Critical Care Review

Paul Wischmeyer M.D.

Associate Professor of Anesthesiology

University of Colorado Health Sciences Center

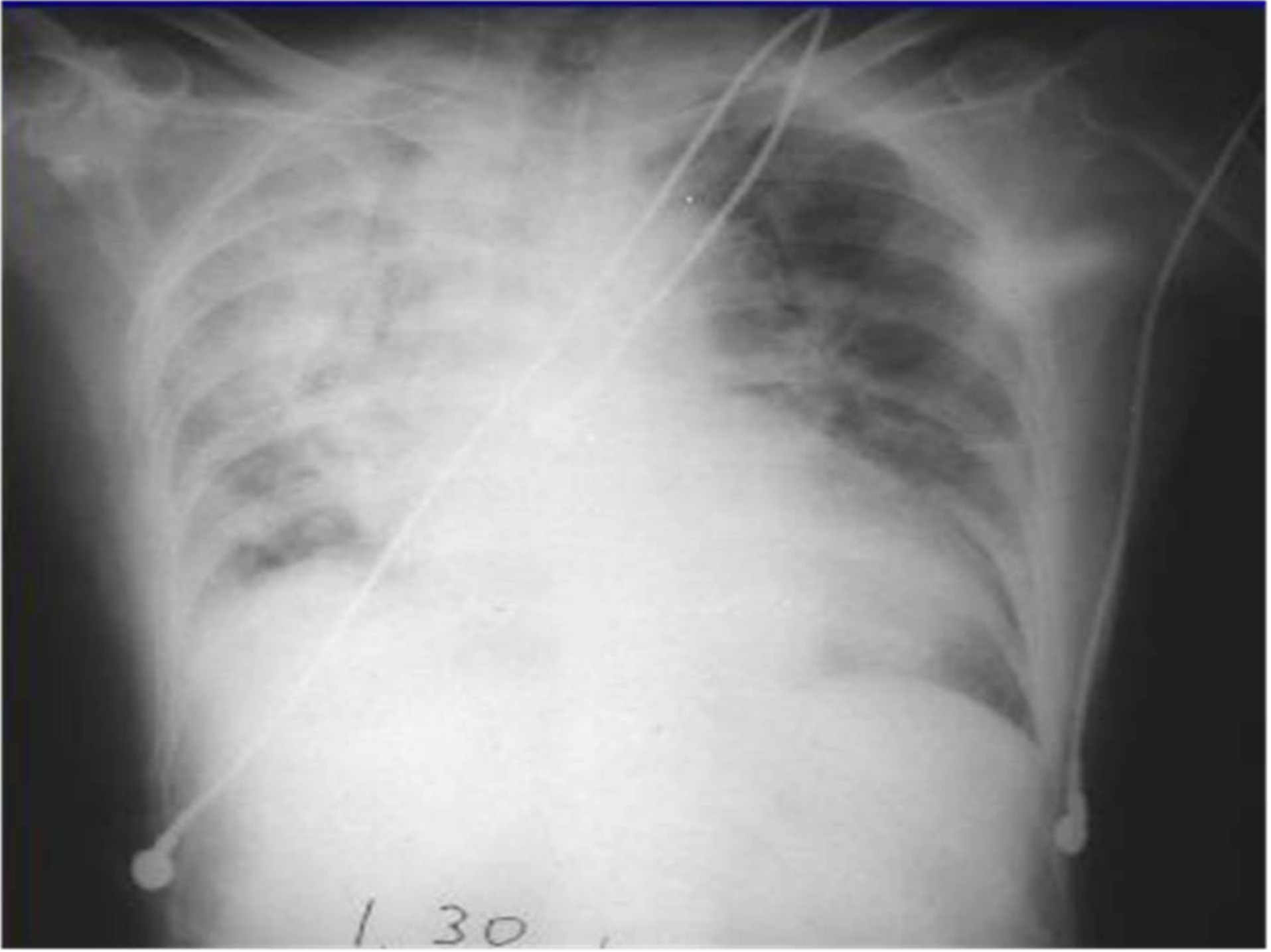
Case Study

☹ **It’s now 3 pm and you get the dreaded call there is an emergency case for an exploratory lap that needs to go now !**


ON
CISATRACURIUM

Case Study

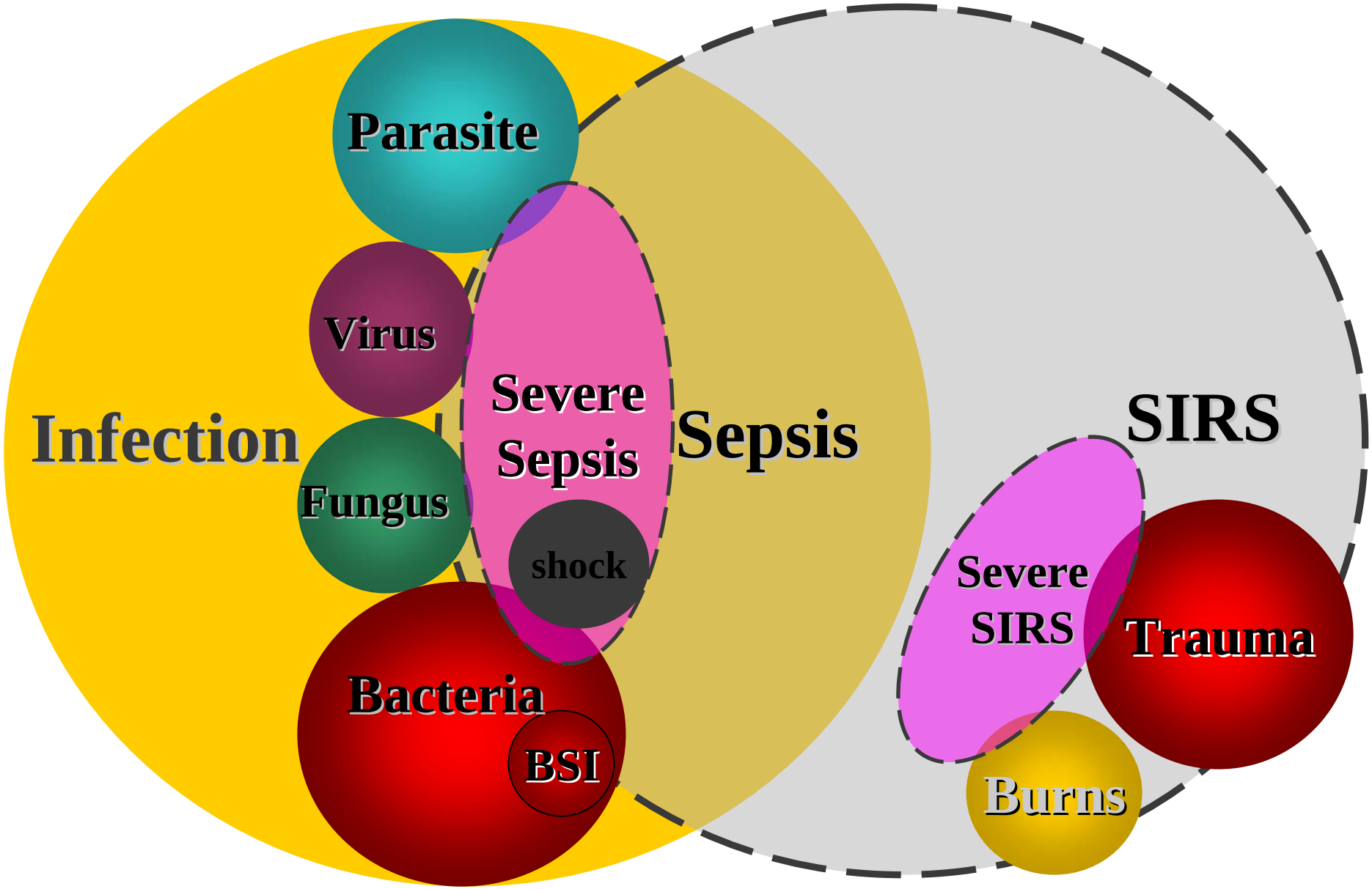
- 58 y.o. male with firm, distended abdomen and severe metabolic acidosis (lactate- 5.0) coming to OR for exploratory laparotomy
- Vent Settings: Pressure Control - 34 Peep- 12 R- 24, FiO2= 100%, PiP- 46
- ABG: 7.20 / pCO_2 - 50 / pO_2 - 65
- CXR- reveals 3 quadrant infiltrates
- HR 110, BP 75/40, C.I. - 4.0 SVR- 458
- Drips: vasopressin and insulin
- U/O - 5 cc last hour


1.30

What can we do to save this patient today… that perhaps we could not have a few years ago ??

But first… is he “critically ill” ?

What makes for a “critically ill” patient ?



Adapted from SCCM/ACCP Consensus Guidelines

The Sepsis Continuum

SIRS due to infection

≥2 of the following:

- **T >38ºC or <36ºC**
- **HR >90**
- **RR >20**
- **WBC >12,000 or <4,000 or >10% bands**

Organ Dysfunction:

- **Shock/hypotension**
- **Acute lung injury**
- **Renal**
- **Hepatic**
- **Hematologic**
- **CNS**
- **Metabolic acidosis**

Bone RC, et al. *Chest* 1992;101:1644-55.

DEFINITIONS

- **MOFS: multiple organ failure syndrome**
  - **Progressive, persistent, hyperdynamic, hypermetabolic state associated with gradual deterioration of multiple organs, lungs usually being the first**
- **MODS: multiple organ dysfunction syndrome**
  - **Organs rarely fail abruptly**

PATHOPHYSIOLOGY

- **The (abnormal?) host response to insult**
- **<u>Prolonged shock state</u>**
  - **Can be from any form of shock (hypovolemic, cardiogenic, distributive/vasodilatory, or obstructive)**
  - **Cellular level: mitochondrial dysfunction and "cytopathic hypoxia"**
  - **Mitochondria "leak" free radicals, and activate nuclear factor kappa B (NF-κB), a transcription factor for many pro-inflammatory mediators**
  - **Mediators may stimulate cytokines (TNF, interleukins), complement system, coagulation and fibrinolytic system, and cellular system (macrophages, neutrophils, endothelial cells, and platelets)**

PATHOPHYSIOLOGY

- **"2nd hit" phenomenon**
  - **The initial insult "primes" inflammatory system, and a second insult amplifies the response**
- **"Gut" hypothesis**
  - **GI tract is the "undrained abscess" causing MODS. The gut leaks bacteria/products**
  - **Possibly via lymphatics (ALI/ARDS)**
  - **GI tract is largest immune organ (GALT)**

CLINICAL MANIFESTATIONS of MOFS

- Patients appear to stabilize after resuscitation to a “hypermetabolic” state
- Lungs usually the first (ALI/ARDS) to injure
- Sequence of other organs influenced by co-morbidities
- Renal dysfunction usually follows second
- Liver failure late
- Usually die from hypotension unresponsive to pressors

