

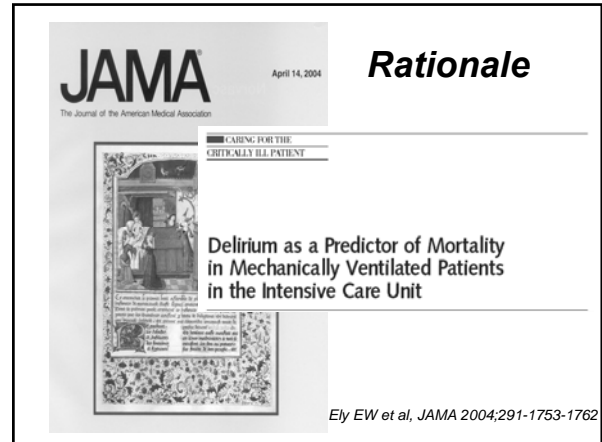
Critical Care and Industry Sponsorship: It Can Work Well

Pratik Pandharipande, M.D., M.S.C.I.
Vanderbilt University Medical Center
Nashville, Tennessee

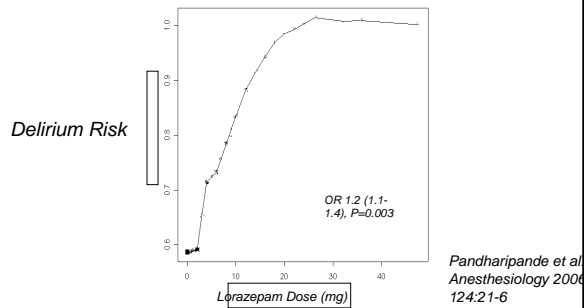


Critical Care and Industry: Making the partnership work!

Pratik Pandharipande, MD, MSCI
Department of Anesthesiology,
Division of Critical Care
Vanderbilt University School of Medicine,
Nashville, TN



Genesis of the Hypothesis



Hypothesis

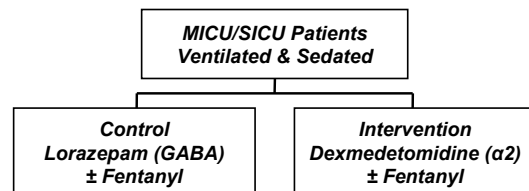
To determine if changing sedation paradigms by targeting α_2 receptors instead of GABA receptors will

- reduce duration and prevalence of acute brain dysfunction (delirium and coma)
- achieve equivalent efficacy of sedation

Navigating the MENDS trial

1. Development of protocol
2. Funding and Contacts
3. FDA
4. Re-negotiating contracts
5. Expanding the study
6. Taking it to publication

MENDS Trial Double-blind, randomized, controlled



Vanderbilt University Medical Center and Washington Hospital Center

Pandharipande PP, et al. JAMA 2007;298:2644-53

Protocol development issues

- *Wanted it to be a real life study*
- *Choice of comparator?*
- *Could we blind the infusion?*
 - *lorazepam dosed as mg/hr*
 - *Dexmedetomidine as mcg/kg/hr*
- *What would be our study population?*
- *What would be maximal dose and duration of dexmedetomidine allowed?*
- *What would be the rescue drug?*
- *Would antipsychotic medications be permitted?*

Quest for Funding

- *Established dialogue between Investigators and Abbot*
- *Visit to Vanderbilt to meet our research group*
 - *Our focus delirium and role of sedation*
 - *Abbot's focus- Can dexmedetomidine be used in the MICU*
- *Abbot not too enthusiastic about "delirium endpoints"*
- *Concern about the higher dose (1.5 mcg/kg/hr) and longer duration (up to 5 days) proposed- ? FDA approval*
- *Better chance if budget <\$200,000*

My own academic development

- *Interested in becoming a clinician-scientist (Drs. Wes Ely, Jeff Balsler and Mervyn Maze as mentors)*
- *Applied for the Masters in Science and Clinical Investigation (MSCI) program*
- *Awarded the Vanderbilt Physician Scientist Award (VPSD)*
- *Guaranteed 80% protected research time for period Sept 2003-June 2005*

Grant In Aid

- *Initial GIA approved late 2003 with a \$180,000 budget for a 40 patient pilot study to evaluate efficacy of sedation*
 - *Study drug*
 - *Research nurse for 1 year*
 - *Pharmacy and IRB administrative costs*
- *No support for Investigators*
 - *Wes Ely- NIH*
 - *Pratik Pandharipande- VPSD award*
 - *Additional personnel- Departmental funds*

FDA IND-early 2004

- *Established communications with the FDA and applied for FDA IND*
- *FDA modifications*
 - *Exclude patients with Child B and C cirrhosis*
 - *Exclude patients with coronary ischemia, including post CABG*
 - *Daily troponins and EKG for all study days and again after end of study drug*
 - *Daily bilirubin and SGPT*
 - *Expansion of endocrine labs beyond cortisol to evaluate LH, prolactin, ACTH, testosterone*
- *Additional cost approx \$150,000*

Re-negotiating contract

- *Needed additional funds for FDA mandated labs*
- *Abbot spins off Hospira as an independent company- new folks take over!!*
- *Protocol revised to include FDA labs and exclusions*
- *Revised GIA submitted and approved by new committee- \$325,000*

The desire to do more!!!

- *Inclusion of surgical and medical patients*
- *Keen on studying the impact on delirium duration and not just efficacy of sedation*
- *Banking DNA*
- *Collection of plasma to study drug plasma levels, cytokines etc*

Re-negotiating contract...again

- *Supportive group at Hospira*
- *Change in primary outcome to duration of delirium*
- *Doubling of sample size to 106*
- *Hospira unable to "double budget"-additional \$150,000- total \$475,000*
- *Separate provision for drug negotiated*
- *Application to GCRC at Vanderbilt for support for genetics and cytokine analysis*

Final Contract

- *Investigator initiated study- research grant provided by Hospira*
 - *Research nurse, safety labs, drug, IRB, misc*
- *Investigator initiated and designed protocol. No modifications by Hospira*
- *Hospira had no access to the raw data*
- *No reporting of AE, SAE, PD etc mandated*
- *Independent DSMB*
- *Independent Vanderbilt statistician*
- *Hospira to get data if no write up occurred 3 years after enrollment ended*

Enrollment and expansion

- *Enrollment started in August 2004*
- *Desired expansion to 2 additional sites*
 - *Washington Hospital Center- Dr. Dan Herr*
 - *Columbia- Dr. Sladen*
- *Viewed with enthusiasm by Hospira, but contract issues*
- *Vanderbilt subcontract with WH*
- *Study drug and randomization provided by our Investigational pharmacy to theirs*
- *Site visit and start up in mid 2005*

Funding issues resurface


- *PI-need for funded protected time (VPSD ended June 2005)*
- *ASCCA-FAER Mentored Research Grant- July 2005-June 2007*
 - *Committee concerned about Industry involvement*
 - *Required assurances from Chair and Investigator about appropriate use of funds*

Taking it to publication

- *Data analysis independent of Industry*
- *No discussion of results till abstract accepted at ATS 2007*
- *Final manuscript provided to Hospira to evaluate for accuracy about "dexmedetomidine" per contract.*
- *Hospira- no role in write up of manuscript*

JAMA
The Journal of the American Medical Association
December 12, 2007

CARING FOR THE CRITICALLY ILL PATIENT



Effect of Sedation With Dexmedetomidine vs Lorazepam on Acute Brain Dysfunction in Mechanically Ventilated Patients: The MENDS Randomized Controlled Trial

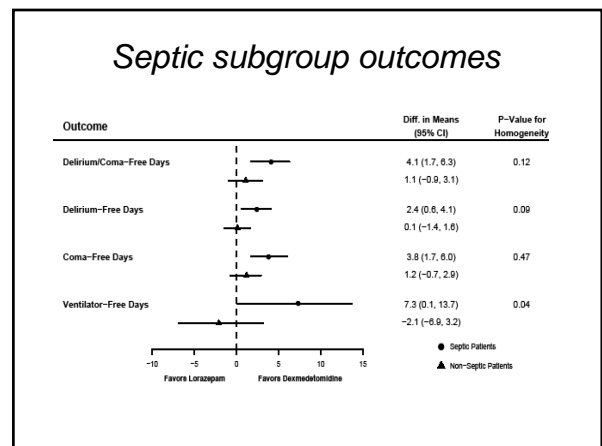
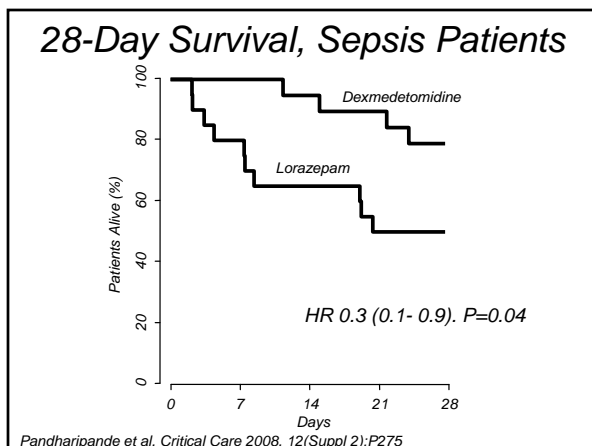
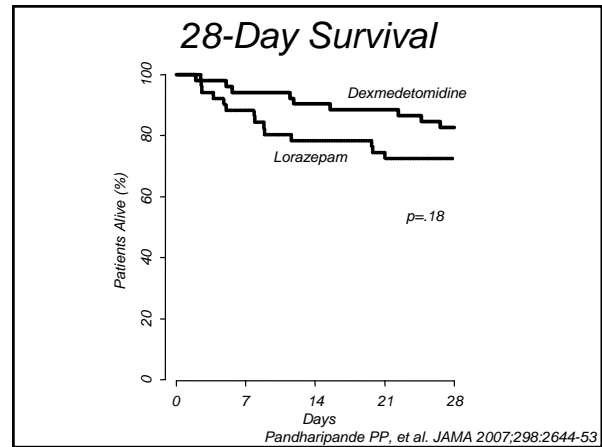
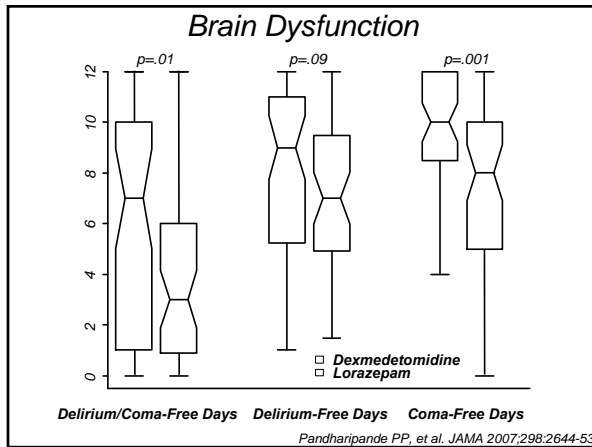
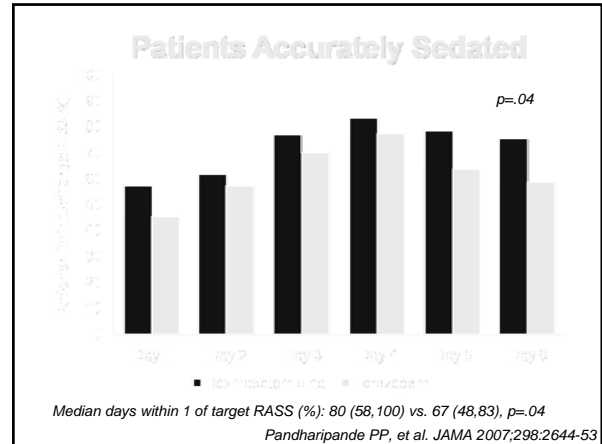
Pratik P. Pandharipande, MD, MSc
Brenda T. Poon, RN, MSN, ACNP
David L. Heron, MD
Mervyn Maze, MR, CChB
Timothy D. Girard, MD, MSc
Russell S. Miller, MD, MPH
Aransi K. Shisani, MPH, PhD
Jennifer L. Thompson, MPH
James C. Jackson, PhD
Stephane A. Durrans, MA, MS
Robert A. Silvers, PhD
Robert S. Utman, MD, MPH
Gordon B. Downard, MD
E. Wesley Ely, MD, MPH

Context: Lorazepam is currently recommended for sustained sedation of mechanically ventilated intensive care unit (ICU) patients, but this and other benzodiazepine drugs may contribute to acute brain dysfunction, ie, delirium and coma, associated with prolonged hospital stays, costs, and increased mortality. Dexmedetomidine induces sedation via different central nervous system receptors than the benzodiazepine drugs and may lower the risk of acute brain dysfunction.

Objective: To determine whether dexmedetomidine reduces the duration of delirium and coma in mechanically ventilated ICU patients while providing adequate sedation as compared with lorazepam.

Design, Setting, Patients, and Intervention: Double-blind, randomized controlled trial of 106 adult mechanically ventilated medical and surgical ICU patients at 2 tertiary care centers between August 2004 and April 2006. Patients were sedated with dexmedetomidine or lorazepam for as many as 120 hours. Study drugs were titrated to achieve the desired level of sedation, measured using the Richmond Agitation Sedation Scale (RASS). Patients were monitored twice daily for delirium using the Confusion Assessment Method for the ICU (CAM-ICU).

Main Outcome Measures: Days alive without delirium or coma and percentage of flow-speak sessions (RASS level of 0-3) without the sedation goal.



Potential pitfalls

- ***Contracts***
 - *Ownership of data*
 - *Publication rights/ control*
 - *Subcontracting with other sites*
- ***Budget negotiations***
 - *Personnel coverage (especially PI, Co-PI)*
 - *University Indirects*
- ***Conflicts of Interest***

Future direction

- ***Can we reduce mortality by altering sedation paradigms***
- ***Does sedative choice matter in sepsis***
- ***Mechanisms for the beneficial effects of dexmedetomidine***
 - *Attenuation of inflammation*
 - *Promotion of sleep*
 - *Anti-apoptosis*
- ***Funding goal- NIH plus Industry***

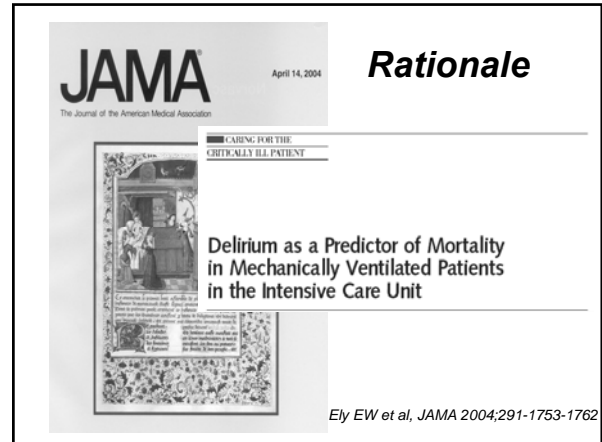
Critical Care and Industry Sponsorship: It Can Work Well

Pratik Pandharipande, M.D., M.S.C.I.
Vanderbilt University Medical Center
Nashville, Tennessee

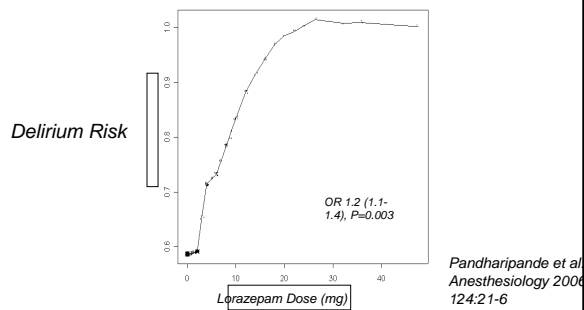


Critical Care and Industry: Making the partnership work!

Pratik Pandharipande, MD, MSCI
Department of Anesthesiology,
Division of Critical Care
Vanderbilt University School of Medicine,
Nashville, TN



Genesis of the Hypothesis



Hypothesis

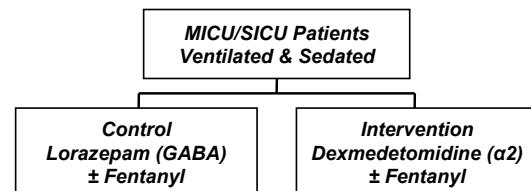
To determine if changing sedation paradigms by targeting α_2 receptors instead of GABA receptors will

- reduce duration and prevalence of acute brain dysfunction (delirium and coma)
- achieve equivalent efficacy of sedation

Navigating the MENDS trial

1. Development of protocol
2. Funding and Contacts
3. FDA
4. Re-negotiating contracts
5. Expanding the study
6. Taking it to publication

MENDS Trial Double-blind, randomized, controlled



Vanderbilt University Medical Center and Washington Hospital Center

Pandharipande PP, et al. JAMA 2007;298:2644-53

Protocol development issues

- *Wanted it to be a real life study*
- *Choice of comparator?*
- *Could we blind the infusion?*
 - *lorazepam dosed as mg/hr*
 - *Dexmedetomidine as mcg/kg/hr*
- *What would be our study population?*
- *What would be maximal dose and duration of dexmedetomidine allowed?*
- *What would be the rescue drug?*
- *Would antipsychotic medications be permitted?*

Quest for Funding

- *Established dialogue between Investigators and Abbot*
- *Visit to Vanderbilt to meet our research group*
 - *Our focus delirium and role of sedation*
 - *Abbot's focus- Can dexmedetomidine be used in the MICU*
- *Abbot not too enthusiastic about "delirium end-points"*
- *Concern about the higher dose (1.5 mcg/kg/hr) and longer duration (up to 5 days) proposed- ? FDA approval*
- *Better chance if budget <\$200,000*

My own academic development

- *Interested in becoming a clinician-scientist (Drs. Wes Ely, Jeff Balsler and Mervyn Maze as mentors)*
- *Applied for the Masters in Science and Clinical Investigation (MSCI) program*
- *Awarded the Vanderbilt Physician Scientist Award (VPSD)*
- *Guaranteed 80% protected research time for period Sept 2003-June 2005*

Grant In Aid

- *Initial GIA approved late 2003 with a \$180,000 budget for a 40 patient pilot study to evaluate efficacy of sedation*
 - *Study drug*
 - *Research nurse for 1 year*
 - *Pharmacy and IRB administrative costs*
- *No support for Investigators*
 - *Wes Ely- NIH*
 - *Pratik Pandharipande- VPSD award*
 - *Additional personnel- Departmental funds*

FDA IND-early 2004

- *Established communications with the FDA and applied for FDA IND*
- *FDA modifications*
 - *Exclude patients with Child B and C cirrhosis*
 - *Exclude patients with coronary ischemia, including post CABG*
 - *Daily troponins and EKG for all study days and again after end of study drug*
 - *Daily bilirubin and SGPT*
 - *Expansion of endocrine labs beyond cortisol to evaluate LH, prolactin, ACTH, testosterone*
- *Additional cost approx \$150,000*

Re-negotiating contract

- *Needed additional funds for FDA mandated labs*
- *Abbot spins off Hospira as an independent company- new folks take over!!*
- *Protocol revised to include FDA labs and exclusions*
- *Revised GIA submitted and approved by new committee- \$325,000*

The desire to do more!!!

- *Inclusion of surgical and medical patients*
- *Keen on studying the impact on delirium duration and not just efficacy of sedation*
- *Banking DNA*
- *Collection of plasma to study drug plasma levels, cytokines etc*

Re-negotiating contract...again

- *Supportive group at Hospira*
- *Change in primary outcome to duration of delirium*
- *Doubling of sample size to 106*
- *Hospira unable to "double budget"-additional \$150,000- total \$475,000*
- *Separate provision for drug negotiated*
- *Application to GCRC at Vanderbilt for support for genetics and cytokine analysis*

Final Contract

- *Investigator initiated study- research grant provided by Hospira*
 - *Research nurse, safety labs, drug, IRB, misc*
- *Investigator initiated and designed protocol. No modifications by Hospira*
- *Hospira had no access to the raw data*
- *No reporting of AE, SAE, PD etc mandated*
- *Independent DSMB*
- *Independent Vanderbilt statistician*
- *Hospira to get data if no write up occurred 3 years after enrollment ended*

Enrollment and expansion

- *Enrollment started in August 2004*
- *Desired expansion to 2 additional sites*
 - *Washington Hospital Center- Dr. Dan Herr*
 - *Columbia- Dr. Sladen*
- *Viewed with enthusiasm by Hospira, but contract issues*
- *Vanderbilt subcontract with WH*
- *Study drug and randomization provided by our Investigational pharmacy to theirs*
- *Site visit and start up in mid 2005*

Funding issues resurface


- *PI-need for funded protected time (VPSD ended June 2005)*
- *ASCCA-FAER Mentored Research Grant- July 2005-June 2007*
 - *Committee concerned about Industry involvement*
 - *Required assurances from Chair and Investigator about appropriate use of funds*

Taking it to publication

- *Data analysis independent of Industry*
- *No discussion of results till abstract accepted at ATS 2007*
- *Final manuscript provided to Hospira to evaluate for accuracy about "dexmedetomidine" per contract.*
- *Hospira- no role in write up of manuscript*

JAMA
The Journal of the American Medical Association
December 12, 2007

CARING FOR THE CRITICALLY ILL PATIENT



Effect of Sedation With Dexmedetomidine vs Lorazepam on Acute Brain Dysfunction in Mechanically Ventilated Patients: The MENDS Randomized Controlled Trial

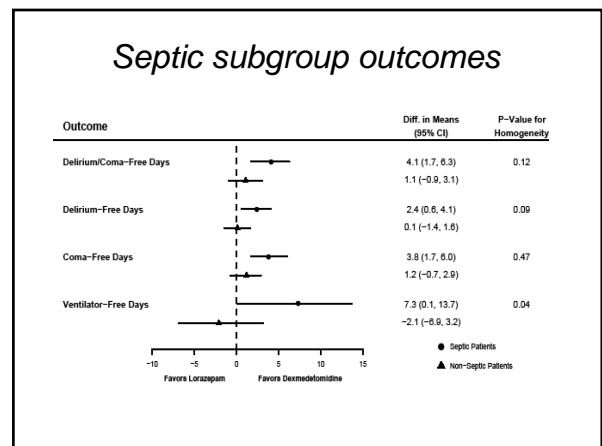
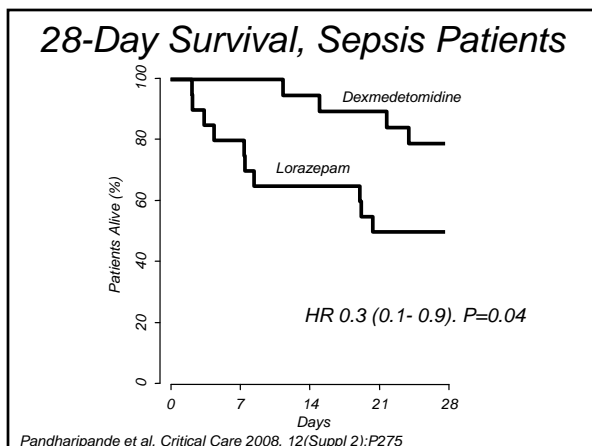
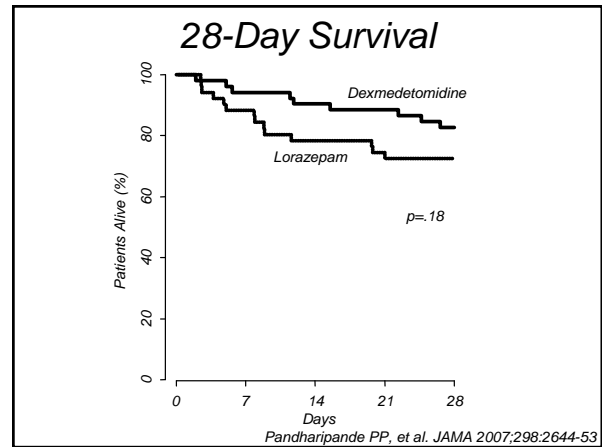
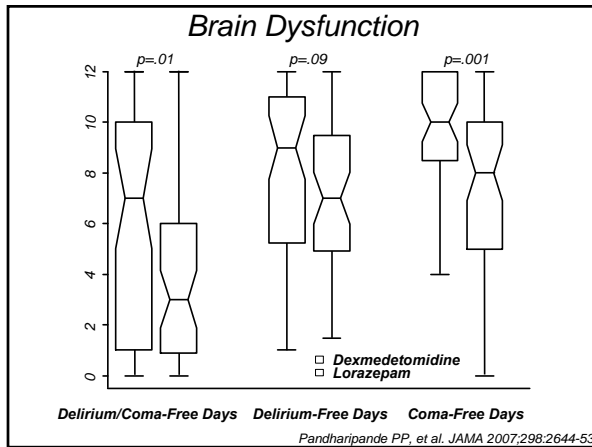
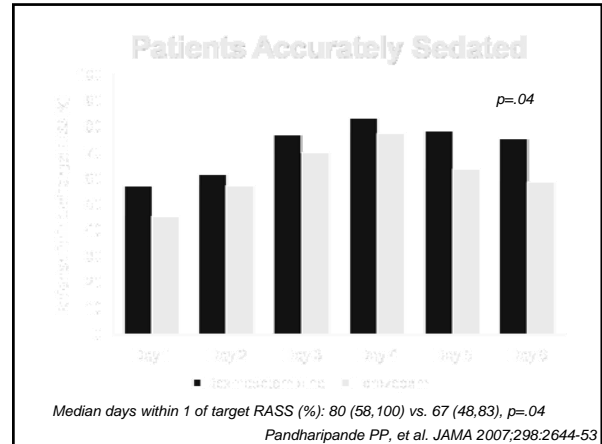
Pratik P. Pandharipande, MD, MSc
Brenda T. Poon, RN, MSN, ACNP
David L. Heron, MD
Mervyn Maze, MR, CChB
Timothy D. Girard, MD, MSc
Russell S. Miller, MD, MPH
Armani K. Shisani, MPH, PhD
Jennifer L. Thompson, MPH
James C. Jackson, PhD
Stephane A. Durrans, MA, MS
Robert A. Silvas, PhD
Robert S. Utman, MD, MPH
Gordon B. Downard, MD
E. Wesley Ely, MD, MPH

Context: Lorazepam is currently recommended for sustained sedation of mechanically ventilated intensive care unit (ICU) patients, but this and other benzodiazepine drugs may contribute to acute brain dysfunction, ie, delirium and coma, associated with prolonged hospital stays, costs, and increased mortality. Dexmedetomidine induces sedation via different central nervous system receptors than the benzodiazepine drugs and may lower the risk of acute brain dysfunction.

Objective: To determine whether dexmedetomidine reduces the duration of delirium and coma in mechanically ventilated ICU patients while providing adequate sedation as compared with lorazepam.

Design, Setting, Patients, and Intervention: Double-blind, randomized controlled trial of 106 adult mechanically ventilated medical and surgical ICU patients at 2 tertiary care centers between August 2004 and April 2006. Patients were sedated with dexmedetomidine or lorazepam for as many as 120 hours. Study drugs were titrated to achieve the desired level of sedation, measured using the Richmond Agitation Sedation Scale (RASS). Patients were monitored twice daily for delirium using the Confusion Assessment Method for the ICU (CAM-ICU).

Main Outcome Measures: Days alive without delirium or coma and percentage of flow speech within 1 RASS level of the sedation goal.



Potential pitfalls

- ***Contracts***
 - *Ownership of data*
 - *Publication rights/ control*
 - *Subcontracting with other sites*
- ***Budget negotiations***
 - *Personnel coverage (especially PI, Co-PI)*
 - *University Indirects*
- ***Conflicts of Interest***

Future direction

- ***Can we reduce mortality by altering sedation paradigms***
- ***Does sedative choice matter in sepsis***
- ***Mechanisms for the beneficial effects of dexmedetomidine***
 - *Attenuation of inflammation*
 - *Promotion of sleep*
 - *Anti-apoptosis*
- ***Funding goal- NIH plus Industry***

Critical Care and Grading Evidence: It Can't Work Well

Brian P. Kavanagh, M.B., B.Sc., M.R.C.P.I., F.R.C.P.C., F.F.A.R.C.S.I.
Hospital for Sick Children
University of Toronto
Toronto, Canada

Evidence based anesthesia appears to be catching on. Evidence based medicine is considered by many to be a very major advance and many involved in anesthesia wish to integrate EBM into their practice, and make it a part of the practice of others. Grading of evidence is central to EBM and new development of this is grading of guidelines which is intended to give the reader (clinician) a better sense of confidence about implementing the guidelines. Unfortunately there is no evidence that grading of guidelines is a useful exercise; in fact the only evidence is that grading of guidelines is inconsistent. In addition, organizations that have used graded guidelines have demonstrable major inconsistencies in what is recommended. Also, there are major concerns with the inherent logic of grading proposals. Finally, highly ranked guidelines have subsequently been shown to be false. Superimposed upon all of this is the finding that anesthesia as a specialty has established an enviable record of safety long before the term 'evidence-based medicine' was conceived. This coupled with the acceptance that evidence based medicine is a rather broad term encompassing that which any responsible clinician would naturally undertake means that "EBM" is too broad a definition for what amounts to an exercise in grading. This talk will discuss the shortcomings in grading evidence and grading guidelines and use examples from the anesthesia and critical care literature to illustrate the points.

Brian P. Kavanagh MB BSc MRCP(I) FRCP(C) FFARCS(I)[Hon]
Chairman, Department of Anesthesia, Faculty of Medicine, University of Toronto
Professor of Anesthesia, Medicine & Physiology
Dr. Geoffrey Barker Chair in Critical Care Medicine

Critical Care: Resuscitation During Modern Conflict

Michael J. Murray, M.D.
Mayo Clinic
Scottsdale, Arizona

Critical Care: Resuscitation During Modern Conflict

**Michael J Murray MD PhD FCCM FCCP
COL MC USAR**
Professor of Anesthesiology
Mayo Clinic Arizona
17 October 2008

Modern Conflicts

- Managing war injury is no longer the exclusive preserve of military physicians
- Increasing numbers of non-combatants are injured in modern conflicts, and peacetime military surgical facilities and expertise may not be available

BMJ 2005;330:1498-1500

Modern Conflicts

Types of injury in modern warfare

- High energy transfer bullet wounds
- Fragmentation injury
- Blast injury
- Burns

BMJ 2005;330:1498-1500

Modern Conflicts

After resuscitation, a careful top to toe survey must be done. Care must be taken to identify any truncal penetrating injury, without forgetting the back and buttocks, perineum, and axillae.

Wound assessment should include:

- Site and size
- Presence of cavity and degree of contamination
- Anatomical structures involved
- Distal perfusion
- Presence of fractures

BMJ 2005;330:1498-1500

Resuscitation

- Airway

Anesth Analg 2007;104:619-23

Resuscitation

Field Airway Management Disasters:

- During a 5-yr study period 149 consecutive out-of-hospital tracheal intubations were performed by primary emergency physicians and later evaluated.
- The mean patient age was 57.0 (22.7) yr and 99 patients (66.4%) were men.
- The tracheal tube was determined by the study physician to have been placed in the right mainstem bronchus or esophagus in 16 (10.7%) and 10 (6.7%) patients, respectively.
- All esophageal intubations were detected and corrected by the physician at the scene, but with a 70 % mortality rate.

Anesth Analg 2007;104:619-23

Resuscitation

Field Airway Management:

Army Field Manuals stressed surgical management but in an editorial:

Providers of emergency resuscitation must recognize the paramount importance of ventilation and the dire risks of failure to ventilate the lungs.

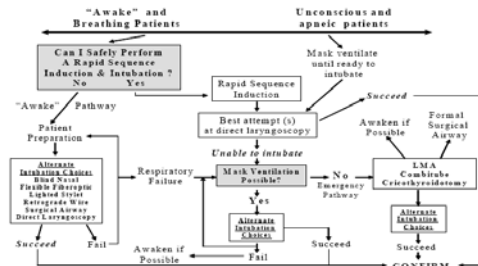
They must have proper equipment to intubate the trachea and to verify tracheal intubation.

They must have alternative airway equipment, such as laryngeal masks, laryngeal tubes, or Combitubes to support ventilation should conventional orotracheal intubation fail.

Anesth Analg 2007 104: 481-483.

Airway Management 2006 Joint Theater Trauma System

JTTS CLINICAL PRACTICE GUIDELINES FOR
TRAUMA AIRWAY MANAGEMENT



The Joint Theater Trauma System Advances In Battlefield Injury Care

- Development and implementation of trauma system modeled after successes of civilian systems, but realistic with respect to the realities of combat
- Utility of trauma systems for medical command decision making and battlefield trauma medicine practice improvement.

6th Annual Battlefield Healthcare
Combat Casualty Care from the Front Line to CONUS
March 31 - April 2, 2008

Resuscitation

- Airway
- Breathing

Anesth Analg 2007;104:619 -23)

NIH ARDS NET

- V_T (mL/kg) 6 - 8 vs. 12
 - Flow > 80 L/min
 - PaO_2 55 - 80 mmHg
 - PEEP titrated to FiO_2
 - 0.5 → 8-10; 0.8-14; 1.0 → 20-24
 - Plateau pressure < 30 cm H_2O
- If > 30, ↓ V_T by 1 mL/kg until 4 mL/kg
- If < 20, ↑ V_T by 1 mL/kg to 8 mL/kg

Mortality Decreased 38 to 31 %

NEJM: 342:1302-1308, 2000

Resuscitation from Injury

- WWI: Hemorrhagic shock
Treatment: Transfusion
- WWII: Acute renal failure
Treatment: Volume resuscitation
- Vietnam: ARDS
Treatment: PEEP
- 1990s-2000s: MODS
Treatment: Sepsis Bundle

Crystalloid

Excessive crystalloid has resulted in a greater incidence of abdominal compartment syndrome (16% vs 8%), multiple organ failure (22% vs 9%) and death (27% vs 11%) in a large series of civilian trauma patients.

Balogh Z, McKinley BA, Cocanour CS, et al: Supra-normal trauma resuscitation causes more cases of abdominal compartment syndrome. *Arch. Surg.* 138:637-643, 2003.
Moore FA, McKinley BA, Moore EE. The next generation in shock resuscitation. *Lancet.* 2004 Jun 12;363(9425):1988-96.

Resuscitation

- A total of 174 articles on prehospital ALS or BLS for trauma were reviewed
- Weighted odds ratio for dying was 2.59 for patients receiving ALS compared with those receiving BLS.
- The aggregated data in the literature have failed to demonstrate a benefit for on-site ALS provided to trauma patients and support the scoop and run approach.

Journal of Trauma-Injury Infection & Critical Care. 49(4):584-599, 1988

Immediate versus Delayed Fluid Resuscitation for Hypotensive Patients with Penetrating Torso Injuries

VARIABLE	IMMEDIATE RESUSCITATION (N = 309)	DELAYED RESUSCITATION (N = 289)	P VALUE
Before arrival at the hospital			
Ringer's acetate (ml)	870±667	92±309	<0.001
Trauma center			
Ringer's acetate (ml)	1608±1201	283±722	<0.001
Packed red cells (ml)	133±393	11±88	<0.001
Operating room†			
Ringer's acetate (ml)	6772±4688	6529±4863	0.31
Packed red cells (ml)	1942±2322	1713±2313	0.07
Fresh-frozen plasma or platelet packs (ml)	357±1002	307±704	0.45
Autologous-transfusion volume (ml)	95±486	111±690	0.76
Headstarch (ml)	499±717	542±696	0.41
Rate of intraoperative fluid administration (ml/min)	117±126	91±88	0.008

*Plus-minus values are means ±SD.

†For these analyses there were 288 patients in the immediate-resuscitation group and 260 patients in the delayed-resuscitation group.

NEJM 1994, 331:1105-1109

Immediate versus Delayed Fluid Resuscitation for Hypotensive Patients with Penetrating Torso Injuries

VARIABLE	IMMEDIATE RESUSCITATION	DELAYED RESUSCITATION	P VALUE
Survival to discharge — no. of patients/total patients (%)	193/309 (62)*	203/289 (70)†	0.04
Estimated intraoperative blood loss — ml‡	3127±4937	2555±3546	0.11
Length of hospital stay — days§	14±24	11±19	0.006
Length of ICU stay — days§	8±16	7±11	0.30

*95 percent confidence interval, 57 to 68 percent.

†95 percent confidence interval, 65 to 75 percent.

‡The estimated intraoperative blood loss was calculated for patients who survived the operation: 268 in the immediate-resuscitation group and 260 in the delayed-resuscitation group.

§The lengths of stays in the hospital and intensive care unit (ICU) were calculated for patients who survived the operation: 227 in the immediate-resuscitation group and 238 in the delayed-resuscitation group.

NEJM 1994, 331:1105-1109

Immediate versus Delayed Fluid Resuscitation for Hypotensive Patients with Penetrating Torso Injuries

COMPLICATION	IMMEDIATE RESUSCITATION		DELAYED RESUSCITATION		P VALUE
	NO. OF PATIENTS	PERCENT (95% CI)	NO. OF PATIENTS	PERCENT (95% CI)	
Adult respiratory distress syndrome	8	4 (2–6)	3	1 (0–3)	0.11
Sepsis syndrome	12	5 (3–9)	11	5 (3–8)	0.74
Acute renal failure	8	4 (2–6)	3	1 (0–3)	0.11
Coagulopathy	24	11 (7–15)	19	8 (5–12)	0.34
Wound infection	21	9 (9–17)	24	10 (7–14)	0.36
Pneumonia	28	12 (9–17)	22	9 (6–13)	0.28
Patients with ≥1 complications	69	30 (25–36)	55	23 (18–29)	0.08

*Several patients had more than one complication. CI denotes confidence interval.

NEJM 1994, 331:1105-1109

Revised UHC Model Guidelines: Hemorrhagic Shock

- Crystalloid and colloid solutions should not be considered substitutes for blood or blood components
- Crystalloids are considered to be the initial resuscitation fluid of choice
- When 4 L of crystalloid fail to produce a response within 2 h in adults, consider non-protein colloids or 5% albumin (when non-protein colloids are contraindicated)

University HealthSystem Consortium. *Technology Assessment: Albumin, Nonprotein Colloid, and Crystalloid Solutions.* May 2000.

Resuscitation

- Airway
- Breathing
- Circulation

Anesth Analg 2007;104:619-23)

Damage Control Resuscitation

New methods of resuscitation utilizes objective criteria to initiate rFVIIa, thawed plasma and RBC use in the ED, within minutes of arrival. Crystalloid infusion is extremely limited.

Maintain Normothermia

The following measures must be immediately implemented across the theater of operations until further notice:

- Monitor temperature on all immediate/urgent litter casualties (forehead) at Level II and during EVAC to Level III
- Keep EMT/OR temp 78-90 degrees F during casualty resuscitation
- -use warmed IV fluids and warm blanket and, forced air warming devices as applicable
- -implement mandatory documentation of patient temperature
- -mandatory use of Hypothermia Prevention/Management Kits for all rotary wing evac/ground evac

Results with Increased FFP

	2000 N=4169	2001 N=4566	2002 N=4387	2003 N=4557	2004 N=4254	2005 N=3666	P-value
% Requiring TX	16.4%	16.7%	17.7%	15.2%	16.6%	16.8%	0.77
% Requiring > 10u TX	11.1%	10.8%	12.1%	6.9%	9.3%	7.9%	0.007
Mean units PRBC TX	8.1±10.4	7.1±9.1	7.4±9.0	6.2±8.6	6.5±7.9	6.2±8.4	0.04
Fresh Frozen Plasma	2.8±5.8	2.2±5.3	2.6±5.5	2.4±7.0	3.1±6.1	4.5±8.5	0.0001
Mortality	19.9%	19.5%	19.8%	19.1%	19.7%	21.1%	0.82

Fresh whole blood: mortality for combat related casualties Description of its use and effect on mortality

Conclusions: The use of FWB for patients sustaining severe traumatic injuries may improve survival. This report also demonstrates that a large-scale FWB transfusion program can be developed and sustained for a large number of patients presenting in hemorrhagic shock related to combat injuries. Prospective trials are needed to confirm if the use of fresh or stored whole blood can improve survival compared to component therapy in patients with severe traumatic injuries.

