 0.40)						
Test for subgroup differences: Chi² = 5.84, df = 2 (P = 0.05), I² = 65.7%						

Figure 6 Impact of initial low energy intake on mortality. CI, confidence interval; LE, low energy; MH, Mantel-Haenszel.

Tian F, et al. Crit Care. 2015

Low Energy vs. Full Nutrition

- 2 groups
- A <u>higher protein intake</u> combined with high energy (≥0.85 g/kg per day) may <u>decrease the infection rate</u>
- No statistical differences were observed in rates of
  - pneumonia
  - gastrointestinal intolerance
  - hospital and ICU LOS
  - mechanical ventilation days



Study or Subgroup	Low energy Events	Low energy Total	High energy Events	High energy Total	Weight	Risk Ratio M-H, Random, 95% CI
2.1.1 Different Protein						
Braunschweig 2014	8	38	5	40	2.6%	1.68 [0.60, 4.70]
Rice 2011	30	98	33	102	13.1%	0.95 [0.63, 1.42]
Rice 2012	59	508	46	492	15.5%	1.24 [0.86, 1.79]
Taylor 1999	35	41	25	41	22.4%	1.40 [1.06, 1.84]
Subtotal (95% CI)		**685**		**675**	**53.7%**	**1.25 [1.04, 1.52]**
Total events	132		109			
Heterogeneity: Tau² = 0.00; Chi² = 2.88, df = 3 (P = 0.41); I² = 0%						
Test for overall effect: Z = 2.32 (P = 0.02)						
2.1.2 Same Protein						
Arabi 2011	53	120	56	120	22.3%	0.95 [0.72, 1.25]
Charles 2014	29	41	32	42	24.1%	0.93 [0.72, 1.20]
Subtotal (95% CI)		**161**		**162**	**46.3%**	**0.94 [0.77, 1.13]**
Total events	82		88			
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.92); I² = 0%						
Test for overall effect: Z = 0.68 (P = 0.50)						
Total (95% CI)		**846**		**837**	**100.0%**	**1.09 [0.92, 1.29]**
Total events	214		197			
Heterogeneity: Tau² = 0.01; Chi² = 7.27, df = 5 (P = 0.20); I² = 31%						
Test for overall effect: Z = 0.99 (P = 0.32)						
Test for subgroup differences: Chi² = 4.50, df = 1 (P = 0.03), I² = 77.8%						

Figure 7 Impact of initial low energy intake on infections. CI, confidence interval; MH, Mantel-Haenszel.

Tian F, et al. Crit Care. 2015

Low Energy vs. Full Nutrition

The Association Between Nutritional Adequacy and Long-Term Outcomes in Critically Ill Patients Requiring Prolonged Mechanical Ventilation: A Multicenter Cohort Study*

Xuejiao Wei, MSc[1]; Andrew G. Day, MSc[1,2]; Hélène Ouellette-Kuntz, PhD[1]; Daren K. Heyland, MD, MSc[2,3]

- Retrospective analysis of data prospectively collected for multicenter randomized controlled trial
- Adult patients who were mechanically ventilated for more than 8 days in the ICU
- Nutritional adequacy was obtained from the average proportion of prescribed calories received over the amount prescribed during the first 8 days
- Survival status and health-related quality of life as assessed using the SF-36 were obtained at 3 and 6 months post ICU admission