TREATMENT

- **THERE IS NO KNOWN TREATMENT!!!!**

PREVENTION

- Best defined by literature that shows improved outcomes or survival in patients typically at risk for MODS
- Prospective, randomized, placebo controlled trials (PRCT's)
- Grade A or B recommendations
  - A: 2 separate Level I trials
  - B: only 1 Level I trial

Once we have a critically ill patient… What does the latest literature say…

1) Does Not Work

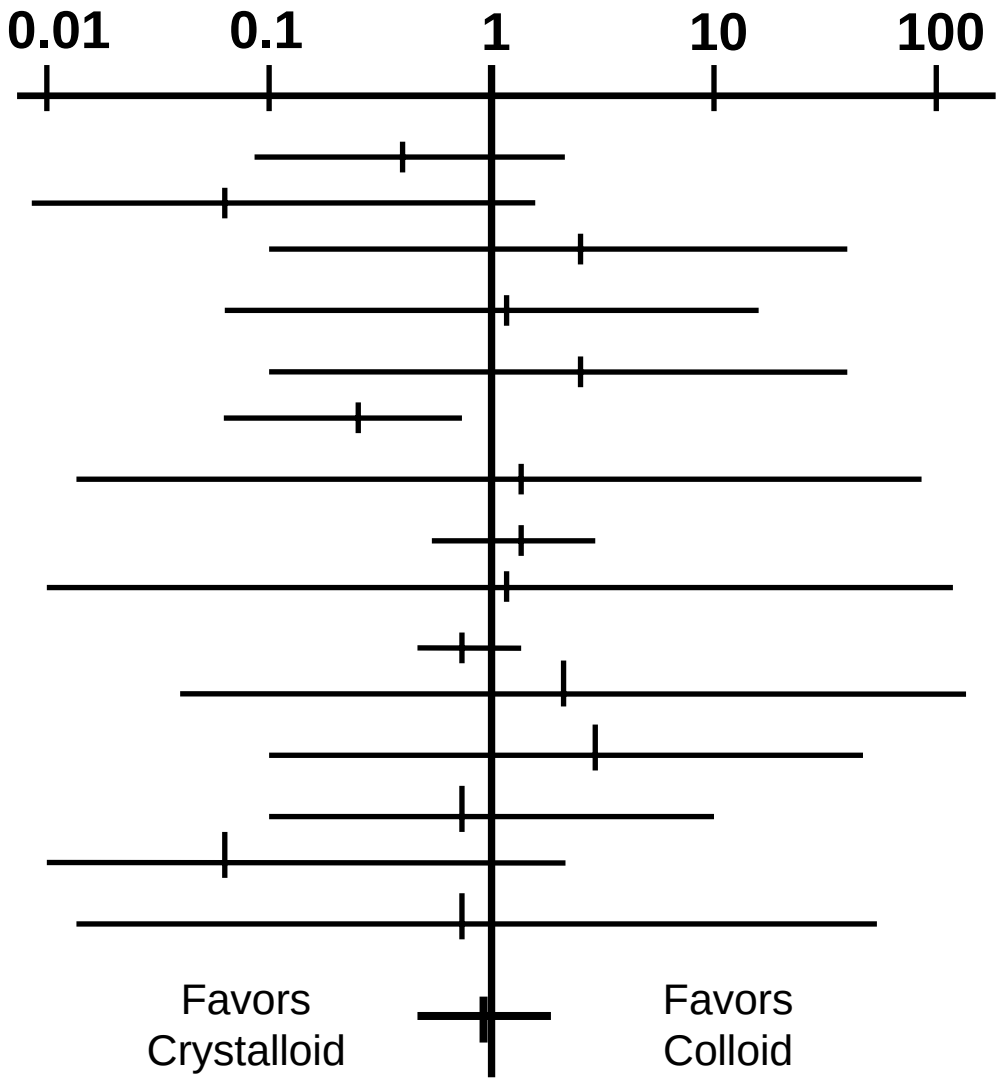
2) May Work

3) Does Work

What Doesn’t Work

Colloid vs Crystalloid Controversy

Lowe	1977	0.68
Lucas	1978	0.07
Butros	1979	2.22
Virgillo	1979	1.07
Moss	1981	2.43
Goodwin	1983	0.27
Modic	1983	1.08
Rackow	1983	1.23
Shires	1983	1.0
Metildi	1984	0.82
Sade	1985	1.83
Karanko	1987	2.37
Davidson	1991	1.0
London	1992	0.22
Pocka	1994	0.90
Overall		0.97



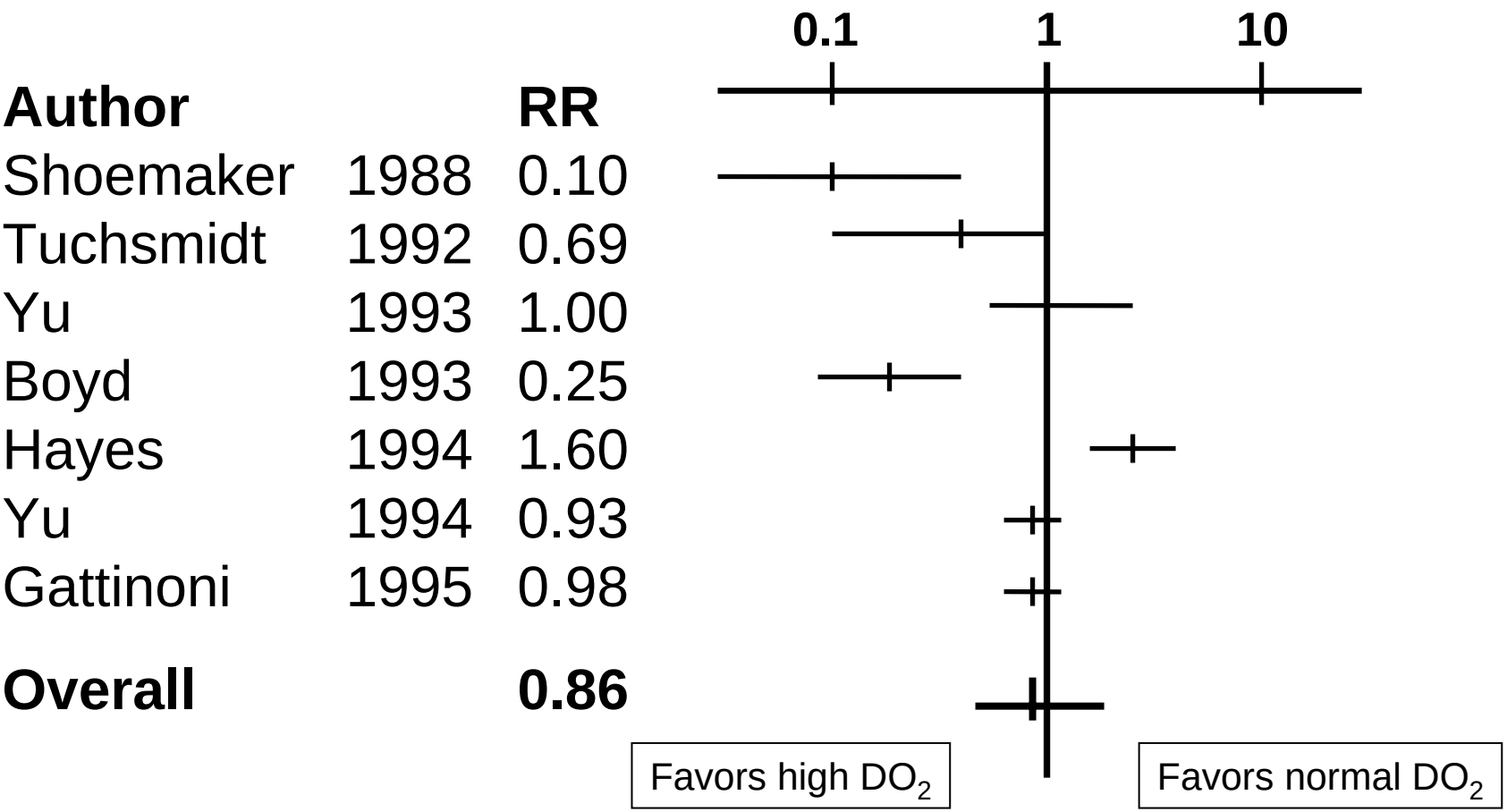
Choi PTL, et al. *Critical Care Med* 1999;27:200-10.
Schierhout G, et al. *BMJ* 1998;316:961-4.

Dopamine for Renal Dysfunction

- RCT, 328 patients
- Included: 2 SIRS criteria *plus* oliguria *or* creatinine >1.7 *or* 24-hour rise in creatinine >0.9
- Dosing: Dopamine 2 μg/kg/min via CVC
- No differences found in
  - Peak creatinine, fraction with creatinine >3.4
  - Percent requiring renal replacement therapy
  - Time to recover renal function
  - Furosemide dose, ICU LOS, hospital LOS
  - Time on ventilator, survival

Bellomo R, et al. *Lancet* 2000;356:2139-43.