Recombinant Factor VIIa

- Newer hemostatic agent that is licensed in the United States only for the management of bleeding in hemophilia patients with factor VIII or factor IX inhibitors.
- Interacts with TF at sites of injury to and induces hemostasis through enhancement of thrombin generation on the surface of thrombin-activated platelets.
- Accumulating anecdotal experience and small case series have generated interest in the use of rFVIIa for other indications, including bleeding after surgery or major trauma

Hoffman: Hematology: Basic Principles and Practice, 4th ed

Recombinant Factor VIIa usefulness in Trauma

- “Coagulopathic” bleeding can occur after major trauma.
- This is multifactorial and may be due to dilution, citrate intoxication, acidosis, hyperfibrinolysis and hypothermia.
- Factor VIIa has been shown to decreased transfusion requirements in trauma patients following massive blood loss. (Grounds RM, 2006)

Thrombosis

- Primary safety concern with the use of rFVIIa is thrombosis.
- Most reported thrombotic events have been associated with other risk factors, such as preexisting atherosclerotic vascular disease or advanced age. (Hedner, 2002)
- Hemophiliacs have a less than 1% chance of thrombosis.

Thromboembolic Adverse Events After Use of Recombinant Human Coagulation Factor VIIa

Kathryn A. O'Connell, MD, PhD
Jennifer J. Wood, PhD, MPH
Robert P. Wise, MD, MPH
Jay N. Lottier, MD, PhD
M. Miles Braun, MD, MPH

JAMA

Figure 3. Number of Thromboembolic Event Reports With Recombinant Human Coagulation Factor VIIa Reported to FDA by Source and Year

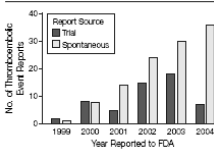
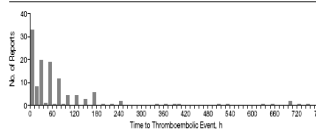


Figure 5. Number of Reports by Time From Last Recombinant Human Coagulation Factor VIIa Dose to Thromboembolic Event



Thromboembolic Adverse Events After Use of Recombinant Human Coagulation Factor VIIa

Table 1. Number of Thromboembolic Event Reports With Use of rFVIIa by Report Source and Reason for Use and Bleeding Status

Reason for use	No. of Reports (%)	
	Trial (n=58)	Spontaneous (n=108)
Surgery (bleeding or prophylaxis)	27 (46)	48 (44)
Intracranial bleeding	19 (32)	5 (4)
Bleeding, nonsurgical	8 (14)	26 (24)
Trauma, nonsurgical	5 (8)	9 (8)
Hemophilia	0	17 (16)
Unknown*	0	4 (4)
Bleeding status		
Active bleeding	35 (60)	80 (73)
Prophylactic	24 (41)	22 (20)
Unknown*	0	7 (7)

Table 2. Number of Thromboembolic Events Reported With Use of rFVIIa by Site and Report Source*

Site	No. of Reports (%)		
	Trial	Spontaneous	Total
Arterial	37 (20.2)	62 (53.9)	99 (54.1)
Non-CFH cardiovascular accident	13 (7.1)	26 (14.3)	39 (21.3)
Acute myocardial infarction	12 (6.5)	22 (12.0)	34 (18.6)
Other arterial thromboembolism†	12 (6.5)	14 (7.6)	26 (14.2)
Venous	28 (15.3)	46 (25.1)	74 (40.4)
Venous other than pulmonary embolism‡	18 (9.8)	24 (13.1)	42 (22.9)
Pulmonary embolism	10 (5.5)	22 (12.0)	32 (17.5)
Device occluded§	1 (0.5)	9 (4.9)	10 (5.5)
Total	66 (36.1)	117 (63.4)	183 (100)

Abbreviations: CFH, intracranial hemorrhage; rFVIIa, recombinant human coagulation factor VIIa.
*Including 2 spontaneous reports with unrelated thromboembolic site.
†Includes femoral, hepatic, pulmonary, renal, splenic, and iliac artery occlusion.
‡Includes deep vein thrombosis and/or leg/leg, mesenteric, portal, renal, and central vein thromboses.
§Device includes endoscopic membrane oxygenation lines, dialysis shunt/tubing, and endotracheal tubes.

Guidelines for Administration of rFVIIa:

The usual trauma dose is 100 mcg/kg IV push

1) Typically, for injured US troops this equals three vials (2.4 mg each) or 90-120 mcg/kg IV push.

2) The dose may be safely repeated as many as three times in 20 minute or greater intervals.

ED/EMT Resuscitation:

rFVIIa and plasma and PRBC (1:1 ratio) are indicated for any one of the following findings:

1. Truncal/axillary/neck or groin bleeding not controlled with tourniquets, hemcon or quickclot dressings
2. Bleeding from Large soft tissue injuries not controlled with tourniquets, hemcon or quickclot.
3. A proximal amputation or mangled extremity
4. > 1000 cc blood out of a chest tube, or > 200 cc/hr for 4 consecutive hours
5. Physical exam findings:
 - a. decreased mental status from injury and shock
 - b. severe head injury
 - c. clinically coagulopathic

ED/EMT Resuscitation:

6. Objective physical exam or Laboratory findings

- a. an INR \geq 1.5
- b. a base deficit \geq 6
- c. a Hgb \leq 12
- d. hypothermic from blood loss (T $<$ 96°F)
- e. hypotensive from blood loss (SBP $<$ 90 mmHg) or a weak/absent radial pulse)

7. Need for fresh whole blood transfusion

- a. Bilateral proximal amputations
- b. Large hemoperitoneum and significant shock

ED/EMT Resuscitation:

Two Caveats:

Casualties with any one of these parameters have $>$ 25% mortality and should be given rFVIIa and RBC:thawed plasma in a 1:1 ratio as soon as possible.

GUIDELINE ONLY—NOT A SUBSTITUTE FOR CLINICAL JUDGEMENT 1 UPDATED NOV 2006

JTTS Updated Nov 2006

New Approaches

- **Maintain Temperature**
- **Fluid Management**
- **Hemostatic Dressings in field**
- **More FFP**
- **Whole Blood**
- **Factor VII**

Critical Care at Altitude: Testing Physiological Limits in Antarctica

Patricia M. Murphy, M.D., F.R.C.P.C.
University of Toronto
Toronto, Canada

Climbers on Headwall



The development of hypoxia is the physiological result of human exposure to high altitudes. Advances in aviation and improved access to remote mountainous regions, has resulted in increased numbers of individuals traveling to moderate (2000-4000 m) or high (> 4000 m) altitude for work or recreational activities. High altitude illnesses, the most common of which is Acute Mountain Sickness (AMS) can occur in susceptible individuals at 2000 meters.ⁱ High altitude pulmonary edema (HAPE) and high altitude cerebral edema (HACE) can also occur in addition to AMS and their occurrence depends upon a number of factors including rate of ascent, the altitude at which the individual sleeps and individual susceptibility. Contrary to public opinion, youth and physical fitness do not confer decreased susceptibility to AMS.^{ii,iii} Obesity, preexisting cardiopulmonary disorders, residence at sea level and heavy exertion upon arrival are all additional risk factors for the development of AMS, HAPE and HACE.^{iv,v,vi} The incidence of AMS becomes significant once altitudes greater than 3000 meters (9842 feet) are attained with reported incidences of 34-42%.^{vii,2}

The limits to human performance at altitude are significantly affected by the adaptation to altitude, i.e. the development of "tolerance" to hypoxia or acclimatization. As a climber ascends from sea level to increasing altitude there is a progressive decrease in barometric pressure. At sea level the barometric pressure is 760 mm HG or torr, whereas on the summit of Everest (8848 m) the barometric pressure is 252 mmHg (torr). Although the percentage of oxygen in the atmosphere remains constant from sea level to stratosphere, the effect of barometric pressure (Boyle's Law) means that the actual amount of oxygen molecules in the air is significantly less, just 32% of what is available at sea level. The inspired pO_2 is 42-43 mm Hg (torr). At the Vinson Massif in Antarctica the altitude at the summit is 4897 meters or 16065 feet. At this altitude it is predicted that there is 55% as much oxygen available as at sea level. However this prediction does not take into account the difference in barometric pressure that occurs as at the equatorial latitudes. A dense band of cold air is present at either pole, with the South Pole being the colder and hence more affected by this phenomenon. This band of cold air results in the barometric pressure being even lower than expected at the altitude.^{viii} Therefore the available oxygen in the atmosphere is even lower than predicted. The unusual barometric pressure-altitude relationship at or near the South Pole has raised the apparent altitude by 23%. The "apparent" altitude of the Vinson Massif in Antarctica can be predicted to be 6023 meters (19,760 feet) and there would be 48% as much oxygen available as at sea level.

Acclimatization at altitude is the physiologic response of humans to the limited availability of oxygen at the cellular level. As altitude increases there is an immediate increase in alveolar ventilation, which is mediated by the Hypoxic Ventilatory Response. The peripheral chemosensor in the carotid body detects the hypoxia and perpetuates the increase in alveolar ventilation. Ventilatory acclimatization is further enhanced over the next 2 weeks at increased altitude as the carotid body chemoreceptors become more sensitive to the hypoxemia. As alveolar ventilation increases, the alveolar oxygen pressure and subsequently the arterial oxygen content increase. The arterial carbon dioxide content also decreases in proportion to the increase in alveolar ventilation resulting in respiratory alkalosis that is only partially corrected by renal compensation. Hypoxemia stimulates the production of erythropoietin, which in turn stimulates the bone marrow to produce more red blood cells. This process results in increased RBC mass within 10-14 days. At the cellular level, hypoxia stimulates the production of Hypoxia-Inducible Factor-1 (HIF-1), which induces the secretion of vascular endothelial growth factor (VEGF).^{ix} The secretion of VEGF stimulates angiogenesis thereby augmenting blood flow and oxygen delivery at the cellular level. The normal cardiovascular response to hypoxia is an increase in cardiac output and a rise in pulmonary artery pressures secondary to pulmonary vasoconstriction.^x An increased plasma secretion of endothelin-1 has also been found in association with the increase in pulmonary artery pressures.^{xi} V/Q mismatch in the lung is decreased as a result of these changes promoting improved oxygenation. These physiological adaptive processes to hypoxemia are all time-dependent and may differ in the magnitude and timing of response between individuals. Hence the differences in rates of acclimatization amongst individuals.

AMS and HACE are now thought to represent differing severities on a continuum of pathophysiology. Many of the nonspecific symptoms of AMS, headache, nausea, vomiting and lethargy, can be attributed to an elevation in intracranial pressure. Physical signs include edema of the face, hands and feet and tachycardia. The cerebral edema is secondary to the presence of extravascular water. MRI's of patients with AMS and HACE have revealed intense T2 signals in white matter particularly in the splenium and corpus callosum.^{xii} This is supportive evidence

that the cerebral edema is due to vasogenic leak. In addition studies in individuals with AMS have demonstrated fluid retention, weight gain and an antidiuresis.^{xiii} The normal physiological response to ascent to altitude is a mild diuresis. Further studies have demonstrated an increase in aldosterone secretion with AMS.^{xiv}

HAPE is a non-cardiogenic pulmonary edema that occurs at high altitude. It usually, but not always, occurs several days after the onset of symptoms of AMS. It begins insidiously as a nonproductive cough that progresses to dyspnea at rest often accompanied by watery, pink sputum. Early and aggressive treatment is needed, as it can be fatal. It has a gender predilection (male) and may have a genetic predisposition. Individuals who have had one episode of HAPE are more likely to have another when reintroduced to altitude. Interestingly the frequency of PFO is 4X higher in individuals who had developed HAPE compared to individuals exposed to the same altitude who did not develop HAPE. The pathogenesis of HAPE has been found to involve exaggerated HPVR to hypoxia with abnormally high pulmonary artery pressures but normal capillary wedge pressure compared to non-HAPE individuals. The cause of this exaggerated response may be secondary to vasoactive mediators including thromboxane B2 and endothelin-1.^{xv, xvi} HAPE individuals have also been found to have increased sympathetic nervous system activity and decreased concentrations of NO.^{xvii} The contributions and importance of these differences in the pathogenesis of HAPE is still unclear.

Treatment of mild AMS is mostly symptomatic with rest as the cornerstone of therapy and use of medications such as acetazolamide, as adjuncts. The individual should not attempt further ascent until symptoms of AMS have abated. The Lake Louise consensus conference in 1991 proposed a scoring system as a guideline for diagnosis and treatment. The development of HACE necessitates more aggressive treatment with descent, supplemental oxygen and medications such as dexamethasone, and acetazolamide. If descent cannot be facilitated supplemental oxygen or the use of Gamow bag is necessary. The treatment of HAPE differs in its reliance on the use of pulmonary vasodilators. The mainstay of therapy is still descent and supplemental oxygen, however nifedipine, sildenafil and tadalafil have all been shown effective in HAPE.^{xviii}

Life Live - Test Your Limits



Dr. Murphy
on headwall
with Mt.
Shinn
backdrop

The Lake Louise Consensus on the Definition of Altitude Illness

The following definitions on the diagnosis of altitude illness were adopted at the 1991 International Hypoxia Symposium, held at Lake Louise in Alberta, Canada.

AMS

In the setting of a recent gain in altitude, the presence of headache and at least one of the following symptoms:

- gastrointestinal (anorexia, nausea or vomiting)
- fatigue or weakness
- dizziness or lightheadedness
- difficulty sleeping

HACE

Can be considered "end stage" or severe AMS. In the setting of a recent gain in altitude, either:

- the presence of a change in mental status and/or ataxia in a person with AMS
- or, the presence of both mental status changes and ataxia in a person without AMS

HAPE

In the setting of a recent gain in altitude, the presence of the following:

Symptoms: at least two of:

- dyspnea at rest
- cough
- weakness or decreased exercise performance
- chest tightness or congestion

Signs: at least two of:

- crackles or wheezing in at least one lung field
- central cyanosis
- tachypnea
- tachycardia

-
- ⁱ Hackett PH, Rennie D. The incidence, importance and prophylaxis of acute mountain sickness. *Lancet* 1976;7996: 1149-1155.
- ⁱⁱ Honigman B, Theis MK, Koziol-McLain J, et al. Acute mountain sickness in a general tourist population at moderate altitudes. *Ann Intern Med* 1993;118:587-592.
- ⁱⁱⁱ Savourey G, Garcia N, Besard Y, et al. Physiological changes induced by pre-adaptation to high altitude. *Eur J Appl Physiol Occup Physiol* 1994; 69:221-227.
- ^{iv} Ri-Li G, Chase PJ, Witkowski S, et al. Obesity: associations with acute mountain sickness. *Ann Intern Med* 2003; 139: 253-257.
- ^v Hackett PH. In: Hornbein TF, Schoene RB, eds. High altitude: an exploration of human adaptation. Vol 161 in Lenfant C, ed. Lung Biology in health and disease series. New York, NY: Marcel Dekker Publishers, 2001:839-885
- ^{vi} Roach RC, Maes D, Sandoval D, et al. Exercise exacerbates acute mountain sickness at simulated altitude. *J Appl Physiol* 2000; 88: 581-585
- ^{vii} Maggiorini M, Buhler B, Walter M, et al. Prevalence of acute mountain sickness in the Swiss Alps. *BMJ* 1990;301:853-855
- ^{viii} West JB. Acute Mountain Sickness at the South Pole. *High altitude Medicine and Biology* 2001;2:559
- ^{ix} Semenza G. HIF-1: mediator of physiological and pathophysiological responses to hypoxia. *J Appl Physiol* 2000;88: 1474-1480
- ^x Wolfel EE, Levine BD. The cardiovascular system at high altitude: heart and systemic circulation. In Hornbein TF, Schoene RB, eds. High altitude: an exploration of human adaptation. Vol 161 in Lenfant C, ed. Lung biology in health and disease series. New York, NY: Marcel Dekker Publishers, New York, 2001:293-342
- ^{xi} Goerre S, Wenk M, Bartsch P, Luscher TF, Niroomand F, Hohenhaus E, Oelz O, Reinhart WH. Endothelin-1 in pulmonary hypertension associated with high altitude exposure. *Circulation* 1995;91:359-364
- ^{xii} Hackett PH, Yarnell PR, Hill R, et al. High-altitude cerebral edema evaluated with magnetic resonance imaging: clinical correlation and pathophysiology. *JAMA* 1998; 280:1920-1925
- ^{xiii} Hackett PH, Rennie D, Hofmeister SE, et al. Fluid retention and relative hypoventilation in acute mountain sickness. *Respiration* 1982;43:321-329
- ^{xiv} Loeppky JA, Icenogle MV, Maes D, et al. Early fluid retention and severe mountain sickness. *J Appl Physiol* 2005; 98: 591-597
- ^{xv} Schoene RB, Hackett PH, Henderson WR, et al. High-altitude pulmonary edema: characteristics of lung lavage fluid. *JAMA* 1986; 256: 63-69
- ^{xvi} Modesti PA, Vanni S, Morabito M, et al. Role of Endothelin-1 in exposure to high altitude ACMI-1 study. *Circ* 2006;114:1410-1416
- ^{xvii} Duplain H, Sartori C, Iepori M, et al. Exhaled nitric oxide in high-altitude pulmonary edema role in regulation of pulmonary vascular tone and evidence for a role against inflammation. *Am J Respir Crit Care Med* 2000; 162:221-224
- ^{xviii} Oelz O, Maggiorini M, Ritter M, et al. Nifedipine for high altitude pulmonary edema. *Lancet* 1989;2:1241-1244

From Everest to the ICU: Understanding Extremes in Physiology

Adapted from an article by the same authors submitted to support a lecture by MG Mythen at The International Anaesthesia Research Society 2008 published as an abstract in Anesth and Analg.

Michael Mythen, M.B., B.S., F.R.C.A., M.D.
Smiths Medical Professor of Anaesthesia and Critical Care
Director of The Joint UCL and Hospitals Biomedical Research Unit
Management Team Caudwell Extreme Everest
University College London, United Kingdom

MP Grocott, M.B., B.S., M.R.C.P., F.R.C.A.
Smiths Medical Senior Lecturer Anaesthesia and Critical Care
Director Centre for Altitude Space and Extreme Environment Medicine
Expedition Leader Caudwell Extreme Everest
University College London, United Kingdom

HIGH ALTITUDE AS A MODEL FOR CRITICAL ILLNESS

The role of hypoxia in critical illness and the possible relationship between responses to hypoxia at high altitude and critical illness have been explored elsewhere. Cellular hypoxia may be both cause and consequence of a variety of conditions common in critically ill patients. Few if any critically ill patients do not have marked cellular hypoxia in at least one organ system. Hypoxia may trigger inflammatory pathways, and inflammation may in turn lead to localized or more generalized hypoxia. Adaptive responses to hypoxemia at altitude in part reflect patterns of response in critical illness. Oxygen consumption and flux (delivery) is commonly increased in the acute phase of critical illness and following the trauma of major surgery; the response to acute hypoxemia during early exposure to altitude is to increase oxygen flux (elevation of cardiac output and hemoglobin). At this stage, augmenting oxygen delivery by increasing blood flow or oxygen content may improve outcome in critically ill and post-surgical patients. Conversely, in established critical illness the reverse is true: oxygen consumption tends to fall and deliberately increasing oxygen delivery has no benefit or may even cause harm. A similar pattern pertains in well-acclimatized individuals where limitation of oxygen consumption seems to be an important feature of the adaptive process. Furthermore, allelic variants of ubiquitously expressed genes (Angiotensin Converting Enzyme) associated with improved outcomes in several critical illnesses (e.g. ARDS) are also associated with improved performance at extreme altitude.

A paradox at the centre of altitude physiology is that variations in performance at altitude are not explained by either sea level performance or resting oxygen delivery at altitude (product of cardiac output and oxygen content). Furthermore, relative differences in physiological variables thought to be responsible for "acclimatization" (e.g. ventilation, cardiac output, and hemoglobin) do not explain differences in observed performance. Changes in tissue or cellular oxygen handling might provide an explanation for this puzzling situation. Possible mechanisms may include alterations in microcirculatory flow leading to impaired cellular oxygen delivery, limitation of oxygen diffusion within the tissues, and variation in relative cellular metabolic efficiency (modification of the relationship between oxygen consumption and work). If cellular metabolic efficiency does change in some subjects, and the underlying mechanisms can be identified, then the implications would be significant. A therapy capable of altering the relative efficiency of cellular oxygen use might allow less aggressive targeting of oxygen delivery in some critically ill patients. This in turn has the potential to reduce the known adverse effects associated with some of the strategies to improve oxygen availability at a cellular level (mechanical ventilation, high-inspired oxygen levels, blood transfusion) and

potentially improve patient outcomes.

The Caudwell Xtreme Everest Expedition in 2007 set out to test the hypotheses that alterations in performance at high altitude might be explained by changes in microcirculation blood flow (and hence local oxygen delivery) or by alterations in cellular “metabolic efficiency,” the ratio between work output and oxygen consumed. We also set out to explore the hypothesis that inter-individual variation in observed adaptive changes would be related to variation in the frequencies of alleles of candidate genes. Specific candidate genes will include those implicated in mediating changes in “metabolic efficiency”, known hypoxia sensitive genes, and genes known to be unregulated during fetal life. The possibility that physiological pathways identified as beneficial or maladaptive in fetal life, may be associated with similar effects in adults exposed to conditions of profound hypoxia/hypoxemia is particularly intriguing. Recent advances in the understanding and investigation of fetal gene expression may give new life to Sir Joseph Barcroft’s oft quoted analogy of “Everest in *utero*”.

Clearly the study of healthy individuals exposed to hypoxia at high altitude has limitations as a model for critical illness. However, alternatives may have equivalent or greater limitations and studies in critically ill patients are fraught with difficulty. Patients with critical illness are a heterogeneous population. They have a variety of presenting complaints, pre-existing illness, and subsequent patterns of organ failures and are receive a variety of treatments. One consequence of this heterogeneity is that separating out the specific effects of an individual variable can be very difficult: the signal to noise ratio is very low. The limitations of animal models have been highlighted by the repeated failure of anti-sepsis treatments that have shown no benefit in humans despite promising results from studies in animals. Cellular and molecular studies are an important component of patient, volunteer and animal studies but on their own are no substitutes for exploring integrated physiology at a whole organism level. Increasingly complex computer models have huge potential but the validity of current models is still uncertain and they rely on iterative process with regular “reality checks” from human data. Studies in hypobaric chambers are a possible alternative to field studies at high altitude but have several disadvantages. Prolonged chambers studies are expensive, not least due to the requirement for continuous medical and technical staffing and capacity is limited (CXE involved more than 11 person years of subject exposure to hypobaric hypoxia). Finally, recruitment of more than 200 healthy volunteers for research during a trek in the Himalaya is feasible; it is doubtful whether the same could be achieved for a 2-week chamber exposure.

THE CAUDWELL XTREME EVEREST STUDY

CXE is the largest human high-altitude experiment ever conducted and builds on work conducted during previous high altitude and chamber studies. The strengths of CXE are the large number of subjects studied, and the unique data collected near to the summit of Everest. During the first 6 months of 2007, more than 200 healthy volunteers were studied at sea level in London and at four field laboratories at increasing altitudes up to 5300 meters (Everest Base Camp) in Nepal. Fifteen climbing investigators went through the same tests and then ascended high on the mountain to make novel measurements up to and above 8000 meters. More than 60 investigators were involved in data collection. The strengths of CXE recruited many more subjects and many more subjects and conducted.

The core studies were designed to map out changes in exercise capacity and exercise efficiency during progressive exposure and adaptation to the hypoxic environment. Oxygen consumption was measured using Cardiopulmonary Exercise Testing (breath-by-breath respiratory gas analysis) whilst pedaling a cycle ergometer. Subjects were exercised to exhaustion to explore exercise capacity (anaerobic threshold and maximum oxygen consumption) whilst exercise efficiency was investigated using a steady-state protocol. During exhaustive exercise cerebral and muscle tissue oxygenation were monitored using Near-Infrared Spectroscopy. Subjects filled in a daily symptom diary and recorded simple physiological variables (including oxygen saturations) before and after a standardized exercise challenge (CXE Step Test). Additional studies on all subjects included spirometry, and a detailed neurological assessment ranged from simple pupillary responses to a complex neurocognitive battery lasting up to 45 minutes.

Sub-groups of the base-camp and climbing investigators were studied in more depth. ECG, echocardiography, trans-cranial doppler recording of the middle cerebral artery and real-time imaging of the microcirculation provided valuable data. Invasive techniques including intra-arterial cannulation, muscle biopsy and gastrointestinal tonometry allowed more precise description of adaptive changes. Arterial access allowed continuous monitoring of cardiac output and blood pressure during exercise as well as serial sampling of biological markers. Muscle biopsies will allow us to explore the transcriptome and proteome in order to explore whether observed variations in allelic frequencies result in changes in gene products. Conversely, the availability of tissue to explore patterns of transcription and expression may allow identification of novel candidate genes to explore the relationship between observed phenotype and allelic variation.

Although complex imaging techniques are impractical in remote environments, several studies involved Magnetic Resonance Imaging (MRI) before and after the altitude exposure. These studies explored both structural predisposition to hypoxia related pathology and, in the climbers, subtle changes associated with prolonged significant hypoxemia. In addition, a small group underwent functional MRI studies and these should contribute substantially to our understanding of the metabolic changes induced by prolonged exposure to hypoxia.

Higher on the mountain, arterial blood gases were obtained at 8400 meters whilst descending from the summit and a novel semi-closed breathing system was evaluated above 6000 meters.

CONCLUSION

The output of these studies so far is a huge amount of novel data. Data entry on the main study database was completed in December 2007, and the dataset is currently being validated and quality controlled. The first of a planned series of primary publications are currently in peer review. The investigators hope that as the data is analyzed and the hypotheses confirmed or refuted, that a new phase of translational clinical studies in critical care and high-risk major surgery will be driven by the novel results.

ACKNOWLEDGEMENTS

Caudwell Xtreme Everest (CXE) is a research project coordinated by the Centre for Altitude, Space and Extreme Environment Medicine, University College London, UK. The aim of CXE is to conduct research into hypoxia and human performance at high altitude in order to improve understanding of hypoxia in critical illness. Membership, roles and responsibilities of the CXE Research Group can be found at www.caudwell-xtreme-everest.co.uk/team. The research was funded from a variety of sources, none of which are public. The entrepreneur John Caudwell, whose name the expedition carries, donated £500 000 specifically to support the research. BOC Medical, now part of Linde Gas Therapeutics, generously supported the research early on and continues to do so. Lilly Critical Care, The London Clinic (a private hospital), Smiths Medical, Deltex Medical and The Rolex Foundation have also donated money to support the research and logistics. All monies were given as unrestricted grants. Specific research grants were awarded by the Association of Anaesthetists of Great Britain and Ireland, and the UK Intensive Care Foundation. The CXE volunteers who trekked to Everest basecamp also kindly donated to support the research.

Reference List

- (1) Grocott M, Richardson A, Montgomery H, Mythen M. Caudwell Xtreme Everest: a field study of human adaptation to hypoxia. *Crit Care* 2007; 11(4):151.
- (2) Grocott MP. Human physiology in extreme environments: lessons from life at the limits? *Postgrad Med J* 2008; 84(987):2-3.
- (3) Grocott M, Montgomery H, Vercueil A. High-altitude physiology and pathophysiology: implications and relevance for intensive care medicine. *Crit Care* 2007; 11(1):203.
- (4) Eastman NJ. Mount Everest in utero. *Am J Obstet Gynecol* 1954; 67(4):701-711.
- (5) West JB, Boyer SJ, Graber DJ., Hackett PH, Maret KH, Milledge JS, Peters RM, Pizzo CJ, Samaja M, Sarnquist FH, Schoene RB, Winslow RM. Maximal exercise at extreme altitudes on Mount Everest. *J. Appl Physiol* 1983;55(3):688-698
- (6) Cymerman A, Reeves JT, Sutton JR, Rock PB, Groves BM, Malconian MK, Young PM, Wagner PD, Houston CS. Operation Everest II: maximal oxygen uptake at extreme altitude. *J. Appl Physiol* 1989;66(5):2446-2453

Nutrition Therapy in Critical Illness: Not Just "Support" Anymore

Paul E. Wischmeyer, M.D.
University of Colorado
Denver, Colorado

Nutrition Therapy: Not Just Support Anymore?



Paul Wischmeyer M.D.
Co-Chair- 2009 Society of Critical Care Medicine Congress
Editor-in-Chief: *Journal of Parenteral and Enteral Nutrition* □
Director of Nutrition Therapy Service
Associate-Chair for Clinical and Translational Research
Professor of Anesthesiology
University of Colorado Health Sciences Center

Why nutrition support has been stuck in antiquity...

No regulation leads to:

- Poor products
- Outrageous claims

Why nutrition support has been stuck in antiquity...

- Lack of high quality research
- Claims based on small, poorly designed trials

Why nutrition support has been stuck in antiquity...

- So...ultimately more questions than answers...

So...as a nutrition researcher what can be done ???

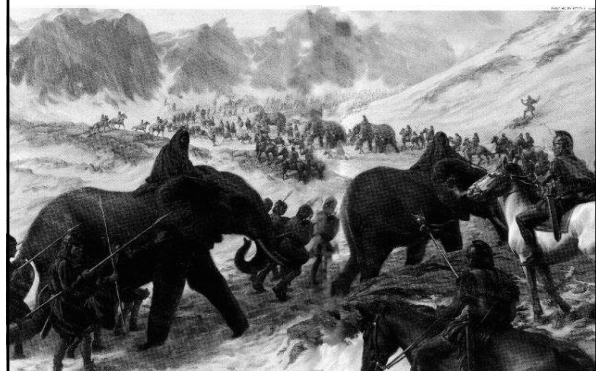
What can *Gladiator* teach us about the evolution of critical care nutrition therapy?



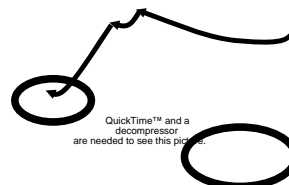


Scipio Africanus ??

Hannibal and the Barbarian Hoards...



Scipio's "Tipping Point"



QuickTime™ and a decompressor are needed to see this picture.

What Can We Learn?

- When no progress is being made in the field (or in a field).. A simple change of tactic can bring great success
- When you want "real results", you must go to the original source (mechanism??) or the fundamental pillars of truth that support your dream or concept...
- Your New Carthage can then be found...

Why nutrition support has been stuck in antiquity...

- Little understanding of mechanism
- Thought of as snake oil rather than science
- Clinical trials conducted like snake oil trials rather than real intervention trials
- We needed to attack the fundamental source/ mechanism of benefit... our New Carthage
- And..
- Plan our trials based on these fundamentals

We have turned the tide...

Take Home Message
Nutrition ~~(Support)~~ Therapy: Modulating the Stress Response and Systemic Immunity



Adjunctive Supportive Therapy



Take Home Message
Nutrition ~~(Support)~~ Therapy: Modulating the Stress Response and Systemic Immunity



Adjunctive Supportive Therapy



Proactive Primary Therapy

Why Should You Believe Me??



How should we make Therapeutic Decisions ?

- Therapy Makes Mechanistic Sense
- Majority of Studies Support Use of Therapy (on clinically relevant endpoints)
- Meta-Analysis Supports Use
- No Evidence of Harm/Low Cost

- Makes Sense in the Developmental History of Mankind...?



First things first...



What evidence should you rely on to guide your clinical decisions...

Evidence-based Medicine is only meaningful when...

WE EXAMINE ENDPOINTS THAT MATTER !

the ONION® Dispatches from the Tenth Circle

Report: Aspirin Taken Daily With Bottle Of Bourbon Reduces Awareness Of Heart Attacks



PHILADELPHIA—In a medical breakthrough that should come as welcome news for millions of at-risk Americans, University of Pennsylvania cardiologists announced Saturday that taking one aspirin tablet and a fifth of bourbon daily can significantly reduce an individual's awareness of heart attacks.

PHILADELPHIA—In a medical breakthrough that should come as welcome news for millions of at-risk Americans, University of Pennsylvania cardiologists announced Saturday that taking one aspirin tablet and a fifth of bourbon daily can significantly reduce an individual's awareness of heart attacks.

see REPORT next page

the ONION® Dispatches from the Tenth Circle

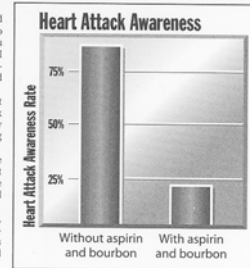
REPORT from previous page

Americans are excited about the findings. "My four heart attacks were all hellish," said Ronald Diering, an Evansville, IN, auto mechanic. "I was aware of everything that was happening, and I was gripped by the fear that I was going to die. But with this new aspirin-bourbon treatment, future heart attacks should be much less traumatic."

"Who wants to spend what could be their last moments on Earth in sheer terror?" said Alex Broadhurst of San Jose, CA. "Better to enjoy another bourbon and lie on the floor waiting for the ambulance to show up."

Researchers said individuals who take aspirin and bourbon in an attempt to prevent heart attacks may experience various side effects, including slurred speech, impaired vision, and vomiting.

Upon waking up from a heart attack, researchers said, there is also a chance of having "a wicked hangover." In such cases, victims are strongly advised to avoid bright lights and not move around too much. ☞



Outline

Clinical Nutrition Therapy in the ICU

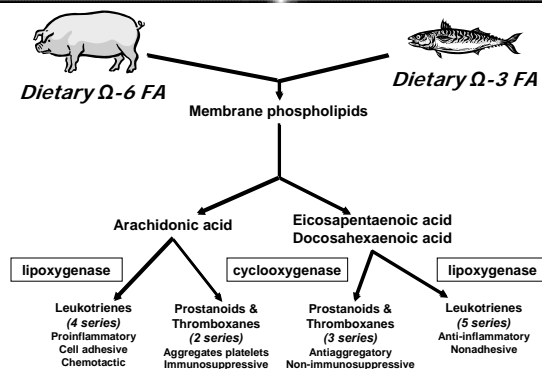
- **Pharmaconutrients**
 - **Pharmaconutrients: Omega-3 Fats**
 - **Pharmaconutrients: Arginine**
 - **Pharmaconutrients: Glutamine**

What Role Might Enteral Nutrition Play in Treating Lung Injury/ARDS?

Why You Should Use a New Therapy in Your ICU?

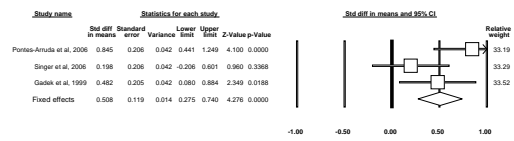
- Therapy Makes Mechanistic Sense
- Majority of Studies Support Use of Therapy (on clinically relevant endpoints)
- Meta-Analysis Supports Use
- No Evidence of Harm/Low Cost

You Are What You Eat



Why You Should Use a New Therapy in Your ICU?

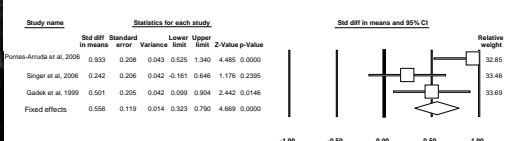
- Therapy Makes Mechanistic Sense
- Majority of Studies Support Use of Therapy (on clinically relevant endpoints)
- Meta-Analysis Supports Use
- No Evidence of Harm/Low Cost



MORE ICU-FREE DAYS

p < 0.0001

Pontes-Arruda et al; JPEN, Accepted 2008.

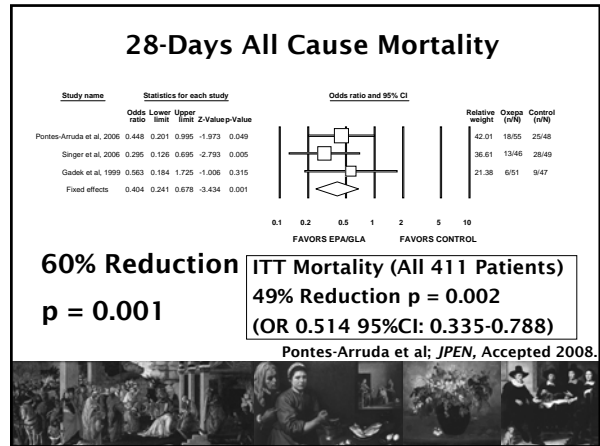
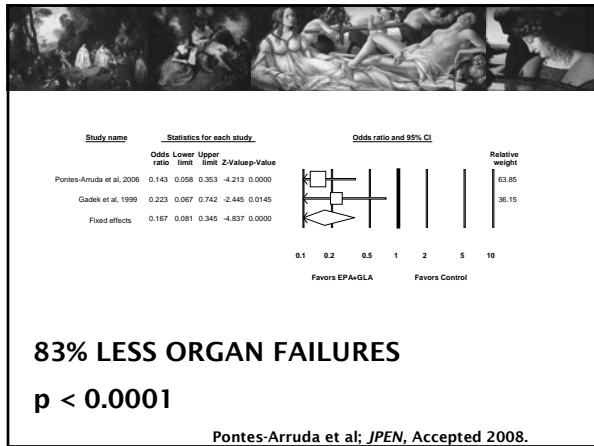


MORE VENTILATOR-FREE DAYS

p < 0.0001

Pontes-Arruda et al; JPEN, Accepted 2008.





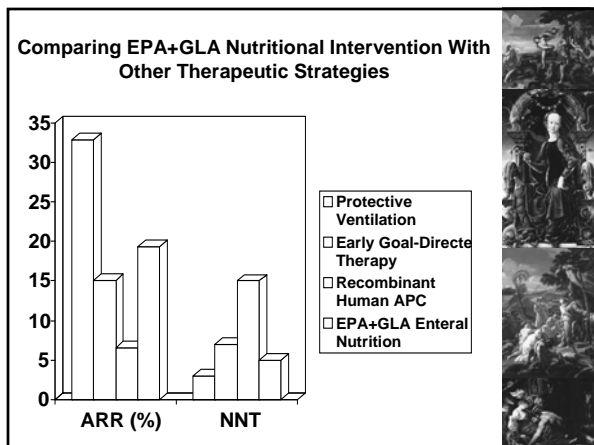
Why You Should Use a New Therapy in Your ICU?

- Therapy Makes Mechanistic Sense
- Majority of Studies Support Use of Therapy (on clinically relevant endpoints)
- Meta-Analysis Supports Use
- No Evidence of Harm/Low Cost

Health Costs

Patient with ARDS	\$ 8500 ¹
ICU Bed	\$ 2500 ²
Ventilatory Assistance	\$ 1000 ³
EN with EPA + GLA	\$25

1. Teres D, Rapoport J, et al: *Crit Care* 2001;5(suppl 1):P258
2. Project Impact CCM, Inc. www.projectimpacticu.cc
3. Salpente DM: *Crit Care Nurse* 2002;22(4):30



Special Interest

The following article is one of two articles offered for continuing education credit in this session. Please see page S82 for details.