Wei X, et al. Crit Care Med. 2015

Low Energy vs. Full Nutrition

- 475 met the inclusion criteria for this study
- 3 groups

TABLE 1. Patient Baseline Characteristics and Short-Term Clinical Outcomes

Variable	Overall	Nutritional Adequacy[a]			
		Low (0% and ≤ 50%)	Moderate (≥ 50% and < 80%)	High (≥ 80%)	p[b]
Number of patients (%)	475	182 (38)	231 (49)	62 (13)	
Baseline characteristics					
Age, yr	62 ± 15	62 ± 15	62 ± 15	65 ± 14	0.53
Female (%)	187 (40)	55 (30)	102 (44)	30 (48)	0.001
Acute Physiology and Chronic Health Evaluation II score	26.9 ± 7.1	27.2 ± 7.4	26.8 ± 7.0	26.6 ± 7.1	0.94
Charlson Comorbidity Index	1.5 ± 1.7	1.4 ± 1.8	1.6 ± 1.7	1.7 ± 1.9	0.44
Baseline Sequential Organ Failure Assessment	8.6 ± 2.8	8.6 ± 3.1	8.5 ± 2.8	8.5 ± 2.4	0.91
Admission category (%)					< 0.001
Medical	372 (78)	116 (64)	203 (88)	53 (86)	
Surgical	103 (22)	66 (36)	28 (12)	9 (14)	
Primary ICU diagnosis (%)					< 0.001
Cardiovascular	78 (16)	44 (24)	24 (10)	10 (15)	
Respiratory	154 (32)	35 (19)	90 (39)	29 (47)	
Gastrointestinal	44 (9)	25 (14)	12 (5)	7 (11)	
Sepsis	149 (31)	58 (32)	75 (33)	16 (24)	
Other	52 (11)	20 (11)	30 (13)	2 (3)	
Treatment arm (%)					0.07
Antioxidants	114 (24)	32 (18)	65 (28)	19 (27)	
Glutamine	124 (26)	46 (25)	66 (29)	12 (19)	
Glutamine + antioxidants	120 (25)	55 (30)	52 (23)	13 (21)	
Placebo	117 (25)	49 (27)	48 (21)	20 (32)	
Body mass index, kg/m^2					0.31
Overall mean	30.0 ± 8.7	29.7 ± 7.9	30.4 ± 9.1	29.3 ± 9.4	
Underweight (< 18.5) (%)	9 (2)	3 (2)	4 (2)	2 (3)	
Normal weight (18.5–24) (%)	139 (29)	48 (26)	73 (32)	18 (29)	
Overweight (25–29) (%)	145 (31)	64 (35)	58 (25)	23 (37)	
Obese I (30–34) (%)	82 (17)	34 (19)	38 (17)	10 (16)	
Obese II (35–40) (%)	42 (9)	15 (8)	23 (10)	4 (7)	
Obese III (> 41) (%)	58 (12)	18 (10)	35 (15)	5 (8)	
Region (%)					0.09
Canada	404 (85)	144 (79)	203 (88)	57 (92)	
Europe	15 (3)	5 (3)	8 (3)	2 (3)	
United States	56 (12)	33 (18)	20 (9)	3 (4)	
Short-term clinical outcomes					
ICU length of stay					
Median (interquartile range)	18 (13–29)	18 (13–28)	19 (13–31)	18 (12–29)	
Mechanical ventilation duration					
Median (interquartile range)	15 (11–25)	15 (10–23)	15 (11–25)	15 (11–25)	
ICU mortality[c] (%)	123 (26)	47 (26)	62 (27)	14 (23)	0.63
Hospital mortality (%)	151 (32)	58 (32)	75 (32)	18 (29)	0.85

[a]Proportion of caloric prescription received by enteral nutrition and parenteral nutrition over first 8 days of mechanical ventilation and ICU stay.
[b]To account for ICU-level clustering, *p* values were calculated by Rao-Scott adjusted chi-square method for categorical variables and the linear generalized estimating equations for continuous variables.
[c]ICU mortality is calculated based on the raw number of deaths prior to ICU discharge.
Data are reported as number (%) or mean ± SD.

Wei X, et al. Crit Care Med. 2015

Low Energy vs. Full Nutrition

- Survival time in those who received low nutritional adequacy <u>was significantly shorter</u> than those who received high nutritional adequacy while adjusting for covariates

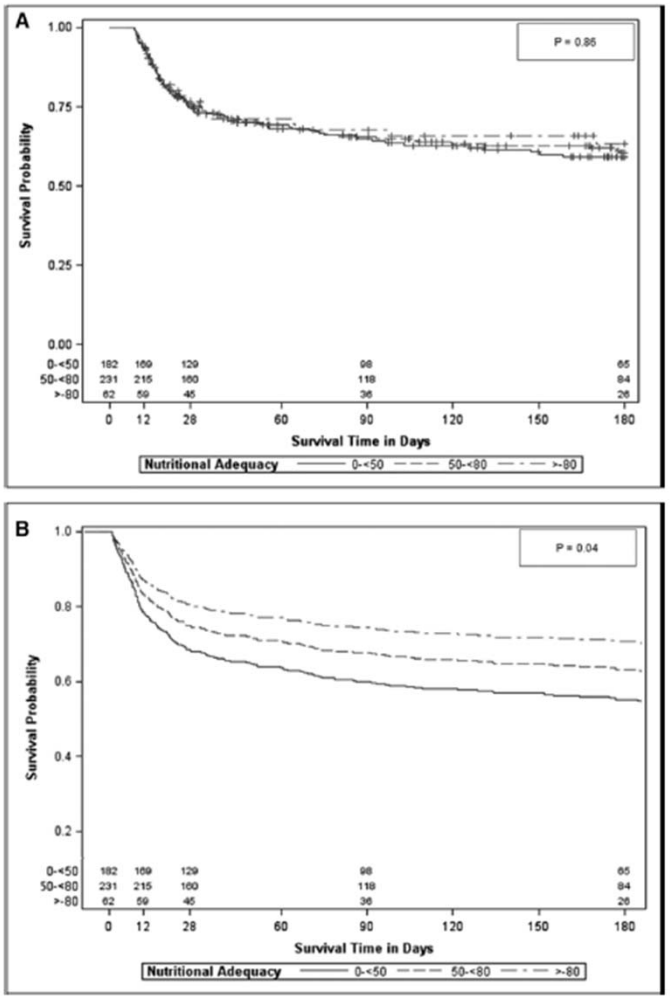


Figure 2. Crude (**A**) and adjusted (**B**) survival curves stratified by nutritional adequacy groups in 475 patients who were mechanically ventilated in the ICU for more than 8 days. Adjusted covariates include age, Acute Physiology and Chronic Health Evaluation II score, baseline Sequential Organ Failure Assessment, Charlson Comorbidity Index, admission category, primary ICU diagnosis, body mass index, and region.