Supranormal Oxygen Delivery



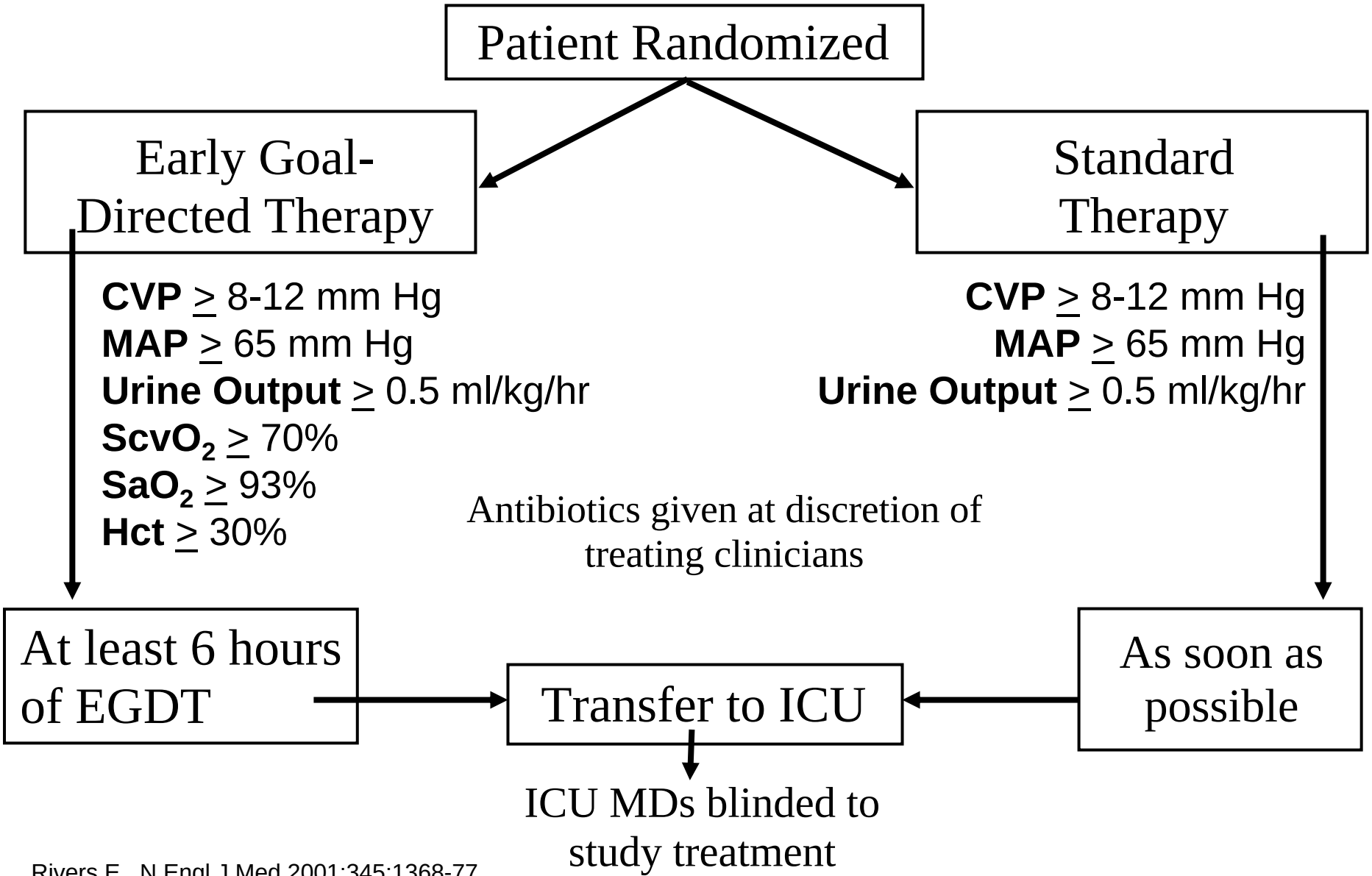
What Might Work

Early Goal-directed Therapy for Septic Shock

- **RCT , n = 263**
- **Septic shock unresp to 20 ml/kg crystalloid *or* lactate > 4**
- **Rx (all patients receive CVP and SvO2 monitor**
  - **Traditional: CVP 8-12, Vasopressor for SBP < 90 mm Hg, keep UOP > 0.5 ml/kg/hr**
  - **Investigation: As above + *RBCs for hct < 30 AND SvO2 < 70, if fails add dobutamine to dose 20 ug/kg/min***

Rivers et al NEJM 345:1368 2001

Early Goal-Directed Therapy



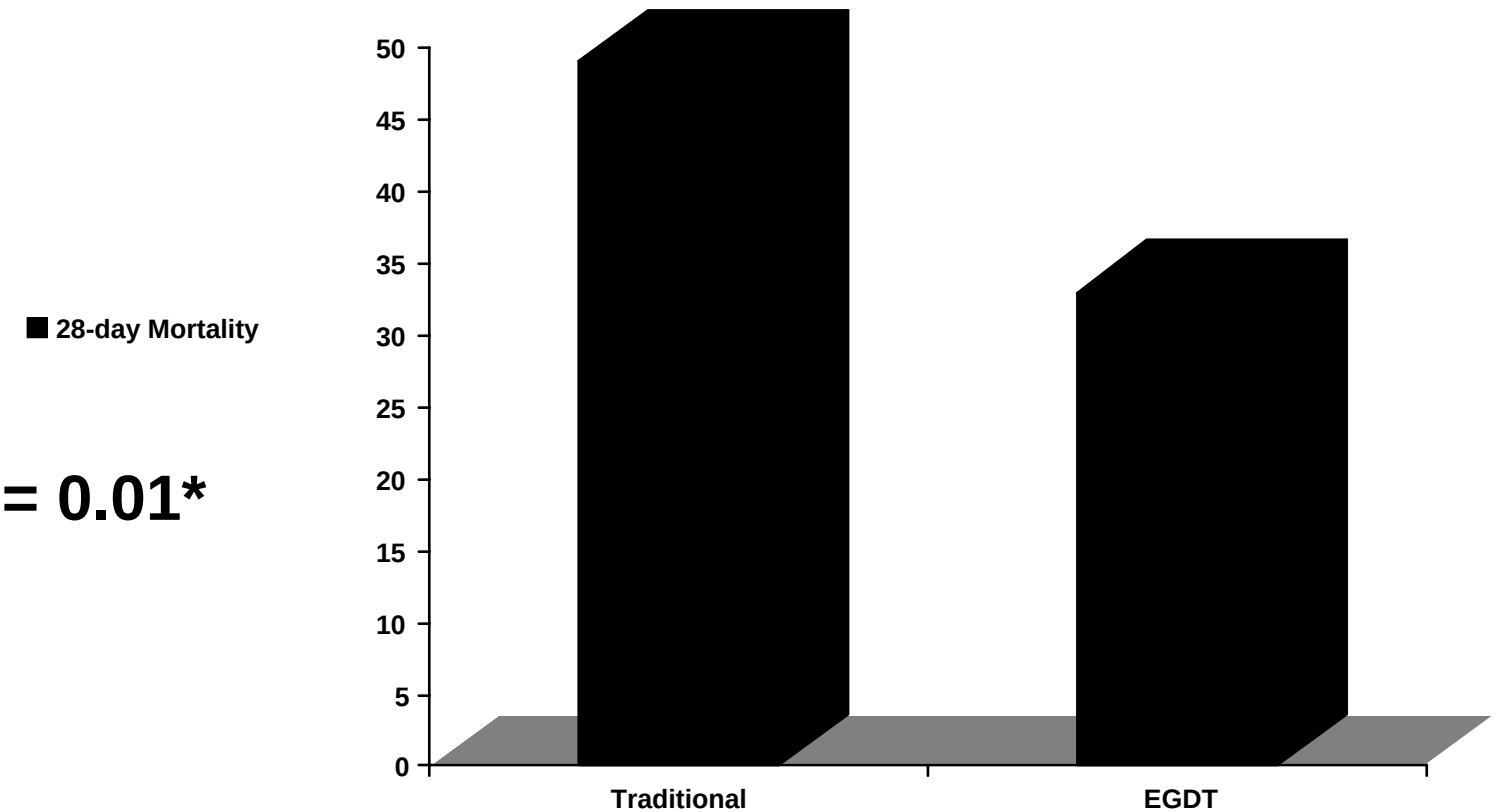
Rivers E. N Engl J Med 2001;345:1368-77.

EGDT in Septic Shock: Treatments actually received (0-6 hrs)

	Traditional	EGDT
• Fluids (mL)	3500	5000
• RBCs (%patients)	19	64
• Vasopressor (%pts)	30	27
• Dobutamine (%pts)	1	14

Rivers et al NEJM 345:1368 2001

EGDT - Outcome



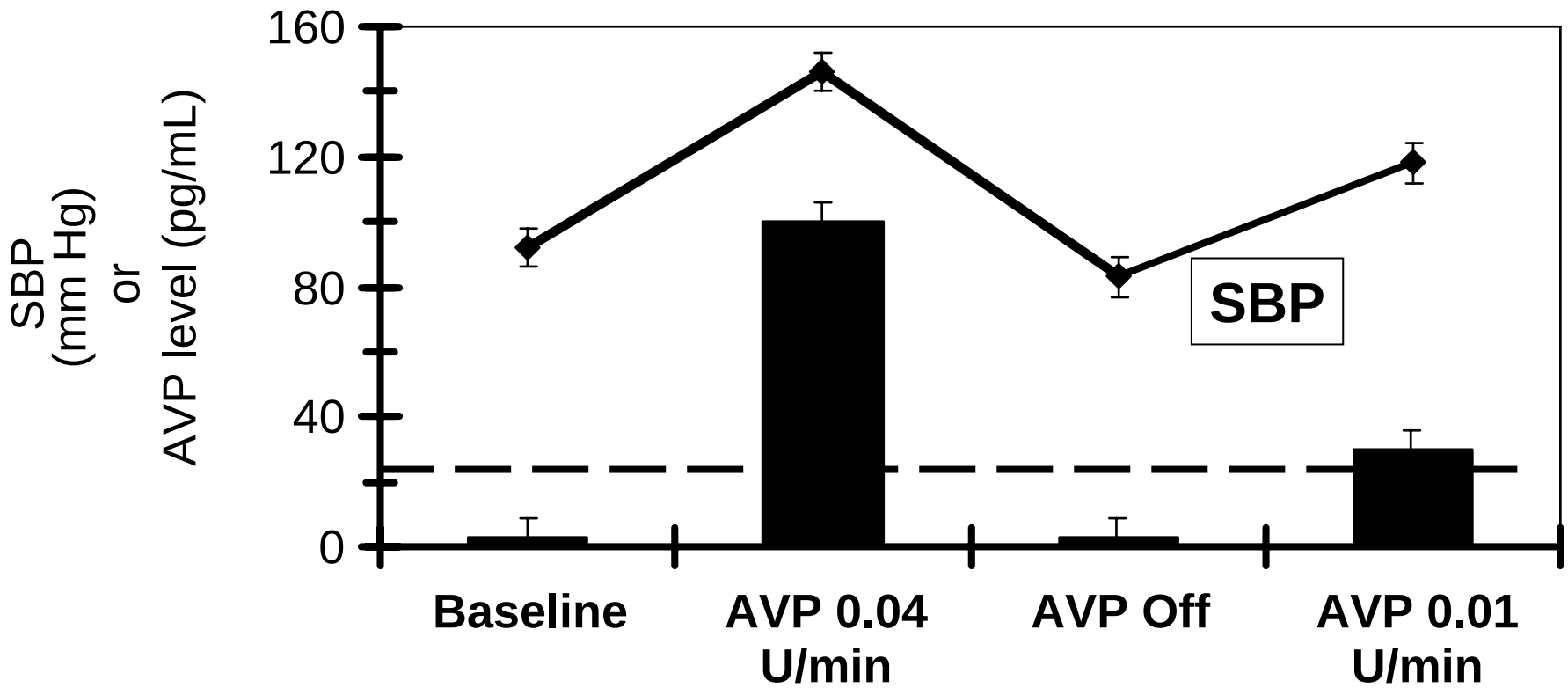
P = 0.01*

*Key difference was in sudden cv collapse not MSOF

Rivers et al NEJM 345:1368 2001


Vasopressin…Why Vasopressin ??


BP and Vasopressin Levels After AVP for Septic Shock



Landry DW, et al. *Circulation* 1997;95:1122-5.
Landry DW, et al. *Crit Care Med* 1997;25:1279-82.

Vasopressin Summary

- No large, randomized controlled trials
- Raises MAP by increasing SVR in vasodilatory shock
- If effective, acts rapidly and at low doses
- Probably synergistic with catecholamines
- At this time, no data suggest improved outcomes

Intensive Insulin Therapy in Critically Ill Patients

The New England Journal of Medicine

VOLUME 345 NOVEMBER 8, 2001 NUMBER 19

INTENSIVE INSULIN THERAPY IN CRITICALLY ILL PATIENTS

GREET VAN DEN BERGHE, M.D., PH.D., PIETER WOUTERS, M.SC., FRANK WEEKERS, M.D., CHARLES VERWAEST, M.D., FRANS BRUYNINCKX, M.D., MIET SCHETZ, M.D., PH.D., DIRK VLASSELAERS, M.D., PATRICK FERDINANDE, M.D., PH.D., PETER LAUWERS, M.D., AND ROGER BOUILLON, M.D., PH.D.