Canadian Clinical Practice Guidelines for Nutrition Support in Mechanically Ventilated, Critically Ill Adult Patients*

Doreen K. Heyland, MD, FRCPC, MSc¹; Roginder Thalwal, RCP, John W. Devore, MD, FRCSC, FACS²; Leah Gramlich, MD, FRCPC³; Peter Dodek, MD, MRCG⁴; and the Canadian Critical Care Clinical Practice Guidelines Committee

Adult ICU Nutrition Guidelines

**SCCM / ASPEN Guidelines 2008
Selection of Appropriate Enteral
Formulation**

- Patients with ARDS should be placed on EF characterized by an anti-inflammatory lipid profile (i.e. omega 3 fish oil) (A)

Currently under "final" review by both SCCM and ASPEN

Similarities in "Guidelines"

	Canada n 2007	ESPE N 2006	SCCM 2008	ASPEN 2008	Austr NZ 2003	EAST 2004	Chest 1997
Fish oil in ARDS/ ALI	Yes	Yes	Yes	Yes	N/A	N/A	N/A

**Do I need to tell you
anymore ??**

**Until Proven
Otherwise...**

Outline

Clinical Nutrition Therapy in the ICU

- **Pharmaconutrients**
 - **Pharmaconutrients: Omega-3 Fats**
 - **Pharamaconutrients: Arginine**
 - **Pharamaconutrients: Glutamine**

**Arginine: The Controversy
Becomes Clear**

Arginine

- **Significant decrease in infection after elective surgery, trauma**
- **Increased mortality with primary diagnosis of sepsis**
- **Why ???**

Kudsk. Ann Surg 1996;224:531-40.
Moore. J Trauma 1994;37:607-15.

Why You Should Use a New Therapy in Your Patients?

- Therapy Makes Mechanistic Sense
- Majority of Studies Support Use of Therapy (on clinically relevant endpoints)
- Meta-Analysis Supports Use
- No Evidence of Harm/Low Cost

Questions ?

- Are infections after severe trauma frequent?
 - 50-100% infection rates in the ICU.
 - Contributes significantly to 25% of all trauma deaths.
 - Produced by multiple types of organisms.
 - Pseudomona, Staphylococcus, Candida
- WHY are infections so frequent and severe?
- Can we prevent them?

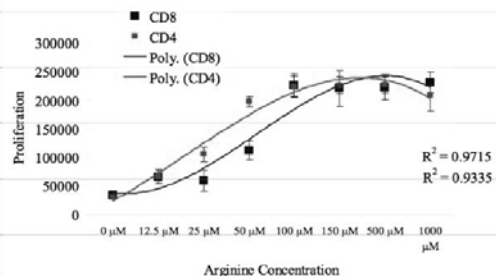
T Helper Cell Count after Trauma



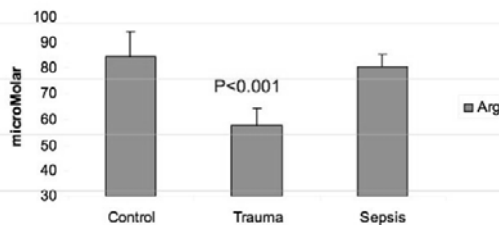
Figure 3. T-helper cell count per cubic centimeter of peripheral blood in the three clinical outcome groups (● = uneventful recovery; ▲ = major infection; ▼ = died).

Cheedle, WG. - J. Trauma 35(6):844-9

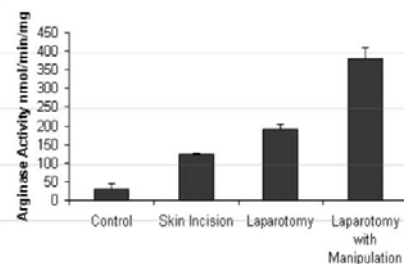
Arginine is essential for Normal T cell proliferation – Matta, B in Preparation



Arginine Plasma Levels and disease Process



Effect of Graded Trauma on Arginase Activity



Physical Injury and Sepsis are Different

- | | |
|--|---|
| <ul style="list-style-type: none"> • Sepsis – <ul style="list-style-type: none"> – Classic Macrophage Act. • Nitric Oxide • Dendritic cells • IL-1 – T helper 1 cytokine Prof. • Interferon γ • IL-2 • TNF | <ul style="list-style-type: none"> • Trauma <ul style="list-style-type: none"> – Alternative Macrophage • Arginase • Poor Antigen Presen. • IL-10 – T helper 2 cytokine Prof. • IL-4 • IL-13 |
|--|---|

Arginine Deficiency is NOT PRESENT in Sepsis

- No drop in Arginine plasma levels (unless previous surgery or trauma).
- Modest increase in Arginase
- Maximum increase in inducible nitric oxide synthase (iNOS)
- T helper 1 activation
- Classic myeloid inflammatory Response
- NO CLINICAL BENEFIT FROM ARGININE TREATMENT

Why You Should Use a New Therapy in Your Patients?

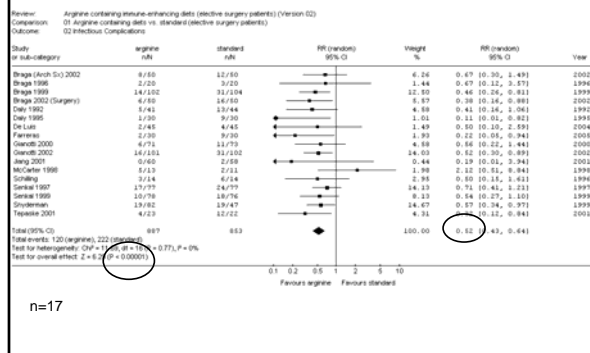
- Therapy Makes Mechanistic Sense
- Majority of Studies Support Use of Therapy (on clinically relevant endpoints)
- Meta-Analysis Supports Use
- No Evidence of Harm/Low Cost

Results

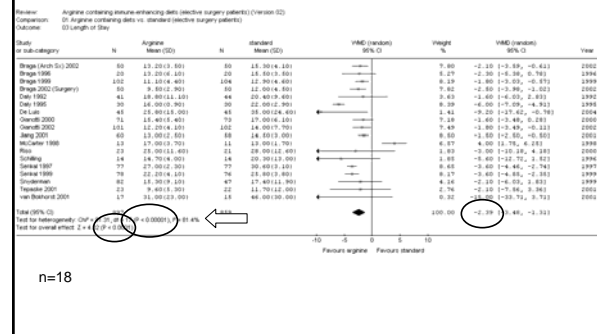
19 RCT's with 2212 patients

- Primary outcome
 - Reduced infections complications (17 trials)
 - RR= -0.52(95%CI: 0.43-0.64), p=0.00001
- Secondary outcomes
 - Reduced length of stay (18 trials)
 - -2.39(95%CI: -3.48 -1.31), p=0.0001
 - Mortality – no difference
 - RR=1.11(95%CI: 0.52-2.37), p=0.78

Results- Infectious Complications

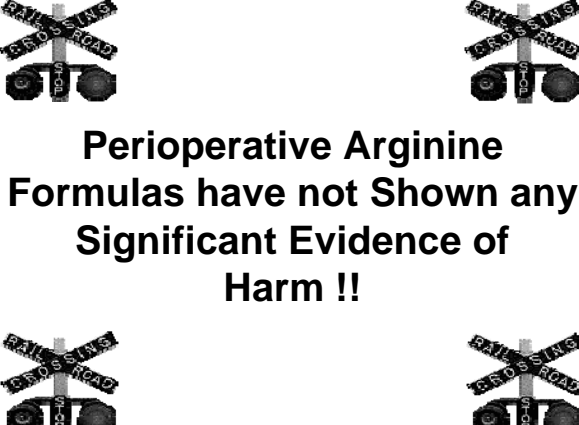


Results- Hospital LOS



Why You Should Use a New Therapy in Your Patients?

- Therapy Makes Mechanistic Sense
- Majority of Studies Support Use of Therapy (on clinically relevant endpoints)
- Meta-Analysis Supports Use
- No Evidence of Harm/Low Cost



Perioperative Arginine Formulas have not Shown any Significant Evidence of Harm !!



The Cost Savings to Millions of Patients Having Surgery Would Be Enormous!!

Do I need to tell you anymore ??

This works !

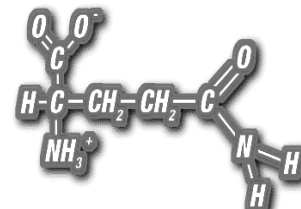
Until Proven Otherwise...

Outline

Clinical Nutrition Therapy in the ICU

- **Pharmaconutrients**
 - Pharmaconutrients: Omega-3 Fats
 - Pharmaconutrients: Arginine
 - Pharmaconutrients: Glutamine

What is Glutamine ?

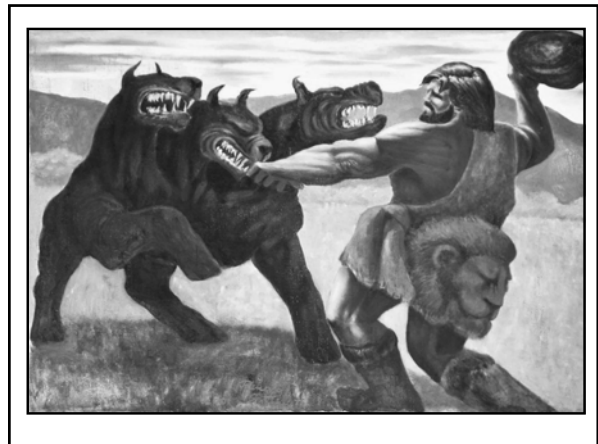


COMMON GROUP ← → SIDE GROUP ("R" GROUP)

Isn't just a metabolic fuel?

So I Will Show You That Glutamine...

- Has multiple strong mechanistic benefits
- Most all single studies show benefit on meaningful outcomes
- Meta-Analysis does support use or consideration of use
- No Evidence of Harm/Low Cost ...and...



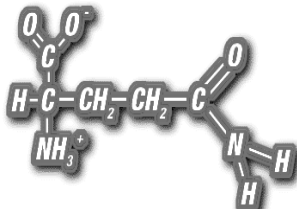
Why You Should Use a New Therapy in Your ICU?

- Therapy Makes Mechanistic Sense
- Majority of Studies Support Use of Therapy (on clinically relevant endpoints)
- Meta-Analysis Supports Use
- No Evidence of Harm/Low Cost
- Makes Sense in the Developmental History of Mankind...?

Does GLN make Mechanistic Sense??



Glutamine in Critical Illness



COMMON GROUP ← → SIDE GROUP ("R" GROUP)

Clearly a deficiency !!

Compensating a deficiency?? Glutamine as a Fuel

- 🔍 "Conditionally essential" amino acid
- 🔍 Vital to gut, immune cells, and kidney
- 🔍 GLN concentrations fall precipitously after injury, illness, and stress (including exercise)
- 🔍 Glutamine (GLN) deficiency at onset of critical illness/sepsis is correlated with increased mortality (Oudemans-van Straaten, HM et al. Intensive Care Med, 2001)

Glutamine, a life-saving nutrient, but why?*

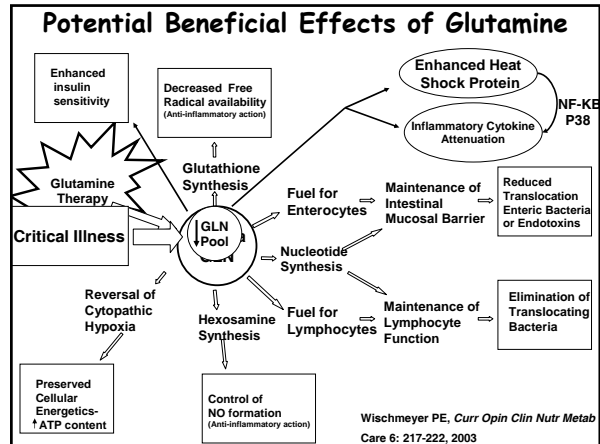
Few several decades there has been considerable and extensive interest in glutamine as an adjunct to the treatment of critical care patients. A rapid depletion of glutamine during critical illness has been reported (1, 2). A plasma glutamine concentration <0.42 mmol/L is a risk factor for poor outcome (3). Therefore, it is likely that during critical illness, the release of glutamine occurs from normally essential to essential, but particularly the essential amino acid arginine, contains very little glutamine (glutamine concentration is not increased) but is not glutamine (released parenterally).

Dr. Carol and coworkers (4) report in this issue of Critical Care Medicine the additional evidence for a role for glutamine supplementation, evidenced by improved survival and a decrease in infectious complications in patients with sepsis. The findings of this study are very consistent with previous findings (5, 6) in which patients with sepsis who were supplemented with parenteral glutamine had a significantly lower mortality rate than those who were not supplemented.

Dr. Carol and coworkers (4) report in this issue of Critical Care Medicine the additional evidence for a role for glutamine supplementation, evidenced by improved survival and a decrease in infectious complications in patients with sepsis. The findings of this study are very consistent with previous findings (5, 6) in which patients with sepsis who were supplemented with parenteral glutamine had a significantly lower mortality rate than those who were not supplemented.

References

1. De Waele JJ, et al. Plasma glutamine concentration and outcome in critically ill patients. *Crit Care Med* 2000; 28: 1000-1004.
2. De Waele JJ, et al. Plasma glutamine concentration and outcome in critically ill patients. *Crit Care Med* 2000; 28: 1000-1004.
3. De Waele JJ, et al. Plasma glutamine concentration and outcome in critically ill patients. *Crit Care Med* 2000; 28: 1000-1004.
4. De Waele JJ, et al. Plasma glutamine concentration and outcome in critically ill patients. *Crit Care Med* 2000; 28: 1000-1004.
5. De Waele JJ, et al. Plasma glutamine concentration and outcome in critically ill patients. *Crit Care Med* 2000; 28: 1000-1004.
6. De Waele JJ, et al. Plasma glutamine concentration and outcome in critically ill patients. *Crit Care Med* 2000; 28: 1000-1004.



New Paradigm

Glutamine as a Vital Drug and Signaling Molecule In Critical Illness

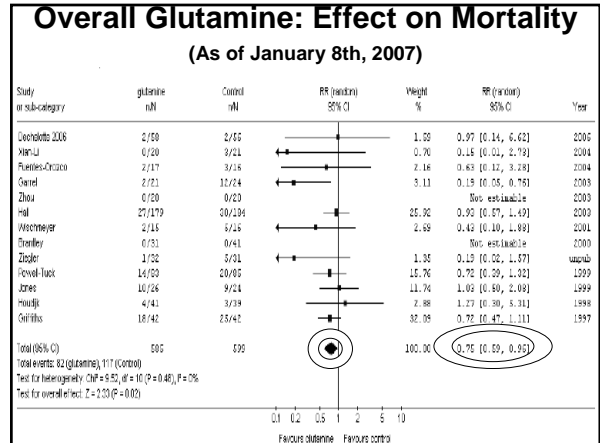
Why You Should Use a New Therapy in Your ICU?

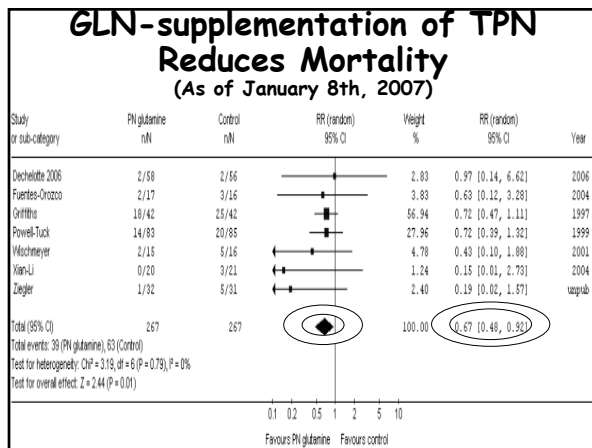
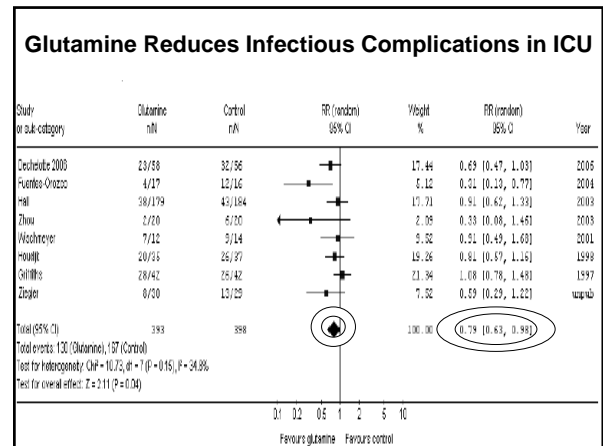
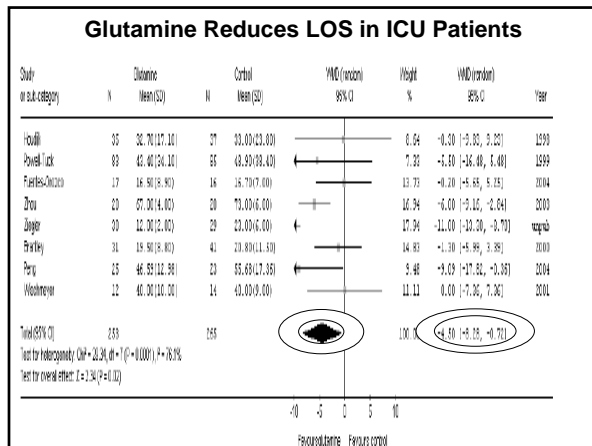
- Therapy Makes Mechanistic Sense
- Majority of Studies Support Use of Therapy (on clinically relevant endpoints)
- Meta-Analysis Supports Use
- No Evidence of Harm/Low Cost
- Makes Sense in the Developmental History of Mankind...?

Effect of Glutamine in Critically Ill: A Systematic Review of the Literature (Criticalcarenutrition.com)

- Comprehensive search
- Selection criteria
 - Randomized
 - Surgical or critically ill adults (not cancer, not VLBW infants)
 - Glutamine (EN or IV) vs. placebo
 - Clinically important outcomes
 - UPDATED regularly (last update January 8th, 2007)

Novak et al, *Critical Care Medicine*, 2007





Effect of Glutamine in Critically Ill: A Systematic Review of the Literature (Criticalcarenutrition.com)

→ Results of subgroup analyses:

- Reduced mortality in ICU patients (particularly in ICU patient on TPN)
- Less complications and shorter LOS in ICU patients
- Greater treatment effect with parenteral, high dose

Good in Theory and Good in Practice ??

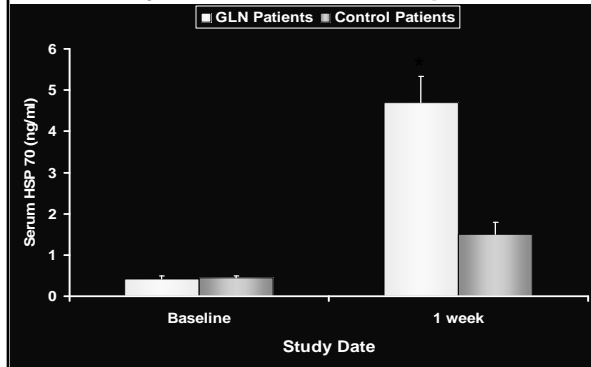
NC(=O)CC(N)C(=O)N
Glutamine

Inducing

**Hsp 70
Protein in
Critically Ill
Patients**

Could this be the answer???

ALA-GLN Enhances Serum HSP-70 in Critically Ill Patients with Sepsis/SIRS



Conclusions

- ✘ ALA-GLN treatment leads to significant enhancement of serum HSP-70 with 7 days of treatment
- ✘ ALA-GLN mediated enhancement of HSP-70 correlates with decreased ICU length of stay and time on ventilator

Ziegler T, Wischmeyer P et al Intensive Care Medicine, 31:1079-1086, 2005

Replacing a Deficiency And...

Inducing a Pharmacologic Effect



Heat Shock Protein and Critical Illness

- Critical Illness leads to a maladaptive (?) deficit in HSP expression
- This may be due to acute GLN deficiency
- Aging and Diabetes worsen defect in HSP expression ([HSP72 protects against obesity-induced insulin resistance. Proc Natl Acad Sci 105:1739-44, 2008.](#))
- Critically ill patient is at great risk for severe deficit in HSP expression which leads to:
 - Defect in organ protection
 - Defect in control of inflammatory response via increased IκBa degradation



Heat Shock Protein and Critical Illness







- Early glutamine is the only known therapeutic intervention that can prevent Heat Shock Protein depletion

Why You Should Use a New Therapy in Your ICU?

- Therapy Makes Mechanistic Sense
- Majority of Studies Support Use of Therapy (on clinically relevant endpoints)
- Meta-Analysis Supports Use
- No Evidence of Harm/Low Cost
- Makes Sense in the Developmental History of Mankind...?



No Study of Glutamine in Critical Illness has Shown any Significant Evidence of Harm

Far Cheaper Than Activated Protein C !!

Or almost any other new pharmacologic agent in the ICU...

About \$100/day

So We Have Shown Glutamine...

- Makes Mechanistic Sense
- Majority of Studies Support Use of Therapy (on clinically relevant endpoints)
- No Evidence of Harm
- Meta-Analysis Supports Use

- Makes Sense in the Developmental History of Mankind...?

How do we Explain Glutamine's Effects in History of Human Development ??



How Do We Explain GLN's Role in Stress and Illness?

- We know that GLN levels fall precipitously following stress and injury
- The magnitude of this fall is predictive of mortality in critical illness
- It appears we have only evolved the ability to store 24-48 hours worth of this vital stress signal and substrate
- This would make sense, as the ER and ICU are recent developments



How Do We Explain GLN's Role in Stress and Illness?

☛ If you did not survive your initial trauma or injury in the first 24-72 hours you died...no ambulance came and scooped you up

☛ Thus... significant stores of stress substrates and signaling molecules would not be necessary

☛ This is supported by the fact that battlefield mortality rates have changed little in the least 150 years.

Champion HR et al. A profile of combat injury. J Trauma. 54:S13-19, 2003

How Do We Explain GLN's Role in Stress and Illness?

☛ Currently many of the therapies we consider standard of care, are having their risk/benefit ratio questioned (I.e. antibiotics)

Singer M et al. Treating Critical Illness: The importance of first doing no harm. PLOS medicine, 2:e167, 2005.

☛ Perhaps we should be looking to the bodies own stress substrates as our "drugs of the future" for critical illness and injury

☛ This is particularly true for substrates that may have a limited supply such as glutamine, which likely need replacement as we know deficiency's correlate with increased death in ICU

1001-0800/09/00000000-0000
Journal of Intensive Care Medicine 24(12)
Copyright © 2009 by the American Society for Parenteral and Enteral Nutrition

Special Interest

The following article is one of two articles offered for continuing education credit in this issue. Please see page 1083 for details.

Canadian Clinical Practice Guidelines for Nutrition Support in Mechanically Ventilated, Critically Ill Adult Patients*

Davey K. Heyland, MD, FRCPC, MSc¹; Rajinder Dhaliwal, BSc²; John W. Dronow, MD, FRCSC, FACHE³; Leah Greenlich, MD, FRCPC⁴; Peter Dodek, MD, MSc⁵; and the Canadian Critical Care Clinical Practice Guidelines Committee

Adult ICU Nutrition Guidelines

Enteral versus Parenteral GLN

Enteral GLN:

Recommendation: Based on 2 level 1 and 5 level 2 studies, enteral glutamine should be considered in burn and trauma patients. There are insufficient data to support the routine use of enteral glutamine in other critically ill patients.

**Canadian Critical Care Nutrition Guidelines
Criticalcarenutrition.com**

Enteral versus Parenteral GLN

Parenteral GLN

Based on 4 level 1 studies and 5 level 2 studies, when parenteral nutrition is prescribed to critically ill patients, parenteral supplementation with glutamine, where available, is recommended.

**Canadian Critical Care Nutrition Guidelines
Criticalcarenutrition.com**

SCCM / ASPEN Guidelines 2008 When Indicated, Maximize Efficacy of Parenteral Nutrition

- When EN not feasible or available and TPN deemed appropriate steps to maximize efficacy should be used
 - Supplemental Glutamine (A- with dipeptide)
- The addition of enteral glutamine should be considered in burn and trauma (B)

Currently under "final" review by both SCCM and ASPEN

Similarities in "Guidelines" for Glutamine Use in ICU Patients

	Canada 2007	ESPEN 2006	SCCM 2008	ASPEN 2008	Austr NZ 2003	EAST 2004	Chest 1997
Glutamine	Yes	Yes	Yes	Yes	Yes	Yes	N/A

Why You Should Change Your Practice ?

- Therapy Makes Mechanistic Sense
- Majority of Studies Support Use of Therapy (on clinically relevant endpoints)
- Meta-Analysis Supports Use
- No Evidence of Harm/Low Cost

- Makes Sense in the Developmental History of Mankind...?

What can I do to change practice??



What Can You and I Do ?

- You are the drivers of change in the hospital

- Epidemics (changes) that save lives are started and transmitted by hosts just like you

- Challenge tradition and intuition-
 - demand data (seeing it yourself is best)
 - ...then demand change

- Believe in—and lead with—a premise that *change is possible.*



Acknowledgements

- Steve McClave M.D.
- Juan Ochoa M.D.
- Daren Heyland M.D.
- Alessando Pontes-Arruda M.D.
- John Drover M.D.
- Scipio Africanus



Questions ??



Nanoparticle Microarrays: The Future of Bedside Pathogen Detection?

Scott M. Ahlbrand, M.D.
Stanford University
Stanford, California

Nanoparticle Gene Array: The Future of Bedside Pathogen Detection?

Scott Ahlbrand, M.D.
Department of Anesthesia
Stanford University Medical Center



Objectives

- Overview the magnitude of antibiotic resistance
- Illustrate how this technology may deliver point of care pathogen identification
- Introduce a nucleotide probe set capable of identifying *Pseudomonas* organisms

Objectives

- Overview the magnitude of antibiotic resistance
- Illustrate how this technology may deliver point of care pathogen identification
- Introduce a nucleotide probe set capable of identifying *Pseudomonas* organisms

Antibiotic Resistance

2 million patients acquire nosocomial infection in the United States each year

NIAID fact sheet, April, 2006

Antibiotic Resistance

2 million patients acquire nosocomial infection in the United States each year



About 90,000 of those patients die each year as a result of their infection

NIAID fact sheet, April, 2006

Antibiotic Resistance

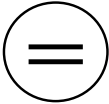


from 13,300 patient deaths in 1992

Antibiotic Resistance



from 13,300 patient deaths in 1992



> 6 fold increase in 14 years

Antibiotic Resistance



(www.sciencemuseum.org,
www.countrytrains.com, img.getactivehub.com,
www.knowmoremedia.com)

Antibiotic Resistance

And the problem is growing . . .

Antibiotic Resistance

Pseudomonas aeruginosa



(www.scienceartfied.com)

Antibiotic Resistance

McGowan, 2007

Second most frequent pathogen recovered among ICU patients in a study in North America



(www.sciencedirect.com)

Antibiotic Resistance

McGowan, 2007

Highest proportion of gram-negative organisms reported in the NNIS System for pneumonia from 1986 to 2003



(www.sciencedirect.com)

Antibiotic Resistance

McGowan, 2007
2004 NNIS System report

Rate of resistance
Quinolones

↑ 9%



2003

(www.sciencedirect.com)

Antibiotic Resistance

McGowan, 2007
2004 NNIS System report

Rate of resistance
Imipenem

↑ 15%



2003

(www.sciencedirect.com)

Antibiotic Resistance

McGowan, 2007
2004 NNIS System report

Rate of resistance
Third-generation cephalosporins

↑ 20%



2003

(www.sciencedirect.com)

Antibiotic Resistance

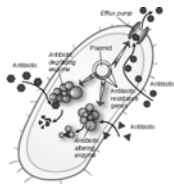
So what is being done ?

NIAID fact sheet, April, 2006

Antibiotic Resistance

Areas of research

Basic Biology of
Resistant Organisms

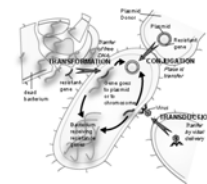


(NIAID fact sheet, April, 2006, www.ssq.ubc.ca)

Antibiotic Resistance

Areas of research

How Resistance is
Developed and Shared



(NIAID fact sheet, April, 2006, www.ssq.ubc.ca)

Antibiotic Resistance

Areas of research

Preventive Measures



(NIAID fact sheet, April, 2006, www.health.gov.au.ca)

Antibiotic Resistance

Areas of research

Novel Therapies

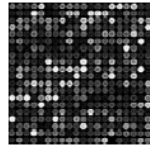


(NIAID fact sheet, April, 2006, www.nature.com)

Antibiotic Resistance

Areas of research

Diagnostic
Techniques



(NIAID fact sheet, April, 2006, www.nature.com)

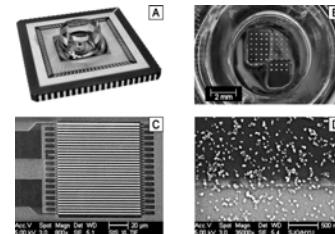
Objectives

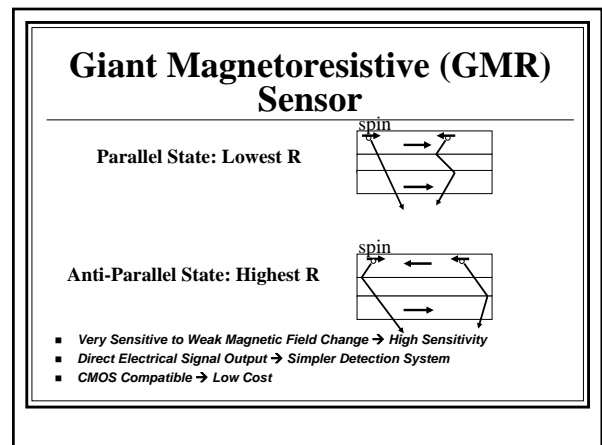
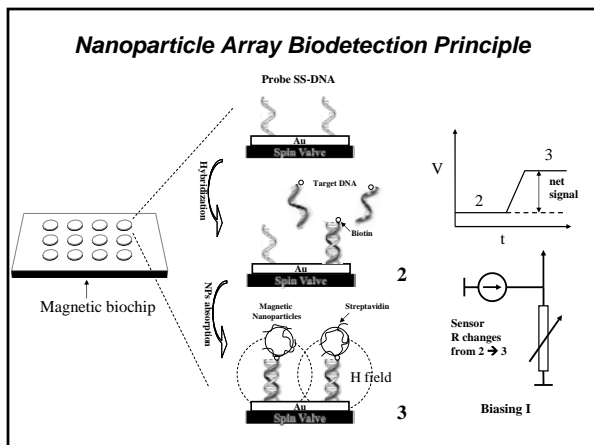
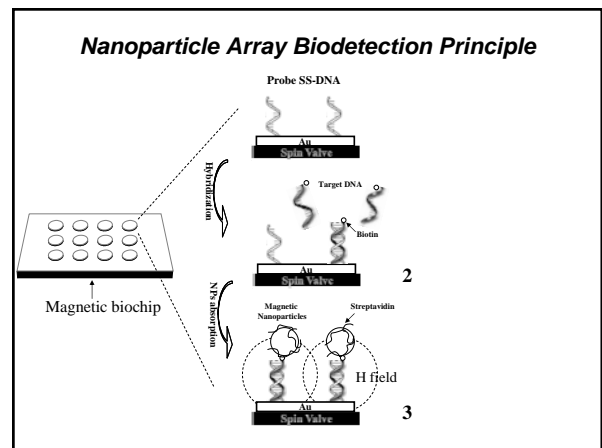
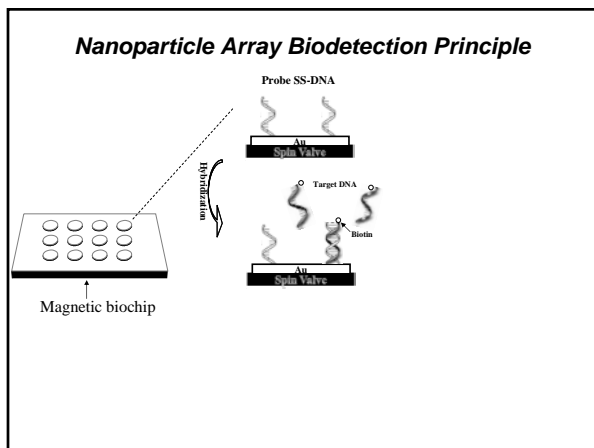
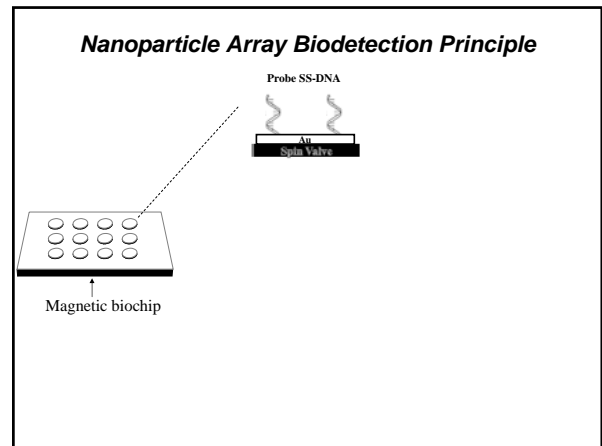
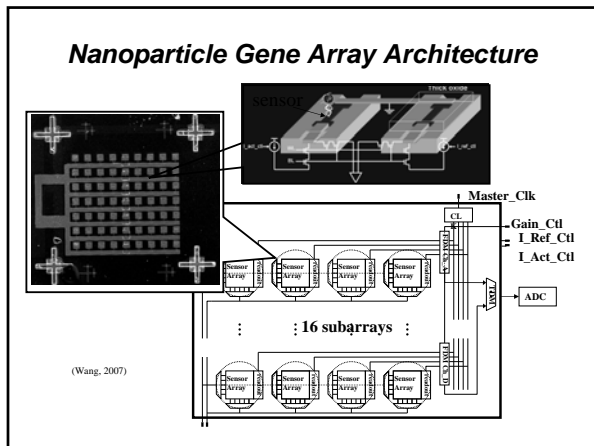
- Overview the magnitude of antibiotic resistance
- Illustrate how this technology may deliver point of care pathogen identification.
- Introduce a nucleotide probe set capable of identifying *Pseudomonas* organisms

Objectives

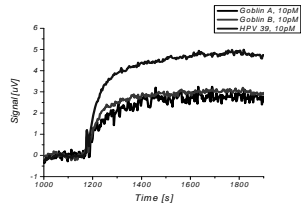
- Overview the magnitude of antibiotic resistance
- Illustrate how this technology may deliver point of care pathogen identification.
- Introduce a nucleotide probe set capable of identifying *Pseudomonas* organisms

Nanoparticle Gene Array





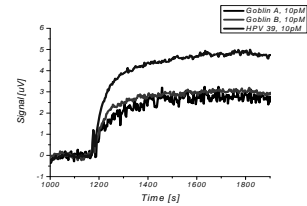
HPV DNA Fragment Quantitation



Noise Level of Signal Traces suggests Analytical Sensitivity below 500 fM is Attainable

(Xu, Yu, et al., unpublished)

HPV DNA Fragment Quantitation



Noise Level of Signal Traces suggests Analytical Sensitivity below 500 fM is Attainable

(Xu, Yu, et al., unpublished)

Objectives

- Overview the magnitude of antibiotic resistance
- Illustrate how this technology may deliver point of care pathogen identification.
- Introduce a nucleotide probe set capable of identifying *Pseudomonas* organisms

Objectives

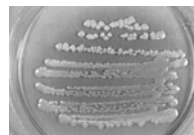
- Overview the magnitude of antibiotic resistance
- Illustrate how this technology may deliver point of care pathogen identification.
- Introduce a nucleotide probe set capable of identifying *Pseudomonas* organisms

Hypothesis

We hypothesized that a set of highly specific nucleotide probes may distinguish Pseudomonas from all other organisms.

Methods

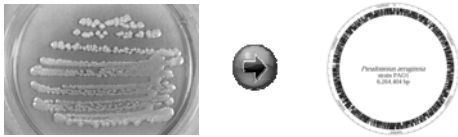
41 *Pseudomonas* colonies collected from the Stanford Hospital Clinical Laboratory



(*pseudomonas.com*, www.bact.wisc.edu/)

Methods

41 *Pseudomonas* colonies collected from the Stanford Hospital Clinical Laboratory
Genomes analyzed for common sequences



(pseudomonas.com, www.bact.wisc.edu)

Methods

9 known *Pseudomonas* groups

Methods

9 known *Pseudomonas* groups



6 groups have been sequenced

Methods

9 known *Pseudomonas* groups



13 genomes known from these groups

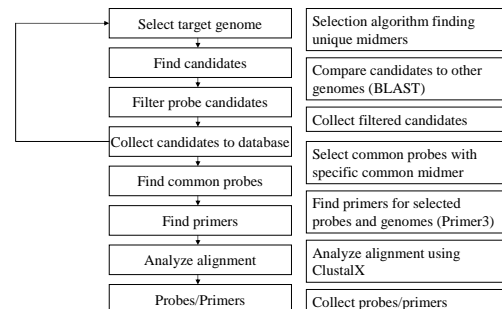
Methods

9 known *Pseudomonas* groups

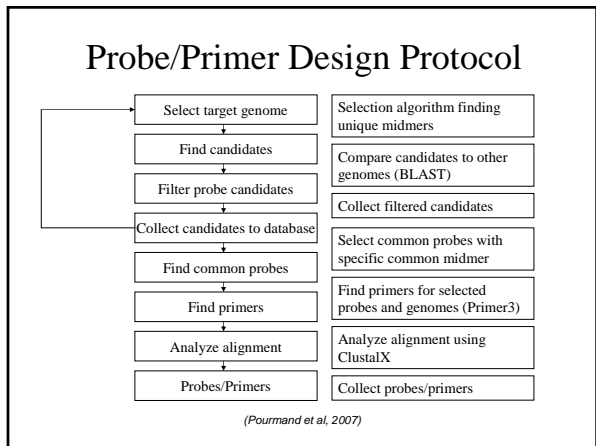
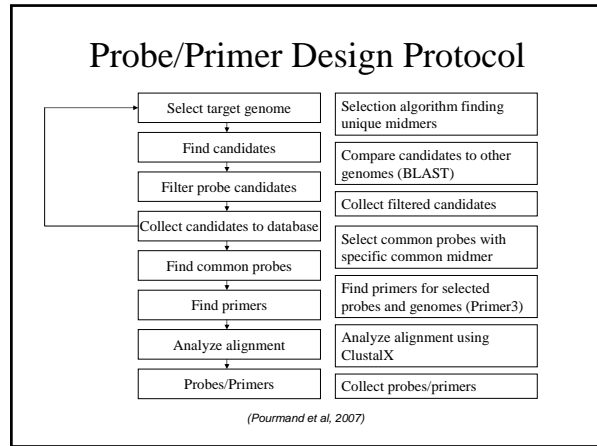
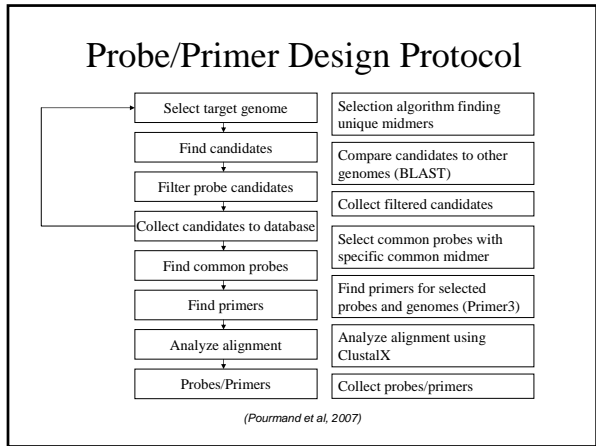


10 genomes have been included so far in our preliminary probe search.