Wei X, et al. Crit Care Med. 2015

Low Energy vs. Full Nutrition

TABLE 4. Estimates of the Effect of Nutritional Adequacy on 36-Item Short-Form Health Survey Scores

36-Item Short-Form Health Survey	Nutritional Adequacy[a] per 25% Increase			
	Crude Estimate[b] (95% CI)	*p*	Adjusted Estimate[b,c] (95% CI)	*p*
Physical Functioning				
3 mo (*n* = 179)[d]	7.7 (2.3–13.1)	0.006	7.3 (1.4–13.2)	0.02
6 mo (*n* = 202)[d]	5.3 (0.0–10.5)	0.05	4.2 (−1.3 to 9.6)	0.14
Role Physical				
3 mo (*n* = 178)[d]	8.3 (3.0–13.5)	0.002	8.3 (2.7–14.0)	0.004
6 mo (*n* = 202)[d]	5.0 (−0.2 to 10.2)	0.06	3.2 (−2.3 to 8.5)	0.25
Physical Component Scale				
3 mo (*n* = 175)[d]	1.8 (−0.1 to 3.7)	0.06	1.8 (−0.2 to 3.8)	0.07
6 mo (*n* = 200)[d]	1.8 (−0.2 to 3.7)	0.07	1.3 (−0.7 to 3.3)	0.19

[a]Proportion of caloric prescription received by enteral nutrition and parenteral nutrition over first 8 days of mechanical ventilation and ICU stay.
[b]The estimate provides the change in 36-Item Short-Form Health Survey (SF-36) scores for every 25% increase in nutritional adequacy.
[c]Adjusted for age, Acute Physiology and Chronic Health Evaluation II score, baseline Sequential Organ Failure Assessment, Functional Comorbidity Index, admission category, body mass index, and region.
[d]*n* provides the number of responders for each SF-36 score.

- Concluded
  - Greater amounts of nutritional intake received during the first week in the ICU were associated with longer survival time and faster physical recovery to 3 months but not 6 months post ICU
  - Current recommendations to underfeed critically ill patients may cause harm in some long-stay patients.

Wei X, et al. Crit Care Med. 2015

Low Energy vs. Full Nutrition

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Permissive Underfeeding or Standard Enteral Feeding in Critically Ill Adults

Yaseen M. Arabi, M.D., Abdulaziz S. Aldawood, M.D., Samir H. Haddad, M.D., Hasan M. Al-Dorzi, M.D., Hani M. Tamim, M.P.H., Ph.D., Gwynne Jones, M.D., Sangeeta Mehta, M.D., Lauralyn McIntyre, M.D., Othman Solaiman, M.D., Maram H. Sakkijha, R.D., Musharaf Sadat, M.B., B.S., and Lara Afesh, M.S.N., for the PermiT Trial Group*

- Looked at permissive underfeeding (40-60% of requirement) with full protein vs. standard enteral feeding (70-100%)
- RCT
- 894 patients

Arabi YM, et al. NEJM. 2015

Low Energy vs. Full Nutrition

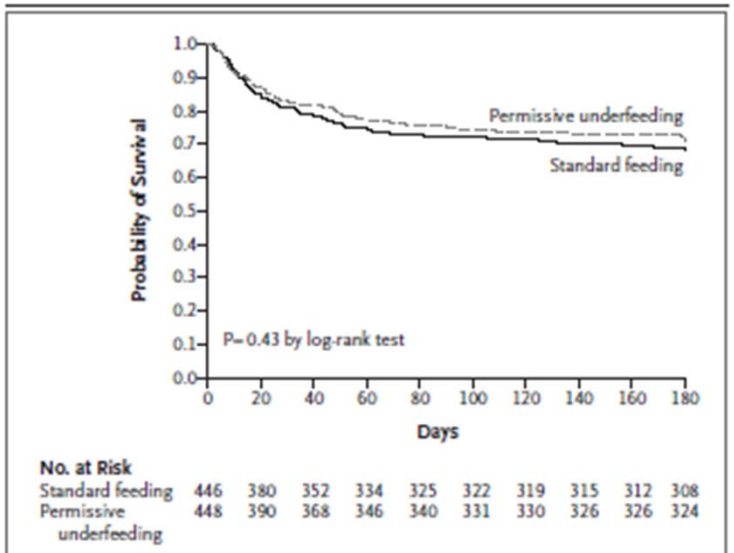


Figure 2. Kaplan–Meier Curves for Survival up to 180 Days after Enrollment.