Van den Berghe G, et al. N Eng J Med 2001;345:1359-1367

Intensive Glucose Control in the Critically ILL

- RCT, n = 1548
- Mechanically ventilated SICU patients
- Treatments
  - Titrate blood glucose 80-110
    - VS
  - Titrate blood glucose 180-200
- All patients received 200-300 gms glucose/d on day - 1 (?$D_{10}W$)
- TPN w/in 24 h of adm (60-80% as glucose cals)

Berghe et al NEJM 345:1359 2001

Intensive Glucose Control
Treatments received

	Conventional	Intensive
• Patients on insulin	39%	99%
• Insulin (median u/d)	33	71
• Duration (%ICU days)	67	100
• AM glucose (all pts)	153	103
• AM glucose (insulin pts)	173	103

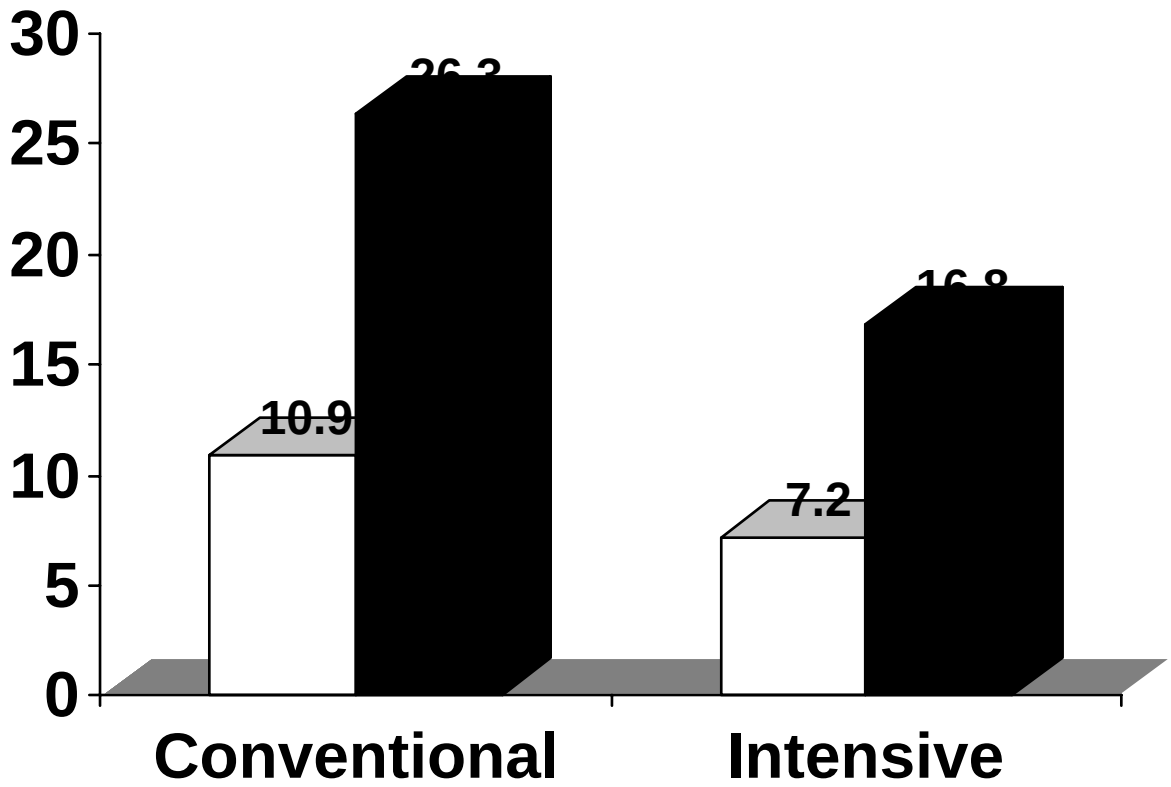
Van Den Berghe et al NEJM 345:1359 2001

Intensive Glucose Control Outcome

In-hospital mortality

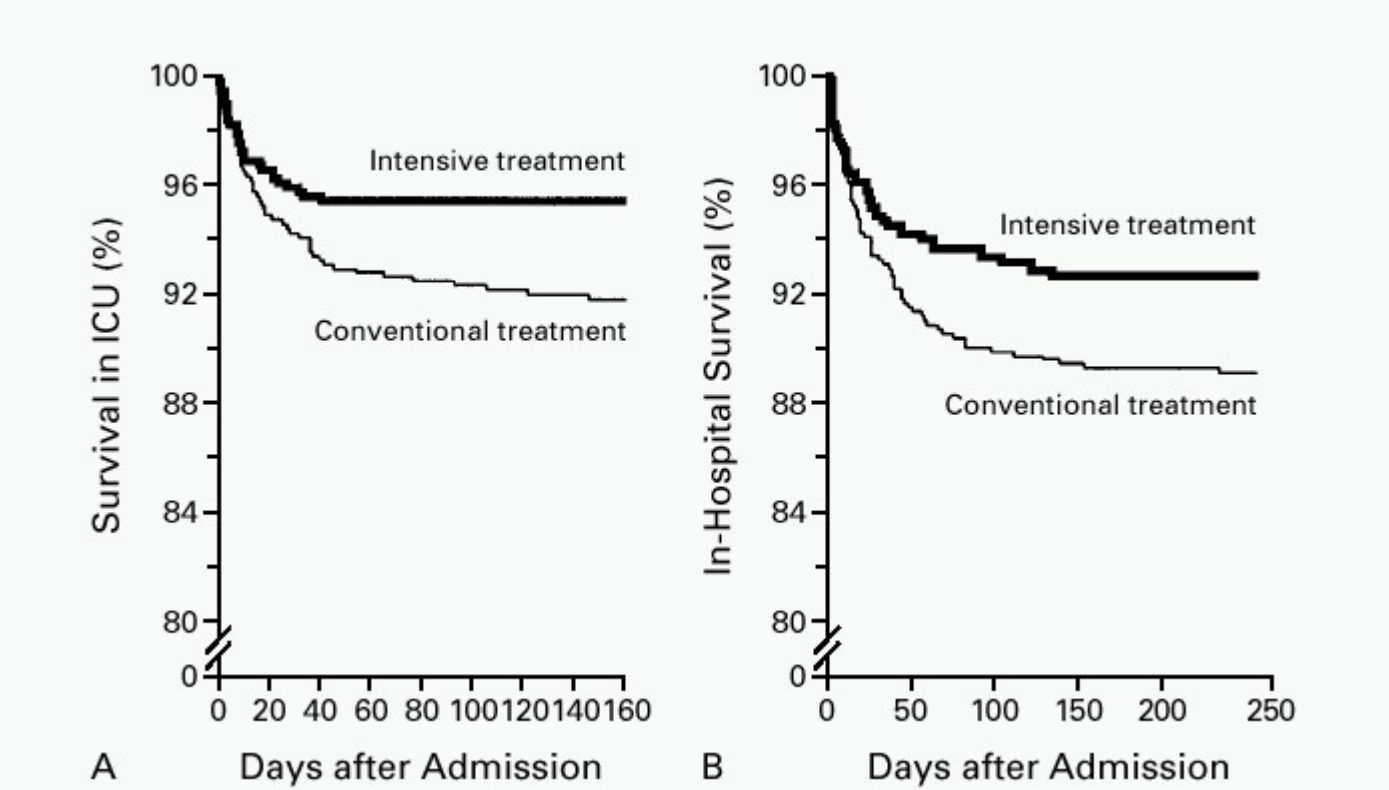
□ **All patients n = 1548**
■ **ICU > 5d n =451**

P = .01
both comparisions



Berghe et al NEJM 345:1359 2001

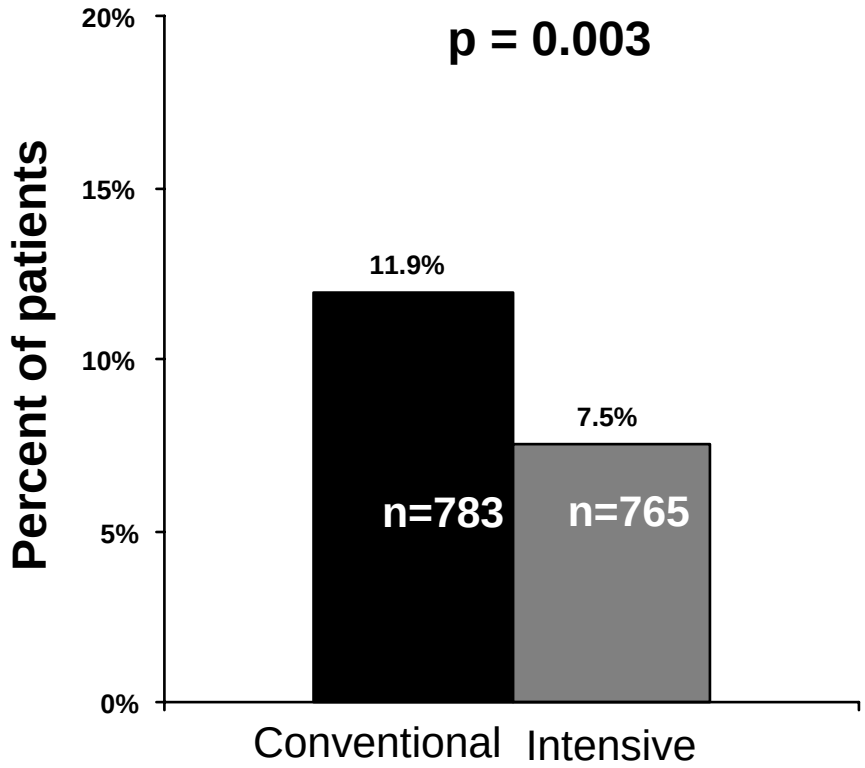
Intensive Insulin Therapy in Critically Ill Patients: Kaplan-Meier Curves



Van den Berghe G, et al. N Eng J Med 2001;345:1363

Intensive Insulin Therapy in Critically Ill Patients: Morbidity

Percent of Patients Requiring >14 Days of Ventilatory Support



Van den Berghe G, et al. N Eng J Med 2001;345:1365

Intensive Insulin Therapy in Critically Ill Patients: Morbidity

- Percent of Patients with Renal Impairment

	Conventional n=783	Intensive n=765	P-value
Peak plasma creatinine >2.5 mg/dL	12.3%	9.0 %	0.04
Peak plasma urea nitrogen >54 mg/dL	11.2 %	7.7 %	0.02
Dialysis or CVVH	8.2 %	4.8 %	0.007

Van den Berghe G, et al. N Eng J Med 2001;345:1359-1367

Intensive Insulin Therapy in Critically Ill Patients: Morbidity

- Percent of Patients with Bloodstream Infections

	Conventional n=783	Intensive n=765	P-value
Septicemia during intensive care	7.8%	4.2%	0.003
Treatment with antibiotics > 10 days	17.1%	11.2%	<0.001