Probe/Primer Design Protocol



(Pourmand et al, 2007)



Methods

Selection criteria

Thiyagarajan et al. 2006

Methods

Selection criteria

Unique midmers with 9 nucleotides in a 25-mer probe sequence

Thiyagarajan et al. 2006

Methods

Selection criteria

Unique midmers with 9 nucleotides in a 25-mer probe sequence

$8n+9n+8n$

Thiyagarajan et al. 2006

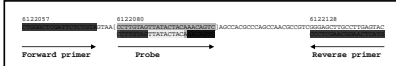
Methods

Selection criteria

Unique midmers with 9 nucleotides in a 25-mer probe sequence

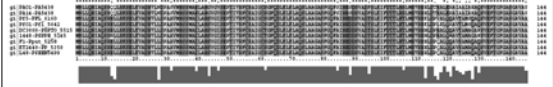
$$8n+9n+8n$$

Using this protocol - 20000 potential probe candidates

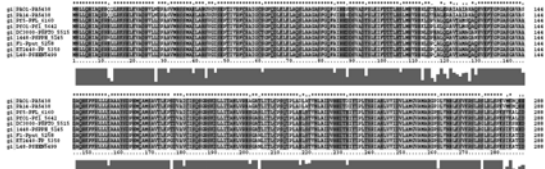


Thyagsajan et al. 2006

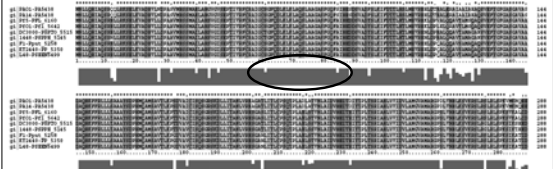
ClustalX Alignment Analysis



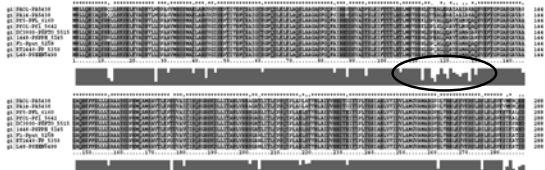
ClustalX Alignment Analysis



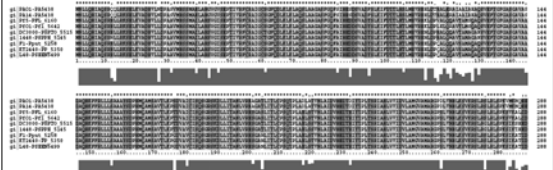
ClustalX Alignment Analysis



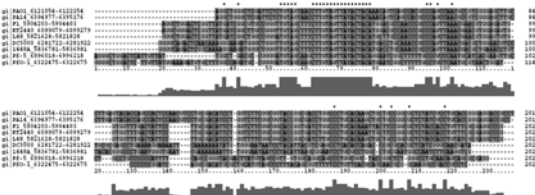
ClustalX Alignment Analysis



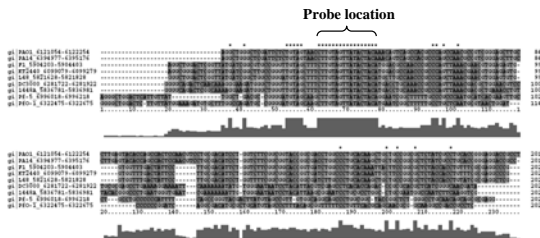
ClustalX Alignment Analysis



ClustalX Alignment Analysis



ClustalX Alignment Analysis



Results

The intron following the gene PA5438 encoding a transcriptional protein regulator contains a homological midmer common to all human pathogenic strains of Pseudomonas.

RpiR family



(dbd.mrc-imb.cam.ac.uk)

Results

CCTTGTACTTATACTAC[REDACTED]
CCTTGTACTTATACTAC[REDACTED]GGAATCC
CCTTGTACTTATACTACATGACCTG
CCTTGTACTTATACTACATGATGC
CCTTGTACTTATACTACATGGACGC
CTTTCCTTAGTTATACATCATGC
GACCGAATATACTTACATCATGC

Objectives

- Overview the magnitude of antibiotic resistance
- Illustrate how this technology may deliver point of care pathogen identification.
- Introduce a nucleotide probe set capable of identifying Pseudomonas organisms

Objectives

- Overview the magnitude of antibiotic resistance
- Illustrate how this technology may deliver point of care pathogen identification.
- Introduce a nucleotide probe set capable of identifying Pseudomonas organisms

Objectives

- Overview the magnitude of antibiotic resistance
- Illustrate how this technology may deliver point of care pathogen identification.
- Introduce a nucleotide probe set capable of identifying *Pseudomonas* organisms

Objectives

- Overview the magnitude of antibiotic resistance
- Illustrate how this technology may deliver point of care pathogen identification.
- Introduce a nucleotide probe set capable of identifying *Pseudomonas* organisms

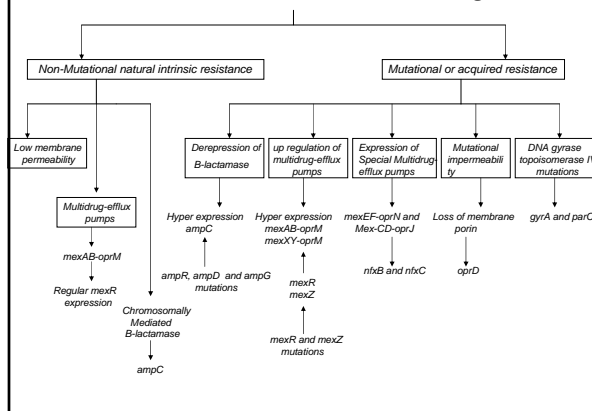
Acknowledgments

Andrew J. Patterson, M.D. Ph.D.
 Nader Pourmand, Ph.D.
 Shan Wang, Ph.D.
 Niaz Banaei, M.D.
 Rani Agrawal, M.S.
 Brooks Rohlen, M.D.
 Joe Hsu, M.D.
 Nancy Federspiel, Ph.D.

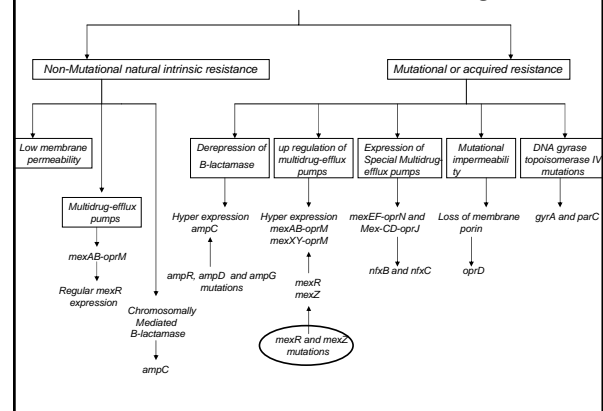
Common Genes of Resistance

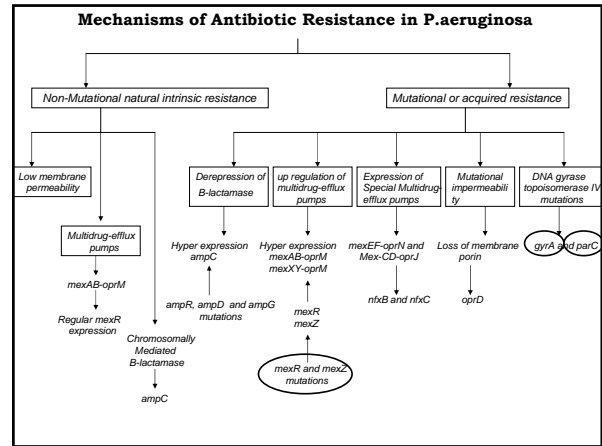
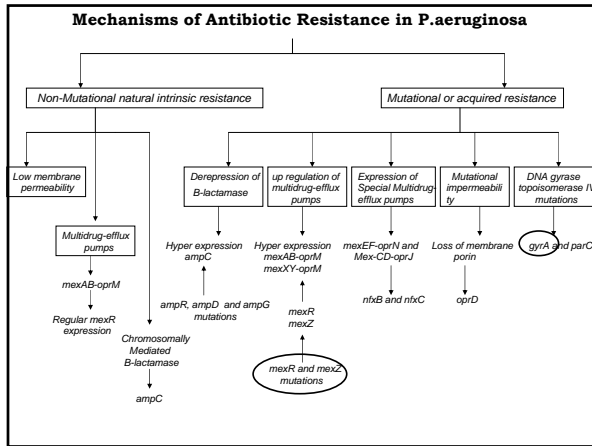
Gene Name	Gene Product	Antibiotic Target
gyrA	A subunit of DNA gyrase enzyme	Fluroquinolones
parC	subunit of Topoisomerase IV enzyme	Fluroquinolones
mexR	Regulatory gene for mexAB-oprM efflux pumps	B-lactames, Fluroquinolones, Chloramphenicol, Trimethoprim
mexZ	Regulatory gene for mexXY-oprM efflux pumps	Aminoglycosides
mexOZ	A region located between mexZ and mexX gene also related to mexXY-oprM expression	Aminoglycosides

Mechanisms of Antibiotic Resistance in *P.aeruginosa*



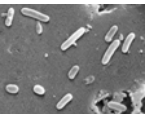
Mechanisms of Antibiotic Resistance in *P.aeruginosa*



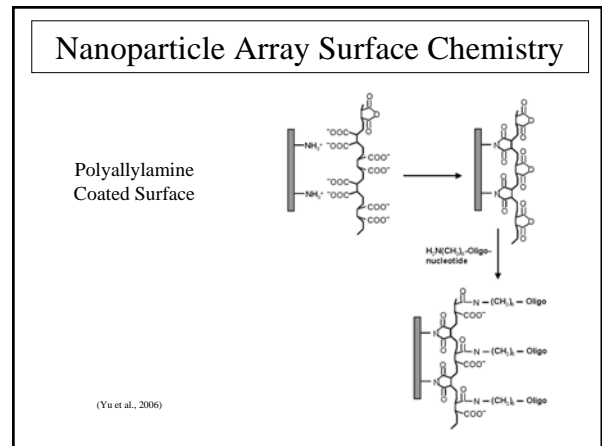


Pseudomonas

- *P. aeruginosa* group (n=4): PAO1, PA14, Mendocina_yp, PA7
- *P. chlororaphis* group: (n=0)
- *P. entomophila* (n=1): Entomophila_L48
- *P. incertae sedis* group: (n=0)
- *P. fluorescens* group (n=2): Pf-5, PFO-1
- *P. pertucinogena* group: (n=0)
- *P. putida* group (n=2): F1, KT2440
- *P. stutzeri* group (n=1): A1501
- *P. syringae* group (n=3): phaseolicola_1448A, pv_B728a, tomato_DC3000



(www.bact.wisc.edu)

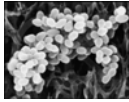


Antibiotic Resistance

And the problem is growing . . .

Antibiotic Resistance

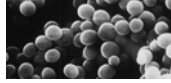
Staphylococcus aureus



(www.forbes.com)

Antibiotic Resistance

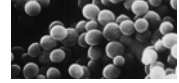
1880 – First identified



(NIAID fact sheet, April, 2006,
www.staphylococcus aureus. blogs

Antibiotic Resistance

1880 – First identified

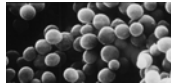


1941 – Penicillin introduced

(NIAID fact sheet, April, 2006,
www.staphylococcus aureus. blogs

Antibiotic Resistance

1880 – First identified



1941 – Penicillin introduced

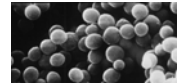


1943 – Resistant strains reported

(NIAID fact sheet, April, 2006,
www.staphylococcus aureus. blogs

Antibiotic Resistance

1880 – First identified



1941 – Penicillin introduced

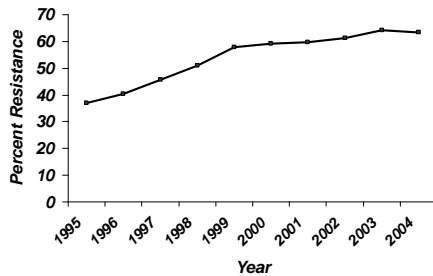


1943 – Resistant strains reported

2 years!!

(NIAID fact sheet, April, 2006,
www.staphylococcus aureus. blogs

MRSA Among ICU Patients



Source: National Nosocomial Infections Surveillance (NNIS) System
(www.bact.wisc.edu)

Antibiotic Resistance

So how do we treat *S.aureus*?

Antibiotic Resistance

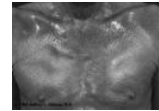
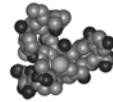


"most effective and reliable drug in these cases"

(NIAID fact sheet, April, 2006, www.abbott.com)

Antibiotic Resistance

Vancomycin



(NIAID fact sheet, April, 2006, www.abbott.com, www.ntif.com)

Antibiotic Resistance



Antibiotic Resistance



Antibiotic Resistance

First reported case of *S. aureus* infection completely resistant to vancomycin

January	February	March
April	May	June
July	August	September
October	November	December

2002

(NIAID fact sheet, April, 2006, www.ntif.com, www.fda.gov)

Antibiotic Resistance

First reported case of *S. aureus* infection completely resistant to vancomycin

January	February	March
April	May	June
July	August	September
October	November	December

2002

(NIAID fact sheet, April, 2006, www.ntif.com, www.fda.gov)

Antibiotic Resistance

First reported case of *S. aureus* infection completely resistant to vancomycin



January	February	March
April	May	June
July	August	September
October	November	December

Second case reported

2002

(NIAID fact sheet, April, 2006, www.nrlf.com,

Antibiotic Resistance

First reported case of *S. aureus* infection completely resistant to vancomycin



January	February	March
April	May	June
July	August	September
October	November	December

Second case reported

2002

(NIAID fact sheet, April, 2006, www.nrlf.com,

Antibiotic Resistance

First reported case of *S. aureus* infection completely resistant to vancomycin



January	February	March
April	May	June
July	August	September
October	November	December

Second case reported



2002

(NIAID fact sheet, April, 2006, www.framehuggers.com,

Antibiotic Resistance



2004 - Third reported case of vancomycin-resistant *S. aureus* (VRSA)

(NIAID fact sheet, April, 2006, www.framehuggers.com,

Antibiotic Resistance



2004 - Third reported case of vancomycin-resistant *S. aureus* (VRSA)



Since then, three additional cases of VRSA, have been reported to CDC

(NIAID fact sheet, April, 2006, www.framehuggers.com,

Antibiotic Resistance

And *S. aureus* is not alone . . .

(NIAID fact sheet, April, 2006, www.framehuggers.com,

Interactive Clinical Forum

Moderator: Avery Tung, M.D.

Discussants: Luca Bigatello, M.D.; Andrew L. Rosenberg, M.D.; Steven J. Lisco, M.D.

A 65 yr F with sarcoidosis, HTN, and CAD is scheduled for thoracotomy with possible wedge resection. Due to a recent two month history of worsening shortness of breath, she had sought medical attention. A subsequent workup revealed a new L upper lobe nodule, resulting in the planned surgery for biopsy and possible resection.

Approximately 6 months ago, a drug eluting coronary stent was placed for exertional angina and a 70% calcified LAD lesion and the patient begun on plavix and aspirin. Aside from mild pulmonary hypertension, her sarcoid was well controlled with prednisone 20 mg qday. Additional medications were lisinopri 10qd, lasix 40mgPOqd, and metoprolol 25POBID.

In the preoperative clinic she notes 1 block exercise tolerance and 1+ LE edema. Vital signs were 150/85, HR 96, RR 25, and SpO₂ 92% on RA. She was 5'4" and 74 kg (BMI =28). Laboratory values included Hct 38%, Cr 1.3, Na⁺ 134, HCO₃⁻ 23, K⁺ = 3.4, INR 1.3. Preoperative echocardiogram revealed LVH, preserved LV systolic function, and mild pulmonary hypertension with RVSP ~ 45 mm Hg.

1. Her heart rate is 96. Controversy exists regarding the role of perioperative beta blockade in reducing the risk of acute myocardial events, with dose, timing, and duration all uncertain. Current data hint that the cardioprotective effect of beta blockade may be associated with HRs<90. Moreover, she is at risk for postoperative tachyarrhythmias. Would you administer additional beta blockade preoperatively?

POISE Study Group, Devereaux PJ, Yang H, Yusuf S, Guyatt G, Leslie K, Villar JC, Xavier D, Chrolavicius S, Greenspan L, Pogue J, Pais P, Liu L, Xu S, Málaga G, Avezum A, Chan M, Montori VM, Jacka M, Choi P. Effects of extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE trial): a randomised controlled trial. Lancet. 2008 May 31;371(9627):1839-47

Beattie WS, Wijeyesundera DN, Karkouti K, McCluskey S, Tait G. Does tight heart rate control improve beta-blocker efficacy? An updated analysis of the noncardiac surgical randomized trials. Anesth Analg. 2008 Apr;106(4):1039-48

Biccard BM, Sear JW, Foëx P. Meta-analysis of the effect of heart rate achieved by perioperative beta-adrenergic blockade on cardiovascular outcomes. Br J Anaesth. 2008 Jan;100(1):23-8

2. This patient is taking aspirin only for prevention of stent-induced coronary thrombosis.
2a. Would you restart the plavix in preparation for the operation?
2b. Post-thoracotomy pain is notable for its intensity and duration. Moreover, aggressive analgesic therapy improves pulmonary function and may reduce the incidence of postoperative dysrhythmias. Would you place an epidural for postoperative pain control?

Hirsh J, Bauer KA, Donati MB, Gould M, Samama MM, Weitz JI; American College of Chest Physicians. Perioperative management of antithrombotic therapy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest. 2008 Jun;133(6 Suppl):141S-159S

Ballantyne JC, Carr DB, deFerranti S, Suarez T, Lau J, Chalmers TC, Angelillo IF, Mosteller F. The comparative effects of postoperative analgesic therapies on pulmonary outcome: cumulative meta-analyses of randomized, controlled trials. Anesth Analg 1998;86:598-612

Oka T, Ozawa Y, Ohkubo Y. Thoracic epidural bupivacaine attenuates supraventricular tachyarrhythmias after pulmonary resection. Anesth Analg. 2001 Aug;93(2):253-9

Jidéus L, Joachimsson PO, Stridsberg M, Ericson M, Tydén H, Nilsson L, Blomström P, Blomström-Lundqvist C. Thoracic epidural anesthesia does not influence the occurrence of postoperative sustained atrial fibrillation. Ann Thorac Surg. 2001 Jul;72(1):65-71

You choose not to place an epidural. Induction, DLT placement, and positioning were uncomplicated. Biopsy of the nodule revealed undifferentiated adenoCA and the L upper lobe was resected. Lymph node dissection resulted in a pulmonary artery tear, a 700cc blood loss, 25 minutes with systolic blood pressures between 60 and 70mmHg, and an extensive surgical repair. U/O for the 4 hour case was 90cc, and the patient received 3000cc LR. Due to concern about the adequacy of the PA repair, a single lumen ETT was placed and she was taken to the ICU.

In the ICU, she was sedated and unresponsive. BP 100/50, HR 105. Her lines included 2 18G IVs and a R radial arterial line. Abg: 7.30/45/82 on 50% with PIP = 32 cm H₂O. BE = -5, Hct = 28, HCO₃ = 19. Her extremities were cool, but capillary refill was good.

3. This patient was on prednisone preoperatively for management of sarcoidosis. Would you administer supplemental steroids?

Sprung CL, Annane D, Keh D, Moreno R, Singer M, Freivogel K, Weiss YG, Benbenishty J, Kalenka A, Forst H, Laterre PF, Reinhart K, Cuthbertson BH, Payen D, Briegel J; CORTICUS Study Group. Hydrocortisone therapy for patients with septic shock. N Engl J Med. 2008 Jan 10;358(2):111-24

Marik PE, Pastores SM, Annane D, Meduri GU, Sprung CL, Arlt W, Keh D, Briegel J, Beishuizen A, Dimopoulou I, Tsagarakis S, Singer M, Chrousos GP, Zaloga G, Bokhari F, Vogeser M; American College of Critical Care Medicine. Recommendations for the diagnosis and management of corticosteroid insufficiency in critically ill adult patients: consensus statements from an international task force by the American College of Critical Care Medicine. Crit Care Med. 2008 Jun;36(6):1937-49

Annane D, Bellissant E, Bollaert PE, Briegel J, Keh D, Kupfer Y. Corticosteroids for treating severe sepsis and septic shock. Cochrane Database Syst Rev. 2004;(1):CD002243

Over the next 2 hours, U/O is low at 10 cc/hr. HR 106, BP 95/45, SpO₂ 96% on 40% FiO₂

4. How would you evaluate the adequacy of her oxygen delivery? PAC, SvO₂, Lactate, Echo? Response to fluid bolus?

After a 500cc albumin bolus, urine output improves to 35 cc/hr. A central line is placed to monitor fluid administration, CVP is 14 mm Hg, and SCVO₂ = 78%. Overnight, the patient receives two additional boluses, both for low urine output.

A chest Xray the next morning demonstrates worsened pulmonary edema. On VCV, TV 600, RR 12, PEEP 10, 50% FiO₂ her arterial PO₂ = 70 mmHg and SCVO₂ = 72%. BP 85/40, HR= 110, CVP =16mmHg, Lasix 40mg IV is given but no increase in urine output results.

5. Her current blood pressures are lower than her preoperative baseline, and may contribute to her low urine output. The thoracic surgeon proposes a vasopressin infusion to increase blood pressure and a lasix drip to decrease intravascular volume. Do you concur?

Boccaro G, Ouattara A, Godet G, Dufresne E, Bertrand M, Riou B, Coriat P. Terlipressin versus norepinephrine to correct refractory arterial hypotension after general anesthesia in patients chronically treated with renin-angiotensin system inhibitors. *Anesthesiology*. 2003 Jun;98(6):1338-44

Brabant SM, Eyraud D, Bertrand M, Coriat P. Refractory hypotension after induction of anesthesia in a patient chronically treated with angiotensin receptor antagonists. *Anesth Analg*. 1999 Oct;89(4):887-8

Morelli A, Tritapepe L, Rocco M, Conti G, Orecchioni A, De Gaetano A, Picchini U, Pelaia P, Reale C, Pietropaoli P. Terlipressin versus norepinephrine to counteract anesthesia-induced hypotension in patients treated with renin-angiotensin system inhibitors: effects on systemic and regional hemodynamics. *Anesthesiology*. 2005 Jan;102(1):12-9.

You begin a vasopressin drip at 40mU/hour and lasix at 10 mg/hr. Blood pressure improves to 120/50. Urine output improves to 60 cc/hr. After 12 hours, however, PO₂ does not improve (now 71 on the same ventilator settings).

Over the next two days, she remains intubated and mechanically ventilated due to poor gas exchange. Her course is complicated by recurrent bouts of atrial fibrillation refractory to amiodarone therapy. You decide to anticoagulate, but her platelet count has dropped from 134k immediately postop to 43k currently.

6a. Would you anticoagulate?

6b. Would you use heparin, argatroban, LMWH, or something else?

Beldi G, Beng L, Siegel G, Bisch-Knaden S, Candinas D. Prevention of perioperative thromboembolism in patients with atrial fibrillation. *Br J Surg*. 2007 Nov;94(11):1351-5

Hirsh J, Bauer KA, Donati MB, Gould M, Samama MM, Weitz JI; American College of Chest Physicians. Perioperative management of antithrombotic therapy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest*. 2008 Jun;133(6 Suppl):141S-159S


2 days later, blood pressure, urine output, and oxygenation improve. The patient is extubated successfully, and her baseline medications restarted. Lines are removed and she is transferred to the floor on POD #5.

CCM in Academics: Job Opportunities, Practice Models, Academic Opportunities

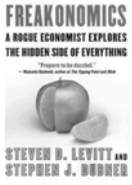
William E. Hurford, M.D.
University of Cincinnati Medical Center
Cincinnati, Ohio

CCM in Academics:
Job Opportunities, Practice Models, Academic Opportunities


William E. Hurford, MD, FCCM
Professor and Chair
Department of Anesthesiology
University of Cincinnati College of Medicine
Cincinnati, Ohio



**A “Freakonomics” approach to
Critical Care**




Economics represents how the world actually works... with apologies to Steven Levitt & Stephen Dubner




No Money; No Mission

- *No matter how much fun, a critical care program cannot be sustained if it doesn't make economic sense.*




Cash Income Statement

- Patient Revenue
- Total Expenses
 - Provider compensation & Benefits
 - Physician Development
 - Insurance
 - Medical Support/Administrative Salaries & Benefits
 - Supplies, Rent, Depreciation
 - Other stuff
- Net Operating Income (Revenue – Expenses)
- Non-Operating Income
 - General and University Funds
 - Contracts & Stipends
 - Grants, Royalties, Licensing
 - Investment Income/Reserves
- Total Net Income (the bottom line!)
= net operating + non-operating income




Premises

- *Critical care physicians, while capable of raising the dead, will not work for free*
- *Physician compensation must be equivalent or greater than the available alternatives to working in the ICU*
- *Because anesthesiologists have greater income requirements, compared to other specialists working in the ICU, they must either be altruistic, highly productive, or have alternative sources of income*



Premises

- *Academic practices are predisposed to developing critical care:*
 - *Available compensation in the OR is less attractive than in private practice*
 - *Stipends for teaching and medical direction are more readily available*
 - *Depts. more commonly have sources of non-operating revenue that can bridge the gap*
 - *Your colleagues are academics, after all, and willing to accept less pay (within limits) simply because its fun to be around really smart people like yourselves*



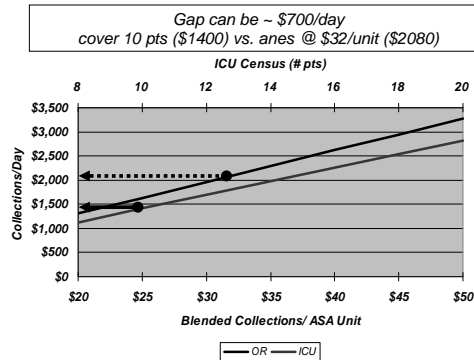
\$\$\$ in OR

- **OR Collections/ASA unit**
 - University \$25
 - Community \$41
 - SAAC Mean \$32.20 (range \$17 - \$37)
- **ASA Units/FTE Workday**
 - 14,000 units/ 214 days = 65 units/day
 - University \$1,700/day
 - Community \$2,780/day

Fewer \$ in ICU

- **Typical Urban Academic Practice**
 - 10 Pts Covered/Provider/Day
 - Payment/Pt = ~ \$140
 - Total Collections = ~ \$1400 /day
- **Variation**
 - Case Mix
 - Simple hospital visit (99231): \$20
 - Initial critical care (99291): \$173
 - Payer Mix
 - 99291 payment varies: \$26 - \$416
 - Procedures

Pt. Revenue Gap: ICU vs. OR



The Nasty Economic Argument for a Multidisciplinary Unit

- There is a reason that small departments do not have large critical care divisions!
- **Example**
 - \$18,400,000 clinical revenue/yr (median revenue, 2007 SAAC)
 - \$700 "revenue gap" per day of ICU coverage
 - "sacrifice" 1% of revenue = \$184,000/year
 - "good of the team" vs. "tax on colleagues" vs. non-operating income
 - Equivalent to 260 days of ICU coverage
- Larger depts. & those with "target rich" ICUs can devote more time to ICU's
- For the remainder of depts...
have anesthesia do 38 weeks coverage (1.2 FTE); other specialists do the rest

Median total compensation Assoc. Prof. (2006 AAMC)

- Assuming 1 FTE = 214 days worked, a "full time" intensivist would gross ~ \$300,000
- **Median Compensation**
 - Anesthesiology \$292,000
 - Surgery Trauma/Crit Care \$265,000
 - Medical CCM \$221,000
 - Emergency Med \$215,000
- **With benefits (26%)**

- Anesthesiology	\$367,920	Gap
- Surgery Trauma/Crit Care	\$333,900	
- Medical CCM	\$278,460	
- Emergency Med	\$270,900	
	\$97,020	

Compensation Gap

- **Compensation Gap – Diff. in Salary + Benefits**
 - Anesthesiology --
 - Surgery Trauma/Crit Care \$34,020
 - Medical CCM \$89,460
 - Emergency Med \$97,020
- **"Free" Days of ICU Coverage (10 pts, 20% overhead = \$1200)**
 - Anesthesiology 0
 - Surgery Trauma/Crit Care 28
 - Medical CCM 75
 - Emergency Med 81

Conclusion: The Money Talks

- *Unless other sources of income are available, it will be difficult for most depts. to support more than about 38 weeks of ICU coverage without affecting the wallets of your colleagues*
- Conclusions
 1. *Let your more cost-effective colleagues pick up the rest*
 2. *Find more money*

Find More Money: Other Clinical/Research Revenue

- *Other clinical activities*
 - More “profitable” ICU’s
 - eICU
 - PACU
 - Anesthesia “on the side”
 - TEE
 - Organ procurement/DCD
 - Hyperbaric medicine
 - Palliative care
- *Clinical Trials/Research Grants*

Find More Money: Hospital Stipends

- *Indigent Care*
- *GME*
- *Programmatic Support (\$\$\$/hour)*
 - *In-house coverage*
 - *eICU*
- *Medical Direction*

Find More Money: Medical Direction

- *Usually good for about 0.2 FTE*
(must document time on activities)
 - *ICU*
 - *PACU*
 - *RRT*
 - *Code call committees*
 - *Quality & Safety*

Value Added

- *Intensivist Value*
 - *Improved mortality*
 - *Shorter LOS*
 - *Less resource utilization*
 - *Reduced # consults*
- *Nice, but not linked to compensation*
- *Fair Market Value*

Fair Market Value

- *Key concept within safe harbor provisions of the Stark law and anti-kickback statutes*
- *Compensation that a physician receives must:*
 - *Not exceed fair market value*
 - *Be “commercially reasonable”*
 - *Not be based on volume or value of referrals*
- *Market approach: Valuation of comparable entities – external benchmarks (AAMC, MGMA)*
 - *Size of institution; type and range of services offered; # & type of personnel; geographic location*
- *Income approach: Projected revenues, expenses, and profit margins*

Find More Money: Nonoperating Revenue

- **Investment income**
 - Independent reserves
 - May depend on cross-subsidies and endowments from group practice plan or common endowment
- **Endowed chairs**
 - 65 chairs nationwide (1999 AUA/SACC data); growing slowly
- **Programmatic Support**
 - Depends on negotiating ability of the chair
 - **MAKE SURE CRITICAL CARE IS CONSIDERED IN ANY NEW CHAIR "PACKAGE" NEGOTIATED FOR YOUR DEPARTMENT!**

Arguments to get your chair (or hospital or dean) to fund the gap

- Promotes departmental visibility, leadership, and professionalism – a face without a mask
- Better management of the perioperative process
- Maintains a highly skilled staff in the OR
- Improves recruitment/retention
- Improves patient care – greater throughput
- Promotes a better environment for teaching and research

- They will invest only if the enterprise ultimately makes more \$\$\$

The Academic Critical Care Workforce – Limited by \$\$\$

- Depts can afford to support ~ 1.2 FTE per department
- 2007 SAAC data – depts assign 1.4 FTEs to ICU
 - 49 depts responding
- 121 departments = 146.5 FTE's
- If average CCM anesthesiologist does 0.2 – 0.25 FTE ICU coverage, we should have a current "market" for 580 to 730 academic CCM anesthesiologists

The Brutal Facts

- Academic anesthesiology CCM is limited by the market:
 - Our salaries are high
 - Maximum hourly compensation is relatively fixed
 - There is a reasonable market of alternative suppliers (trauma surgeons; pulmonologists; EM)

The Brutal Facts

- In the typical dept, more revenue per additional FTE can be earned in the OR compared to the ICU
- Shortfalls can be made up by other revenue, but profitability is limited by "fair market value" compensation
- Dept chairs tend to reserve endowment income for research and academic activities. Any remaining shortfall in income is taken from the wallets of your colleagues
- Devoting 1.2 FTE's is a financially reasonable "sacrifice" for a typical dept

Survival Skills for Academic CCM

- Define a rigorous business plan – most likely, there will be a shortfall in ICU clinical revenue
- Develop a multi-disciplinary collaborative model with your more cost-effective colleagues
- Identify additional clinical opportunities
- Provide visible and valuable medical direction
- Define the fair market value of all services provided
- Work with your university to develop your endowment
- Make sure programmatic support for critical care is included in your next chair's "package"
- Demonstrate your value and clinical outcomes to your hospital, your chair, and, most importantly, to your colleagues

CCM in Private Practice: Does It Exist?

Kenneth Papier, M.D.
Mary Washington Hospital
Fredericksburg, Virginia

I. How our ICU service began

II. How our ICU service grew into a 24X7 management service

III. How our Anesthesia Group worked out coverage for the ICU

IV. How the hospital administration PAID US for ICU service

V. Epilogue: Why our ICU service is ending in Jan '09

Hospital and Provider Group Collaboration: What is Needed?

Walter A. Boyle, III, M.D., FCCM
Washington University School of Medicine
St. Louis, Missouri

An important issue facing medical planners and leaders is the present and growing shortage of qualified providers of in-hospital critical care services.^{1,2} The shortage of hospital-based critical care practitioners is increasingly viewed as a priority, as data accumulate indicating that intensivist-run ICUs, compared with ICUs in which care is rendered by non-critical care trained physicians, are better able to provide high quality critical care, as judged by both better patient outcomes and a substantially lower cost.^{3,4} This presents an opportunity for anesthesiologists to contribute significantly to fill the growing manpower gap in critical care. Indeed, the OR and ICU represent a clinical continuum that differ very little for the most unstable, critically-ill, one-on-one patient. Anesthesiology residency thus provides an ideal background for subspecialty training and practice in critical care. Additionally, board eligibility in critical care following anesthesiology residency requires only one additional year of training, thereby representing an investment strategy for residents attempting to prepare for the needs and opportunities of the future.

In medicine you can only deliver care which is affordable for the providers, and one main drawback for most anesthesiology groups - in terms of getting involved in critical care - is the continued belief that such involvement will represent an expense or cost center for the group. As a result, there are relatively few private practice anesthesiology groups looking specifically for anesthesiologists with critical care training. The value of such training is thereby diminished, and the cycle continues. What is needed is for anesthesiologists to more fully embrace critical care medicine as *their* sub-specialty, and this can only be achieved if anesthesiologists can more clearly see the benefits of doing so. It is fairly obvious that involvement in critical care can more fully integrate an anesthesiology group into the perioperative and acute care culture of the hospital, which may thereby enhance the perceived prestige and value of the group to the hospital. However, the group also needs to be able to show the financial value, or at least fiscal neutrality, of such involvement. To achieve this latter goal will likely require partnership with the hospital at some level. [It should be pointed out, however, the hospital is likely already paying for less than optimal critical care coverage, and hospital administrators are therefore likely to be receptive to discussions about support for higher quality critical care service.] After a careful assessment of what is needed and appropriate, an important issue for the anesthesiology group considering getting involved in critical care will be the kind of provider support that is needed from the hospital, and what strategies can be employed to achieve success that are the most cost effective for both the hospital and the provider group.

One option for critical care delivery that can be both high quality and cost effective is to employ a two tier provider model, utilizing physician intensivist providers that are on-site, available and involved, as well as "mid-level" providers or non-physician critical care practitioners (NPCCPs). From a practical standpoint, NPCCPs [which include both acute care nurse practitioners (ACNPs) and physician assistants (PAs)], may only have the education and training to manage some critically ill patients, but unit-dedicated NPCCPs can learn on the job and function over time at a very high level, permitting broader coverage and effective "flex-up" when there are multiple simultaneous emergencies. This approach allows for most effective utilization of the expensive intensivist tier for care of the least stable and higher risk critically ill patients. Coupled with sound billing practices, this approach can also provide the basic financial resources that permit the attending tier to be self-sufficient, covering the salaries and benefits of the physician intensivists, as well as the administrative expenses required to run the group, and the costs of billing and collections.

Requests for hospital resources in critical care in this two tier model are primarily directed in support of the mid-level provider tier, and specifically in support of NPCCPs. There are, however, a number of advantages if the NPCCPs are *not* hired by the hospital, but rather by the provider group (or department). Having both the physician and non-physician providers in a single group has important positive effects on

morale and culture. Moreover, this arrangement - with collaborative practice agreements between the physician intensivist providers and the NPCCPs – permits the provider group to take advantage of billing opportunities that are not easily achieved if these providers are hospital employees.

As independent practitioners, NPCCPs are reimbursed by the Center for Medicare Services (CMS), as well as virtually every other third party payor, for evaluation and management services (including critical care), and the procedures they perform. However, the NPCCPs are reimbursed at a slightly lower rate by some payors (including CMS), and the NPCCPs also do a lot of non-remunerative leg work, family counseling, and the multifaceted coordination of care that is required for chronically ill ICU patients, or ICU patients moving to lower acuity areas or outside facilities. This non-billable time prevent the NPCCP tier from being entirely self-sufficient. However, these non-billable services are also hospital services, and it is thus both reasonable and appropriate for the hospital to reimburse the provider group for that portion of the NPCCPs' salaries.

Overall, this two tier approach – with mid-level providers extending coverage for the intensivist-led group, and support of the NPCCPs provided by their own income and hospital reimbursement – allows the critical care provider group and the hospital to meet their shared missions of providing consistent and appropriate clinical care to critically ill patients, and to support patients' families, in a cost sensitive and effective manner. Again, critical care trained anesthesiologists are in an excellent position to prepare for the needs and opportunities of the future, and to help fill the growing manpower gap in critical care.

¹Angus DC, Kelley MA, et al. COMPACCS Study of Workforce Requirements for Critically Ill Patients. JAMA 2000; 284:2762-2770.

²2005 US Department of Health and Human Services, HRSA Report to Congress on the Critical Care Workforce: A Study of the Supply and Demand of Critical Care Physicians.

³Provonost, PJ, Angus DC, et al., Physician Staffing Patterns and Critical Care Outcomes. JAMA 2002; 288:2151-2162.

⁴Pronovost, P.J. Needham DM, et. al., Critical Care Medicine 2004. 32(6):1247-1253.

Interactive Journal Club

Moderator: Avery Tung, M.D.

Linda Liu, M.D.
Brenda Fahy, M.D.

Introduction:

An increasing focus on evidence based medicine has led to a corresponding increase in the importance of systematically reviewing the medical literature. Increased scrutiny of literature findings, however, has suggested that interpreting this literature, and translating it into clinical practice, may be extremely challenging. In the area of perioperative care, startling reversals of previously held concepts regarding glucose control, steroid replacement, beta blockade, and even ICU staffing patterns demonstrate that optimal clinical care is an elusive and rapidly moving target.

This session will reproduce a classic journal club, but with the addition of voting machines to allow audience members to indicate their opinions and preferences to clarify how literature findings influence clinical management. We hope that integrating the opinion of a cohort of anesthesia-based intensivists will enhance our review of these papers and allow for a more nuanced interpretation of potentially controversial findings.

Format:

We have selected 4 recent papers, and plan to have you (the audience) vote on which three to review during this 40 minute period. Once chosen, we will present the paper in standard journal club style, highlighting rationale, methods, results, and the author's interpretation. Intermixed with the presentation will be audience votes on pertinent questions: appropriateness, believability, perceived validity, relevance, etc.

After the paper is presented, one discussant will argue in favor of the paper, and another will then argue against. The audience will vote both before and after the arguments. After a period of audience discussion, we will move on to the next paper.