Table 3. Outcomes in the Permissive-Underfeeding and Standard-Feeding Groups.*

Outcome	Permissive Underfeeding (N=448)	Standard Feeding (N=446)	Relative Risk (95% CI)	P Value
Death by 90 days — no./total no. (%)	121/445 (27.2)	127/440 (28.9)	0.94 (0.76–1.16)	0.58
Death in the ICU — no. (%)	72 (16.1)	85 (19.1)	0.84 (0.63–1.12)	0.24
Death by 28 days — no./total no. (%)	93/447 (20.8)	97/444 (21.8)	0.95 (0.74–1.23)	0.7
Death in the hospital — no./total no. (%)	108/447 (24.2)	123/445 (27.6)	0.87 (0.70–1.09)	0.24
Death by 180 days — no./total no. (%)	131/438 (29.9)	140/436 (32.1)	0.93 (0.76–1.14)	0.48
Duration of mechanical ventilation — days				
Median	9	10		0.49†
Interquartile range	5–15	5–16		
Days free from mechanical ventilation				
Median	77	75		0.48†
Interquartile range	0–84	0–84		
ICU length of stay — days				
Median	13	13		0.46†
Interquartile range	8–21	8–20		
ICU-free days				
Median	72	71		0.28†
Interquartile range	0–81	0–79		
Hospital length of stay — days				
Median	28	30		0.24†
Interquartile range	15–54	14–63		
Hypoglycemia — no. (%)	6 (1.3)	7 (1.6)	0.85 (0.29–2.52)	0.77
Hypokalemia — no. (%)	101 (22.5)	91 (20.4)	1.10 (0.86–1.42)	0.44
Hypomagnesemia — no. (%)	127 (28.3)	131 (29.4)	0.97 (0.79–1.19)	0.74
Hypophosphatemia — no. (%)	267 (59.6)	261 (58.5)	1.01 (0.91–1.14)	0.74
Transfusion of packed red cells — no. (%)	141 (31.5)	142 (31.8)	0.99 (0.82–1.20)	0.91
Incident renal-replacement therapy — no./total no. (%)	29/406 (7.1)	45/396 (11.4)	0.63 (0.40–0.98)	0.04
ICU-associated infection — no. (%)	161 (35.9)	169 (37.9)	0.95 (0.80–1.13)	0.54
Urinary tract infection — no. (%)	45 (10.0)	48 (10.8)	0.93 (0.64–1.37)	0.73
Catheter-related infection — no. (%)	11 (2.5)	19 (4.3)	0.58 (0.28–1.20)	0.13
Ventilator-associated pneumonia — no. (%)	81 (18.1)	90 (20.2)	0.90 (0.68–1.17)	0.43
ICU-associated severe sepsis or septic shock — no. (%)	61 (13.6)	58 (13.0)	1.05 (0.75–1.46)	0.79
Feeding intolerance — no. (%)	67 (15.0)	79 (17.7)	0.84 (0.63–1.14)	0.26
Diarrhea — no. (%)	97 (21.7)	117 (26.2)	0.83 (0.65–1.04)	0.11

- Baseline characteristics were similar
- The permissive underfeeding group received fewer mean calories than the standard feeding group
- Protein intake was similar
- The 90-day mortality was <u>no different</u>
- There were <u>no significant differences</u> with respect to feeding intolerance, diarrhea, infections acquired in the ICU, or ICU or hospital LOS

Arabi YM, et al. NEJM. 2015

Now, what do we do?

Enteral vs. Parenteral Nutrition

- Pragmatic, randomized trial involving adults with an unplanned admission to 33 English ICUs
- Randomly assigned patients who could be fed through either the parenteral or the enteral route to a delivery route, with nutritional support initiated within 36 hours after admission and continued for up to 5 days

- The primary outcome was all-cause mortality at 30 days.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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*

ABSTRACT

Harvey SE, et al. NEJM. 2014

Enteral vs. Parenteral Nutrition

- Enrolled 2400 patients
  - 1191 in the parenteral group
  - 1197 in the enteral group
- At 30 days, 33.1% mortality in the parenteral group and 34.2% in the enteral group