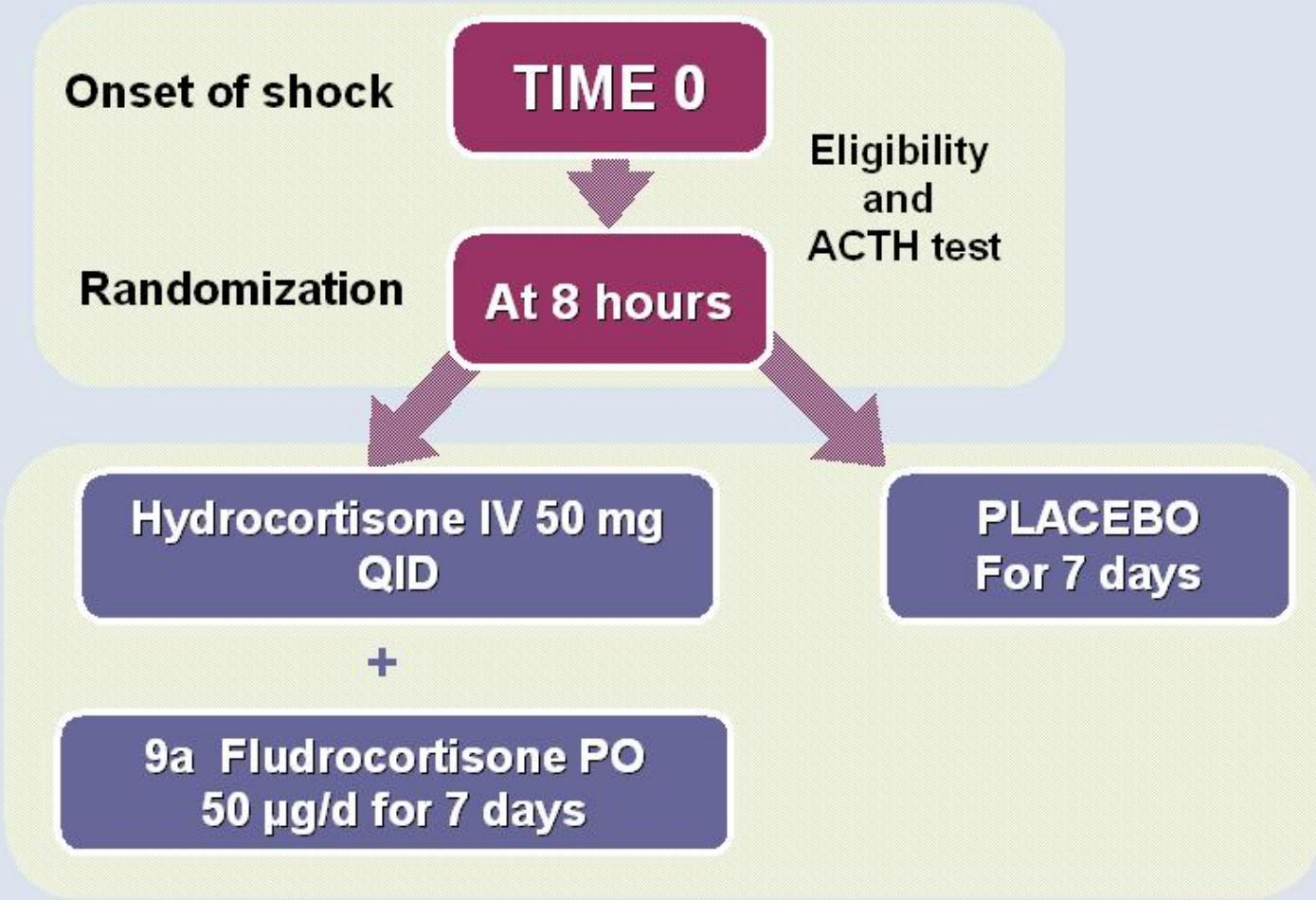
Van den Berghe G, et al. N Eng J Med 2001;345:1365

Intensive Insulin Therapy in Critically Ill Patients: Author's Conclusion

"Intensive insulin therapy to maintain blood glucose at or below 110 mg per deciliter reduces morbidity and mortality among critically ill patients in the surgical intensive care unit."

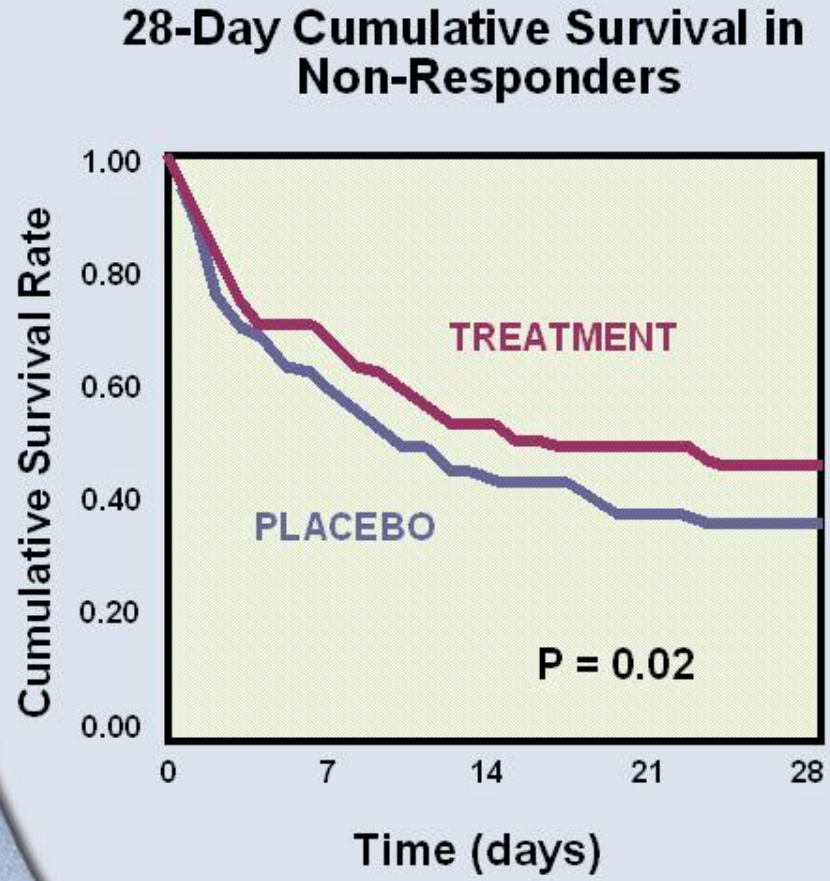
Van den Berghe G, et al. N Eng J Med 2001;345:1359

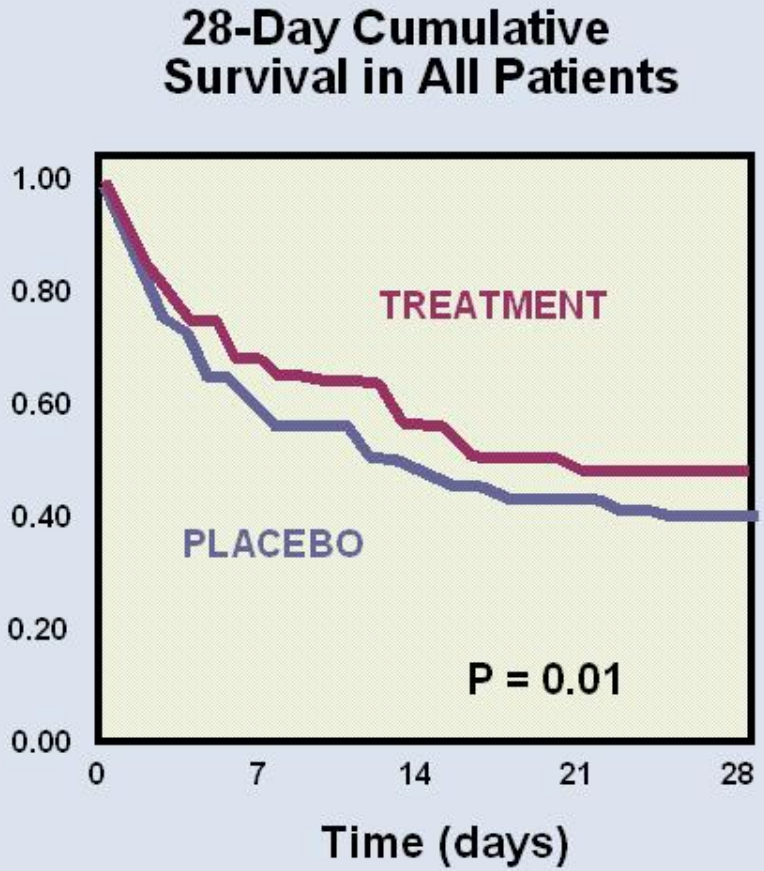
Steroids in Septic Shock with Adrenal Insufficiency: Study Design



Annane D. *Crit Care Med* 2000;28(suppl): Abstract 63.

Effect of Steroids in Septic Shock with Adrenal Insufficiency: Results

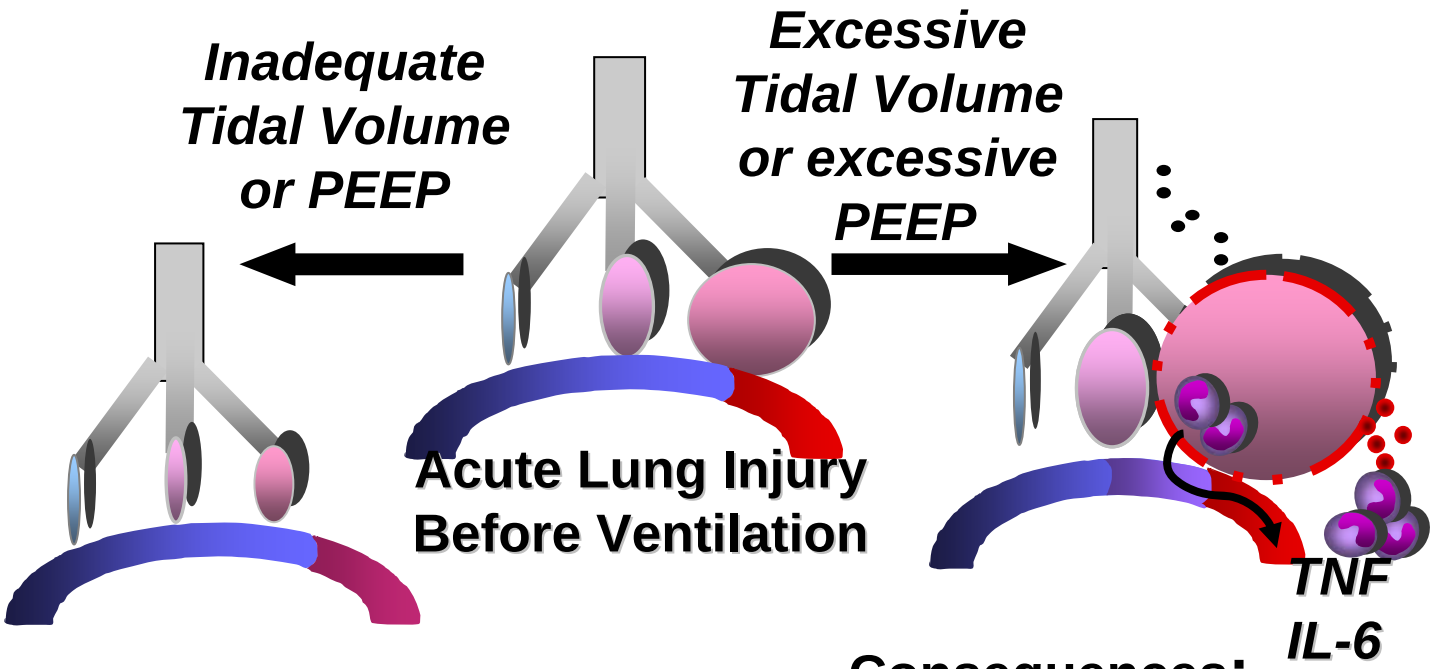




Annane D. *Crit Care Med* 2000;28(suppl): Abstract 63.