Source material:

The audience will choose from among the following 4 papers:

Permission has been granted by the American College of Physicians (*Annals of Internal Medicine*) for ASCCA to reprint the following article in this meeting syllabus:

1. Levy MM, Rapoport J, Lemeshow S, Chalfin DB, Phillips G, Danis M.
Association between critical care physician management and patient mortality in the intensive care unit. *Ann Intern Med.* 2008 Jun 3;148(11):801-9

Permission has been granted by Elsevier (*The Lancet*) for ASCCA to reprint the following article in this meeting syllabus:

2. Girard TD, Kress JP, Fuchs BD, Thomason JW, Schweickert WD, Pun BT, Taichman DB, Dunn JG, Pohlman AS, Kinniry PA, Jackson JC, Canonico AE, Light RW, Shintani AK, Thompson JL, Gordon SM, Hall JB, Dittus RS, Bernard GR, Ely EW. Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomised controlled trial. *Lancet.* 2008 Jan 12;371(9607):126-34.

3. Pandharipande PP, Pun BT, Herr DL, Maze M, Girard TD, Miller RR, Shintani AK, Thompson JL, Jackson JC, Deppen SA, Stiles RA, Dittus RS, Bernard GR, Ely EW. Effect of sedation with dexmedetomidine vs lorazepam on acute brain dysfunction in mechanically ventilated patients: the MENDS randomized controlled trial. *JAMA*. 2007 Dec 12;298(22):2644-53.

Permission has been granted by the Publishing Division of the Massachusetts Medical Society (*The New England Journal of Medicine*) for ASCCA to reprint the following article in this meeting syllabus:

4. Brunkhorst FM, Engel C, Bloos F, Meier-Hellmann A, Ragaller M, Weiler N, Moerer O, Gruendling M, Oppert M, Grond S, Olthoff D, Jaschinski U, John S, Rossaint R, Welte T, Schaefer M, Kern P, Kuhnt E, Kiehntopf M, Hartog C, Natanson C, Loeffler M, Reinhart K; German Competence Network Sepsis (SepNet). Intensive insulin therapy and pentastarch resuscitation in severe sepsis. *N Engl J Med*. 2008 Jan 10;358(2):125-39

Reprints of these papers follow.

Association between Critical Care Physician Management and Patient Mortality in the Intensive Care Unit

Mitchell M. Levy, MD; John Rapoport, PhD; Stanley Lemeshow, PhD; Donald B. Chalfin, MD, MS; Gary Phillips, MAS; and Marion Danis, MD

Background: Critically ill patients admitted to intensive care units (ICUs) are thought to gain an added survival benefit from management by critical care physicians, but evidence of this benefit is scant.

Objective: To examine the association between hospital mortality in critically ill patients and management by critical care physicians.

Design: Retrospective analysis of a large, prospectively collected database of critically ill patients.

Setting: 123 ICUs in 100 U.S. hospitals.

Patients: 101 832 critically ill adults.

Measurements: Through use of a random-effects logistic regression, investigators compared hospital mortality between patients cared for entirely by critical care physicians and patients cared for entirely by non-critical care physicians. An expanded Simplified Acute Physiology Score was used to adjust for severity of illness, and a propensity score was used to adjust for differences in the probability of selective referral of patients to critical care physicians.

Results: Patients who received critical care management (CCM) were generally sicker, received more procedures, and had higher hospital mortality rates than those who did not receive CCM. After adjustment for severity of illness and propensity score, hospital mortality rates were higher for patients who received CCM than for those who did not. The difference in adjusted hospital mortality rates was less for patients who were sicker and who were predicted by propensity score to receive CCM.

Limitation: Residual confounders for illness severity and selection biases for CCM might exist that were inadequately assessed or recognized.

Conclusion: In a large sample of ICU patients in the United States, the odds of hospital mortality were higher for patients managed by critical care physicians than those who were not. Additional studies are needed to further evaluate these results and clarify the mechanisms by which they might occur.

Ann Intern Med. 2008;148:801-809.

www.annals.org

For author affiliations, see end of text.

The extent of involvement and supervision by critical care physicians varies somewhat in U.S. intensive care units (ICUs) (1–6). Some ICUs are organized as strictly closed services, in which critical care physicians, or intensivists, assume control and decision-making ability over all aspects of patient care, whereas in some “hybrid” ICUs, mandated consultation and management by critical care physicians is the primary administrative model. Most ICUs, however, are structured as completely open units, in which the admitting physicians retain full clinical and decisional responsibility and thus have the option to care for their patients with or without input from critical care physicians.

Evidence from several settings suggests improved outcomes when critical care physicians assume substantial responsibility over the care and triage of ICU patients (1, 7–22). These studies, however, have methodological limitations and limited generalizability. Most are small, use historical controls or before–after study designs, and are limited to specific ICUs (for example, medical or surgical) in 1 or 2 centers. They have the usual risks for confounding by illness severity commonly seen in cross-sectional studies (7, 8, 14–21) and retrospective analyses of administrative databases that were limited to certain diagnostic categories (12, 13).

Recognizing the limitations of previously published studies and considerable variability in critical care management (CCM) in the United States, we examined data from

123 ICUs across the United States to assess the relationship between management by critical care physicians and hospital mortality rates of critically ill patients. These data were derived from a large national project that examined resource use in intensive care (2). At the beginning of our analysis, we hypothesized that CCM would be associated with improved outcomes in critically ill patients.

METHODS

Patients

Patients were identified through Project IMPACT (Cerner, Bel Air, Maryland), a national database of ICU patients. The Project IMPACT database is a large administrative database originally developed by the Society of Critical Care Medicine in 1996. Participation is voluntary. All data are collected at each institution by on-site data

See also:

Print

Editors' Notes 802
Editorial comment 877

Web-Only

Appendix
Conversion of graphics into slides

Context

Critical care physicians or physicians without specialized critical care training may manage patients in intensive care units.

Contribution

This study described 101 832 patients in 123 intensive care units in the United States. Patients managed by critical care physicians were sicker, had more procedures, and had higher hospital mortality rates than those managed by other physicians. Analyses that adjusted for severity of illness and the tendency for sicker patients to be managed by critical care specialists still showed higher mortality among patients managed by the specialists.

Caution

Unrecognized confounders might diminish or invalidate the unexpected finding of higher mortality among patients managed by critical care specialists.

—The Editors

collectors who are certified in advance by Project IMPACT to assure standardization and uniformity in data definitions and database definitions and entry. The database for 2000 to 2004 included 142 392 patients admitted to 123 ICUs in 100 U.S. hospitals. We excluded patients with missing data for variables of interest from our analysis, leaving 111 907 patients. We included only the first ICU admission, reducing the number of patients to 106 623, and then excluded patients who were managed only part time during their ICU stay, reducing the total observations to 101 832.

Variables

Our primary outcome variable was hospital mortality. Our key exposure or “risk factor” was the same regardless of whether a patient was managed by a critical care physician during his or her ICU stay. This was ascertained in Project IMPACT by using the survey question, “Was the patient managed by a critical care physician/team?” Trained data entry personnel for Project IMPACT define CCM as treatment occurring when the physician is asked to take responsibility for the overall management of a patient in the critical care unit without having to first provide expertise about a single organ system. A physician should meet 1 or more of the following criteria to be considered a critical care physician: 1) be recognized by the institution as a critical care specialist within a specialty unit, even without a specialty board certification (such as burn or neurointensivist), and must treat the total patient and not a single organ system; 2) have passed critical care medicine board examinations or be qualified to take the examination; and 3) be trained in an accredited critical care fellowship.

When a patient received CCM, it was documented, regardless of whether the treatment was for all or part of

the ICU stay. Covariates included patient characteristics, such as demographic characteristics, diagnosis, and clinical condition at ICU admission. We also controlled for ICU and hospital characteristics. Severity of illness was measured by the Simplified Acute Physiology Score (SAPS) II. Through use of recently published work on SAPS (23), we added additional variables to SAPS II and modified coefficients in the logit model to derive a better fit. These included the patient’s age (<40 years, 40 to 59 years, 60 to 69 years, 70 to 79 years, and >79 years), sex, duration of hospital stay before ICU admission (<24 hours, 1 day, 2 days, 3 to 9 days, >9 days), patient’s location before ICU (transfer from outside emergency department, rehabilitation or skilled nursing facility, wards, or another hospital), clinical category (medical patient or other), and intoxication (yes or no). For this expanded SAPS II, the Hosmer–Lemeshow goodness-of-fit *P* value was 0.38. (The **Appendix**, available at www.annals.org, provides more detail on the expanded SAPS II.)

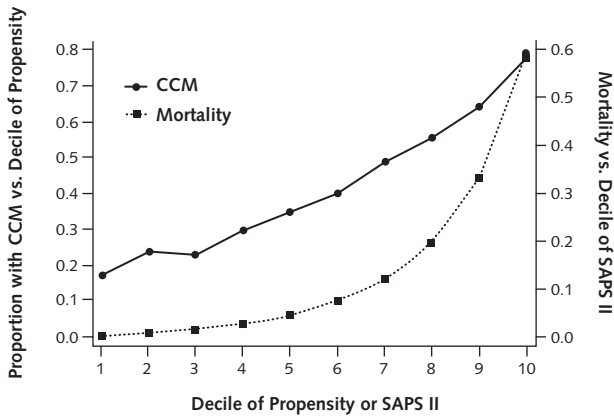
Statistical Analysis

We divided ICUs into 3 groups based on the percentage of patients receiving CCM for the entire stay: 95% of patients or more, 5% to 95% of patients, and 5% of patients or fewer.

We excluded 4793 patients who received CCM for only part of the ICU stay from the analysis, leaving 2 patient management types: CCM for the entire stay and no CCM. For each of the 6 categories defined by the combination of patient management type and ICU group, we computed expected and actual mortality rates. Expected mortality was the mean SAPS II probability of mortality. Actual mortality was the percentage of patients who did not survive the hospital stay. We computed the standardized mortality ratio and its 95% CI, based on an exact Poisson distribution, as the ratio of actual to expected mortality.

We developed a score to measure the propensity that a patient would be selected for CCM. We derived our score from a logistic regression model, with CCM as the dependent variable. The model was estimated on patients only from ICUs not mandating CCM. We screened all available patient characteristics known at the time of ICU admission and ICU characteristics for inclusion in the model. A propensity score was then estimated for each patient. Variables used to create the propensity score were age, Glasgow Coma Score, number of licensed hospital beds, insurance (commercial, Medicaid or Medicare, or self-pay), ventilation at ICU admission, tracheostomy at ICU admission, gastrointestinal bleeding, noninvasive ventilation at ICU admission, cerebrovascular event, chronic immunosuppression, chronic respiratory disease, acute renal failure, hospital location (rural, suburban, or urban), continuous sedation, and admission source (emergency department, another hospital, invasive procedures, or other non-ICU location). **Figure 1** shows the proportion of patients man-

Figure 1. Critical care management (CCM) and mortality.



SAPS = Simplified Acute Physiology Score.

aged by critical care physicians. Hospital mortality rates tend to increase from the first decile to the last decile of propensity and SAPS II. More details of the score and the sensitivity of results to changes in the propensity score are shown in the **Appendix** (available at www.annals.org).

We performed random-effects logistic regressions on the entire sample, using hospital death as the dependent variable. This method uses the within- and between-ICU variability inherent in the nesting of the patients into 123 ICUs. The crude model included only the risk factor “CCM for the entire stay” versus no CCM. Severity of illness (as measured by the expanded SAPS II score) and likelihood of selection for CCM (as measured by the propensity score) were then added to the model as control variables, along with all interactions of the control variables and risk factor. Where a statistically significant interaction term indicated that a control variable was an effect modifier, the regression was estimated within each quartile of the control variable.

We repeated random-effects logistic regression analysis of mortality on several subsamples. The “no-choice” subsample included 2 groups of patients: those from ICUs in which 95% or more or 5% or fewer patients received CCM. In addition, the following subsamples were examined: patients not transferred from another hospital, patients with a respiratory diagnosis with ventilator support at ICU admission, patients with respiratory diagnosis without ventilator support at ICU admission, patients with ventilator support at ICU admission, patients with a diagnosis other than respiratory and no ventilator at ICU admission, patients with a circulatory diagnosis, patients with a diagnosis of infection, patients with at least 1 ICU procedure, and patients with no ICU procedures. The **Appendix** (available at www.annals.org) presents additional details of regression analyses.

Role of the Funding Source

Eli Lilly and the Department of Bioethics at the National Institutes of Health Clinical Center funded the study. The funding services had no role in the design, conduct, and analysis of the study and did not participate in the decision to submit the manuscript for publication.

RESULTS

Table 1 shows that ICUs that manage 95% or more of their patients with critical care physicians for the entire stay were, on average, larger and in larger hospitals than other ICUs. A greater percentage of ICUs had academic affiliation or activity and were only medical, surgical, or trauma, as opposed to a mixed model. A smaller percentage had staffing policies that permitted either licensed practical nurses or registered nurses.

Table 2 shows patient characteristics by ICU category and CCM status. Among the 123 ICUs, 23 (18 618 patients) had at least 95% of patients managed for the entire stay by critical care physicians, whereas 21 (22 870 patients) had 5% or fewer managed by critical care physicians. These 2 groups together make up the “no-choice” group. The remaining 60 344 patients were treated in the 79 ICUs in which 5% to 95% of patients received CCM for the entire stay (the “choice” group).

Comparison of patients managed for the entire stay by

Table 1. Characteristics of Critical Care Management in Intensive Care Units*

Characteristic	Critical Care Management for Patients†		
	≥95%	5%–95%	≤5%
ICUs, n	23	79	21
ICU beds, n			
Mean	17.3	17.5	13.5
Median	16	16	12.9
Minimum–maximum	10–32	7–66	4–25
Hospital beds, n			
Mean	668	468	404
Median	570	430	375
Minimum–maximum	257–1389	70–1049	130–774
Urban location, %	61	47	43
Academic hospital, %	52	5	0
Primary medical school hospital, %	61	6	0
Primary hospital for critical care fellowship, %	87	6	5
Critical care fellows rotate, %	48	8	19
ICU type, %			
Medical only	30	8	10
Surgical or trauma only	22	9	0
Mixed or other	48	83	90
Nursing policy, %			
RN or LPN	4	15	14
RN only	96	81	86
RN with CCRN	0	4	0

* CCRN = critical care registered nurse; ICU = intensive care unit; LPN = licensed practical nurse; RN = registered nurse.
 † For the entire stay for patients in the ICU.

Table 2. Patient Characteristics*

Characteristic	Critical Care Management†			No Critical Care Management		
	≥95%	5%–95%	≤5%	≥95%	5%–95%	≤5%
Patients, <i>n</i>	18 601	23 324	261	17	37 020	22 609
Mean age, <i>y</i>	59.9	59.6	63.2	65.7	61	63.6
Men, %	54.3	53.1	50.2	58.8	52.4	51.9
Race, %						
Black	16.6	13.5	18.0	5.9	12.1	16.5
Other or unknown	5.5	8.5	5.0	5.9	9.6	6.4
White	77.9	78.0	77.0	88.2	78.3	77.1
Full code, %	95.6	94.9	97.3	94.1	94.4	93.6
ICU procedure, %	80.5	72.5	72.4	64.7	52.4	60.8
Intravenous drugs, %	93.2	94.7	96.2	100.0	89.3	93.1
Surgery during ICU, %	51.3	42.5	59.8	64.7	43.8	44.2
Ventilation during the first 24 h in ICU, %	36	33.5	28	11.8	13.9	17.6
Postoperative, %	40.2	30.3	37.9	58.8	33.6	35.3
Continuous sedation, %	11.9	18.7	11.9	5.9	10	6.8
Origin, %						
Another hospital	8.8	5.3	3.4	0	5.7	5.1
Emergency department	30.2	42.1	29.5	11.8	42.3	39.6
Invasive procedure	36.3	27.2	45.6	64.7	33.1	34.3
Other unit (not ICU)	20.7	21.4	17.6	23.5	15.4	17.1
Major disease category, %						
Circulatory system	19.4	20.9	32.6	52.9	30.1	26.1
Digestive system	14.4	12	14.9	17.6	13.5	15.4
Nervous system	15.2	12.9	9.2	11.8	19.1	16.9
Respiratory system	27.3	28.9	25.7	11.8	16.2	19.7
Infection	7.8	8.1	7.7	0	5.2	6
Trauma	6.6	5.1	5.7	0	2.5	2.8
Payment, %						
Medicare	49.5	50.2	60.2	58.8	52.9	59.8
Medicaid	7.8	7.5	3.4	0	6.6	7.2
Self-pay	8.3	10.2	7.3	11.8	8.6	5.3
Commercial or managed care	34.4	32.1	29.1	29.4	32	27.7

* ICU = intensive care unit.

† For the entire stay for patients in the ICU.

critical care physicians versus those managed by other physicians shows that more patients treated by critical care physicians received interventions, such as ICU procedures, intravenous drugs, mechanical ventilation, and continuous sedation. They were less likely to be postoperative patients or to receive surgery while in the ICU. Respiratory system disease, infections, and trauma occurred more among patients treated by critical care physicians. Intensive care units managing 95% or more of patients with critical care physicians had somewhat more admissions from other hospitals and from invasive procedures and somewhat fewer admissions from the emergency department than other ICUs did.

Table 3 provides the discharge destination according to CCM status of patients who survived their hospital stay. More than 59% of patients who did not receive CCM were discharged home (including those with home health care and those leaving against medical advice) compared with 58% of patients who received CCM. About 16% of patients were discharged to an extended care facility for CCM and no CCM, whereas 13% and 9% were discharged to a rehabilitation center for CCM and no CCM, respectively. More than 13% of patients who did not re-

ceive CCM were discharged to an unknown location compared with about 9% of those who received CCM.

Table 4 shows that patients managed by critical care physicians for the entire stay had a higher mean severity of illness (SAPS II probability of mortality) than patients who

Table 3. Hospital Discharge Destination*

Hospital Discharge Destination	No Critical Care Management, %	Critical Care Management, %	Total, %
Extended-care facility	15.78	16.41	16.03
Another hospital	1.50	1.53	1.41
Rehabilitation center	8.55	13.21	10.36
Home	49.29	44.12	47.26
Home with home health care	9.43	13.04	10.85
Home (against medical advice)	0.38	0.48	0.42
Hospice	1.01	1.25	1.10
Long-term acute care	0.06	0.29	0.15
Other	0.66	0.88	0.75
Unknown	13.33	8.80	11.55
Total	100.00	100.00	100.00

* Percentages exclude patients who died in the hospital.

Table 4. Expected and Actual Hospital Mortality*

Variable	Critical Care Management†			No Critical Care Management		
	≥95%	5%–95%	≤5%	≥95%	5%–95%	≤5%
Patients, <i>n</i>	18 601	23 324	261	17	37 020	22 609
Mean SAPS II probability	0.1650	0.1733	0.1511	0.0585	0.1102	0.1368
Mean mortality rate	0.1800	0.1884	0.1801	0.0588	0.1004	0.1244
SMR (95% CI)	1.09 (1.05–1.13)	1.09 (1.05–1.12)	1.19 (0.88–1.58)	1.01 (0.03–5.60)	0.91 (0.88–0.94)	0.91 (0.88–0.94)

* SAPS = Simplified Acute Physiology Score; SMR = standardized mortality ratio.

† For the entire stay for patients in the intensive care unit.

did not receive CCM. These patients also had higher hospital mortality. The standardized mortality ratio for patients who received CCM in ICUs that managed 95% or more patients was 1.09 (95% CI, 1.05 to 1.13) compared with a standardized mortality ratio of 0.91 (CI, 0.88 to 0.94) for patients who did not receive CCM in ICUs in which critical care physicians managed 5% or fewer patients. Among patients who received CCM in ICUs that managed 5% to 95% of patients, the standardized mortality ratio was 1.09 (CI, 1.05 to 1.12) for patients who received CCM for the entire stay compared with 0.91 (CI, 0.88 to 0.94) for patients who did not receive CCM.

A random-effects logistic regression model including only CCM as a predictor of hospital mortality produced a crude odds ratio (OR) of 2.13 ($P < 0.001$). The addition of SAPS II to this model reduced this OR to 1.42 ($P < 0.001$). Further inclusion of the propensity score decreased the OR to 1.40 ($P < 0.001$). For additional regression results, see the **Appendix** (available at www.annals.org).

Interaction terms were statistically significant, indicating that severity and propensity were acting as effect modifiers. Models were estimated for each quartile of severity and propensity score (Table 5). For 11 of 16 resulting groups, the OR for mortality was statistically significant ($P < 0.05$). All statistically significant ORs were greater than 1.0, ranging from 2.83 (severity quartile 1 and propensity quartile 1) to 1.18 (severity quartile 4 and propensity quartile 4). Within each severity quartile, ORs tended to decrease as propensity quartiles increased.

Table 6 shows results of subgroup analysis through use of a random-effects logistic regression. When interaction variables were not significant, the ORs reported for CCM are from a model adjusted for SAPS II and propensity score. When 1 or both of these are effect modifiers, we report results by quartiles of the relevant variables. All of the ORs reported for the subgroup analyses are greater than 1.0, with 4 of 22 not significantly greater than 1.0. These analyses are a respiratory diagnosis of patients with

Table 5. Random-Effects Logistic Regression Odds Ratio for Mortality, Stratified by SAPS II and Propensity Score*

Quartile of SAPS II Probability†	Propensity Score Quartile‡	No CCM Count	CCM Count	CCM Odds Ratio (95% CI)§	P Value	ρ
1	1	6011	1200	2.83 (1.28–6.27)	0.010	0.08
1	2	5974	2013	1.98 (1.07–3.66)	0.028	0.06
1	3	3664	2586	1.45 (0.82–2.58)	0.21	0.05
1	4	1224	3005	1.11 (0.52–2.37)	0.79	0.21
2	1	6335	1428	2.12 (1.48–3.05)	<0.001	0.05
2	2	4749	1989	1.88 (1.40–2.55)	<0.001	0.02
2	3	3189	2576	1.25 (0.93–1.69)	0.143	0.03
2	4	1580	3671	0.86 (0.63–1.18)	0.34	0.07
3	1	5135	1457	2.26 (1.78–2.87)	<0.001	0.06
3	2	4078	1876	1.76 (1.42–2.19)	<0.001	0.05
3	3	3320	2967	1.50 (1.24–1.81)	<0.001	0.04
3	4	2147	4342	1.19 (0.99–1.43)	0.064	0.05
4	1	2874	1201	1.53 (1.27–1.83)	<0.001	0.05
4	2	2770	1959	1.36 (1.16–1.58)	<0.001	0.04
4	3	3487	3621	1.36 (1.19–1.54)	<0.001	0.04
4	4	3109	6295	1.18 (1.05–1.32)	<0.001	0.04

* CCM = critical care management; ICU = intensive care unit; SAPS = Simplified Acute Physiology Score.

† Quartile 1 includes the lowest SAPS II probabilities of death, whereas quartile 4 includes the highest probabilities.

‡ Quartile 1 is the lowest propensity of being seen by a critical care physician, whereas quartile 4 is the highest propensity.

§ Random-effects logistic regression results, in which outcome is hospital mortality, adjusted for SAPS II probability of mortality and propensity to see a critical care physician.

|| ρ is the ratio of the between-ICU variance to the total variance. Zero indicates that all variability is within the ICU, and 1.0 indicates that all variability is between ICUs.

Table 6. Subgroup Analysis: Random-Effects Logistic Regression Odds Ratios for Mortality*

Group	Quartile of Propensity Score† or SAPS II Probability‡	No CCM	CCM	CCM Odds Ratio (95% CI)§	P Value
Respiratory diagnosis and ventilation at ICU admission	–	3075	4822	1.22 (1.01–1.46)	0.034
Respiratory diagnosis and no ventilation at ICU admission	–	7363	7074	1.11 (0.97–1.26)	0.121
Ventilation at ICU admission	–	9121	14 581	1.28 (1.15–1.43)	<0.001
Circulatory diagnosis	–	17 035	8572	1.55 (1.37–1.77)	<0.001
Infection diagnosis	–	3258	3351	1.12 (0.96–1.31)	0.140
“No-choice” ICU¶	–	22 624	18 862	1.47 (1.21–1.77)	<0.001
Patients not transferred from another hospital¶	1	19 146	4779	1.70 (1.46–1.99)	<0.001
	2	16 690	7235	1.50 (1.31–1.71)	<0.001
	3	12 896	11 026	1.33 (1.19–1.48)	<0.001
	4	7643	16 281	1.25 (1.12–1.39)	<0.001
Diagnosis other than respiratory and no ventilation at ICU admission**	1	11 326	4617	2.39 (1.39–4.11)	0.002
	2	11 365	4552	1.95 (1.44–2.64)	<0.001
	3	11 026	4884	2.00 (1.67–2.39)	<0.001
	4	9444	6478	1.57 (1.43–1.73)	<0.001
≥1 ICU procedures¶	1	12 180	4131	1.73 (1.47–2.02)	<0.001
	2	9510	6800	1.16 (1.03–1.31)	0.019
	3	7087	9222	1.28 (1.14–1.43)	<0.001
	4	4384	11 926	1.16 (1.02–1.32)	0.021
No ICU procedures**	1	6506	2647	2.11 (0.80–5.51)	0.129
	2	6714	2445	1.53 (0.92–2.52)	0.101
	3	6692	2440	1.38 (1.01–1.87)	0.042
	4	6572	2575	1.24 (1.06–1.45)	0.006

* CCM = critical care management; ICU = intensive care unit; SAPS = Simplified Acute Physiology Score.
 † Quartile 1 is the lowest propensity of being seen by a critical care physician, whereas quartile 4 is the highest propensity.
 ‡ Quartile 1 includes the lowest SAPS II probabilities of death, whereas quartile 4 includes the highest probabilities.
 § Random-effects logistic regression results, in which outcome is hospital mortality, adjusted for SAPS II probability of mortality and propensity to see a critical care physician.
 ¶ “No choice” is defined as an ICU that manages ≥95% of its patients by a critical care physician or an ICU that manages ≤5% of its patients by a critical care physician.
 ¶ Statistically significant interactions between propensity score and CCM variable; thus, the analysis is run individually over the propensity score quartiles.
 ** Statistically significant interactions between SAPS II probability of mortality and CCM variable; thus, the analysis is run individually over the SAPS II probability quartiles.

no ventilator in place when admitted to the ICU (OR, 1.11; *P* = 0.121) and the first 2 quartiles of no ICU procedures (ORs, 2.11 and 1.53; *P* = 0.129 and 0.101).

We conducted 2 sensitivity analyses to determine whether transferring patients to another location (for example, a new hospital, rehabilitation center, hospice care, or extended care) determined the reduced mortality rate seen in the group that did not receive CCM (Table 7). In the first case, the operational definition of mortality included in-hospital mortality, transfer to another hospital, a rehabilitation center, extended care, hospice, or a long-term acute care facility versus home. Patients whose discharge destination was unknown were omitted from the sensitivity analysis. The second sensitivity analysis included only in-hospital mortality versus discharge to home. The crude OR, the OR adjusted for expanded SAPS II, and the OR adjusted for both expanded SAPS II and propensity for patients to receive CCM are similar. The ORs are greater for the group that received CCM than the group that did not for both sensitivity analyses, demonstrating the robustness of our results. The Appendix (available at www.annals.org) shows additional sensitivity analyses involving changes to the propensity score. Conditional logistic regression analyses for the 19 largest ICUs generated an OR

greater than 1.0 in 18 of 19 ICUs. In 50% of these ICUs, the difference was statistically significant. In the remaining ICUs, the difference was not statistically significant because of the small sample size within the individual ICUs.

DISCUSSION

By using a database of more than 100 000 patients, we identified 3 types of ICUs: ICUs in which all patients are required to receive management by critical care physicians, ICUs in which no patients are managed by critical care physicians, and ICUs in which patients may or may not be managed by critical care physicians. Despite adjustment for severity of illness, we cannot demonstrate any survival benefit with management by critical care physicians. In fact, patients managed by critical care physicians had higher odds of mortality than patients managed by physicians not trained in critical care medicine.

Our results are surprising and completely contrary to previously published findings (7–21). Almost all published studies on the impact of critical care physicians have demonstrated decreased morbidity or mortality with management by critical care specialists (24–28).

To control for potential confounders by severity of

illness and the tendency for sicker patients to be transferred to physicians trained in critical care, we used an expanded SAPS II (23) and developed a propensity score. The expanded SAPS II was designed to better estimate the probability of mortality of patients admitted to ICUs than was possible with the older SAPS II system. To explore the possibility that some subgroups of patients might benefit from CCM more than others, we conducted several subgroup analyses. For almost all of the subgroups analyzed, risk for mortality associated with management by critical care physicians statistically significant increased.

What could account for these unexpected results? Several possible explanations must be considered. First, there may be residual confounders of severity not covered by either the expanded SAPS II or the propensity score. Our data indicate that patients cared for by pulmonary or critical care physicians for their entire ICU stay were sicker, as evidenced by higher median SAPS II scores. Our results are based on the ability to adjust the increased severity in patients managed by pulmonary or critical care physicians. Despite our attempts to adjust for severity to match patients in both groups for the purposes of comparison, no severity adjustment is perfect, and thus, there may be substantial unrecognized markers of severity in patients cared for by critical care physicians that remain unaccounted for. Some examples of residual unrecognized confounding include comorbid conditions and additional diagnoses not reported in the Project IMPACT database; responses to therapy; presence of protocols in some ICUs; presence and responsibilities of nonintensivist physicians, nurses, and other clinicians; and the influence of where and how long the patient received treatment before ICU admission (lead-time bias).

Second, we must consider the possibility that, for the patients in the Project IMPACT database, management by critical care physicians was associated with worse outcomes. Despite compelling evidence in the literature that care pro-

vided by trained critical care physicians leads to better outcomes, our data raise an important point: Although we believe that critical care physicians are trained and expertly skilled in the management of critically ill patients, perhaps some routine critical care practices and procedures may not be beneficial or cumulative use of more interventions may take a negative toll. Although further analyses and studies are needed to understand the possibility that care from critical care physicians is associated with higher hospital mortality, we speculate that there may be several plausible explanations. First, critical care physicians may use their own judgment to manage patients instead of using standardized protocols that may be associated with better outcomes. Second, because of their familiarity and expertise with procedures, they may use more procedures that subsequently lead to more complications. Their use of more procedures, such as placement of catheters and other invasive devices, may make critically ill patients more susceptible to life-threatening infections. Third, patients who receive care from a critical care physician may be transferred to different, unfamiliar physicians, whereas patients who receive care from non-critical care physicians may be more likely to receive ongoing care from physicians already familiar with them. Transfers may, be associated with greater chances of disruption in management and medical orders and create a greater likelihood of miscommunication and errors, all of which can have adverse consequences. This last possible explanation would be more noticeable in patients whose illnesses require less critical care expertise.

We do not claim that this list is exhaustive, but each speculation could be explored by future studies that examine the rates of protocol use, procedures, drug-resistant infections, and care for large groups of patients among physicians who are trained in critical care and those who are not.

Our study has several limitations. First, hospital mortality, rather than 30-day mortality, is the end point.

Table 7. Sensitivity Analysis on the Robustness of the Results to Changes in Mortality Definition*

Variable	Hospital Mortality†	Hospital Mortality Combined with Other Discharge Locations‡	Hospital Mortality versus Discharge to Home§
Main-effects model 			
Crude OR (95% CI); P value	2.13 (2.03–2.24); <0.001	1.80 (1.73–1.87); <0.001	2.42 (2.30–2.56); <0.001
OR adjusted for expanded SAPS II (95% CI); P value	1.42 (1.34–1.52); <0.001	1.31 (1.25–1.37); <0.001	1.59 (1.48–1.71); <0.001
OR adjusted for expanded SAPS II and propensity score (95% CI); P value	1.40 (1.32–1.49); <0.001	1.34 (1.28–1.40); <0.001	1.58 (1.47–1.70); <0.001
Deaths, n (%)			
Yes	14 318 (14.1)	39 890 (39.2)	14 318 (14.1)
No	87 514 (85.9)	51 223 (50.3)	51 223 (50.3)
Not used in analysis	0 (0.0)	10 719 (10.5)	36 291 (35.6)

* OR = odds ratio; SAPS = Simplified Acute Physiology Score.

† Hospital mortality (yes vs. no), as used in this study.

‡ “Hospital mortality” is defined as patients who died in the hospital in combination with those discharged to another hospital, rehabilitation center, hospice care, or long-term acute care vs. those who were discharged home. If the discharge location was unknown, these participants were left out of the sensitivity analysis.

§ “Hospital mortality” is defined as patients who died in the hospital vs. those who were discharged home. All others were excluded from the analysis.

|| Random-effects logistic regression, in which expanded SAPS II probability and propensity score are added into the model as main effects without interaction terms.

Project IMPACT measures only ICU and hospital mortality. No information on the patients was collected after they left the hospital. Thus, the database contains no information on 30-day mortality. This allows for the possibility that the outcome between the 2 groups may be different at 30 days compared with hospital discharge. If more patients managed by non-critical care physicians died between hospital discharge and 30 days, our results might be very different. For this to be the case, non-critical care physicians would have to routinely discharge patients when they are sicker and at higher risk for death. The fact that more patients were discharged home by non-critical care physicians, rather than to extended care facilities, would seem to argue against this possibility.

Second, the process for identifying the management of patients has limitations. Data collectors at each institution decided, on the basis of training and instructions from Project IMPACT staff, whether to classify patients as managed by critical care physicians. Ultimately, this is a subjective process and may have led to unrecognized bias in the classification of patients.

Third, data elements for analysis are limited to those available in the Project IMPACT database. Limited information is available about the internal structure of each ICU in the database. For example, the presence of protocols, order sets, the length of experience of the nursing staff, the nurse-patient ratio on any particular day, and how many different groups of critical care physicians function within each ICU remain unknown. These and other factors may have had a strong, unrecognized influence on the outcomes of patients in a given ICU. In addition, the Project IMPACT database was not established to address the impact of critical care physician management on patient outcome.

Finally, the percentage of patients managed by full-time intensivists cannot be identified in the Project IMPACT database, and we therefore cannot assess the benefit of full-time, on-site management by ICU physicians. Treatment designated as “management entire stay by critical care physicians” includes all models of management in the ICU by board-certified or board-eligible critical care physicians, including full-time intensivists, office-based pulmonary critical care physicians seeing patients on rounds in the ICU once or twice a day, and private consulting groups with responsibility for critical care patients. Therefore, our study does not identify 1 particular model of critical care practice but rather a broad array of practice management styles provided by trained, board-certified or board-eligible critical care physicians. In the Project IMPACT database, we know little about the non-critical care physicians who manage patients in the ICU or the ICUs in which no patients are managed by critical care.

Future prospective studies should be designed to better answer the questions raised by our study, including characteristics that identify high-performing critical care units.

In conclusion, our study, which to our knowledge is

based on the largest cohort ever analyzed to examine the relationship of CCM to survival of critically ill patients, found some unexpected results. Patients managed by critical care physicians for the entire ICU stay had a higher risk for death than patients managed by non-critical care physicians. Although all of the possible explanatory mechanisms we have mentioned may seem to portend badly for the practice of critical care medicine, we suggest that, if true, they are amenable to correction or mitigation through such efforts as guideline development and adherence, quality improvement, and systematic efforts to reduce errors. Given the complexity of critical illness, the need for dedicated critical care physicians seems inevitable, and strategies to assure best practices will help them to guarantee the best outcomes possible. Further research is needed to explain these findings and determine whether these results may be explained by unrecognized residual confounders of illness severity.

From Brown University, Providence, Rhode Island; Mount Holyoke College, South Hadley, Massachusetts; Ohio State University College of Health, Columbus, Ohio; Albert Einstein College of Medicine, New York, New York; and National Institutes of Health, Bethesda, Maryland.

Disclaimer: The opinions expressed in this paper are those of the authors and do not reflect policies of the National Institutes of Health or the U.S. Department of Health and Human Services.

Acknowledgment: The authors thank Rito Bergemann MD, PhD; Laura Katz, MPH; Lisa Siegartel, MPH; and J.J. Doyle, PhD, whose initial statistical support contributed to the initial observation, and Barbara Shott, who assisted in preparing the manuscript.

Grant Support: By the National Institutes of Health Clinical Center and an unrestricted educational grant from Eli Lilly.

Potential Financial Conflicts of Interest: *Consultancies:* D.B. Chalfin (Project IMPACT).

Reproducible Research Statement: *Study protocol:* Not available. *Statistical code:* Available from Mr. Phillips (gary.phillips@osumc.edu). *Data set:* Available for purchase from Cerner Corporation (www.cerner.com/piccm).

Requests for Single Reprints: Mitchell M. Levy, MD, Rhode Island Hospital, 593 Eddy Street, Providence, RI 02903; e-mail, Mitchell_Levy@brown.edu.

Current author addresses and author contributions are available at www.annals.org.