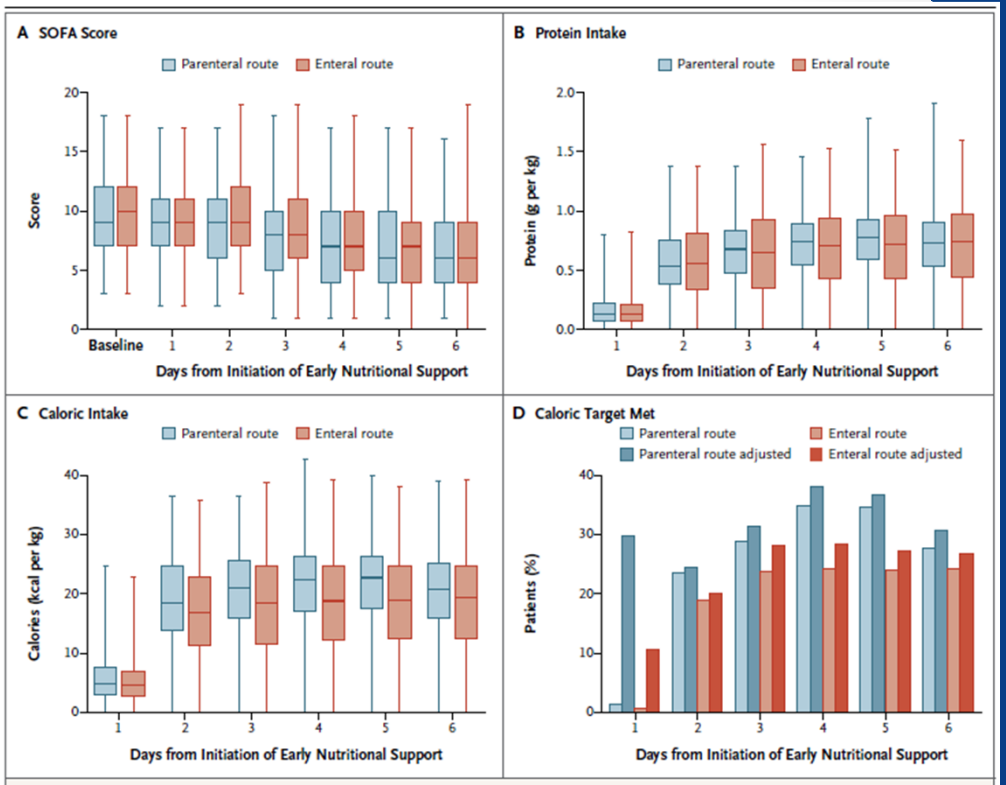


Figure 2. Daily SOFA Score and Protein and Caloric Intake from Days 1 to 6.
Panel A shows the Sequential Organ Failure Assessment (SOFA) scores for the 24 hours before randomization (baseline) and from day 1 to day 6. SOFA scores range from 0 to 24, with higher scores indicating a greater degree of organ failure. Also shown are the total amounts of protein (Panel B) and calories (Panel C) received per kilogram of actual or estimated body weight. Panel D shows the percentage of patients in whom the target of 25 kcal per kilogram of body weight per day was met. The dark-colored bars show the percentage of patients in whom the target was met after adjustment for partial days of feeding (e.g., after the death of a patient). Day 1 data are the values from the time of initiation to the end of the day of initiation of nutritional support. In Panels A to C, the horizontal lines within the boxes indicate medians, the lower and upper ends of the boxes the 25th and 75th percentiles, respectively, and the I bars the 1st and 99th percentiles.

Harvey SE, et al. NEJM. 2014

Enteral vs. Parenteral Nutrition

- There were significant reductions in the parenteral group, as compared with the enteral group, in rates of hypoglycemia and vomiting
- There were no significant differences between the parenteral group and the enteral group in
  - the mean number of treated infectious complications
  - 90-day mortality
  - other secondary outcomes
  - rates of adverse events

Table 3. Primary and Secondary Outcomes.*

Outcome	Parenteral Group (N=1191)	Enteral Group (N=1197)	Absolute Difference between Groups (95% CI)	Relative Risk (95% CI)	P Value
Primary outcome: death within 30 days — no./total no. (%)	393/1188 (33.1)	409/1195 (34.2)	1.15 (−2.65 to 4.94)†	0.97 (0.86 to 1.08)‡	0.57§
Secondary outcomes					
No. of days alive and free of specified organ support up to 30 days¶					
Free of advanced respiratory support	14.3±12.1	14.3±12.2	0.04 (−0.94 to 1.01)		0.94
Free of advanced cardiovascular support	18.9±13.5	18.5±13.6	0.41 (−0.63 to 1.53)		0.44
Free of renal support	19.1±13.9	18.8±14.0	0.26 (−0.85 to 1.47)		0.66
Free of neurologic support	19.2±13.8	18.9±14.0	0.34 (−0.81 to 1.36)		0.57
Free of gastrointestinal support	13.0±11.7	13.2±11.8	−0.12 (−1.05 to 0.80)		0.81
No. of treated infectious complications per patient‖	0.22±0.60	0.21±0.56	0.01 (−0.04 to 0.06)		0.72
Noninfectious complications — no./total no. (%)					
Episodes of hypoglycemia	44/1191 (3.7)**	74/1197 (6.2)††	2.49 (0.75 to 4.22)†		0.006§
Elevated liver enzymes	212/1191 (17.8)	179/1197 (15.0)	−2.85 (−5.81 to 0.12)†		0.07§
Nausea requiring treatment	44/1191 (3.7)	53/1197 (4.4)	0.73 (−0.85 to 2.32)†		0.41§
Abdominal distention	78/1191 (6.5)	99/1197 (8.3)	1.72 (−0.38 to 3.82)†		0.12§
Vomiting	100/1191 (8.4)	194/1197 (16.2)	7.81 (5.20 to 10.43)†		<0.001§
New or substantially worsened pressure ulcers	181/1190 (15.2)	179/1195 (15.0)	−0.23 (−3.10 to 2.64)†		0.91§
Median no. of days in the ICU (IQR)‡‡	8.1 (4.0–15.8)	7.3 (3.9–14.3)			0.15
Median no. of days in acute care hospital (IQR)§§	17 (8–34)	16 (8–33)			0.32
Death — no./total no. (%)¶¶					
In the ICU	317/1190 (26.6)	352/1197 (29.4)		0.91 (0.80 to 1.03)	0.13§
In acute care hospital	431/1185 (36.4)	450/1186 (37.9)		0.96 (0.86 to 1.06)	0.44§
By 90 days	442/1184 (37.3)	464/1188 (39.1)		0.96 (0.86 to 1.06)	0.40§