What Works

Balancing Ventilation Priorities



Consequences:

- Atelectasis
- Hypoxemia
- Hypercapnia

Consequences:

- V/Q mismatch
- Alveolar-capillary injury
- Inflammation
- Pulmonary hypertension
- “Barotrauma”

Ventilator Management

- **Assist control mode**
- **Reduce TV to 6 mL/kg predicted body weight**
- **Keep plateau airway pressure <30 cm H_2O**
- **Maintain SaO_2 / SpO_2 88%-95% using this scale:**

FiO_2	.3	.4	.4	.5	.5	.6	.7	.7	.7	.8	.9	.9	.9	1.0
PEEP	5	5	8	8	10	10	10	12	14	14	14	16	18	20-24

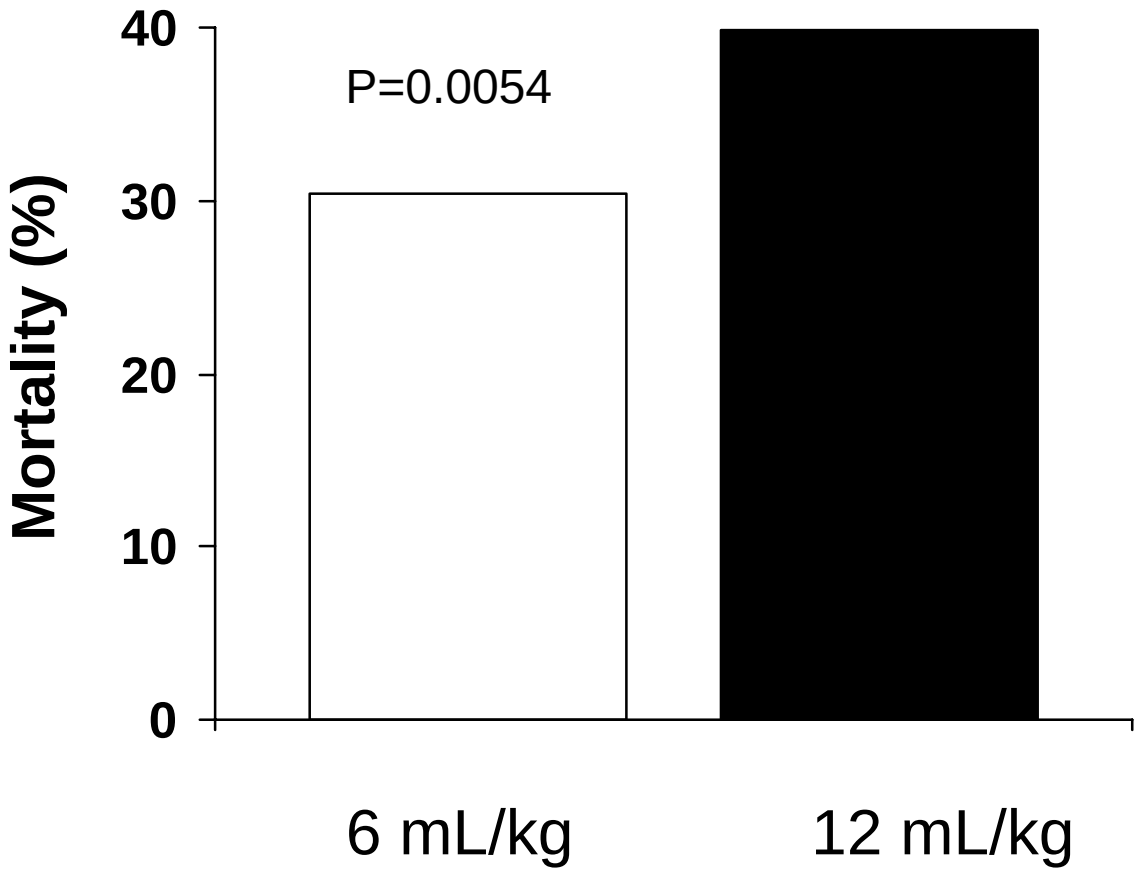
The Acute Respiratory Distress Syndrome Network. *N Engl J Med* 2000;342:1301-8.

Ventilator Management

- Accept mild respiratory acidosis
  - If pH <7.30 increase rate (max 35)
  - If acidosis persists and rate = 35, consider $NaHCO_3$
  - If acidosis refractory/unresponsive, may raise TV to achieve pH >7.15
- Perform a spontaneous breathing trial daily if
  - Shock absent
  - Spontaneous efforts present
  - $FiO_2 \leq 0.4$ and PEEP = 8

The Acute Respiratory Distress Syndrome Network. *N Engl J Med* 2000;342:1301-8.

Mortality Prior to Discharge



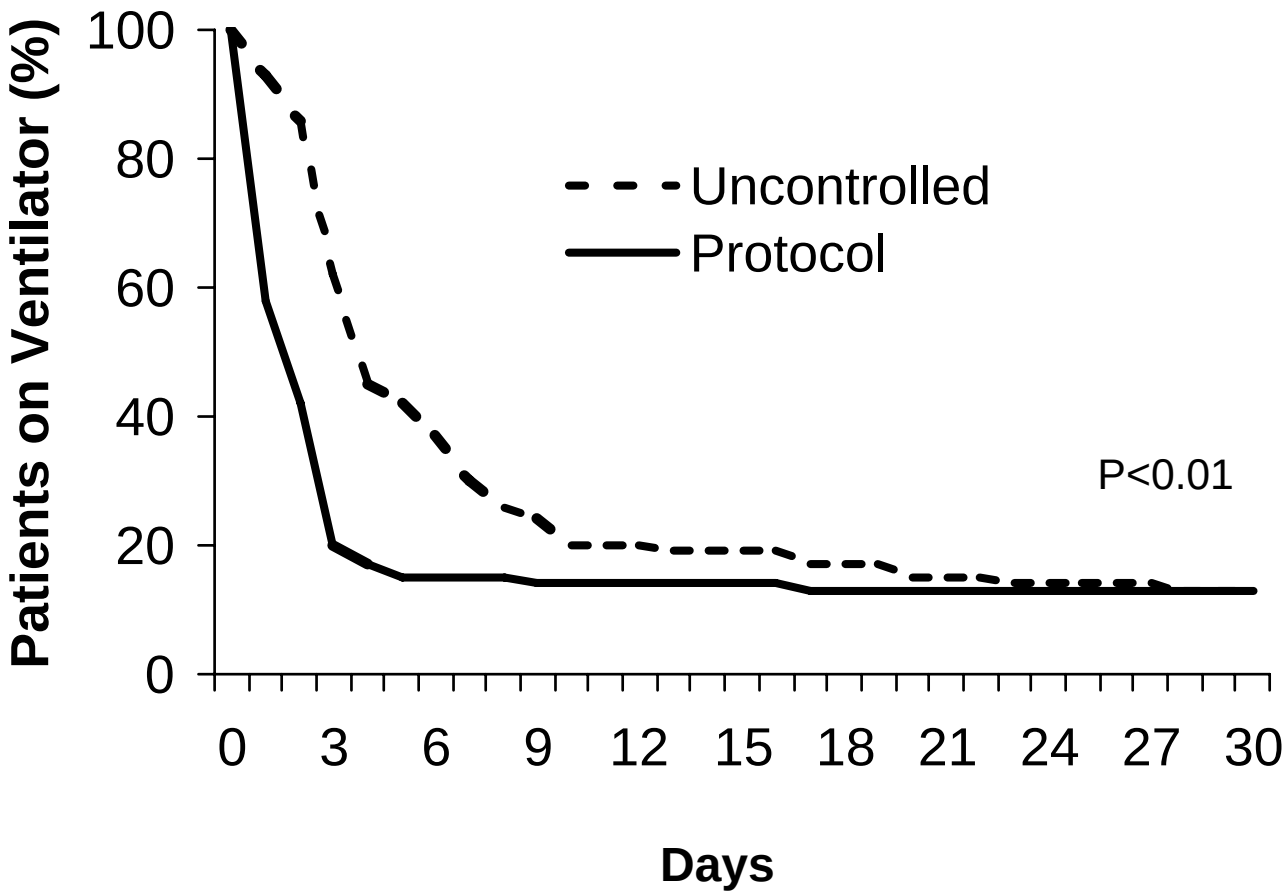
The Acute Respiratory Distress Syndrome Network. *N Engl J Med* 2000;342:1301-8.

Spontaneous Breathing Trials

- Respiratory therapy driven protocol
- Daily screening of all ventilated patients:
  - No shock
  - $FIO_2 \leq 0.4$, PEEP ≤ 8
  - Awake, not-paralyzed
- Two hour spontaneous breathing trial
- Extubation decision by primary team

Ely EW, et al. *N Engl J Med* 1996;335:1864-9.

Value of Spontaneous Breathing Trials



Ely EW, et al. *N Engl J Med* 1996;335:1864-9.