References

1. The Leapfrog Group. Leapfrog Hospital Quality and Safety Survey Results. Accessed at www.leapfroggroup.org/cp on 17 April 2008.
2. Danis M, Chalfin DB, Doyle JJ, Bergemann R, Katz LM, Siegartel LR et al. Development of model-based computer software for ICU resource allocation [Abstract]. *Crit Care Med*, 2004; 32:A94.
3. Groeger JS, Guntupalli KK, Strosberg M, Halpern N, Raphaely RC, Cerra F, et al. Descriptive analysis of critical care units in the United States: patient

- characteristics and intensive care unit utilization. *Crit Care Med*. 1993;21:279-91. [PMID: 8428482]
4. Groeger JS, Strosberg MA, Halpern NA, Raphaely RC, Kaye WE, Guntupalli KK, et al. Descriptive analysis of critical care units in the United States. *Crit Care Med*. 1992;20:846-63. [PMID: 1597041]
 5. Groeger JS, Strosberg MA, Halpern NA, Raphaely RC, Kaye WE, Guntupalli KK, et al. Descriptive analysis of critical care units in the United States. *Crit Care Med*. 1992;20:846-63. [PMID: 1597041]
 6. Kelley MA, Angus DC, Chalfin DB. The critical care crisis in the United States: a report from the profession. *Crit Care Med* 2004;32:1219-1222.
 7. Multz AS, Chalfin DB, Samson IM, Dantzker DR, Fein AM, Steinberg HN, et al. A "closed" medical intensive care unit (MICU) improves resource utilization when compared with an "open" MICU. *Am J Respir Critic Care Med* 1998;157:1468-73. [PMID: 9603125]
 8. Carson SS, Stocking C, Podsadecki T, Christenson J, Pohlman A, MacRae S, et al. Effects of organizational change in the medical intensive care unit of a teaching hospital: a comparison of 'open' and 'closed' formats. *JAMA*. 1996;276:322-8. [PMID: 8656546]
 9. Carlson RW, Weiland DE, Srivathsan K. Does a full-time, 24-hour intensivist improve care and efficiency? *Crit Care Clin*. 1996;12:525-51. [PMID: 8839588]
 10. Barie PS, Bacchetta MD, Eachempati SR. The contemporary surgical intensive care unit. Structure, staffing, and issues. *Surg Clin North Am*. 2000;80:791-804, vii. [PMID: 10897261]
 11. Pronovost PJ, Angus DC, Dorman T, Robinson KA, Dremsizov TT, Young TL. Physician staffing patterns and clinical outcomes in critically ill patients: a systematic review. *JAMA* 2002;288:2151-62. [PMID: 12413375]
 12. Dimick JB, Pronovost PJ, Heitmiller RF, Lipssett PA. Intensive care unit physician staffing is associated with decreased length of stay, hospital cost, and complications after esophageal resection. *Crit Care Med*. 2001;29:753-8. [PMID: 11373463]
 13. Pronovost PJ, Jenckes MW, Dorman T, Garrett E, Breslow MJ, Rosenfeld BA, et al. Organizational characteristics of intensive care units related to outcomes of abdominal aortic surgery. *JAMA*. 1999;281:1310-7. [PMID: 10208147]
 14. Brown JJ, Sullivan G. Effect on ICU mortality of a full-time critical care specialist. *Chest*. 1989;96:127-9. [PMID: 2736969]
 15. Reynolds HN, Haupt MT, Thill-Baharozian MC, Carlson RW. Impact of critical care physician staffing on patients with septic shock in a university hospital medical intensive care unit. *JAMA*. 1988;260:3446-50. [PMID: 3210284]
 16. Lima C, Levy MM. The impact of an on-site intensivist on patient charges and length of stay in the medical intensive care unit [Abstract]. *Crit Care Med* 1995; 23:A238
 17. Ghorra S, Reinert SE, Cioffi W, Buczko G, Simms HH. Analysis of the effect of conversion from open to closed surgical intensive care unit. *Ann Surg*. 1999;229:163-71. [PMID: 10024095]
 18. Li TC, Phillips MC, Shaw L, Cook EF, Natanson C, Goldman L. On-site physician staffing in a community hospital intensive care unit. Impact on test and procedure use and on patient outcome. *JAMA*. 1984;252:2023-7. [PMID: 6481908]
 19. Manthous CA, Amoaeng-Adjepong Y, al-Kharrat T, Jacob B, Alnuaimat HM, Chatila W, et al. Effects of a medical intensivist on patient care in a community teaching hospital. *Mayo Clin Proc*. 1997;72:391-9. [PMID: 9146680]
 20. Pollack MM, Katz RW, Ruttimann UE, Getson PR. Improving the outcome and efficiency of intensive care: the impact of an intensivist. *Crit Care Med*. 1988;16:11-7. [PMID: 3338276]
 21. Hanson CW 3rd, Deutschman CS, Anderson HL 3rd, Reilly PM, Behringer EC, Schwab CW, et al. Effects of an organized critical care service on outcomes and resource utilization: a cohort study. *Crit Care Med*. 1999;27:270-4. [PMID: 10075049]
 22. Milstein A, Galvin RS, Delbanco SF, Salber P, Buck CR Jr. Improving the safety of health care: the Leapfrog initiative. *Eff Clin Pract*. 2000;3:313-6. [PMID: 11151534]
 23. Varelas PN, Conti MM, Spanaki MV, Potts E, Bradford D, Sunstrom C, et al. The impact of a neurointensivist-led team on a semiclosed neurosciences intensive care unit. *Crit Care Med*. 2004;32:2191-8. [PMID: 15640630]
 24. Angus DC, Kelley MA, Schmitz RJ, White A, Popovich J Jr. Committee on Manpower for Pulmonary and Critical Care Societies (COMPACCS). Caring for the critically ill patient. Current and projected workforce requirements for care of the critically ill and patients with pulmonary disease: can we meet the requirements of an aging population? *JAMA*. 2000;284:2762-70. [PMID: 11105183]
 25. Dara SI, Afessa B. Intensivist-to-bed ratio: association with outcomes in the medical ICU. *Chest*. 2005;128:567-72. [PMID: 16100139]
 26. Fuchs RJ, Berenholtz SM, Dorman T. Do intensivists in ICU improve outcome? *Best Pract Res Clin Anaesthesiol*. 2005;19:125-35. [PMID: 15679063]
 27. Higgins TL, McGee WT, Steingrub JS, Rapoport J, Lemeshow S, Teres D. Early indicators of prolonged intensive care unit stay: impact of illness severity, physician staffing, and pre-intensive care unit length of stay. *Crit Care Med*. 2003;31:45-51. [PMID: 12544992]
 28. Young MP, Birkmeyer JD. Potential reduction in mortality rates using an intensivist model to manage intensive care units. *Eff Clin Pract*. 2000;3:284-9. [PMID: 11151525]

Current Author Addresses: Dr. Levy: Rhode Island Hospital, 593 Eddy Street, Providence, RI 02903.

Dr. Rapoport: Department of Economics, Mount Holyoke College, 50 College Street, South Hadley, MA 01077.

Dr. Lemeshow: Ohio State University College of Health, M116 Starling Loving Hall, 320 West 10th Avenue, Columbus, OH 43210-1240.

Dr. Chalfin: Abbott Point of Care, 104 Windsor Center Boulevard, East Windsor, NJ 08520.

Mr. Phillips: Ohio State University Center for Biostatistics, M410 Starling Loving Hall, 320 West 10th Avenue, Columbus, OH 43210.

Dr. Danis: Department of Bioethics, National Institutes of Health, Building 10 Room 1C118, Bethesda, MD 20892-1156.

Author Contributions: Conception and design: J. Rapoport, D.B. Chalfin, M. Danis, M.M. Levy.

Analysis and interpretation of the data: J. Rapoport, S. Lemeshow, D.B. Chalfin, G. Phillips, M. Danis, M.M. Levy.

Drafting of the article: J. Rapoport, D.B. Chalfin, G. Phillips, M.M. Levy.

Critical revision of the article for important intellectual content: J. Rapoport, S. Lemeshow, D.B. Chalfin, G. Phillips, M. Danis, M.M. Levy.

Final approval of the article: J. Rapoport, S. Lemeshow, M. Danis, M.M. Levy.

Statistical expertise: J. Rapoport, S. Lemeshow, G. Phillips.

Obtaining of funding: M. Danis.

Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomised controlled trial

Timothy D Girard, John P Kress, Barry D Fuchs, Jason W W Thomason, William D Schweickert, Brenda T Pun, Darren B Taichman, Jan G Dunn, Anne S Pohlman, Paul A Kinniry, James C Jackson, Angelo E Canonico, Richard W Light, Ayumi K Shintani, Jennifer L Thompson, Sharon M Gordon, Jesse B Hall, Robert S Dittus, Gordon R Bernard, E Wesley Ely

Summary

Background Approaches to removal of sedation and mechanical ventilation for critically ill patients vary widely. Our aim was to assess a protocol that paired spontaneous awakening trials (SATs)—ie, daily interruption of sedatives—with spontaneous breathing trials (SBTs).

Methods In four tertiary-care hospitals, we randomly assigned 336 mechanically ventilated patients in intensive care to management with a daily SAT followed by an SBT (intervention group; n=168) or with sedation per usual care plus a daily SBT (control group; n=168). The primary endpoint was time breathing without assistance. Data were analysed by intention to treat. This study is registered with ClinicalTrials.gov, number NCT00097630.

Findings One patient in the intervention group did not begin their assigned treatment protocol because of withdrawal of consent and thus was excluded from analyses and lost to follow-up. Seven patients in the control group discontinued their assigned protocol, and two of these patients were lost to follow-up. Patients in the intervention group spent more days breathing without assistance during the 28-day study period than did those in the control group (14·7 days vs 11·6 days; mean difference 3·1 days, 95% CI 0·7 to 5·6; p=0·02) and were discharged from intensive care (median time in intensive care 9·1 days vs 12·9 days; p=0·01) and the hospital earlier (median time in the hospital 14·9 days vs 19·2 days; p=0·04). More patients in the intervention group self-extubated than in the control group (16 patients vs six patients; 6·0% difference, 95% CI 0·6% to 11·8%; p=0·03), but the number of patients who required reintubation after self-extubation was similar (five patients vs three patients; 1·2% difference, 95% CI -5·2% to 2·5%; p=0·47), as were total reintubation rates (13·8% vs 12·5%; 1·3% difference, 95% CI -8·6% to 6·1%; p=0·73). At any instant during the year after enrolment, patients in the intervention group were less likely to die than were patients in the control group (HR 0·68, 95% CI 0·50 to 0·92; p=0·01). For every seven patients treated with the intervention, one life was saved (number needed to treat was 7·4, 95% CI 4·2 to 35·5).

Interpretation Our results suggest that a wake up and breathe protocol that pairs daily spontaneous awakening trials (ie, interruption of sedatives) with daily spontaneous breathing trials results in better outcomes for mechanically ventilated patients in intensive care than current standard approaches and should become routine practice.

Introduction

A third of patients in intensive care worldwide are mechanically ventilated.¹ Although instituted to save lives, mechanical ventilation is nearly universally accompanied by the administration of large doses of sedatives;² together these interventions are associated with significant morbidity.³⁻⁶ Efforts to reduce the duration of mechanical ventilation in intensive-care populations via ventilator weaning protocols and sedation protocols can improve clinical outcomes.⁷⁻⁹ Unfortunately, only a few patients are managed with these strategies since there is ongoing disagreement among health-care professionals with regard to benefits and risks and because weaning protocols and sedation protocols are viewed as separate concerns—often handled in a cumbersome fashion by different members of the patient-care team (eg, sedation by nurses and ventilator

weaning by respiratory therapists and physicians). Since the process of discontinuing ventilatory support is affected by heavy use of sedatives, there is an unmet need to combine approaches to sedation and ventilator weaning and to optimise their management.

Numerous randomised trials support the use of ventilator weaning protocols that include daily spontaneous breathing trials (SBTs) as their centrepiece; such protocols are standard of care, having reduced the duration of mechanical ventilation in diverse populations of patients with acute respiratory failure.^{7,10-14} Recent clinical trials, seeking to identify ways to manage sedation that might also facilitate earlier extubation, have shown that both intermittent use of sedatives and spontaneous awakening trials (SATs)—ie, daily interruption of sedatives—can reduce the duration of mechanical ventilation without compromising patient comfort or

Lancet 2008; 371: 126-34

See [Comment](#) page 95

Department of Medicine (A E Canonico MD) and Saint Thomas Research Institute (J G Dunn RN), Saint Thomas Hospital, Nashville, TN, USA; Department of Medicine, Division of Allergy, Pulmonary, and Critical Care

Medicine (T D Girard MD, J W W Thomason MD, B T Pun RN, J C Jackson PsyD, Prof R W Light MD, Prof G R Bernard MD, Prof E W Ely MD), Center for Health Services Research (T D Girard, J C Jackson, S M Gordon PsyD, Prof R S Dittus MD, E W Ely), and Department of Biostatistics (A K Shintani PhD, J L Thompson MPH), Vanderbilt University School of Medicine, Nashville, TN, USA; VA Tennessee Valley Geriatric Research, Education and Clinical Center (GRECC), VA

Service, Department of Veterans Affairs Medical Center, Tennessee Valley Healthcare System, TN, USA (S M Gordon, R S Dittus, E W Ely); Department of Medicine, Section of Pulmonary and Critical Care, University of Chicago, Chicago, IL, USA (J P Kress MD, W D Schweickert MD, A S Pohlman RN, Prof J B Hall MD); and Department of Medicine, Division of Pulmonary, Allergy and Critical Care Medicine, University of Pennsylvania School of Medicine, Philadelphia, PA, USA (B D Fuchs MD, D B Taichman MD, P A Kinniry MD)

Medicine, Section of Pulmonary and Critical Care, University of Chicago, Chicago, IL, USA (J P Kress MD, W D Schweickert MD, A S Pohlman RN, Prof J B Hall MD); and Department of Medicine, Division of Pulmonary, Allergy and Critical Care Medicine, University of Pennsylvania School of Medicine, Philadelphia, PA, USA (B D Fuchs MD, D B Taichman MD, P A Kinniry MD)

Medicine, Section of Pulmonary and Critical Care, University of Chicago, Chicago, IL, USA (J P Kress MD, W D Schweickert MD, A S Pohlman RN, Prof J B Hall MD); and Department of Medicine, Division of Pulmonary, Allergy and Critical Care Medicine, University of Pennsylvania School of Medicine, Philadelphia, PA, USA (B D Fuchs MD, D B Taichman MD, P A Kinniry MD)

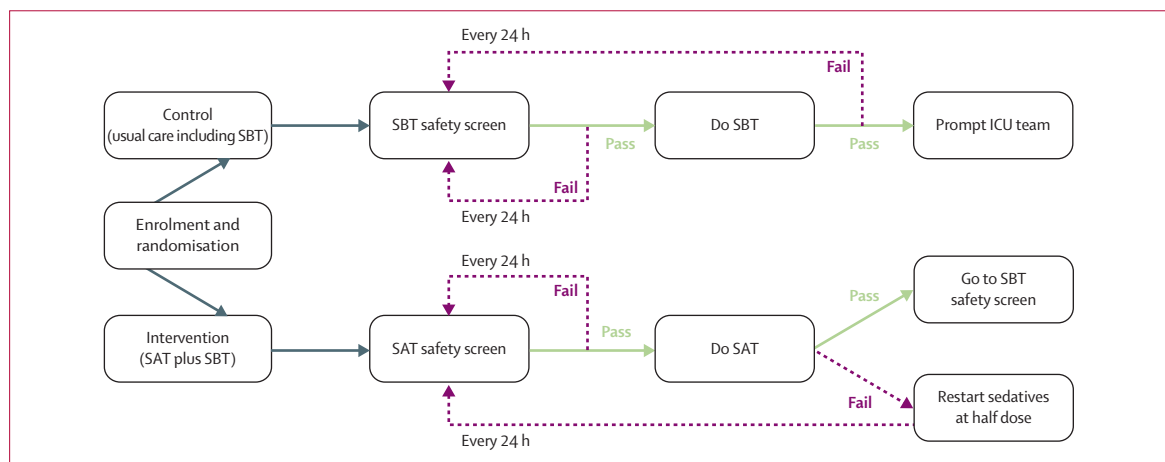


Figure 1: Treatment protocols

ICU=intensive-care unit. SAT=spontaneous awakening trial. SBT=spontaneous breathing trial.

safety.^{8,9,15} The paucity of additional evidence supporting the routine use of SATs, however, as well as anecdotal concerns regarding patient safety and agitation, have led to limited use of this sedation strategy. Whereas some intensive-care practitioners report only lightly sedating patients during most of their time on the ventilator, less than half of practitioners worldwide have implemented daily interruption of sedatives—eg, 34% in Germany,¹⁶ 40% in Canada,¹⁷ and 40% in the USA.^{18,19} Also, proponents of patient-targeted sedation strategies argue that titration of sedatives according to patients' needs produces outcomes equivalent to those resulting from a protocol that promotes daily SATs.^{20,21}

To test our hypothesis that routine SATs improve patient outcomes when combined with routine SBTs, we undertook the Awakening and Breathing Controlled (ABC) trial, a multicentre, randomised controlled trial in which we assessed the efficacy and safety of a protocol of daily SATs paired with SBTs versus a standard SBT protocol in patients receiving patient-targeted sedation as part of usual care.

Methods

Patients

We recruited participants at four large medical centres: Saint Thomas Hospital (Nashville, TN, USA), University of Chicago Hospitals (Chicago, IL, USA), Hospital of the University of Pennsylvania (Philadelphia, PA, USA), and Penn Presbyterian Medical Center (Philadelphia). Vanderbilt Coordinating Center (Nashville, TN, USA) supervised the trial; a Vanderbilt investigator was available 24 h a day to answer questions and respond to reports of adverse events.

Study personnel screened all patients in intensive care every day to identify adult patients (≥ 18 years old) who required mechanical ventilation for 12 h or more. Patients receiving full ventilatory support and those whose support was being weaned were eligible. Patients were

excluded from enrolment for the following reasons: admission after cardiopulmonary arrest, continuous mechanical ventilation for 2 weeks or longer, moribund state (ie, death was perceived to be imminent), withdrawal of life support, profound neurological deficits (eg, large stroke or severe dementia), or current enrolment in another trial.

The institutional review boards at each participating centre approved the study protocol, and written informed consent was obtained from participants or their authorised surrogates.

Procedures

Patients were randomly assigned in a 1:1 manner to management with paired SAT and SBT protocols (the intervention group) or usual care, including patient-targeted sedation and an SBT protocol (the control group). A computer-generated, permuted-block randomisation scheme was stratified according to study centre by a Vanderbilt biostatistician. Each assignment was designated on a tri-folded piece of paper enclosed in a consecutively numbered, sealed, opaque envelope. After informed consent was obtained, before data were collected, the appropriate envelope was opened by local study personnel.

According to each study centre intensive-care unit's usual practice of care, physicians and nurses managed all patients with patient-targeted sedation, titrating sedative and analgesic doses to maintain the level of arousal and comfort deemed clinically appropriate for each patient. Each intensive-care unit used a validated sedation scale to monitor depth of sedation. Beginning the morning after enrolment, intensive-care nurses and respiratory therapists or study personnel managed patients according to the study protocols. Figure 1 displays the steps in each study protocol.

In accordance with the SBT protocol, patients in the control group were assessed every morning with an SBT

Correspondence to:
Dr Timothy D Girard, Division of Allergy, Pulmonary, and Critical Care Medicine, Center for Health Services Research, 6th Floor MCE 6110, Vanderbilt University School of Medicine, Nashville, TN 37232-8300, USA
timothy.girard@vanderbilt.edu

safety screen. Patients passed the screen if they had adequate oxygenation (oxygen saturation [SpO_2] $\geq 88\%$ on a fraction of inspired oxygen [F_iO_2] $\leq 50\%$ and a positive end-expiratory pressure [PEEP] ≤ 8 cm H_2O), any spontaneous inspiratory effort in a 5-min period, no agitation, no evidence of myocardial ischaemia in the previous 24 h, no significant use of vasopressors or inotropes (dopamine or dobutamine ≥ 5 $\mu\text{g}/\text{kg}$ per min, norepinephrine ≥ 2 $\mu\text{g}/\text{min}$, or vasopressin or milrinone at any dose), and no evidence of increased intracranial pressure. Patients who failed the screen were reassessed the following morning.

Patients who passed underwent an SBT: ventilatory support was removed, and the patient was allowed to breathe through either a T-tube circuit or a ventilatory circuit with continuous positive airway pressure of 5 cm H_2O or pressure support ventilation of less than 7 cm H_2O .²² No change was made in F_iO_2 or PEEP during the SBT. Patients failed the SBT if they developed a respiratory rate of more than 35 or less than eight breaths per min for 5 min or longer, hypoxaemia ($\text{SpO}_2 < 88\%$ for ≥ 5 min), abrupt changes in mental status, an acute cardiac arrhythmia, or two or more signs of respiratory

distress, including tachycardia (>130 bpm), bradycardia (<60 bpm), use of accessory muscles, abdominal paradox, diaphoresis, or marked dyspnoea. Patients who failed the SBT were ventilated immediately with the ventilator settings used before the trial. Patients passed the SBT if they did not develop any failure criteria during a 120-min trial. If the SBT was successful, the patients' physicians were notified verbally. Study personnel did not participate in decisions to extubate patients.

In accordance with the SAT protocol, patients in the intervention group were assessed every morning with an SAT safety screen. SATs were prescribed by protocol only for patients in the intervention group, although patients in the control group were not prevented from undergoing SATs if the managing clinician felt that they were indicated. Patients passed the screen unless they were receiving a sedative infusion for active seizures or alcohol withdrawal, were receiving escalating sedative doses due to ongoing agitation, were receiving neuromuscular blockers, had evidence of active myocardial ischaemia in the previous 24 h, or had evidence of increased intracranial pressure. Patients who failed the screen were reassessed the following morning.

Patients who passed the screen underwent an SAT: all sedatives and analgesics used for sedation were interrupted. Analgesics needed for active pain were continued. Patients were monitored by intensive-care staff or study personnel for up to 4 h. Patients passed the SAT if they opened their eyes to verbal stimuli or tolerated sedative interruption for 4 h or more without exhibiting failure criteria. Patients failed the SAT if they developed sustained anxiety, agitation, or pain, a respiratory rate of more than 35 breaths per min for 5 min or longer, an SpO_2 of less than 88% for 5 min or longer, an acute cardiac dysrhythmia, or two or more signs of respiratory distress, including tachycardia, bradycardia, use of accessory muscles, abdominal paradox, diaphoresis, or marked dyspnoea. When patients failed an SAT, intensive-care staff restarted sedatives at half the previous dose and then titrated the medications to achieve patient comfort. Patients who passed the SAT were immediately managed with the SBT protocol.

The primary endpoint was defined a priori as the number of days patients were breathing without assistance (ventilator-free days) during the 28-day study period, which began at the time of enrolment. Patients who died during the study period were assigned 0 ventilator-free days.²³ A period of unassisted breathing began with extubation (or removal of ventilatory support for patients with tracheostomies) if the period of unassisted breathing lasted at least 48 consecutive hours. Secondary endpoints included time to discharge from the intensive-care unit and from the hospital, all-cause 28-day mortality, 1-year survival, and duration of coma and delirium.

Trained study personnel did neurological assessments every day with two well-validated instruments: level of

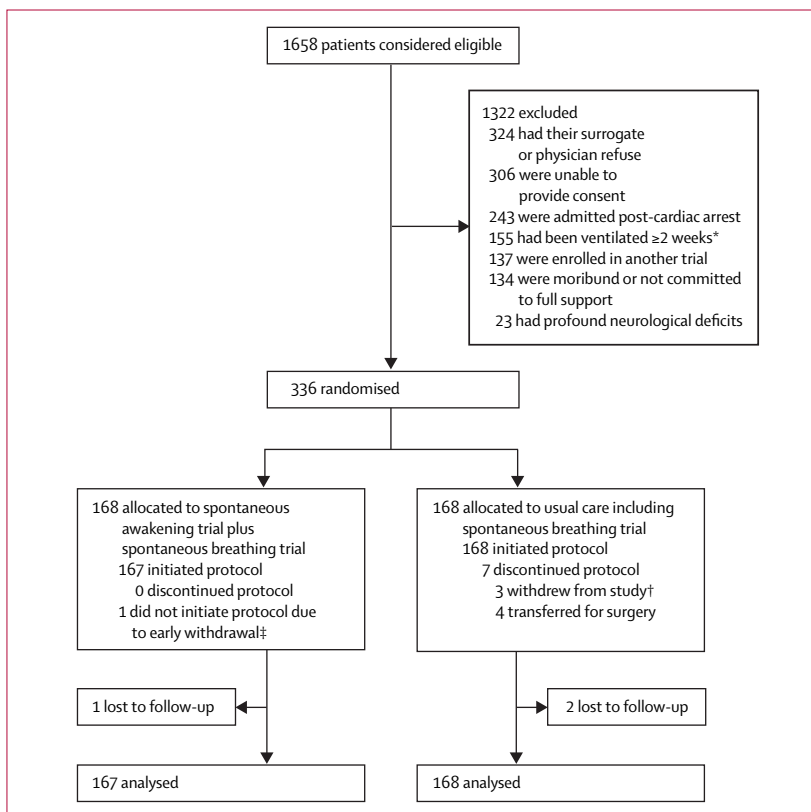


Figure 2: Trial profile

*Patients who were excluded because of ≥ 2 weeks of mechanical ventilation were transferred from other intensive-care units after periods of prolonged mechanical ventilation. †Withdrew from the study: discontinued the study protocol but allowed study personnel to track study outcomes, which were included in analysis. ‡One person was excluded from analysis due to study withdrawal by the surrogate immediately after randomisation, before any data collection.

arousal was assessed with the Richmond agitation-sedation scale (RASS),^{24,25} and delirium was diagnosed with the confusion assessment method for the intensive-care unit (CAM-ICU).^{26–28} Duration of coma was defined as the number of days in the study period that patients had no response to verbal or physical stimulation (RASS –5) or responded to physical or painful stimulation with movement but without eye opening (RASS –4). Duration of delirium was defined as the number of days in the study period during which patients were CAM-ICU positive and were not comatose.

Patients were followed up from enrolment until death or discharge, and survivors were followed up for vital status until 1 year after enrolment using the hospitals' electronic record systems, telephone calls, in-person visits, and a commercial version of the Social Security Death Master File.²⁹

Study personnel monitored patients for adverse events during the trial and reported all serious, unexpected, and study-related adverse events to an independent data and safety monitoring board. Self-extubation and reintubation were tracked as safety endpoints. The data and safety monitoring board reviewed two interim analyses of adverse events after enrolment of 30 and 100 patients. No interim analysis of efficacy was done.

Statistical analysis

On the basis of a pilot database, we expected a mean of 12·9 (SD 10·4) ventilator-free days in the control group. Thus, we calculated that a sample size of 334 patients would be needed to detect a 25% increase in ventilator-free days to 16·1 days within the intervention group with 80% power and a two-sided significance level of 0·05.³⁰

Data were analysed with an intention-to-treat approach. We used χ^2 tests to compare categorical variables between the study groups, and the Wilcoxon-Mann-Whitney two-sample rank-sum test to compare continuous variables, including the primary endpoint. We also used bootstrapping with 2000 samples to calculate a non-parametric 95% CI for the difference in mean ventilator-free days, because the variable had an unusual distribution.³¹ Specifically, we calculated the difference in mean ventilator-free days in each of 2000 samples randomly generated from the original data using resampling with replacement and determined the 95% CI using the 2·5 and 97·5 percentiles of the results of these calculations.

To compare the effects of the two treatment protocols on length of stay in the intensive-care unit and in the hospital, we used time-to-event analyses. Patient data were censored at time of death. Medians and IQRs were obtained with Kaplan-Meier analyses, and the log-rank test was used to assess the effect of the treatment protocols. Kaplan-Meier analysis and the log-rank test were also used to assess the effect of the treatment protocols on 1-year survival; patients were censored at the time of last contact alive or at 1 year from enrolment,

whichever was first. The unadjusted hazard ratio (HR) of death up to 1 year was obtained with Cox proportional hazards regression. We assessed the proportional hazards assumption by examining scaled Schoenfeld's partial residuals³² for the independent variable included in the model; no violation of the assumption was detected. To

	Intervention group (n=167)	Control group (n=168)
Age (years)	60 (48 to 71)	64 (51 to 75)
Sex (female)	77 (46%)	83 (49%)
APACHE II score	26 (21 to 33)	26·5 (21 to 31)
SOFA score	9 (6 to 11)	8 (6 to 11·5)
Diagnosis on admission to intensive care		
Sepsis/acute respiratory distress syndrome	79 (47%)	87 (52%)
Myocardial infarction/congestive heart failure	22 (13%)	29 (17%)
Chronic obstructive pulmonary disease/asthma	17 (10%)	12 (7%)
Altered mental status	18 (11%)	12 (7%)
Hepatic or renal failure	9 (5%)	5 (3%)
Malignancy	3 (2%)	2 (1%)
Alcohol withdrawal	1 (1%)	1 (1%)
Other*	18 (11%)	20 (12%)
RASS on first study day	–4 (–5 to –2)	–4 (–5 to –2)
Sedation before enrolment		
Benzodiazepines (mg)†	8 (4 to 34)	10 (2 to 41)
Opiates (µg)‡	815 (184 to 4380)	850 (142 to 4685)
Propofol (mg)	5102 (2340 to 9720)	3248 (1455 to 7420)
Time from admission to enrolment (days)	2·2 (1·1 to 3·9)	2·2 (1·1 to 3·9)

Data are n (%) or median (IQR). APACHE II=acute physiology and chronic health evaluation II. RASS=Richmond agitation-sedation scale. SAT=spontaneous awakening trial. SBT=spontaneous breathing trial. SOFA=sequential organ failure assessment. *Including gastrointestinal bleeding, metabolic disarray, haemoptysis, pulmonary embolism, and status epilepticus. †Expressed in lorazepam equivalents.³⁴ ‡Expressed in fentanyl equivalents.³⁴

Table 1: Baseline characteristics

	Intervention group (n=167)	Control group (n=168)	p value
Underwent an SAT	150 (90%)*	0 (0%)	<0·0001
Sedatives held before any SBT	150 (90%)*	52 (31%)	<0·0001
Underwent an SBT	136 (81%)†	146 (87%)†	0·17
Benzodiazepine use post-enrolment			
Patients treated	120 (72%)	111 (66%)	0·25
Total dose (mg)‡	20 (5–93)	39 (8–213)	0·02
Average daily dose (mg)‡	2 (0–8)	3 (1–17)	0·12
Opiate use post-enrolment			
Patients treated	130 (78%)	128 (76%)	0·87
Total dose (µg)§	2662 (431–9875)	3700 (772–16 306)	0·07
Average daily dose (µg)§	327 (49–891)	301 (69–1555)	0·28
Propofol use post-enrolment			
Patients treated	117 (70%)	115 (69%)	0·88
Total dose (mg)	8950 (3070–17 159)	8380 (2250–18 980)	0·90
Average daily dose (mg)	1230 (431–2070)	987 (373–2158)	0·40

Data are n (%) or median (IQR). SAT=spontaneous awakening trial. SBT=spontaneous breathing trial. *17 patients in the intervention group never passed an SAT safety screen or underwent an SAT. †22 patients in the control group and 31 in the intervention group never passed an SBT safety screen or underwent an SBT. ‡Expressed in lorazepam equivalents.³⁴ §Expressed in fentanyl equivalents.³⁴

Table 2: Protocol adherence and sedative use

	Intervention group (n=167)	Control group (n=168)	p value
Ventilator-free days*			
Mean	14.7 (0.9)	11.6 (0.9)	0.02
Median	20.0 (0 to 26.0)	8.1 (0 to 24.3)	
Time to discharge (days)			
From intensive care	9.1 (5.1 to 17.8)	12.9 (6.0 to 24.2)	0.01
From hospital	14.9 (8.9 to 26.8)	19.2 (10.3 to NA)†	0.04
28-day mortality	47 (28%)	58 (35%)	0.21
1-year mortality	74 (44%)	97 (58%)	0.01
Duration of brain dysfunction (days)			
Coma	2 (0 to 4)	3 (1 to 7)	0.002
Delirium	2 (0 to 5)	2 (0 to 6)	0.50
RASS at first successful SBT	-1 (-3 to 0)	-2.5 (-4 to 0)	0.0001
Complications			
Any self-extubation	16 (10%)	6 (4%)	0.03
Self-extubation requiring reintubation‡	5 (3%)	3 (2%)	0.47
Reintubation‡	23 (14%)	21 (13%)	0.73
Tracheostomy	21 (13%)	34 (20%)	0.06

Data are mean (SD), n (%), or median (IQR). RASS=Richmond agitation-sedation scale. SAT=spontaneous awakening trial. SBT=spontaneous breathing trial. *Ventilator-free days from study day 1 to 28. †Greater than 25% of patients in the SBT group remained in the hospital at study day 28. ‡Reintubation within 48 hours of extubation.

Table 3: Main outcomes

assess for an interaction between study centre and treatment with respect to the primary endpoint, we included an interaction term in a proportional odds logistic regression model with ventilator-free days as the dependent variable. We used R (version 2.4 patched) for all statistical analyses.³³ An independent biostatistician re-analysed the final dataset and verified all our results.

This study is registered with ClinicalTrials.gov, number NCT00097630.

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the manuscript. The corresponding author had full access to all the data and had final responsibility for the decision to submit for publication.

Results

1658 patients were considered eligible for enrolment between October, 2003, and March, 2006. We enrolled and randomised 336 of these individuals (figure 2). 168 patients were randomly assigned to each group. Seven (4%) patients in the control group discontinued the protocol: surrogates withdrew three patients from the study, and four patients were transferred to another service not participating in the trial. No patient in the intervention group discontinued the protocol; a surrogate withdrew one patient before protocol initiation or any data collection, and this patient was excluded from analyses.

The two groups were similar at baseline (table 1). On day 1, 87 (52%) patients in the control group and 94 (56%)

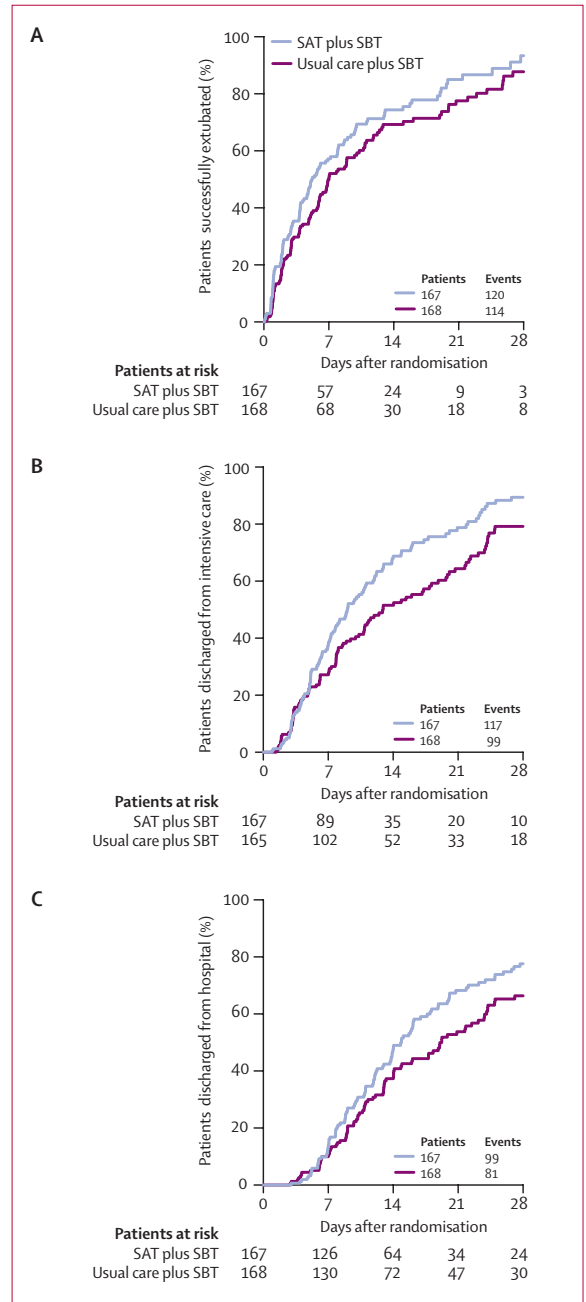


Figure 3: Probability of successful extubation (A), discharge from intensive care (B), and hospital discharge (C) during the first 28 days after randomisation

Events indicate total number of successful extubations (A), discharges from intensive care (B), and discharges from the hospital (C) in each treatment group during the 28 days from enrolment.

patients in the intervention group were comatose. Before enrolment, the two groups were treated with similar doses of benzodiazepines and opiates, although patients in the intervention group received more propofol (p=0.02). Propofol dose before enrolment, however, was not associated with study outcomes (data not shown).

150 (90%) patients in the intervention group passed an SAT safety screen; these patients underwent 895 SATs (table 2). Analgesics were continued for pain during 132 (15%) of these SATs. Clinicians discontinued the sedatives administered to 52 (31%) patients in the control group before at least one SBT (table 2). The number of patients in each group treated with benzodiazepines, opiates, or propofol was similar, as was the cumulative dose of propofol (table 2). The cumulative benzodiazepine dose was higher in the control group than in the intervention group. Only 45 (27%) patients in the control group and 31 (18%) patients in the intervention group received haloperidol ($p=0.07$).

Patients in the intervention group spent more days breathing without assistance than those in the control group (3.1 mean ventilator-free days difference, 95% CI 0.7–5.6; $p=0.02$; table 3). Additionally, the intervention protocol resulted in discharge about 4 days earlier from both intensive care and from the hospital (table 3 and figure 3). There was no significant interaction between study centre and treatment with respect to the number of ventilator-free days (data not shown).

The duration of coma was significantly shorter in the intervention group than in the control group, whereas the duration of delirium was similar between the two groups (table 3). Of the assessable patients, delirium occurred in 124 (74%) in the intervention group and 119 (71%) in the control group ($p=0.66$).

Patients in the two treatment groups progressed to the point of passing an SBT at the same rate (median number of days to first passed SBT 3.8 [IQR 1.1–14.0] days in the intervention group vs 3.9 [1.0–11.8] days in the control group; $p=0.49$). Patients in the intervention group, however, were more alert than were those in the control group on the day they first passed an SBT safety screen (median RASS –2 [IQR –3 to 0] vs –3 [–4 to –1]; $p=0.0003$) and an SBT (–1 [–3 to 0] vs –2.5 [–4 to 0]; $p=0.0001$). 59 (54%) of the 109 patients in the intervention group who ever passed an SBT were extubated on the day they first passed an SBT compared with 49 (40%) of the 124 patients in the control group (14.6% difference, 95% CI 1.0–26.0; $p=0.03$).

Analysis of 1-year survival showed that, at any instant during the year after enrolment, patients managed with the SAT plus SBT strategy were 32% less likely to die than were patients in the control group (HR 0.68, 95% CI 0.50 to 0.92; $p=0.01$; figure 4). For every seven patients treated with the SAT plus SBT protocol, one life was saved (number needed to treat 7.4, 95% CI 4.2–35.5).

Tracheostomies, which no patient had at enrolment, were placed in 21 (13%) patients in the intervention group and in 34 (20%) of those in the control group (absolute risk reduction 7.6%, 95% CI –0.3% to 15.6%; $p=0.06$). Median time to tracheostomy placement was similar in the two groups (12.7 [IQR 5.9–13.4] days in the intervention group vs 12.9 [8.0–18.1] days in the control group; $p=0.32$).

More patients in the intervention group self-extubated than in the control group (6.0% difference, 95% CI 0.6–11.8; $p=0.03$; table 3). Only five individuals in the intervention group self-extubated, however, during or within 12 h of an SAT. Also, five patients in the intervention group required reintubation within 48 h of self-extubation,

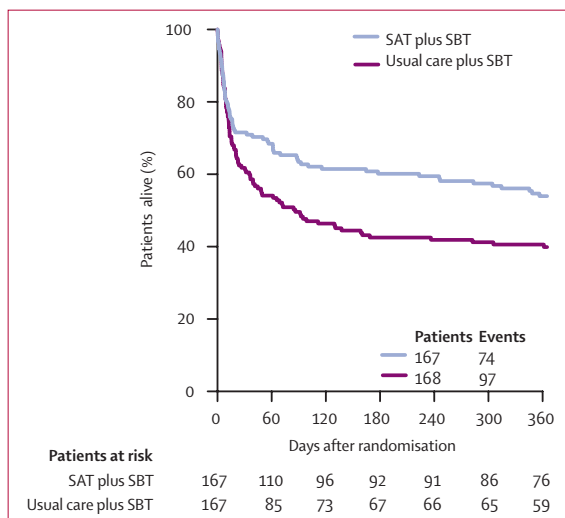


Figure 4: Survival at 1 year

Events indicate the number of deaths in each group in the year after enrolment.

	Intervention group	Control group	p value
SAT			
Total	895	0	
Passed	837 (94%)	NA	NA
Opened eyes to verbal stimuli	731 (82%)	NA	NA
Tolerated SAT for ≥ 4 h	106 (11%)	NA	NA
Failed*	58 (7%)	NA	NA
Anxiety, agitation, or pain	42 (5%)	NA	NA
Signs of respiratory distress	25 (3%)	NA	NA
Tachypnoea	20 (2%)	NA	NA
Hypoxaemia	12 (1%)	NA	NA
Dysrhythmia	1 (0%)	NA	NA
SBT			
Total	603	948	
Passed	319 (53%)	492 (52%)	0.70
Failed*	284 (47%)	456 (48%)	..
Tachypnoea	221 (37%)	351 (37%)	0.75
Signs of respiratory distress	125 (37%)	217 (23%)	0.27
Hypoxaemia	33 (6%)	51 (5%)	0.98
Abrupt change in mental status	13 (2%)	17 (2%)	0.64
Bradypnoea	8 (1%)	19 (2%)	0.31
Dysrhythmia	15 (3%)	9 (1%)	0.02

Data are n (%). NA=not applicable. SAT=spontaneous awakening trial. SBT=spontaneous breathing trial. *Some patients had more than one reason for failure.

Table 4: Results of the spontaneous awakening trials and spontaneous breathing trials

compared with three patients in the control group (1.2% difference, 95% CI -5.2% to 2.5%; $p=0.47$). The overall rate of reintubation was similar between the two groups (1.3% difference, 95% CI -8.6% to 6.1%; $p=0.73$).