* Plus–minus values are means ±SD.
† This value is the absolute risk reduction between event rates.
‡ The adjusted odds ratio from multiple logistic regression was 0.95 (95% CI, 0.79 to 1.13; P=0.55).
§ This P value was calculated with the use of Fisher's exact test.
¶ Data on the number of days alive and free of organ support were not available for 5 patients in the parenteral group and 2 in the enteral group.
‖ Infectious complications in 224 of 262 patients (85.5%) in the parenteral group and in 215 of 253 patients (85.0%) in the enteral group were confirmed on laboratory testing.
** A total of 25 these episodes occurred during the first 6 days, and the mean (±SD) of the lowest blood glucose levels was 57±15 mg per deciliter (3.2±0.8 mmol per liter).
†† A total of 48 of these episodes occurred during the first 6 days, and the mean of the lowest blood glucose levels was 54±15 mg per deciliter (3.0±0.8 mmol per liter).
‡‡ The number of days in the ICU was not available for 1 patient in the parenteral group.
§§ The numbers of days in an acute care hospital were not available for 6 patients in the parenteral group and 11 in the enteral group.
¶¶ The adjusted odds ratios from multiple logistic regression were 0.86 (95% CI, 0.71 to 1.04; P=0.12) for death in the ICU, 0.93 (95% CI, 0.78 to 1.11; P=0.43) for death in an acute care hospital, and 0.93 (95% CI, 0.77 to 1.11; P=0.39) for death by 90 days.

Harvey SE, et al. NEJM. 2014

Timing of Parenteral Nutrition

Bost *et al. Annals of Intensive Care* 2014, **4**:31
http://www.annalsofintensivecare.com/content/4/1/31

Annals of Intensive Care
a SpringerOpen Journal

REVIEW **Open Access**

Timing of (supplemental) parenteral nutrition in critically ill patients: a systematic review

Rianne BC Bost[1], Dave HT Tjan[1] and Arthur RH van Zanten[1,2*]

- Systematic review summarizing results of prospective studies among adult ICU patients addressing the best timing of supplemental parenteral nutrition (SPN)
  - initiation of SPN <48 h after admission (EPN)
  - initiation of SPN until day 8 after ICU admission (LPN)
- 4 RCTs and 2 prospective observational studies

Bost RBC, et al. Ann Intensive Care. 2014

Timing of Parenteral Nutrition

- 1 RCT found a higher percentage of alive discharge from the ICU at day 8 in the LPN group compared to EPN group ($p = 0.007$) but no differences in ICU and in-hospital mortality.
- None of the other RCTs found differences in ICU or in-hospital mortality rates.
- Contradicting or divergent results on other secondary outcomes were found for
  - ICU length of stay
  - hospital length of stay
  - infection rates
  - nutrition targets
  - duration of mechanical ventilation
  - glucose control
  - duration of renal replacement therapy
  - muscle wasting and fat loss.

- It is reasonable to assume that in adult critically ill patients, there <u>are no clinically relevant benefits of EPN compared with LPN</u> with respect to morbidity or mortality end points, when full enteral support is contraindicated or fails to reach caloric targets.

Bost RBC, et al. Ann Intensive Care. 2014

Nutritional Supplements

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Randomized Trial of Glutamine and Antioxidants in Critically Ill Patients

Daren Heyland, M.D., John Muscedere, M.D., Paul E. Wischmeyer, M.D., Deborah Cook, M.D., Gwynne Jones, M.D., Martin Albert, M.D., Gunnar Elke, M.D., Mette M. Berger, M.D., Ph.D., and Andrew G. Day, M.Sc., for the Canadian Critical Care Trials Group

- REDOXS
- Blinded 2-by-2 factorial trial
- 1223 critically ill adults in 40 ICUs
- Patients with multiorgan failure and were receiving mechanical ventilation
- Radomized to receive glutamine, antioxidants, both, or placebo.
- Supplements were started within 24 hours after admission to the ICU and were provided both intravenously and enterally.
- The primary outcome was 28-day mortality.

Heyland D, et al. NEJM. 2013

Nutritional Supplements

- There was a trend toward increased mortality at 28 days among patients who received glutamine
- In-hospital mortality and mortality at 6 months were significantly higher among those who received glutamine
- Glutamine had no effect on rates of organ failure or infectious complications.

- Early provision of glutamine or antioxidants did not improve clinical outcomes, and <u>glutamine was associated with an increase in mortality</u> among critically ill patients with multiorgan failure.