Sepsis Specific Therapy

At Last a Reality

The PROWESS Trial:
Drotrecogin Alfa (Activated) in Patients with Severe Sepsis

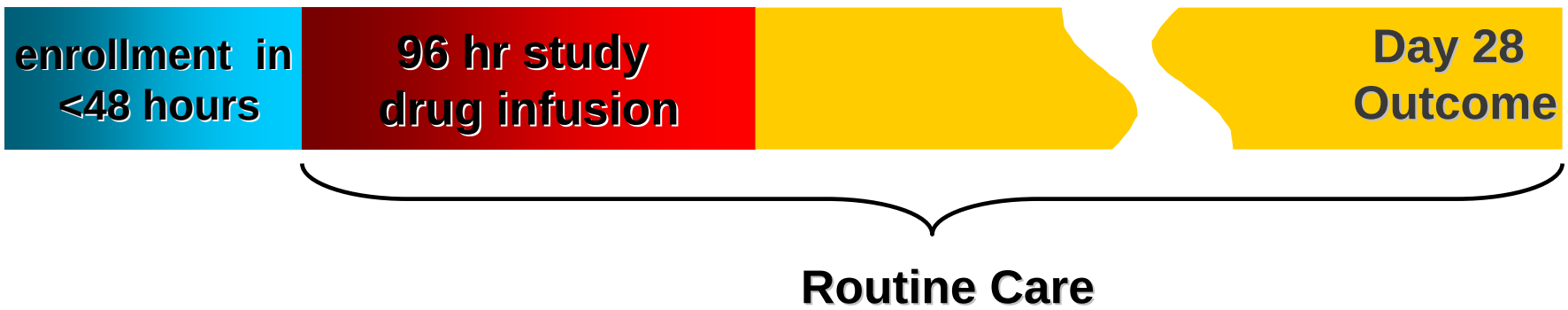
- **Anticoagulant**
  - **Inactivates coagulation factors Va, VIIIa**
  - **Inhibits formation of thrombin**
- **Pro-fibrinolytic**
  - **Allows activity of tissue plasminogen activator (endogenous TPA)**
- **Antiinflammatory**
  - **Reduces IL-6 and proinflammatory cytokines**

Drotrecogin Alfa (Activated) in Severe Sepsis: Phase III Study

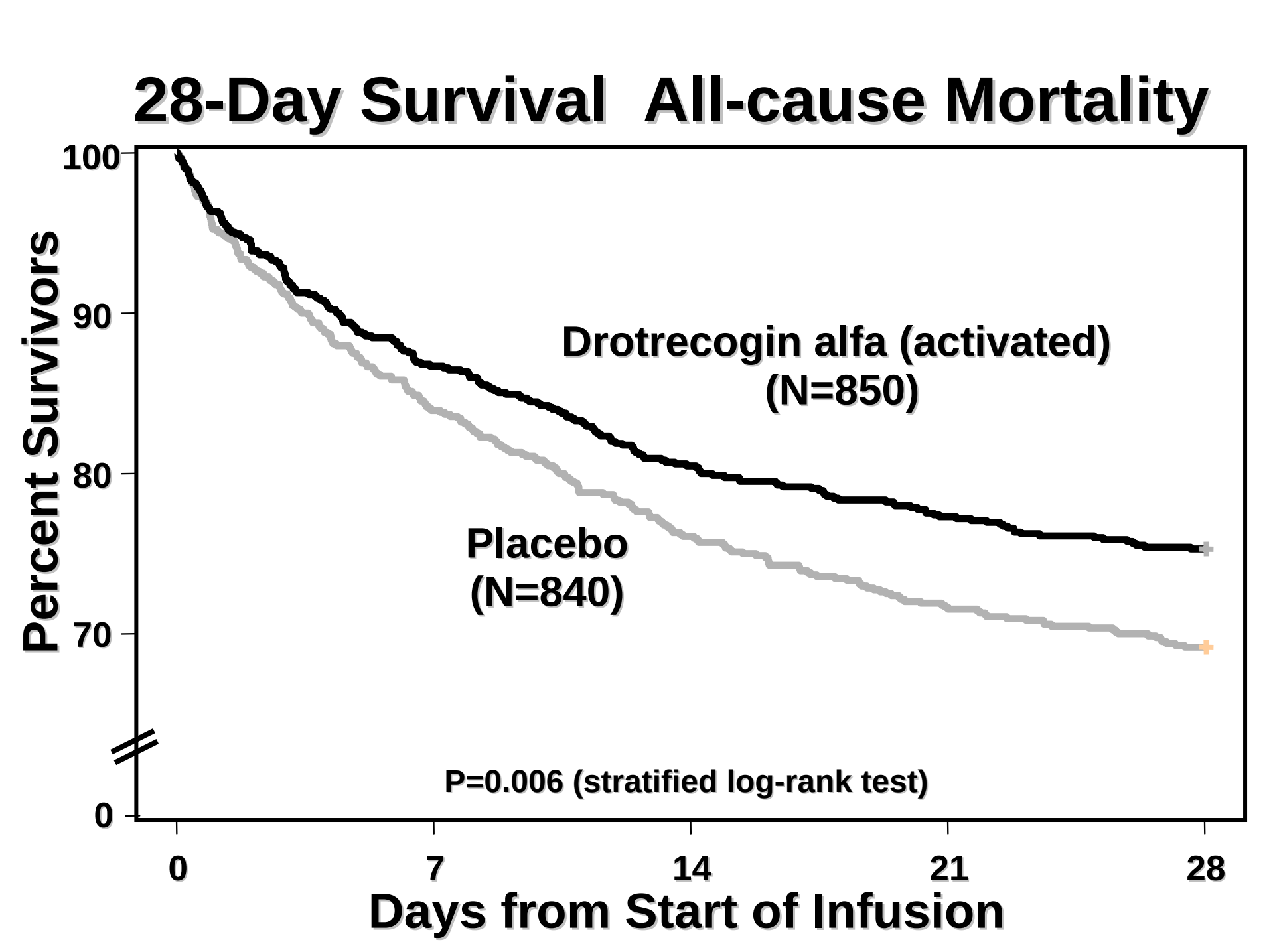
- **Randomized 1:1**
- **Blinded**
- **Large N=1690**

- **Placebo-controlled**
- **164 centers**
- **11 countries**
- **Severe sepsis**

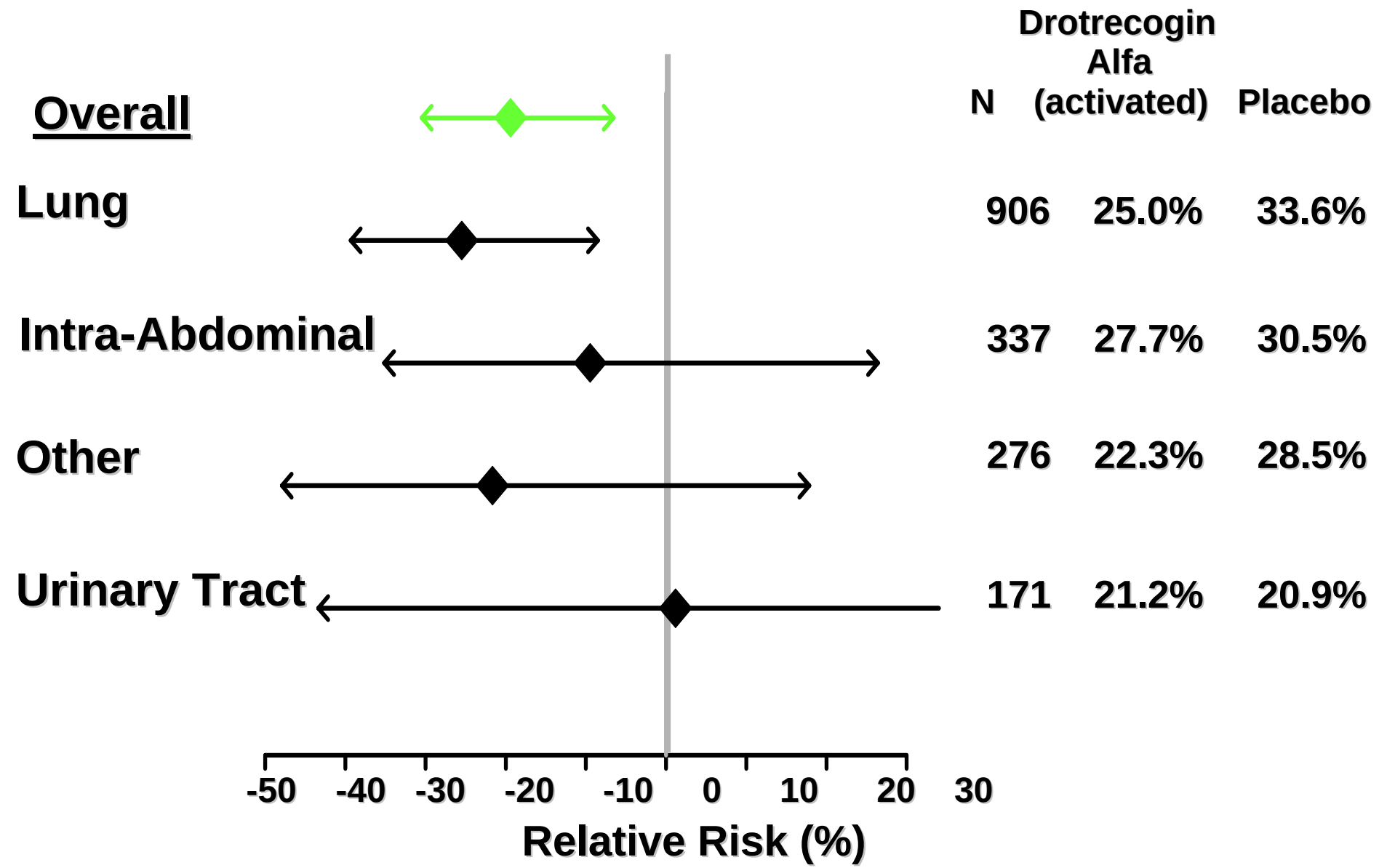
Infection + 3 SIRS criteria
and acute (<24 hr) organ failure



Bernard GR, et al. *N Engl J Med* 2001;344:699-709.


28-Day Survival All-cause Mortality
100
90
80
70
0
Percent Survivors
Drotrecogin alfa (activated)
(N=850)
Placebo
(N=840)
P=0.006 (stratified log-rank test)
0
7
14
21
28
Days from Start of Infusion

Mortality by Site of Infection



Other Important New Data You Should Be Aware Of !!

“Appropriate” antibiotics Kollef, Chest 1999

- **Inadequate antimicrobial treatment of infection**
- **Defined as microbiologic documentation of infection (*ie*, positive culture result) not being effectively treated at time of identification**
- **Absence of antimicrobial agents directed at specific class of microorganisms (absence of tx for fungemia due to *Candida*) and administration of agent to which microorganism responsible for infection were resistant (*eg*, empiric tx with methacillen for pneumonia subsequently attributed to methacillen-resistant *Staphylococcus aureus* [MRSA] based on culture results).**

“Appropriate” antibiotics Kollef, Chest 1999

- 169 patients out of 2000 surveyed were “inappropriately treated” at diagnosis of infection
- Mortality rate in this group was 52.1 %
- 12.2% mortality in appropriately treated group versus 52.1% (NNT = 2.5)

“Invasive” strategy for VAP diagnosis Fagon, Ann Int Med 2000

- Examined diagnosis of ventilator associated pneumonia via bronchoscopic BAL samples and their quantitative cultures

- Versus noninvasive isolation of microorganisms by nonquantitative analysis of endotracheal aspirates, and clinical practice guidelines.

“Invasive” strategy for VAP diagnosis Fagon, Ann Int Med 2000

Patients who recv’d invasive diagnosis had:

- **Reduced mortality at day 14 (16.2% vs. 25.8%; p < 0.02)**
- **Decreased Sepsis-related Organ Failure Assessment scores at day 3 and day 7**
- **Decreased antibiotic use (mean number of antibiotic-free days, 5.0+/-5.1 and 2.2+/-3.5; P < 0.001).**

“Invasive” strategy for VAP diagnosis Fagon, Ann Int Med 2000

Conclusions-

“Compared with noninvasive management strategy, invasive management strategy was significantly associated with fewer deaths at 14 days, earlier attenuation of organ dysfunction, and less antibiotic use in patients suspected of having ventilator-associated pneumonia.”