Patients in the intervention group failed 201 (18%) of the 1140 SAT safety screens that were done, most often due to agitation, which was noted during 151 (13%) safety screens. An SAT was done after 895 (95%) of the 939 SAT safety screens that were passed. Patients passed 837 (94%) of these SATs. Patients who failed SATs most often did so due to anxiety, agitation, or pain, which occurred only during 42 (5%) SATs (table 4).

Two-thirds of all SBT safety screens were passed (647 [66%] of 983 screens done in the intervention group vs 1036 [65%] of 1599 in the control group; $p=0.59$), and half of all SBTs were passed by patients in both groups (table 4). The most common reasons for SBT failure in both groups were tachypnoea and other signs of respiratory distress. Patients failed a small number of SBTs in both groups due to acute dysrhythmias; this occurred more frequently in patients in the intervention group (1.6% difference, 95% CI 0.3–3.2; $p=0.02$). None of these dysrhythmias were deemed to be serious, since none resulted in clinically adverse sequelae other than termination of the SBT.

Discussion

Our results show that a paired sedation and ventilator weaning protocol consisting of daily SATs plus SBTs resulted in patients spending more time off mechanical ventilation, less time in coma, and less time in intensive care and the hospital, and the protocol improved 1-year survival compared with usual care. This wake up and breathe strategy was effective and was associated with few adverse events in a diverse population in intensive care in both community and university hospitals.

Respiratory failure and mechanical ventilation frequently result in anxiety and pain.^{35,36} Thus, clinicians use sedatives and analgesics to alleviate patient discomfort, decrease oxygen consumption, facilitate nursing care, and ensure patient safety.³⁷ These medications, however, are associated with adverse effects, including oversedation,³⁸ delirium,⁵ and prolongation of mechanical ventilation.⁶ The most appropriate pattern and dose of administration is often difficult to determine, and many intensive-care practitioners have the perception that their patients are not oversedated, even though observational studies in Europe² and the USA³⁸ found that nearly half of intensive-care patients are deeply sedated and unarousable.

In 2000, Kress and colleagues⁹ reported that a protocol of daily SATs reduced duration of mechanical ventilation and length of stay in intensive care. This study showed that SATs are safe; self-extubation,⁹ intensive-care-related complications,³⁹ myocardial ischaemia,⁴⁰ and post-traumatic stress disorder⁴¹ did not occur more frequently in patients managed with daily SATs than in

those managed without SATs. Kress and colleagues' trial was limited, however, being a single-centre trial that did not mandate daily SBTs. Because of the absence of a multicentre trial supporting the efficacy of SATs and persistent concerns regarding the safety of this sedation strategy, most intensive-care patients are not managed with routine SATs; intensive-care practitioners often opt instead for individualised, patient-targeted sedation.^{16–19}

In the current investigation, daily SATs reduced the likelihood of oversedation so that patients were neurologically ready for extubation once their respiratory failure had improved. Patients in the intervention group were more alert than were patients in the control group on first passing both an SBT safety screen and SBT. Thus, these patients were more likely to be extubated shortly after first passing a breathing trial. Accompanying this earlier neurological recovery in the intervention group was a higher rate of self-extubation. Since these events did not result in more reintubations, the patients were apparently ready to come off the ventilator earlier than the intensive-care team had expected. Self-extubation within the intervention group did not substantially affect the results of the trial; after excluding all patients who self-extubated, the difference in ventilator-free days between treatment groups remained significant (data not shown).

In both the current trial and that by Kress and colleagues,⁹ patients managed with daily SATs were treated with less total benzodiazepine medication than were patients who did not undergo SATs, a difference in drug dose that was considerable over the entire stay in intensive care but small on any given day of treatment. Total propofol doses, however, were similar between groups in both studies, suggesting that a reduction in drug dose was not the sole factor leading to improved outcomes. The pattern of administration is apparently an important factor; the interruption of a sedative infusion—during the wake up component of the SAT plus SBT protocol—probably facilitates a decline in plasma drug concentration and reduces the likelihood of drug accumulation.

Major strengths of the ABC trial included the parallel format of the SAT plus SBT protocol, which includes specific safety screens and failure criteria, making it easy to replicate; participation by intensive-care staff, including nurses and respiratory therapists; use of patient-targeted sedation and an SBT protocol in both groups; assessment of coma and delirium with validated and reliable instruments; and a multicentre study design with enrolment in both open and closed intensive-care units. Also, the liberal SBT safety screen criteria used ($F_iO_2 \leq 50\%$ and $PEEP \leq 8$ cm H_2O) facilitated the observation that many patients might be ready to breathe without assistance sooner than previously expected. Likewise, the simple criteria for passing an SAT were part of an SAT plus SBT protocol that was easy to implement yet effective. The

format of the SAT plus SBT protocol (ie, linkage of SATs and SBTs) should facilitate its use, making the typical practice of devising and implementing sedation protocols and ventilator weaning protocols as independent constructs unnecessary, thereby avoiding emphasis on one or the other depending on local strengths and personnel. Lastly, the patients and critical care communities that participated in the ABC trial were heterogeneous, greatly enhancing the generalisability of these findings.

Several limitations should be noted. Research personnel and intensive-care staff were not blinded to patient allocation because blinding is not possible in a study of this kind. Knowledge of group allocation can bias study results, so we randomly assigned patients to treatment groups, managed patients in both groups with formal protocols, followed well-defined outcomes, and used a statistical analysis plan designed a priori. Although each participating intensive-care unit used patient-targeted sedation strategies, we did not mandate the use of a specific sedation protocol in the control group or particular short-acting or long-acting sedatives in either group but—to compare the SAT plus SBT protocol with usual care—allowed clinicians to use their judgment with regard to the most appropriate medications and levels of sedation for individual patients. A detailed description of sedation practices used to manage patients in the control group is therefore not available except that sedative doses were recorded. By chance, patients in the intervention group received more propofol before enrolment than did those in the control group, whereas benzodiazepine and opiate doses were similar between groups. Although increased propofol doses before enrolment in the intervention group might have biased the results against showing improved outcomes in the intervention group, our analysis indicated that pre-enrolment propofol dose was not associated with study outcomes. Because we did not track the time spent executing the SAT plus SBT protocol, we cannot report the amount of personnel time needed to implement this intervention. The protocol was designed to be done by bedside nurses and respiratory therapists during the course of routine care, and it was implemented largely by clinical staff during the trial. Lastly, we did not enrol surgical patients because of their potential need for continuous analgesia; thus, the wake up and breathe protocol should be tested separately in a surgical intensive-care population.

At any instant during the year following enrolment, patients managed with the wake up and breathe protocol were about a third less likely to die than were patients in the control group. Patients with more severe critical illness, who tend to have prolonged stays in intensive care—ie, those who accrue the largest cumulative exposure to sedative medications—could receive the greatest benefit from management with the SAT plus SBT strategy, but we are limited in our ability to draw such conclusions since no data exist to elucidate the mechanism of the observed survival benefit.

In conclusion, our results suggest that use of a so-called wake up and breathe protocol that pairs daily spontaneous awakening trials (ie, interruption of sedatives) with daily spontaneous breathing trials for the management of mechanically ventilated patients in intensive care results in better outcomes than current standard approaches and should become routine practice.

Contributors

JJWT and EWE conceived the trial. TDG, JPK, BDF, JJWT, BTP, DBT, JCY, AKS, SMG, JBH, RSD, GRB, and EWE participated in study design. TDG, JPK, BDF, JJWT, WDS, BTP, DBT, JGD, ASP, PAK, JCY, AEC, RWL, and EWE recruited patients and collected data, and TDG, AKS, JLT, and EWE analysed the data. All authors participated in interpretation of results. TDG drafted the manuscript, and all authors contributed to the critical review and revision of the manuscript. All authors have seen and approved the final version of the manuscript.

Conflict of interest statement

EWE has received grant support or honoraria from Pfizer, Hospira, Lilly, and Aspect Medical. All other authors declare that they have no conflict of interest.

Acknowledgments

We thank the Saint Thomas Foundation (Nashville, TN, USA), the National Institutes of Health (AG001023, HL007123, and RR024975), the Veterans Affairs Tennessee Valley Geriatric Research, Education, and Clinical Center (GRECC), the Hartford Geriatrics Health Outcomes Research Scholars Award Program, and the Vanderbilt Physician Scientist Development Program for financial support. We thank the ABC trial study personnel at University of Chicago Hospitals (Joseph Levitt, Celerina Nigos, Stacey Sandbo, and Ajeet Vinayak), Hospital of the University of Pennsylvania (Megan Carr-Lettieri, Joan Hoch, and Edward Tollok), and Penn Presbyterian Medical Center (Hernan Alvarado Jr, Sandra Kaplan, William E Laury, and Jennifer Shin); the members of the data and safety monitoring board (Daniel W Byrne, Brian W Christman, and John H Newman); Frank E Harrell Jr for his expert statistical guidance; Daniel W Byrne for independently verifying all statistical results; and the staff of the intensive care units at Saint Thomas Hospital, the University of Chicago Hospitals, the Hospital of the University of Pennsylvania, and Penn Presbyterian Medical Center for their invaluable participation in the ABC trial.

References

- 1 Esteban A, Anzueto A, Frutos F, et al. Characteristics and outcomes in adult patients receiving mechanical ventilation: a 28-day international study. *JAMA* 2002; **287**: 345–55.
- 2 Payen JF, Chanques G, Mantz J, et al. Current practices in sedation and analgesia for mechanically ventilated critically ill patients: a prospective multicenter patient-based study. *Anesthesiology* 2007; **106**: 687–95.
- 3 Cook DJ, Walter SD, Cook RJ, et al. Incidence of and risk factors for ventilator-associated pneumonia in critically ill patients. *Ann Intern Med* 1998; **129**: 433–40.
- 4 Pinhu L, Whitehead T, Evans T, Griffiths M. Ventilator-associated lung injury. *Lancet* 2003; **361**: 332–40.
- 5 Pandharipande P, Shintani A, Peterson J, et al. Lorazepam is an independent risk factor for transitioning to delirium in intensive care unit patients. *Anesthesiology* 2006; **104**: 21–26.
- 6 Kollef MH, Levy NT, Ahrens TS, Schaiff R, Prentice D, Sherman G. The use of continuous i.v. sedation is associated with prolongation of mechanical ventilation. *Chest* 1998; **114**: 541–48.
- 7 Ely EW, Baker AM, Dunagan DP, et al. Effect on the duration of mechanical ventilation of identifying patients capable of breathing spontaneously. *N Engl J Med* 1996; **335**: 1864–69.
- 8 Brook AD, Ahrens TS, Schaiff R, et al. Effect of a nursing-implemented sedation protocol on the duration of mechanical ventilation. *Crit Care Med* 1999; **27**: 2609–15.
- 9 Kress JP, Pohlman AS, O'Connor MF, Hall JB. Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. *N Engl J Med* 2000; **342**: 1471–77.

- 10 MacIntyre NR, Cook DJ, Ely EW Jr, et al. Evidence-based guidelines for weaning and discontinuing ventilatory support: a collective task force facilitated by the American College of Chest Physicians; the American Association for Respiratory Care; and the American College of Critical Care Medicine. *Chest* 2001; **120**: 375S–95S.
- 11 Esteban A, Frutos F, Tobin MJ, et al. A comparison of four methods of weaning patients from mechanical ventilation. Spanish Lung Failure Collaborative Group. *N Engl J Med* 1995; **332**: 345–50.
- 12 Kollef MH, Shapiro SD, Silver P, et al. A randomized, controlled trial of protocol-directed versus physician-directed weaning from mechanical ventilation. *Crit Care Med* 1997; **25**: 567–74.
- 13 Marelich GP, Murin S, Battistella F, Inciardi J, Vierra T, Roby M. Protocol weaning of mechanical ventilation in medical and surgical patients by respiratory care practitioners and nurses: effect on weaning time and incidence of ventilator-associated pneumonia. *Chest* 2000; **118**: 459–67.
- 14 Lellouche F, Mancebo J, Joliet P, et al. A multicenter randomized trial of computer-driven protocolized weaning from mechanical ventilation. *Am J Respir Crit Care Med* 2006; **174**: 894–900.
- 15 Carson SS, Kress JP, Rodgers JE, et al. A randomized trial of intermittent lorazepam versus propofol with daily interruption in mechanically ventilated patients. *Crit Care Med* 2006; **34**: 1326–32.
- 16 Martin J, Franck M, Sigel S, Weiss M, Spies CD. Changes in sedation management in German intensive care units between 2002 and 2006: a national follow up survey. *Crit Care* 2007; **11**: R124.
- 17 Mehta S, Burry L, Fischer S, et al. Canadian survey of the use of sedatives, analgesics, and neuromuscular blocking agents in critically ill patients. *Crit Care Med* 2006; **34**: 374–80.
- 18 Taniot MA, Devlin JW, Epstein SK. Perceived barriers to implementing strategy of daily interruption of sedative in the intensive care unit for critically ill patients. *Proc Am Thorac Soc* 2005; **2**: A793.
- 19 Devlin JW, Taniot MA, Epstein SK. Intensive care unit sedation: waking up clinicians to the gap between research and practice. *Crit Care Med* 2006; **34**: 556–57.
- 20 Heffner JE. A wake-up call in the intensive care unit. *N Engl J Med* 2000; **342**: 1520–22.
- 21 Hong JJ, Mazuski JE, Shapiro MJ. Daily interruption of sedative infusions in critically ill patients. *N Engl J Med* 2000; **343**: 814–15.
- 22 Esteban A, Alia I, Gordo F, et al. Extubation outcome after spontaneous breathing trials with T-tube or pressure support ventilation. *Am J Respir Crit Care Med* 1997; **156**: 459–65.
- 23 Schoenfeld DA, Bernard GR. Statistical evaluation of ventilator-free days as an efficacy measure in clinical trials of treatments for acute respiratory distress syndrome. *Crit Care Med* 2002; **30**: 1772–77.
- 24 Sessler CN, Gosnell MS, Grap MJ, et al. The Richmond agitation-sedation scale: validity and reliability in adult intensive care unit patients. *Am J Respir Crit Care Med* 2002; **166**: 1338–44.
- 25 Ely EW, Truman B, Shintani A, et al. Monitoring sedation status over time in ICU patients: reliability and validity of the Richmond agitation-sedation scale (RASS). *JAMA* 2003; **289**: 2983–91.
- 26 Ely EW, Inouye SK, Bernard GR, et al. Delirium in mechanically ventilated patients: validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU). *JAMA* 2001; **286**: 2703–10.
- 27 Ely EW, Margolin R, Francis J, et al. Evaluation of delirium in critically ill patients: validation of the confusion assessment method for the intensive care unit (CAM-ICU). *Crit Care Med* 2001; **29**: 1370–79.
- 28 Ely EW, Pun BT. The Confusion assessment method for the ICU (CAM-ICU) training manual. <http://www.icudelirium.org/delirium/CAM-ICUTraining.html> (accessed Sept 20, 2006).
- 29 Anon. Social security death index. <http://ssdi.rootsweb.com> (accessed July 3, 2007).
- 30 Dupont WD, Plummer WD. PS power and sample size program available for free on the Internet. *Controlled Clin Trials* 1997; **18**: 274.
- 31 Efron B, Tibshirani RJ. An introduction to the bootstrap. New York, NY: Chapman & Hall/CRC, 1993.
- 32 Schoenfeld D. Partial residuals for the proportional hazards regression model. *Biometrika* 1982; **69**: 239–41.
- 33 Ihaka R, Gentleman R. R: a language for data analysis and graphics. *J Comput Graph Stat* 1996; **5**: 299–314.
- 34 Wilson WC, Smedira NG, Fink C, McDowell JA, Luce JM. Ordering and administration of sedatives and analgesics during the withholding and withdrawal of life support from critically ill patients. *JAMA* 1992; **267**: 949–53.
- 35 Novaes MA, Knobel E, Bork AM, Pavao OF, Nogueira-Martins LA, Ferraz MB. Stressors in ICU: perception of the patient, relatives and health care team. *Intensive Care Med* 1999; **25**: 1421–26.
- 36 Puntillo KA. Pain experiences of intensive care unit patients. *Heart Lung* 1990; **19**: 526–33.
- 37 Jacobi J, Fraser GL, Coursin DB, et al. Clinical practice guidelines for the sustained use of sedatives and analgesics in the critically ill adult. *Crit Care Med* 2002; **30**: 119–41.
- 38 Weinert CR, Calvin AD. Epidemiology of sedation and sedation adequacy for mechanically ventilated patients in a medical and surgical intensive care unit. *Crit Care Med* 2007; **35**: 393–401.
- 39 Schweickert WD, Gehlbach BK, Pohlman AS, Hall JB, Kress JP. Daily interruption of sedative infusions and complications of critical illness in mechanically ventilated patients. *Crit Care Med* 2004; **32**: 1272–76.
- 40 Kress JP, Vinayak AG, Levitt J, et al. Daily sedative interruption in mechanically ventilated patients at risk for coronary artery disease. *Crit Care Med* 2007; **35**: 365–71.
- 41 Kress JP, Gehlbach B, Lacy M, Pliskin N, Pohlman AS, Hall JB. The long-term psychological effects of daily sedative interruption on critically ill patients. *Am J Respir Crit Care Med* 2003; **168**: 1457–61.

ORIGINAL ARTICLE

Intensive Insulin Therapy and Pentastarch Resuscitation in Severe Sepsis

Frank M. Brunkhorst, M.D., Christoph Engel, M.D., Frank Bloos, M.D., Ph.D., Andreas Meier-Hellmann, M.D., Max Ragaller, M.D., Norbert Weiler, M.D., Onnen Moerer, M.D., Matthias Gruending, M.D., Michael Oppert, M.D., Stefan Grond, M.D., Derk Olthoff, M.D., Ulrich Jaschinski, M.D., Stefan John, M.D., Rolf Rossaint, M.D., Tobias Welte, M.D., Martin Schaefer, M.D., Peter Kern, M.D., Evelyn Kuhnt, M.Sc., Michael Kiehntopf, M.D., Christiane Hartog, M.D., Charles Natanson, M.D., Markus Loeffler, M.D., Ph.D., and Konrad Reinhart, M.D., for the German Competence Network Sepsis (SepNet)

ABSTRACT

BACKGROUND

The role of intensive insulin therapy in patients with severe sepsis is uncertain. Fluid resuscitation improves survival among patients with septic shock, but evidence is lacking to support the choice of either crystalloids or colloids.

METHODS

In a multicenter, two-by-two factorial trial, we randomly assigned patients with severe sepsis to receive either intensive insulin therapy to maintain euglycemia or conventional insulin therapy and either 10% pentastarch, a low-molecular-weight hydroxyethyl starch (HES 200/0.5), or modified Ringer's lactate for fluid resuscitation. The rate of death at 28 days and the mean score for organ failure were coprimary end points.

RESULTS

The trial was stopped early for safety reasons. Among 537 patients who could be evaluated, the mean morning blood glucose level was lower in the intensive-therapy group (112 mg per deciliter [6.2 mmol per liter]) than in the conventional-therapy group (151 mg per deciliter [8.4 mmol per liter], $P < 0.001$). However, at 28 days, there was no significant difference between the two groups in the rate of death or the mean score for organ failure. The rate of severe hypoglycemia (glucose level, ≤ 40 mg per deciliter [2.2 mmol per liter]) was higher in the intensive-therapy group than in the conventional-therapy group (17.0% vs. 4.1%, $P < 0.001$), as was the rate of serious adverse events (10.9% vs. 5.2%, $P = 0.01$). HES therapy was associated with higher rates of acute renal failure and renal-replacement therapy than was Ringer's lactate.

CONCLUSIONS

The use of intensive insulin therapy placed critically ill patients with sepsis at increased risk for serious adverse events related to hypoglycemia. As used in this study, HES was harmful, and its toxicity increased with accumulating doses. (ClinicalTrials.gov number, NCT00135473.)

The authors' affiliations are listed in the Appendix. The investigators who participated in the Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis (VISEP) study are listed in the Supplementary Appendix, available with the full text of this article at www.nejm.org. Address reprint requests to Dr. Reinhart at the Department of Anesthesiology and Intensive Care Medicine, Friedrich Schiller University of Jena, Erlanger Allee 101, 07747 Jena, Germany, or at konrad.reinhart@med.uni-jena.de.

Drs. Brunkhorst and Engel contributed equally to the article.

N Engl J Med 2008;358:125-39.

Copyright © 2008 Massachusetts Medical Society.

IN A STUDY BY VAN DEN BERGHE ET AL. involving critically ill surgical patients, intensive insulin therapy to maintain euglycemia (glucose level, 80 to 110 mg per deciliter [4.4 to 6.1 mmol per liter]) lowered in-hospital mortality from 10.9% to 7.2%, mostly by reducing deaths from multiple organ failure with a proven septic focus.¹ This beneficial effect occurred predominantly in cardiac surgical patients who received high glucose challenges immediately after surgery (8 to 12 g of glucose intravenously per hour) and was associated with an unusually high rate of death (5.1%) among controls.

Furthermore, in a follow-up study by Van den Berghe et al., involving critically ill patients who had not undergone surgery and had not received a high glucose challenge, intensive insulin therapy had no beneficial effect on survival rates. However, such therapy was associated with an increase in hypoglycemic events (mean glucose level, 31 mg per deciliter [1.7 mmol per liter]) by a factor of 5 to 6.² Although it is unknown whether intensive insulin therapy improves the outcome during critical illness with severe sepsis, such therapy has been widely advocated.³

Few data are available to guide the choice of either colloid or crystalloid for fluid resuscitation in patients with septic shock.⁴ In animal models, hydroxyethyl starch (HES), as compared with crystalloids, improved microcirculation during endotoxemia⁵ and lessened tissue damage.⁶ On the other hand, HES was associated with serious side effects, including coagulopathy and acute renal failure.^{7,8} We assessed the safety and efficacy of intensive insulin therapy as compared with conventional insulin therapy (on the basis of the Leuven titration protocol) as well as the safety and efficacy of HES as compared with Ringer's lactate in patients with severe sepsis or septic shock.

METHODS

STUDY DESIGN

In this multicenter, randomized study, called the Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis (VISEP) study, we compared intensive insulin therapy with conventional insulin therapy and HES with Ringer's lactate, using a two-by-two factorial, open-label design. There was no a priori reason to expect interactions between the two types of treatment.

STUDY PATIENTS

From April 2003 to June 2005, we recruited patients in multidisciplinary intensive care units (ICUs) at 18 academic tertiary hospitals in Germany. Patients with severe sepsis or septic shock who were at least 18 years of age were eligible to enroll in the study. Severe sepsis and septic shock were defined according to criteria reported previously (for details, see the Supplementary Appendix, available with the full text of this article at www.nejm.org).⁹ Patients were deemed to be eligible if the onset of the syndrome was less than 24 hours before admission to the ICU or less than 12 hours after admission if the condition developed in the ICU. The treatment period was ended at 21 days after randomization or at discharge from the ICU or at the time of death (see the Supplementary Appendix).

The trial was approved by the ethics committee at each participating institution. Written informed consent was obtained from all patients or their legal representatives. In cases in which previous consent could not be obtained from the patient because of critical illness or the use of sedatives or anesthetic drugs and in order to permit early resuscitation, the ethics committee approved a provision for delayed consent. In such cases, a surrogate decision maker was fully informed as soon as possible. Consent was then obtained or the patient was removed from the study and all study procedures were ended.

The study's sponsors — B. Braun, Novo Nordisk, and HemoCue — provided drugs and glucometers but had no role in the design of the study, the gathering or analysis of data, or the preparation of the manuscript. The sponsors also had no responsibility for the conduct of the trial, had no access to the data, and did not control the decision to publish the results. The authors accept full responsibility for the conduct of the trial, had complete and unrestricted access to the data, and vouch for the completeness and accuracy of the data.

INSULIN THERAPY

In the conventional-therapy group, a continuous insulin infusion (50 IU of Actrapid HM, Novo Nordisk) in 50 ml of 0.9% saline solution was delivered through a perfusion pump when the blood glucose level exceeded 200 mg per deciliter (11.1 mmol per liter); the insulin level was then adjusted to maintain a blood glucose level of

180 mg per deciliter (10.0 mmol per liter) to 200 mg per deciliter. In the intensive-therapy group, infusion of insulin was started when blood glucose levels exceeded 110 mg per deciliter; the insulin level was then adjusted to maintain euglycemia (80 to 110 mg per deciliter).

The insulin dose was adjusted to whole-blood glucose levels, which were measured at intervals of 1 to 4 hours with the use of either arterial or capillary blood samples and a glucometer (HemoCue). ICU nurses calculated insulin adjustments with the use of the Leuven titration guidelines.¹⁰

FLUID RESUSCITATION

Patients were not eligible to participate in the study if they had received more than 1000 ml of HES in the 24 hours before randomization. (For details on fluid composition and hemodynamic management, see the Supplementary Appendix.) Renal-replacement therapy was instituted, regardless of the study-group assignment, in the case of acute renal failure or in the presence of another indication, such as volume overload or hyperkalemia.¹¹

OUTCOME MEASURES AND SAFETY END POINTS

The coprimary end points were the rate of death from any cause at 28 days and morbidity, as measured during the intervention by the mean score on the Sequential Organ Failure Assessment (SOFA), on a scale ranging from 0 to 4 for each of six organ systems, with an aggregate score of 0 to 24 and higher scores indicating more severe organ dysfunction. Secondary end points were the rate of acute renal failure (defined as a doubling of the baseline serum creatinine level or the need for renal-replacement therapy), the time to hemodynamic stabilization, the frequency of vasopressor therapy, mean SOFA subscores, the need for red-cell transfusion, the duration of mechanical ventilation, the length of stay in the ICU, and mortality at 90 days. The occurrence of severe hypoglycemia (≤ 40 mg of glucose per deciliter [2.2 mmol per liter]) was defined as a safety end point. Serious adverse events were reported according to standard definitions.¹² One safety analysis was planned and performed before the first interim analysis.

STATISTICAL ANALYSIS

The study was designed to detect a reduction in mortality from 40% to 30% at 28 days. Such an

effect was expected to reduce the mean SOFA score by 1.2 points.¹³ To permit early termination of the study in case of futility or unexpectedly large effects, as well as modifications of the sample size and end points on the basis of interim results, we used a two-stage adaptive design with mortality and the mean SOFA score as coprimary end points.¹⁴ To detect a difference of 1.2 in the mean SOFA score with a power of 80%, we needed to enroll 600 patients in the first stage of the adaptive study design. Therefore, the first interim efficacy analysis was performed after inclusion of 600 patients. We used the chi-square test and the t-test to assess differences in mortality at 28 days and the mean SOFA score, respectively, in the intention-to-treat population. Details on the stopping strategy, as well as the analyses of secondary end points, are described in the Supplementary Appendix. Cox regression analysis with time-dependent covariates was used to identify risk factors for the time to death. All reported P values are two-sided. Statistical analyses were performed with the use of SAS software, version 9.13.

RESULTS

TRIAL SUSPENSION

After the first safety analysis, involving 488 patients,¹⁵ intensive insulin therapy was terminated early by the data and safety monitoring board, owing to an increased number of hypoglycemic events, as compared with conventional insulin therapy; hypoglycemia was reported in 30 of 247 patients in the intensive-therapy group (12.1%) and in 5 of 241 patients in the conventional-therapy group (2.1%, $P < 0.001$). The comparison between HES and Ringer's lactate was continued with all patients receiving conventional insulin therapy until the planned interim analysis involving 537 patients. The additional 49 patients, who underwent randomization after the first safety analysis, were not different with respect to baseline characteristics or the conduct of insulin treatment.

The planned interim analysis after the enrollment of 600 patients showed a significantly greater incidence of renal failure and a trend toward higher 90-day mortality among patients who received HES than among those who received Ringer's lactate. The study was suspended by the data and safety monitoring board, and the second stage of the adaptive design was aborted.

Enrollment and outcomes are shown in Figure 1 of the Supplementary Appendix.

ANALYSES OF INTERACTION

There were no significant interactions between the two study interventions with respect to the rate of death at 28 days (P=0.55) and the rate at 90 days (P=0.71). However, we found a sugges-

tion of an interaction for the mean SOFA score (P=0.07) and the development of acute renal failure (P=0.06). There was no interaction for the mean SOFA score if the renal subscore was excluded (P=0.11). Comparisons between single study groups suggested that the risk of acute renal failure in the intensive-therapy group was higher among patients who received HES than among

Table 1. Baseline Characteristics of the Patients.*

Variable	Insulin Therapy				Fluid Resuscitation		
	All Patients (N=537)	Conventional (N=290)	Intensive (N=247)	P Value†	Ringer's Lactate (N=275)	HES (N=262)	P Value‡
Age — yr	64.6±13.7	65.2±13.2	64.0±14.3	0.35	64.9±14.1	64.4±13.3	0.72
Male sex — no. (%)	322 (60.0)	171 (59.0)	151 (61.1)	0.61	164 (59.6)	158 (60.3)	0.87
Body-mass index§	27.3±5.5	27.5±5.3	26.9±5.8	0.22	27.2±5.5	27.3±5.6	0.74
APACHE II score¶	20.2±6.7	20.3±6.8	20.2±6.6	0.84	20.3±6.7	20.1±6.7	0.72
Preexisting condition — no. (%)							
Hypertension	249 (46.4)	144 (49.7)	105 (42.5)	0.10	134 (48.7)	115 (43.9)	0.26
Diabetes mellitus							
Either type	163 (30.4)	91 (31.4)	72 (29.1)	0.58	83 (30.2)	80 (30.5)	0.93
Type 1	73 (13.6)	41 (14.1)	32 (13.0)	0.69	37 (13.5)	36 (13.7)	0.92
Type 2	90 (16.8)	50 (17.2)	40 (16.2)	0.75	46 (16.7)	44 (16.8)	0.98
Heart failure	80 (14.9)	44 (15.2)	36 (14.6)	0.85	34 (12.4)	46 (17.6)	0.09
Renal dysfunction	44 (8.2)	23 (7.9)	21 (8.5)	0.81	30 (10.9)	14 (5.3)	0.02
COPD	82 (15.3)	44 (15.2)	38 (15.4)	0.95	46 (16.7)	36 (13.7)	0.34
Liver cirrhosis	12 (2.2)	7 (2.4)	5 (2.0)	0.76	6 (2.2)	6 (2.3)	0.93
Cancer							
Previous disease	49 (9.1)	27 (9.3)	22 (8.9)	0.87	26 (9.5)	23 (8.8)	0.79
Current disease	34 (6.3)	23 (7.9)	11 (4.5)	0.10	23 (8.4)	11 (4.2)	0.05
Immunosuppression	10 (1.9)	7 (2.4)	3 (1.2)	0.36	5 (1.8)	5 (1.9)	1.00
Site of infection — no. (%)							
Lung	221 (41.2)	123 (42.4)	98 (39.7)	0.58	124 (45.1)	97 (37.0)	0.04
Abdomen	207 (38.5)	112 (38.6)	95 (38.5)	0.93	103 (37.5)	104 (39.7)	0.64
Bone or soft tissue	61 (11.4)	34 (11.7)	27 (10.9)	0.79	29 (10.5)	32 (12.2)	0.55
Surgical wound	42 (7.8)	21 (7.2)	21 (8.5)	0.58	23 (8.4)	19 (7.3)	0.62
Urogenital	47 (8.8)	29 (10.0)	18 (7.3)	0.27	18 (6.5)	29 (11.1)	0.07
Primary bacteremia	22 (4.1)	10 (3.4)	12 (4.9)	0.41	11 (4.0)	11 (4.2)	0.92
Other	23 (4.3)	10 (3.4)	13 (5.3)	0.29	10 (3.6)	13 (5.0)	0.45
Recent surgical history — no. (%)				0.47			0.04
Elective surgery	86 (16.0)	49 (16.9)	37 (15.0)		50 (18.2)	36 (13.7)	
Emergency surgery	198 (36.9)	100 (34.5)	98 (39.7)		88 (32.0)	110 (42.0)	
No history of surgery	252 (46.9)	140 (48.3)	112 (45.3)		137 (49.8)	115 (43.9)	
Missing data	1 (0.2)	1 (0.3)	0		0	1 (0.4)	

Table 1. (Continued.)

Variable	Insulin Therapy			P Value†	Fluid Resuscitation		P Value‡
	All Patients (N=537)	Conventional (N=290)	Intensive (N=247)		Ringer's Lactate (N=275)	HES (N=262)	
Laboratory values							
Blood glucose — mg/dl				0.05			0.13
Median	134	138	130		136	133	
Interquartile range	110–178	111–184	108–167		112–184	106–168	
Glycated hemoglobin — %				0.04			0.58
Median	5.9	6.0	5.9		6.0	5.8	
Interquartile range	5.3–6.3	5.4–6.4	5.2–6.2		5.3–6.3	5.3–6.3	
Plasma C-reactive protein — mg/liter				0.99			0.97
Median	200	204	198		199	203	
Interquartile range	127–290	126–289	131–290		127–307	127–280	
Serum creatinine — mg/dl				0.45			0.68
Median	1.43	1.44	1.40		1.39	1.47	
Interquartile range	0.96–2.13	0.95–2.20	0.96–2.07		0.94–2.20	0.96–2.07	
Creatinine clearance — ml/min				0.72			0.77
Median	51.8	51.7	51.9		52.3	51.7	
Interquartile range	32.8–83.3	31.0–84.6	35.3–81.0		30.7–86.5	34.7–76.7	
Lactate — mmol/liter				0.14			0.93
Median	2.2	2.4	2.1		2.2	2.2	
Interquartile range	1.5–4.0	1.6–4.0	1.4–3.8		1.5–4.3	1.5–3.8	
Hemodynamic variables							
Heart rate — bpm				0.95			0.82
Median	104	104	104		104	103	
Interquartile range	90–118	90–118	90–118		90–117	90–118	
Central venous pressure — mm Hg				0.30			0.32
Median	12.0	12.0	12.0		12.0	12.0	
Interquartile range	8.0–15.0	8.0–15.0	8.0–15.0		8.0–14.5	8.0–15.0	
Mean arterial pressure — mm Hg				0.82			0.64
Median	75.0	75.0	77.0		75.0	75.5	
Interquartile range	68.0–85.0	68.0–84.0	67.0–85.0		68.0–85.0	67.0–85.0	
Central venous oxygen saturation — %				0.88			0.20
Median	75.0	75.0	75.0		74.0	75.0	
Interquartile range	68.0–80.0	68.0–80.0	68.0–81.0		68.0–79.0	69.0–81.0	

* Plus–minus values are means \pm SD. P values were calculated with the t-test or the Mann–Whitney test and the chi-square test or Fisher's exact test, as appropriate. To convert the values for glucose to millimoles per liter, multiply by 0.05551. To convert the values for creatinine to micromoles per liter, multiply by 88.4. COPD denotes chronic pulmonary obstructive disease, and HES hydroxyethyl starch (pentastarch).

† P values are for the comparison between conventional insulin therapy and intensive insulin therapy.

‡ P values are for the comparison between Ringer's lactate and HES.

§ The body-mass index is the weight in kilograms divided by the square of the height in meters.

¶ Missing subscores on the Acute Physiology and Chronic Health Evaluation (APACHE II) were counted as 0. This scale ranges from 0 to 71, with higher scores indicating a greater severity of illness.

|| Multiple responses per patient were possible.

those who received Ringer's lactate (odds ratio, 2.65; 95% confidence interval [CI], 1.51 to 4.68). However, the risk was also increased among patients in the HES group who received intensive insulin therapy, as compared with those who received conventional therapy (odds ratio, 1.69; 95% CI, 1.01 to 2.83).

INSULIN THERAPY

The characteristics of the patients and indicators of the severity of disease were well balanced between the intensive-therapy group and the conventional-therapy group (Table 1, and Table 1 of the Supplementary Appendix). The numbers of patients were also well balanced with respect to the receipt of concomitant medications relevant to hyperglycemia (Table 2 of the Supplementary Appendix).

Nutrition and Blood Glucose Control

Data regarding nutritional intake and blood glucose levels are shown in Figure 1 and in Table 4 of the Supplementary Appendix. In the intensive-therapy group, 243 of 247 patients (98.4%) received insulin on at least one study day for glucose values above the target range (>110 mg per deciliter), whereas only 215 of 290 patients (74.1%) in the conventional-therapy group needed insulin because glucose values were outside the target range (≥ 200 mg per deciliter) ($P < 0.001$). During the study period, mean morning blood glucose levels were lower in the intensive-therapy group (mean, 112 mg per deciliter [6.2 mmol per liter]; 95% CI, 110 to 114 [6.1 to 6.3]) than in the conventional-therapy group (mean, 151 mg per deciliter [8.4 mmol per liter]; 95% CI, 148 to 155 [8.2 to 8.6]; $P < 0.001$). The median insulin dose that was administered per patient per day was higher in the intensive-therapy group (32 IU; interquartile range, 20 to 50) than in the conventional-therapy group (5 IU; interquartile range, 0 to 22; $P < 0.001$).

Mortality

The rate of death did not differ significantly between the intensive-therapy group and the conventional-therapy group at 28 days (24.7% vs. 26.0%, $P = 0.74$) or at 90 days (39.7% vs. 35.4%, $P = 0.31$) (Table 2 and Fig. 2A). In a Cox regression analysis, intensive insulin therapy was not an independent risk factor for death (hazard ratio, 0.95; 95% CI, 0.70 to 1.28; $P = 0.72$). However, identi-

fied risk factors were the patient's score on the Acute Physiology and Chronic Health Evaluation (APACHE II, ranging from 0 to 71, with higher scores indicating a greater severity of illness) with the exclusion of the age subscore (hazard ratio, 1.07; 95% CI, 1.05 to 1.09; $P < 0.001$), an age of at least 60 years (hazard ratio, 2.45; 95% CI, 1.68 to 3.57; $P < 0.001$), and hypoglycemia (hazard ratio, 3.31; 95% CI, 2.23 to 4.90; $P < 0.001$).

In unplanned subgroup analyses that evaluated the APACHE II score before randomization, the reasons for ICU admission, the presence or absence of diabetes, and the presence or absence of empirical or appropriate antimicrobial therapy, there was no significant difference in survival between the intensive-therapy group and the conventional-therapy group. In addition, an analysis that excluded all patients who were discharged from the ICU before the 3rd, 5th, or 10th day did not show significant differences between the two study groups (Table 3A of the Supplementary Appendix).

Exploratory analyses that stratified data according to the mean morning blood glucose level (<110 mg per deciliter, 110 to 150 mg per deciliter, or >150 mg per deciliter) did not show significant differences in survival rates between the two study groups (Fig. 2 of the Supplementary Appendix).

Morbidity

There was no significant difference between the intensive-therapy group and the conventional-therapy group in mean SOFA scores (7.8 and 7.7 points, respectively; $P = 0.88$). Likewise, SOFA subscores were similar in both groups. There were also no significant differences between the two study groups in secondary end points, including the rate of acute renal failure, the need for renal-replacement therapy, the use of vasopressors, and the number of ventilator-free days. Patients in the intensive-therapy group tended to have longer stays in the ICU than did patients in the conventional-therapy group (Table 2).