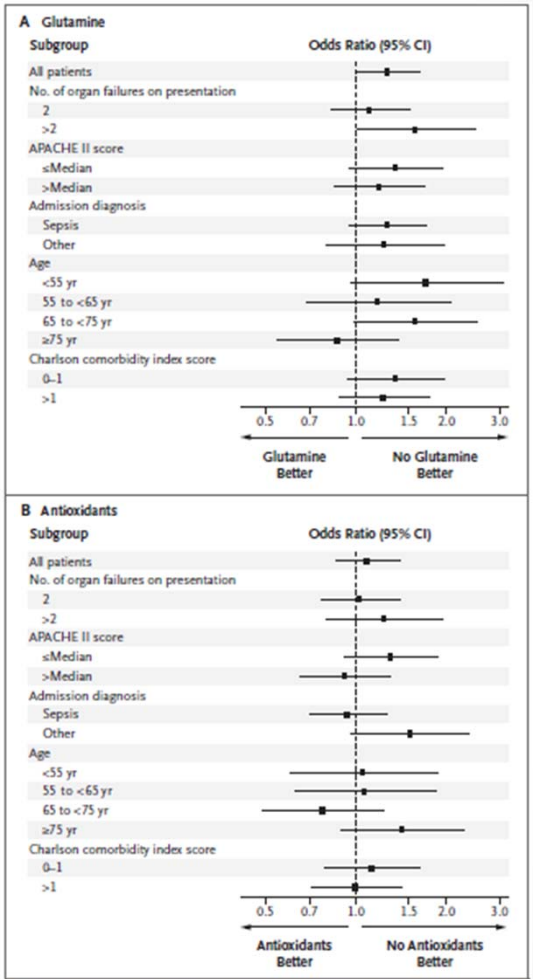


Figure 2. Prespecified Subgroup Analyses of Death at 28 Days, According to Study Group.
Odds ratios and 95% confidence intervals are shown for the primary outcome in each prespecified subgroup. Higher Acute Physiology and Chronic Health Evaluation II (APACHE II) scores indicate greater disease severity. CI denotes confidence interval.

Heyland D, et al. NEJM. 2013

Topic	CCPG 2015	CCPG 2013	ASPEN/SCCM 2009
Enteral vs. Parenteral Nutrition	Recommend the use of enteral nutrition over parenteral nutrition	**Strongly** recommend the use of enteral nutrition over parenteral nutrition	EN is the preferred route of feeding over PN for the critically ill patient who requires nutrition support therapy
Early vs. Delayed	No change	Recommend early enteral nutrition (within 24-48) hours	Enteral feeding should be started early within the first 24 – 48 hours following admission
Trophic vs. Full Feeds	No change	In patients with ALI, and initial strategy of trophic feeds for 5 days should NOT be considered	Efforts to provide 50% to 65% of goal calories should be made to achieve the clinical benefit of EN over the first week of hospitalization
Hypocaloric Enteral Nutrition	Intentional underfeeding of calories (not protein) should be considered in patients with low nutritional risk. This does not apply to patients with high nutritional risk	Insufficient data to make recommendations	Efforts to provide 50% to 65% of goal calories should be made to achieve the clinical benefit of EN over the first week of hospitalization

Canadian Clinical Practice Guidelines 2015

Summary of Revisions to the Recommendations

Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: Society of Critical Care Medicine and American Society for Parenteral and Enteral Nutrition*

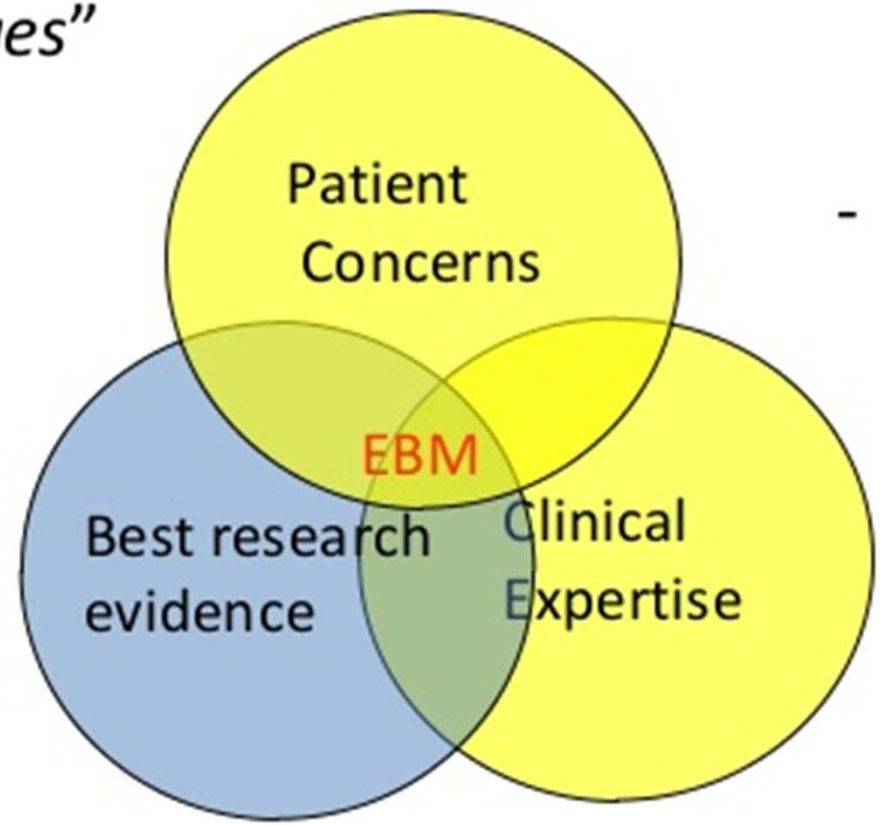
Robert G. Martindale, MD, PhD; Stephen A. McClave, MD; Vincent W. Vanek, MD; Mary McCarthy, RN, PhD; Pamela Roberts, MD; Beth Taylor, RD; Juan B. Ochoa, MD; Lena Napolitano, MD; Gail Cresci, RD; American College of Critical Care Medicine; the A.S.P.E.N. Board of Directors

Topic	CCPG 2015	CCPG 2013	ASPEN/SCCM 2009
Enteral vs. Parenteral Immune Enhancing Diets: Glutamine	Recommend that glutamine NOT be used	Enteral glutamine should be considered in trauma and burn patients	Immune-modulating enteral formulations should be used for the appropriate patient population
Early vs. Delayed Supplemental Parenteral Nutrition	No change	**Strongly** recommend that early supplemental PN NOT be used in unselected patients. Insufficient data for patients not tolerating EN	If early EN is not feasible for 7 days following admission no nutrition support therapy should be provided. In the patient who was previously healthy with no evidence of protein-calorie malnutrition, use of PN should be initiated only after the first 7 days of hospitalization
Small Bowel vs. Gastric Feeding	No change	Small bowel feeding may be associated with a reduction in pneumonia. In units where small bowel access is feasible, we **recommend** the routine use of small bowel feedings. Small bowel feedings **should be considered** for those select patients that demonstrate high gastric residuals and are not tolerating adequate amounts of EN intragastrically.	Either gastric or small bowel feeding is acceptable in the ICU setting. Critically ill patients should be fed via an enteral access tube placed in the small bowel if at high risk for aspiration or after showing intolerance to gastric feeding

Evidence Based Medicine

"Evidence-based medicine is the integration of best *research evidence* with *clinical expertise* and *patient values*"

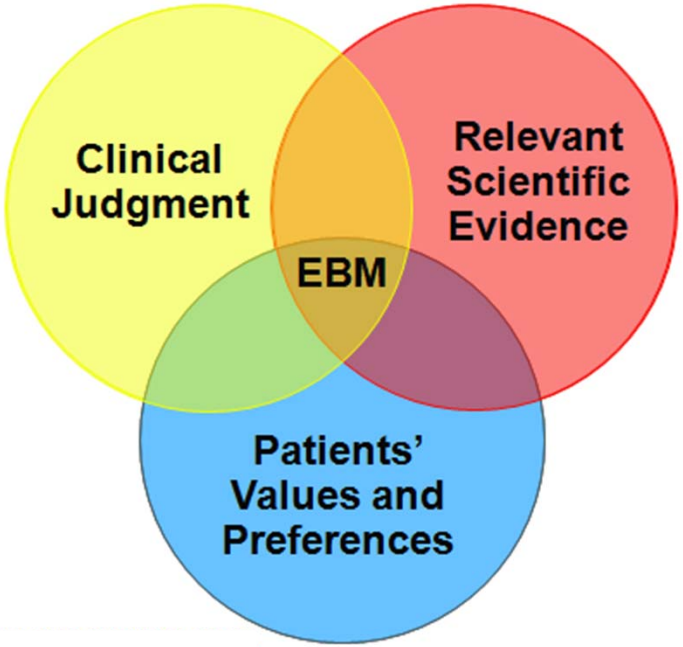
- *Dave Sackett*



Sackett D, et al. Brit Med J. 1996

Evidence Based Medicine

- "…it transforms the complex process of clinical decision making—which includes data gathering, years of medical knowledge, experience, and astute intuition—into an algorithmic exercise that is not individualized for specific clinical scenarios and therefore subject to error in patient care."



Sur RL and Dahm P. Indian J Urol. 2011
Sackett DL, et al. BMJ. 1996

Ten big mistakes in intensive care medicine.

1. **We focus too much on syndromes** — prominently the acute respiratory distress syndrome (ARDS), sepsis, and acute kidney injury (AKI)—and we spend much time redefining them.

2. **We jump to prospective randomized clinical trials**, before fully identifying the right patient population, and then struggle to interpret the results.

6. **We don't use protocols enough, and we use protocols too much**.

Physicians may blindly rely on protocols, and no longer critically evaluate their patients.

7. We have been **too aggressive with many of our interventions**, often with the goal of normalizing the patient's ''physiology'' (too many calories, too much invasive monitoring, too many transfusions, too much tidal volume, etc.)

By being so aggressive, we inadvertently undermine the dictum of primum non nocere.

Vincent JL, et al. Intensive Care Med. 2015

An email…

- *"Evidence based medicine has a life expectancy of 5 years on average for each disease process.!!*
  - *Anti arrhythmic for asymptomatic arrhythmia*
  - *Blood sugar control in ICU*
  - *Carotid endarterectomy for asymptomatic carotid stenosis*
  - *Stress test for asymptomatic middle age male*
  - *Early goal directed therapy!*
  - *Goals of lipid lowering therapy!!*
- *This is an ever growing list.*
- *We still have to be doctors who use commonsense and diligence to care for the sick in the society.*
- *Dogma of evidence [based] medicine shouldn't prevail but be an additional tool for us to use.“*

-Dr. Siva, 2015

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