Safety End Points

At least one episode of severe hypoglycemia occurred in 42 patients in the intensive-therapy group (17.0%) and in 12 patients in the conventional-therapy group (4.1%, $P < 0.001$). Significantly more serious hypoglycemic episodes were reported in the intensive-therapy group (in 19 patients)

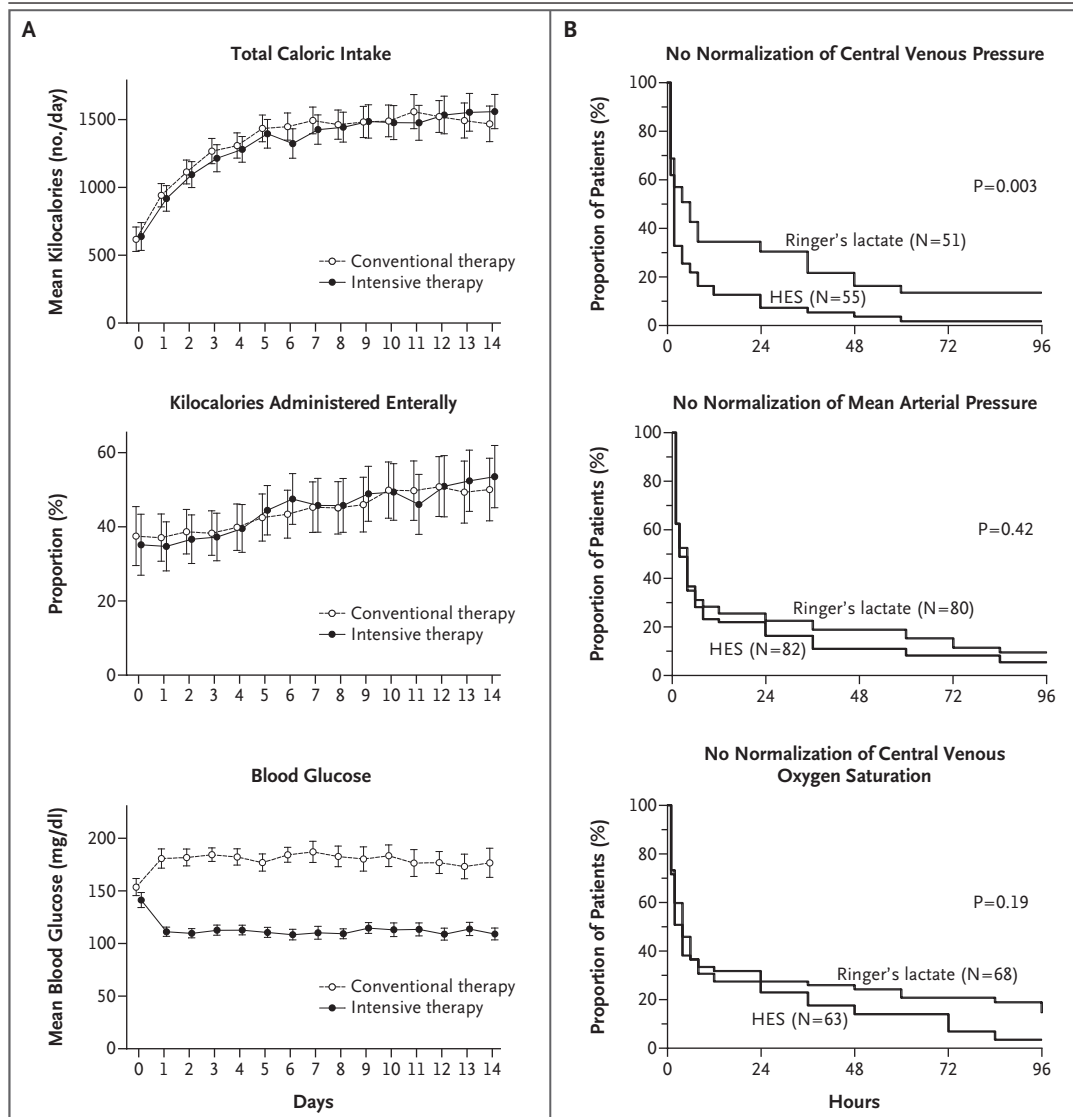


Figure 1. Nutrition, Blood Glucose, Systemic Pressures, and Central Venous Oxygen Saturation, According to the Type of Insulin and Fluid Therapy.

Panel A shows caloric intake and daily morning blood glucose levels in all 537 patients during the first 14 days of the study, according to whether patients received intensive insulin therapy or conventional insulin therapy. Day 0 represents the time at randomization until the start of the next full 24-hour study day; I bars denote 95% confidence intervals. The mean daily caloric intake (both parenteral and enteral) and the fraction of kilocalories administered by the enteral route, respectively, were calculated only for days on which nutrition was given. The type of nutrition was similar in the two study groups. The mean morning blood glucose level in both study groups was calculated only for patients receiving insulin therapy on the respective study day ($P < 0.001$). Panel B shows the results of volume resuscitation in patients receiving either 10% pentastarch, a low-molecular-weight hydroxyethyl starch (HES), or Ringer's lactate, with P values calculated by the log-rank test. Indicated are the proportions of patients who did not have normalization of hemodynamic values for central venous pressure, mean arterial pressure, and central venous oxygen saturation.

than in the conventional-therapy group (7 patients), a difference of 7.7% versus 2.4% ($P = 0.005$). Although no serious adverse event was found to result directly in death, the hypoglycemic episodes were more often classified as life-threaten-

ing in the intensive-therapy group than in the conventional-therapy group (in 13 vs. 6 patients; 5.3% vs. 2.1%; $P = 0.05$) and as requiring prolonged hospitalization (6 patients vs. 1 patient; 2.4% vs. 0.3%; $P = 0.05$) (Table 3).

FLUID RESUSCITATION

Before randomization, the characteristics of patients were well balanced between the group that received HES and the group that received Ringer's lactate (Table 1, and Table 1 of the Supplementary Appendix). Patients in the two study groups received similar fluids in the 12 hours before randomization (Table 5 of the Supplementary Appendix).

Patients in the Ringer's lactate group received significantly more total resuscitation fluid than

did patients in the HES group. The ratio of total fluid in the Ringer's lactate group to that in the HES group was 1.32 for the entire study period (1.58 on day 1 and 1.44 on days 1 to 4). Patients in the HES group received a median cumulative dose of 70.4 ml per kilogram of body weight (interquartile range, 33.4 to 144.2). The median central venous pressure was 11.8 mm Hg (interquartile range, 9.5 to 14.2) in the HES group and 10.7 mm Hg (interquartile range, 8.6 to 12.7) in the Ringer's lactate group ($P<0.001$); the median

Table 2. Primary and Secondary Outcomes.*

Variable	Insulin Therapy			P Value†	Fluid Resuscitation		P Value‡
	All Patients (N=537)	Conventional (N=290)	Intensive (N=247)		Ringer's Lactate (N=275)	HES (N=262)	
Death							
At 28 days§				0.74			0.48
No./total no.	136/536	75/289	61/247		66/274	70/262	
Percent (95% CI)	25.4 (21.7–29.1)	26.0 (20.9–31.0)	24.7 (19.3–30.1)		24.1 (19.0–29.2)	26.7 (21.4–32.1)	
At 90 days				0.31			0.09
No./total no.	200/535	102/288	98/247		93/274	107/261	
Percent (95% CI)	37.4 (33.3–41.5)	35.4 (29.9–40.9)	39.7 (33.6–45.8)		33.9 (28.3–39.6)	41.0 (35.0–47.0)	
SOFA score¶							
Mean	7.8	7.7	7.8	0.88	7.5	8.0	0.16
95% CI	7.4–8.1	7.3–8.2	7.3–8.3		7.1–8.0	7.5–8.5	
SOFA subscores							
Cardiovascular				0.96			0.51
Median	1.78	1.75	1.82		1.76	1.80	
Interquartile range	1.00–2.67	1.00–2.67	1.00–2.74		1.00–2.71	0.86–2.67	
Respiratory				0.24			0.58
Median	2.53	2.57	2.50		2.57	2.50	
Interquartile range	2.00–2.89	2.17–2.92	2.00–2.86		2.00–2.89	2.00–2.90	
Coagulation				0.90			<0.001
Median	0.21	0.21	0.21		0.11	0.46	
Interquartile range	0–1.00	0–1.00	0–1.08		0–0.83	0–1.30	
Renal				0.90			0.02
Median	0.50	0.50	0.53		0.42	0.67	
Interquartile range	0–1.60	0–1.60	0–1.59		0–1.33	0–1.94	
Hepatic				0.74			1.00
Median	0.10	0.08	0.11		0.11	0.09	
Interquartile range	0–0.87	0–0.88	0–0.85		0–0.90	0–0.85	
Central nervous system				0.82			0.50
Median	1.00	1.00	1.00		1.00	1.00	
Interquartile range	0.08–2.10	0–2.00	0.10–2.33		0.05–2.00	0.09–2.43	

Table 2. (Continued.)							
Variable	Insulin Therapy			P Value†	Fluid Resuscitation		
	All Patients (N=537)	Conventional (N=290)	Intensive (N=247)		Ringer's Lactate (N=275)	HES (N=262)	P Value‡
Hypoglycemia (≤ 40 mg/dl)				<0.001			0.85
No. of patients/total no.	54/537	12/290	42/247		27/275	27/262	
Percent (95% CI)	10.1 (7.5–12.6)	4.1 (1.9–6.4)	17.0 (12.3–21.7)		9.8 (6.3–13.3)	10.3 (6.6–14.0)	
Acute renal failure				0.25			0.002
No. of patients/total no.	153/533	77/289	76/244		62/272	91/261	
Percent (95% CI)	28.7 (24.9–32.6)	26.6 (21.6–31.7)	31.1 (25.3–37.0)		22.8 (17.8–27.8)	34.9 (29.1–40.7)	
Renal-replacement therapy				0.19			0.001
No. of patients/total no.	132/533	65/289	67/244		51/272	81/261	
Percent (95% CI)	24.8 (21.1–28.4)	22.5 (17.7–27.3)	27.5 (21.9–33.1)		18.8 (14.1–23.4)	31.0 (25.4–36.7)	
Red-cell transfusion				0.02			0.06
No. of patients/total no.	388/537	197/290	191/247		189/275	199/262	
Percent (95% CI)	72.3 (68.5–76.0)	67.9 (62.6–73.3)	77.3 (72.1–82.6)		68.7 (63.3–74.2)	76.0 (70.8–81.1)	
No. of red-cell transfusion units				0.95			<0.001
Median	5	5	5		4	6	
Interquartile range	2–10	3–10	2–10		2–8	4–12	
Length of stay in ICU (days)				0.06			0.32
Median	14	14	16		14	16	
Interquartile range	8–28	7–25	8–30		7–28	8–28	
Vasopressor-free (days)				0.24			0.52
Median	17	18	16		17	17	
Interquartile range	7–20	8–20	6–20		8–20	6–20	
Ventilator-free (days)				0.83			0.06
Median	3	3	3		3	2	
Interquartile range	1–6	1–6	1–7		1–7	1–6	

* P values were calculated with the t-test or the Mann–Whitney test and the chi-square test or Fisher's exact test, as appropriate. HES denotes hydroxyethyl starch (pentastarch), and SOFA Sequential Organ Failure Assessment.

† P values are for the comparison between conventional insulin therapy and intensive insulin therapy.

‡ P values are for the comparison between Ringer's lactate and HES.

§ This category is a coprimary outcome of the study. All other categories are secondary outcomes.

¶ Subscores on SOFA range from 0 to 4 for each of six organ systems, with an aggregate score of 0 to 24 and with higher scores indicating more severe organ dysfunction.

|| This category applies to days during the study period.

central venous oxygen saturation was 73.6% (interquartile range, 70.0 to 76.9) in the HES group and 72.4% (interquartile range, 69.3 to 75.9) in the Ringer's lactate group ($P=0.04$). The use of nonstudy colloid fluids is discussed in the Supplementary Appendix.

Among patients who entered the study with values for central venous pressure that were below the hemodynamic target values (≥ 8 mm Hg),

the target values were achieved faster in patients receiving HES than in those receiving Ringer's lactate ($P=0.003$) (Fig. 1B).

Mortality

The rate of death at 28 days did not differ significantly between the HES group and the Ringer's lactate group (26.7% and 24.1%, respectively; $P=0.48$). However, there was a trend toward a

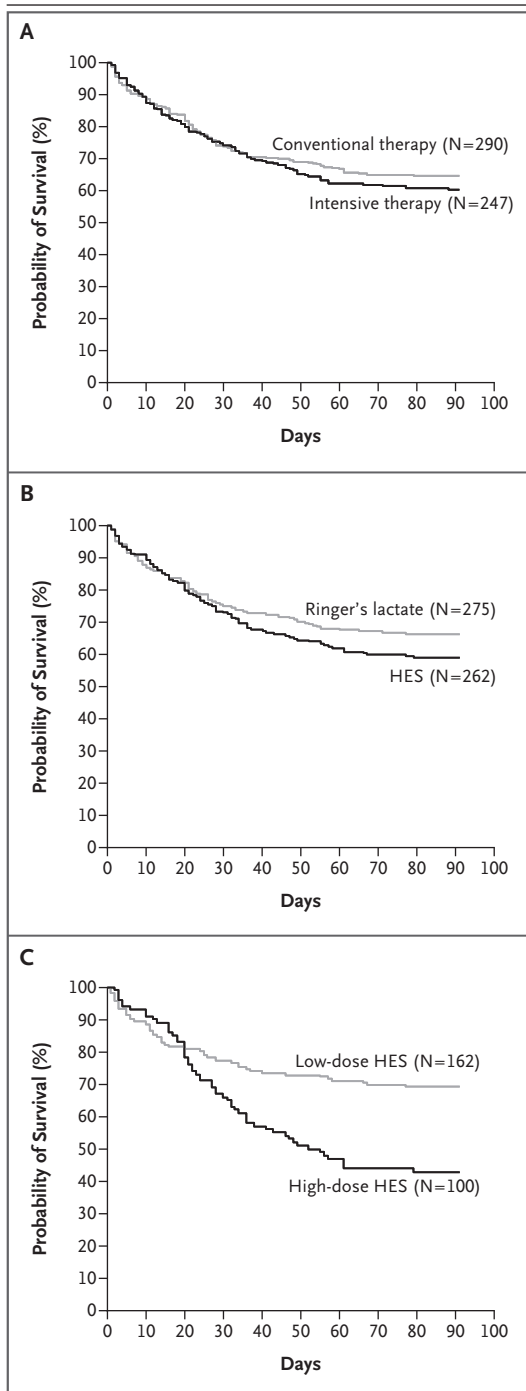


Figure 2. Kaplan–Meier Curves for Overall Survival.

Panel A shows the comparison of overall survival between patients receiving intensive insulin therapy and those receiving conventional insulin therapy ($P=0.36$ by the log-rank test). Panel B shows the comparison between patients receiving pentastarch (HES) for volume resuscitation and those receiving Ringer's lactate ($P=0.14$ by the log-rank test). Panel C shows the comparison between patients in the low-dose HES subgroup (≤ 22 ml per kilogram of body weight per day), who received a median cumulative dose of 48.3 ml per kilogram (interquartile range, 21.9 to 96.2), and those in the high-dose subgroup (>22 ml per kilogram for at least 1 day during the study period), who received a median cumulative dose of 136.0 ml per kilogram (interquartile range, 79.0 to 180.0) ($P<0.001$ by the log-rank test).

tate group (8.0 and 7.5 points, respectively; $P=0.16$) (Table 2). However, the HES group had a significantly higher rate of acute renal failure (34.9% vs. 22.8%, $P=0.002$) and more days on which renal-replacement therapy was required (650 of 3554 vs. 321 of 3471 total days; 18.3% vs. 9.2%). Patients in the HES group had a lower median platelet count (179,600 per cubic millimeter; interquartile range, 122,000 to 260,000) than did those in the Ringer's lactate group (224,000 per cubic millimeter; interquartile range, 149,800 to 314,800; $P<0.001$) and received more units of packed red cells than did patients in the Ringer's lactate group (Table 2).

SUBGROUP AND MULTIVARIATE ANALYSES

In post hoc univariate analysis, there was a direct correlation between the cumulative dose of HES and both the need for renal-replacement therapy and the rate of death at 90 days; there was no corresponding correlation with the cumulative dose of Ringer's lactate (Fig. 3). The dose limit for HES (20 ml per kilogram per day) was exceeded by more than 10% on at least 1 day in 100 of 262 patients in the HES group. In 74 of these 100 patients, the dose escalation occurred within the first 24 hours. Before randomization, the median APACHE II scores and ages of these patients were similar to those of patients who did not receive a dose escalation; however, patients who received a dose escalation had lower initial values for central venous pressure (median, 11.0 mm Hg; interquartile range, 6.0 to 15.0) than did patients who did not receive a dose escalation (median, 12.0 mm Hg; interquartile range, 9.0 to 15.0; $P=0.03$). They also received more crystalloid

rate of death at 90 days that was higher in the HES group than in the Ringer's lactate group (41.0% vs. 33.9%, $P=0.09$) (Table 2 and Fig. 2B).

Morbidity

The mean SOFA scores did not differ significantly between the HES group and the Ringer's lac-

Table 3. Adverse and Serious Adverse Events.*

Variable	Insulin Therapy			Fluid Resuscitation			
	All Patients (N=537)	Conventional (N=290)	Intensive (N=247)	P Value†	Ringer's Lactate (N=275)	HES (N=262)	P Value‡
Adverse event							
Patients with at least one adverse event				<0.001			0.81
No. of patients	80	25	55		40	40	
Percent (95% CI)	14.9 (11.9–17.9)	8.6 (5.4–11.9)	22.3 (17.1–27.5)		14.5 (10.4–18.7)	15.3 (10.9–19.6)	
Hypoglycemia (≤ 40 mg/dl)							
No. of patients	54	12	42	<0.001	27	27	0.85
Percent (95% CI)	10.1 (7.5–12.6)	4.1 (1.9–6.4)	17.0 (12.3–21.7)		9.8 (6.3–13.3)	10.3 (6.6–14.0)	
Bleeding							
No. of patients	23	10	13	0.30	10	13	0.45
Percent (95% CI)	4.3 (2.6–6.0)	3.4 (1.4–5.6)	5.3 (2.5–8.1)		3.6 (1.4–5.9)	5.0 (2.3–7.6)	
Other§							
No. of patients	10	5	5	1.0	8	2	0.11
Percent (95% CI)	1.9 (0.7–3.0)	1.7 (0.2–3.2)	2.0 (0.3–3.8)		2.9 (0.9–4.9)	0.8 (0–1.8)	
Serious adverse event							
Patients with at least one serious adverse event				0.01			0.63
No. of patients	42	15	27		20	22	
Percent (95% CI)	7.8 (5.6–10.1)	5.2 (2.6–7.7)	10.9 (7.0–14.8)		7.3 (4.2–10.3)	8.4 (5.0–11.8)	
Hypoglycemia (≤ 40 mg/dl)¶							
Any							
No. of patients	26	7	19	0.005	13	13	0.90
Percent (95% CI)	4.8 (3.0–6.7)	2.4 (0.7–4.2)	7.7 (4.4–11.0)		4.7 (2.2–7.2)	5.0 (2.3–7.6)	
Life-threatening							
No. of patients	19	6	13	0.05	10	9	0.90
Percent (95% CI)	3.5 (2.0–5.1)	2.1 (0.4–3.7)	5.3 (2.5–8.1)		3.6 (1.4–5.9)	3.4 (1.2–5.6)	
Resulting in prolonged hospitalization							
No. of patients	7	1	6	0.05	3	4	0.72
Percent (95% CI)	1.3 (0.3–2.3)	0.3 (0–1.0)	2.4 (0.5–4.4)		1.1 (0–2.3)	1.5 (0–3.0)	
Bleeding							
No. of patients	13	7	6	0.99	4	9	0.14
Percent (95% CI)	2.4 (1.1–3.7)	2.4 (0.7–4.2)	2.4 (0.5–4.4)		1.5 (0–2.9)	3.4 (1.2–5.6)	
Other§							
No. of patients	5	1	4	0.19	4	1	0.37
Percent (95% CI)	0.9 (0.1–1.7)	0.3 (0–1.0)	1.6 (0–3.2)		1.5 (0–2.9)	0.4 (0–1.1)	

* P values were calculated with the chi-square test or Fisher's exact test, as appropriate. Definitions of all adverse events are listed in the Supplementary Appendix.

† P values are for the comparison between conventional insulin therapy and intensive insulin therapy.

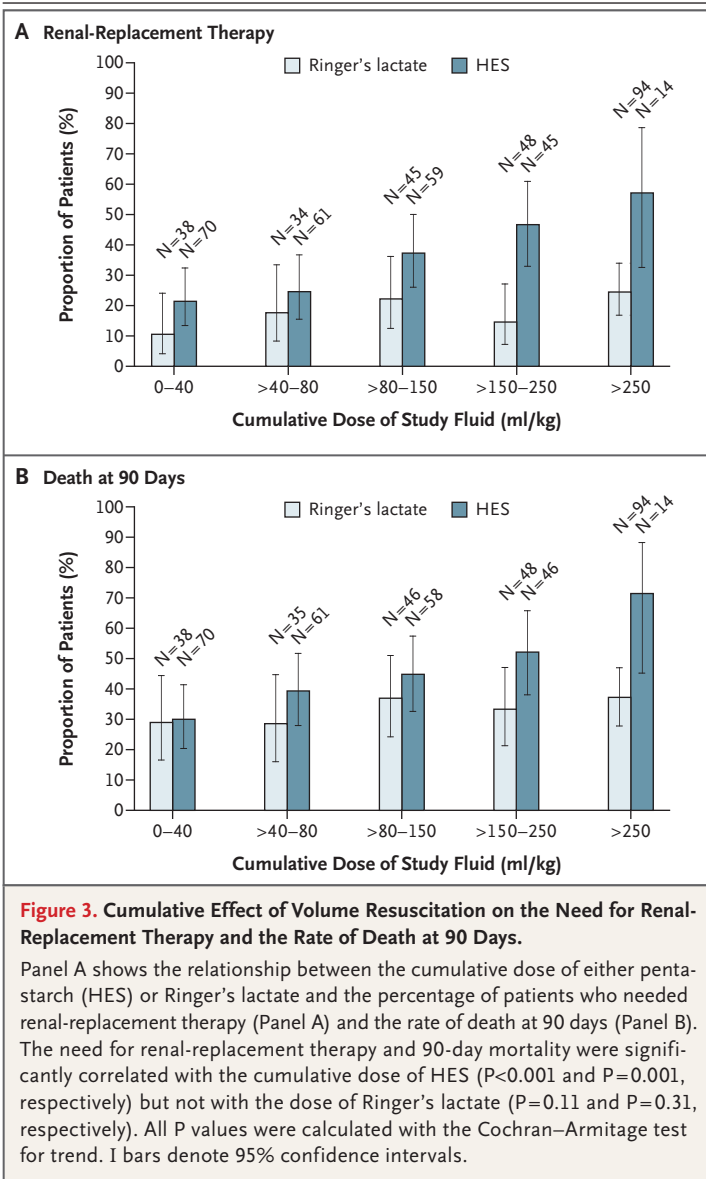
‡ P values are for the comparison between Ringer's lactate and HES.

§ Other conditions included acute worsening of oxygenation, ventricular fibrillation, cardiac arrest, hyperosmolarity, hyperkalemia, and hypernatremia.

¶ Severe hypoglycemia did not result directly in death or in persistent or substantial disability or incapacity in any patient.

in the 12 hours preceding study entry (median, 2400 ml; interquartile range, 1000 to 3500) than did those who did not receive a dose escalation (median, 1135 ml; interquartile range, 500 to 2560; $P=0.002$). The rate of death at 90 days was

significantly increased among patients who received a higher dose of HES, as compared with those who received a lower dose (57.6% vs. 30.9%, $P<0.001$) (Fig. 2C). Detailed analyses of antimicrobial therapy showed no imbalances that could



easily explain these study results (Table 3B and Table 7 of the Supplementary Appendix).

In a multivariate post hoc logistic-regression model that was adjusted for insulin therapy, the total dose of Ringer's lactate, baseline creatinine clearance, mean arterial pressure, and total dose of colloids administered 12 hours before the start of therapy, the total dose of HES was a significant independent predictor of both the need for renal-replacement therapy and the rate of death at 90 days (Table 6 of the Supplementary Appendix). At 90 days, patients who had received a lower dose of HES were more likely to have renal failure than those who had received Ringer's lac-

tate (30.9% vs. 21.7%, $P = 0.04$) and were more likely to need renal-replacement therapy (25.9% vs. 17.3%, $P = 0.03$).

DISCUSSION

In 537 patients with septic shock, we found no beneficial effect of intensive insulin treatment (administered according to the Leuven protocol) with respect to the rate of death at 28 days and the mean SOFA score; we also found no benefit with respect to any of the secondary end points. Moreover, our study was stopped early, at the first planned safety analysis, because intensive insulin therapy was associated with a significantly increased rate of severe hypoglycemic events and a trend toward a prolonged stay in the ICU.

Cox regression analysis identified the occurrence of hypoglycemia as an independent risk factor for death from any cause. Hypoglycemia may be only a marker of a poor outcome, independently of insulin therapy. On the other hand, it is possible that unrecognized adverse effects of hypoglycemia on the brain or heart offset potential beneficial effects of intensive insulin therapy.¹⁶ The full extent of hypoglycemic events in our study is unknown, since the usual clinical warning signs and symptoms of hypoglycemia in the patients we studied may have been masked by critical illness and sedation.

Our findings are similar to those of the second study by Van den Berghe et al.,² which assessed the use of intensive insulin therapy in maintaining euglycemia in critically ill patients in a medical ICU. In our study, the nonsignificant differences in the rates of death at 28 days and at 90 days in the intensive-therapy group and the conventional-therapy group were similar to those in the study by Van den Berghe et al., as was the magnitude of the significant increase in hypoglycemic episodes in the intensive-therapy group, as compared with the conventional-therapy group (18.7% vs. 3.1% in the study by Van den Berghe et al. and 17.0% vs. 4.1% in our study). The mean blood glucose levels during hypoglycemia in the intensive-therapy group and the conventional-therapy group were also similar in the study by Van den Berghe et al. (32 mg and 31 mg per deciliter, respectively; $P = 0.50$) and in our study (31 mg and 28 mg per deciliter, respectively; $P = 0.30$). Moreover, in the study by Van den Berghe et al., mean morning blood glucose

levels in the intensive-therapy group and in the conventional-therapy group (111 ± 29 mg and 153 ± 31 mg per deciliter, respectively) were similar to the levels in our study (112 ± 18 mg and 151 ± 33 mg per deciliter, respectively). In their second study of medical ICU patients, Van den Berghe et al. performed exploratory subgroup analyses regarding the length of the ICU stay and the resolution of organ injury. The beneficial effects that were shown in these subgroup analyses were not confirmed in our study.

Taken together, our study and the medical ICU study by Van den Berghe et al. establish that intensive insulin therapy has no measurable, consistent benefit in critically ill patients in a medical ICU, regardless of whether the patients have severe sepsis, and that such therapy increases the risk of hypoglycemic episodes. The results of these two studies are in marked contrast to the results of the first study by Van den Berghe et al.,¹ which showed a beneficial effect of intensive insulin therapy on postoperative survival rates among critically ill surgical patients. In that study, the beneficial effect was predominantly seen in cardiac surgical patients (accounting for 62% of the study population) who were given intravenous glucose loads (200 to 300 g per 24 hours) on admission to the ICU. It is possible that intensive insulin therapy was beneficial in these patients because it decreased the adverse effect of this high glucose load.

In sedated, severely ill patients with sepsis, the benefits of intensive insulin therapy (administered according to the Leuven protocol) are unproven, but the risk of hypoglycemia is increased by a factor of 5 to 6. We cannot exclude the possibility that patients with sepsis may benefit from other less strict insulin protocols,¹⁷ given that variability in the glucose level was a stronger independent predictor of death in the ICU than was the mean glucose concentration.¹⁸

After the first planned interim analysis, our trial was suspended because of increased rates of renal failure and death at 90 days in the group receiving HES. Adverse effects of HES on renal function have been reported in patients who have undergone renal transplantation and in critically ill patients.^{19,20} Schortgen et al.²¹ reported adverse renal effects associated with a starch solution that had a higher degree of molar substitution (0.6) than that used in our study (0.5). Other

studies did not detect adverse effects except for impaired coagulation, even with large doses of starch solutions; however, these studies were limited by their design, small size, and short observation periods.²²⁻²⁷ Even though we used a "modern" HES solution²⁸ that was designed to have fewer side effects, we found an even higher incidence of acute renal failure than that reported by Schortgen et al. Our study showed that HES was associated with an increased need for renal-replacement therapy in patients with sepsis, even when it was administered at recommended daily doses, and that higher cumulative doses were associated with an increased rate of death at 90 days. Our results should not be used to address the effect of rapid volume expansion on the outcome in patients with sepsis, nor should our findings be extrapolated to other volume expanders.

The differences between the hemodynamic effects of HES and those of Ringer's lactate were minor (e.g., a more rapid return to normal central venous pressure in the HES group). However, we observed marked adverse effects of HES therapy on kidney function, coagulation, transfusion requirements, and survival. The ability of HES to interfere with coagulation has already prompted warning labels and dose limitations.^{29,30} Furthermore, long-term storage of the colloid is potentially toxic and may be responsible (beyond the adverse effects on renal function) for the observed increase in the rate of death at 90 days, particularly with higher doses.^{21,31-36}

Fluid resuscitation with 10% HES 200/0.5 is harmful in patients with severe sepsis. At recommended doses, it causes renal impairment, and at high doses, it impairs long-term survival. Since adverse effects have been attributed to various HES solutions,³⁷ until long-term studies with adequate numbers of patients show that a particular HES solution is safe in critically ill patients, HES solutions should be avoided.

Supported by a grant (01 KI 0106) from the German Federal Ministry of Education and Research and by unrestricted grants from B. Braun, HemoCue, and Novo Nordisk.

Dr. Bloos reports receiving lecture fees from B. Braun, and Dr. Reinhart reports receiving lecture and consulting fees from B. Braun. No other potential conflict of interest relevant to this article was reported.

We thank the members of the data and safety monitoring board: Charles L. Sprung, M.D., Hadassah Hebrew University Medical Center, Jerusalem; Waheedullah Karzai, M.D., Zentral-klinik Bad Berka, Bad Berka, Germany; and Herbert Witte, Ph.D., Institute of Medical Statistics, Informatics and Documentation, University of Jena, Germany.

APPENDIX

The authors' affiliations are as follows: the Department of Anesthesiology and Intensive Care Medicine (F.M.B., F.B., C.H., K.R.) and the Institute of Clinical Chemistry and Laboratory Medicine (M.K.), Friedrich Schiller University, Jena; the Institute of Medical Informatics, Statistics and Epidemiology (C.E., M.L.) and the Coordination Center for Clinical Trials (E.K.), University of Leipzig, Leipzig; the Department of Anesthesiology and Intensive Care Medicine, Helios Klinikum, Erfurt (A.M.-H.); the Department of Anesthesiology and Intensive Care Medicine, University Hospital of the Technical University of Dresden, Dresden (M.R.); the Department of Anesthesiology and Intensive Care Medicine, University Hospital Schleswig-Holstein, Campus Kiel, Kiel (N.W.); the Department of Anesthesiology and Intensive Care Medicine, University of Goettingen, Goettingen (O.M.); the Department of Anesthesiology and Medical Intensive Care, Charite, Campus Virchow-Klinikum, University Medical Center, Berlin (M.O.); the Department of Anesthesiology and Intensive Care Medicine, Martin Luther University, Halle-Wittenberg (S.G.); the Department of Anesthesiology and Intensive Care Medicine, University Hospital, Leipzig (D.O.); the Department of Anesthesiology and Critical Care Medicine, Klinikum Augsburg, Augsburg (U.J.); the Department of Nephrology and Hypertension, University of Erlangen-Nuremberg, Erlangen (S.J.); the Department of Anesthesiology and Intensive Care Medicine, University Hospital Aachen, Rheinisch-Westfaelische Technische Hochschule, Aachen (R.R.); the Department of Pulmonary and Critical Care Medicine, University Otto von Guericke, Magdeburg, and the Department of Pulmonary and Critical Care Medicine, Medizinische Hochschule Hannover, Hannover (T.W.); the Department of Anesthesiology and Intensive Care Medicine, Staetisches Klinikum Brandenburg, Brandenburg (M.S.); and the Department of Anesthesiology and Intensive Care Medicine, Staetisches Krankenhaus Dresden-Friedrichstadt, Dresden (P.K.) — all in Germany; and the Critical Care Medicine Department, National Institutes of Health, Bethesda, MD (C.N.).

REFERENCES

1. Van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in critically ill patients. *N Engl J Med* 2001; 345:1359-67.
2. Van den Berghe G, Wilmer A, Hermans G, et al. Intensive insulin therapy in the medical ICU. *N Engl J Med* 2006;354:449-61.
3. Dellinger RP, Carlet JM, Masur H, et al. Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock. *Crit Care Med* 2004;32:858-73. [Errata, *Crit Care Med* 2004;32:1448, 2169-70.]
4. Roberts I, Alderson P, Bunn F, Chinnock P, Ker K, Schierhout G. Colloids versus crystalloids for fluid resuscitation in critically ill patients. *Cochrane Database Syst Rev* 2004;4:CD000567.
5. Hoffmann JN, Vollmar B, Laschke MW, Inthorn D, Schildberg FW, Menger MD. Hydroxyethyl starch (130 kD), but not crystalloid volume support, improves microcirculation during normotensive endotoxemia. *Anesthesiology* 2002;97:460-70.
6. Morisaki H, Bloos F, Keys J, Martin C, Neal A, Sibbald WJ. Compared with crystalloid, colloid therapy slows progression of extrapulmonary tissue injury in septic sheep. *J Appl Physiol* 1994;77:1507-18.
7. Barron ME, Wilkes MM, Navickis RJ. A systematic review of the comparative safety of colloids. *Arch Surg* 2004;139:552-63.
8. Wilkes MM, Navickis RJ, Sibbald WJ. Albumin versus hydroxyethyl starch in cardiopulmonary bypass surgery: a meta-analysis of postoperative bleeding. *Ann Thorac Surg* 2001;72:527-33.
9. American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference: definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Crit Care Med* 1992;20:864-74.
10. Van den Berghe G, Wouters PJ, Bouillon R, et al. Outcome benefit of intensive insulin therapy in the critically ill: insulin dose versus glycemic control. *Crit Care Med* 2003;31:359-66.
11. Thadhani R, Pascual M, Bonventre JV. Acute renal failure. *N Engl J Med* 1996;334:1448-60.
12. What is a serious adverse event? Rockville, MD: MedWatch, FDA Safety Information and Adverse Event Reporting Program, 2004. (Accessed December 14, 2007, at <http://www.fda.gov/medwatch/report/DESK/advevnt.htm>.)
13. Moreno R, Vincent JL, Matos R, et al. The use of maximum SOFA score to quantify organ dysfunction/failure in intensive care: results of a prospective, multicentre study. *Intensive Care Med* 1999;25:686-96.
14. Bauer P, Köhne K. Evaluation of experiments with adaptive interim analyses. *Biometrics* 1994;50:1029-41.
15. Brunkhorst FM, Kuhnt E, Engel C, et al. Intensive insulin therapy in patients with severe sepsis and septic shock is associated with an increased rate of hypoglycemia: results from a randomized multicenter study (VISEP). *Infection* 2005;33:Suppl 1:19.
16. Cryer PE. Diverse causes of hypoglycemia-associated autonomic failure in diabetes. *N Engl J Med* 2004;350:2272-9.
17. Wilson M, Weinreb J, Hoo GW. Intensive insulin therapy in critical care: a review of 12 protocols. *Diabetes Care* 2007; 30:1005-11.
18. Egi M, Bellomo R, Stachowski E, French CJ, Hart G. Variability of blood glucose concentration and short-term mortality in critically ill patients. *Anesthesiology* 2006;105:244-52.
19. Winkelmayr WC, Glynn RJ, Levin R, Avorn J. Hydroxyethyl starch and change in renal function in patients undergoing coronary artery bypass graft surgery. *Kidney Int* 2003;64:1046-9.
20. Citanova ML, Leblanc I, Legendre C, Mouquet C, Riou B, Coriat P. Effect of hydroxyethylstarch in brain-dead kidney donors on renal function in kidney-transplant recipients. *Lancet* 1996;348:1620-2.
21. Schortgen F, Lacherade JC, Bruneel F, et al. Effects of hydroxyethylstarch and gelatin on renal function in severe sepsis: a multicentre randomised study. *Lancet* 2001;357:911-6.
22. Wiesen P, Canivet JL, Ledoux D, Roediger L, Damas P. Effect of hydroxyethylstarch on renal function in cardiac surgery: a large scale retrospective study. *Acta Anaesthesiol Belg* 2005;56:257-63.
23. Liet JM, Bellouin AS, Boscher C, Lejus C, Rozé JC. Plasma volume expansion by medium molecular weight hydroxyethyl starch in neonates: a pilot study. *Pediatr Crit Care Med* 2003;4:305-7.
24. Beyer R, Harmening U, Rittmeyer O, et al. Use of modified fluid gelatin and hydroxyethyl starch for colloidal volume replacement in major orthopaedic surgery. *Br J Anaesth* 1997;78:44-50.
25. Vogt N, Bothner U, Brinkmann A, de Petriconi R, Georgieff M. Peri-operative tolerance to large-dose 6% HES 200/0.5 in major urological procedures compared with 5% human albumin. *Anaesthesia* 1999;54:121-7.
26. Arellano R, Gan BS, Salpeter MJ, et al. A triple-blinded randomized trial comparing the hemostatic effects of large-dose 10% hydroxyethyl starch 264/0.45 versus 5% albumin during major reconstructive surgery. *Anesth Analg* 2005;100:1846-53.
27. Sakr Y, Payen D, Reinhart K, et al. Effects of hydroxyethyl starch administration on renal function in critically ill patients. *Br J Anaesth* 2007;98:216-24.
28. Perazella MA. Drug-induced renal failure: update on new medications and unique mechanisms of nephrotoxicity. *Am J Med Sci* 2003;325:349-62.
29. Haynes GR, Havidich JE, Payne KJ. Why the Food and Drug Administration changed the warning label for hetastarch. *Anesthesiology* 2004;101:560-1.
30. Jonville-Béra AP, Autret-Leca E, Gruel Y. Acquired type I von Willebrand's disease associated with highly substituted hydroxyethyl starch. *N Engl J Med* 2001; 345:622-3.
31. Legendre C, Therivet E, Page B, Percheron A, Noël LH, Kreis H. Hydroxyethylstarch and osmotic-nephrosis-like lesions

- in kidney transplantation. *Lancet* 1993; 342:248-9.
32. Pillebout E, Nochy D, Hill G, et al. Renal histopathological lesions after orthotopic liver transplantation (OLT). *Am J Transplant* 2005;5:1120-9.
33. van Rijen EA, Ward JJ, Little RA. Effects of colloidal resuscitation fluids on reticuloendothelial function and resistance to infection after hemorrhage. *Clin Diagn Lab Immunol* 1998;5:543-9.
34. Christidis C, Mal F, Ramos J, et al. Worsening of hepatic dysfunction as a consequence of repeated hydroxyethylstarch infusions. *J Hepatol* 2001;35:726-32.
35. Auwerda JJ, Wilson JH, Sonneveld P. Foamy macrophage syndrome due to hydroxyethyl starch replacement: a severe side effect in plasmapheresis. *Ann Intern Med* 2002;137:1013-4.
36. Schmidt-Hieber M, Loddenkemper C, Schwartz S, Arntz G, Thiel E, Notter M. Hydrops lysosomal generalisatus — an underestimated side effect of hydroxyethyl starch therapy? *Eur J Haematol* 2006; 77:83-5.
37. Wiedermann CJ. Hydroxyethyl starch — can the safety problems be ignored? *Wien Klin Wochenschr* 2004;116:583-94.

Copyright © 2008 Massachusetts Medical Society.

Pro-Con Debate
Checklists - Can They Transform Critical Care?

Pro: Todd Dorman, M.D., FCCM
Con: Avery Tung, M.D.

Todd Dorman, M.D., FCCM
Johns Hopkins University Medical Center
Baltimore, Maryland

Avery Tung, M.D.
University of Chicago
Chicago, Illinois

NOTES