Intensivist led multidisciplinary ICU team

- Young, Effective Clinical Practice 2000
- Concept of closed ICU service led by ICU physician
- Up to 60% reduction in mortality

Optimal Hemoglobin in the Critically Ill Patient !?!

- ? Clearly higher Hgb achieved via transfusion is not helpful and may be harmful

- ? Is there a lower threshold?

Transfusion Requirements in Critical Care

- Multicenter, RCT
- Subjects
  - Acutely ill in ICU, Hgb < 9.0
  - Excluded if: chronic anemia, ongoing bleeding, admission after CABG

Hebert et al. NEJM 1999; 340:409-17

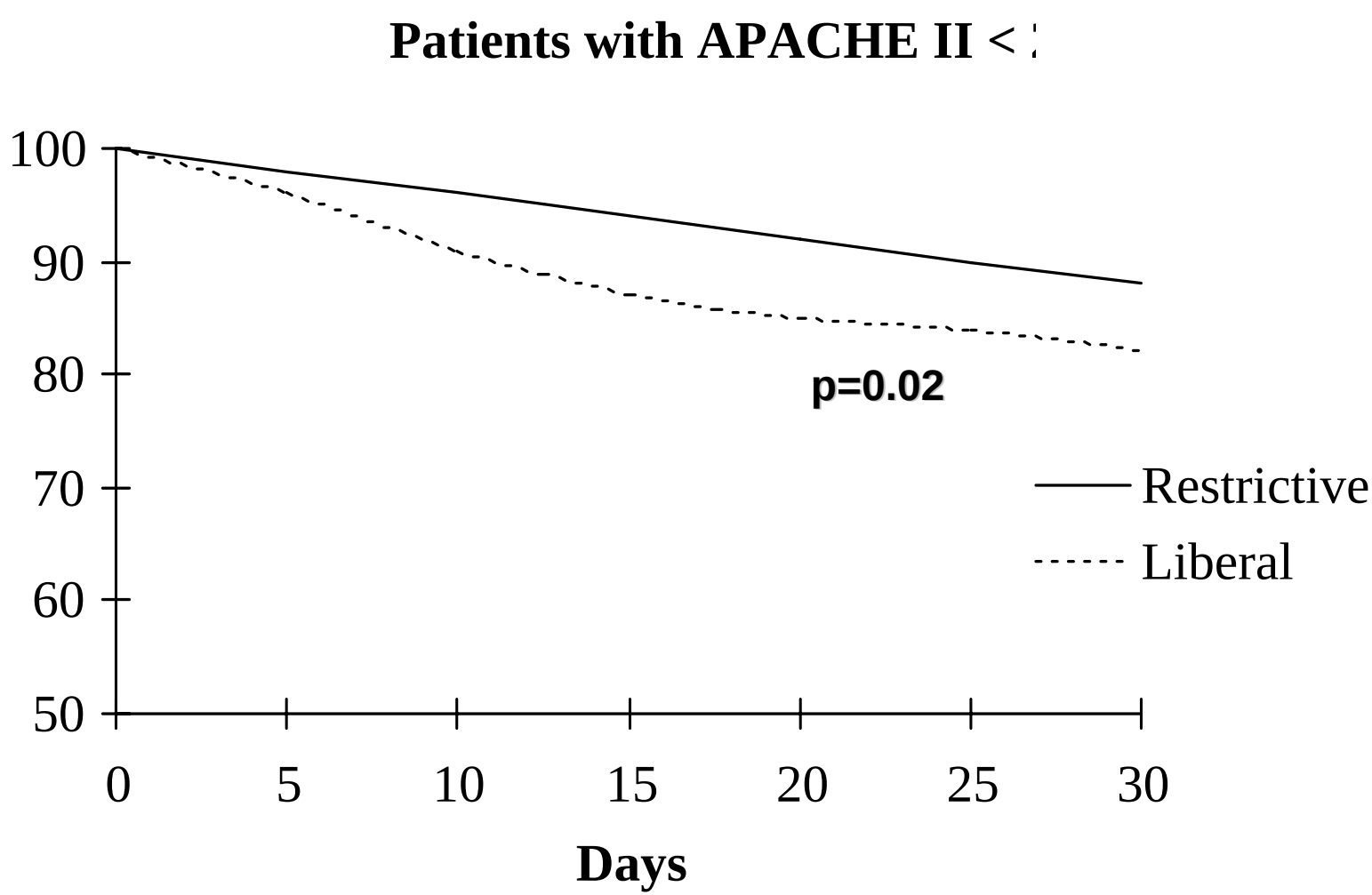
Transfusion Requirements in Critical Care

- Randomized to 2 strategies
- Liberal strategy:
  - Maintain Hgb between 10-12
- Restrictive strategy:
  - Maintain Hgb between 7-9
- Endpoints
  - All cause mortality, MSOF
  - Predefined subgroups: age > 55, CAD, APACHE II > 20

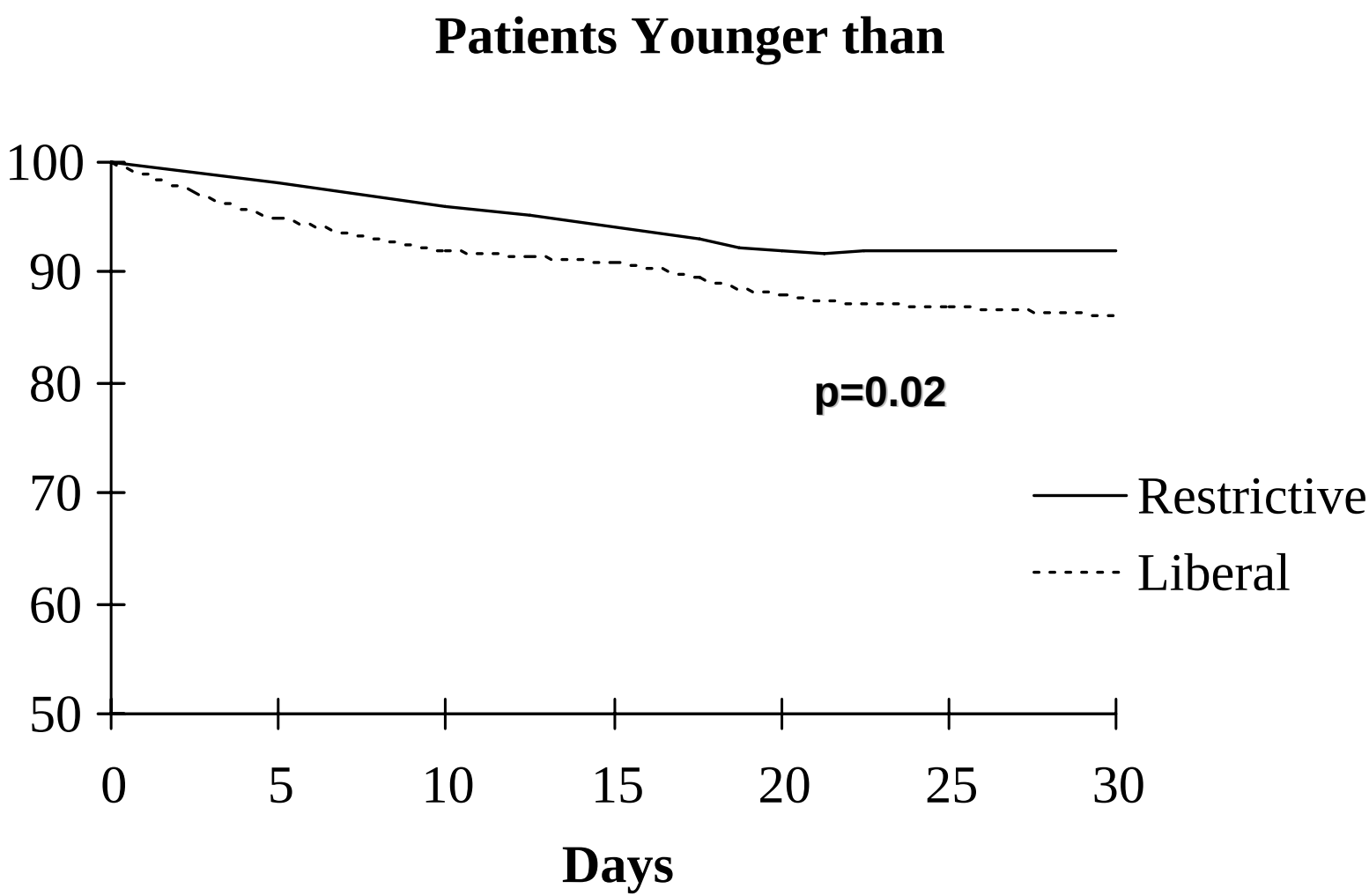
Transfusion Requirements in Critical Care

	Restrictive (n=418)	Liberal (n=420)	p
ICU mortality	13.4%	16.2%	0.29
Death (30d)	18.7%	23.3%	0.11
ICU LOS	11.0	11.5	0.53
MODS	8.3	8.8	0.10
MI	0.7%	2.9%	0.02

Transfusion Requirements in Critical Care



Transfusion Requirements in Critical Care



Transfusion Requirements in Critical Care

- **Conclusions**
  - **- Lower transfusion threshold was as effective as higher trigger**
  - **- Lower threshold superior in some subgroups**
  - **- Mechanism of worse outcomes with liberal strategy unclear (? promotes cytokine cascade, increased risk of ARDS)**

Transfusion Requirements in Critical Care

- **Editorial comment in NEJM**

  "This study has made it clear that a single threshold for transfusion in all patients is not appropriate…… With this knowledge, more physicians will be able to follow the dictum "first do no harm," and we will have a surplus of blood rather than a shortage."

Ely et al. NEJM 1999: 340: 468.

Neuro Critical Care

Just one paper…

But may be very important !

LIPPINCOTT WILLIAMS & WILKINS

Neurology

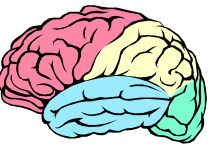
Volume 61(8) 28 October 2003 pp 1047-1051

Detrimental effect of blood pressure reduction in the first 24 hours of acute stroke onset

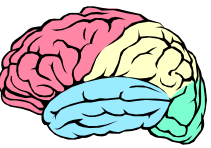
Oliveira-Filho, J. MD, PhD; Silva, S.C.S. MD; Trabuco, C.C. MD; Pedreira, B.B. MD; Sousa, E.U. MD; Bacellar, A. MD

From the Department of Biomorphology (Dr. Oliveira-Filho), Health Sciences Institute, Federal University of Bahia; the Neurology Service (Drs. Oliveira-Filho, Silva, Trabuco, Pedreira, and Bacellar), Hospital Sao Rafael, Monte Tabor Foundation; and the Bahian School of Medicine and Public Health (Dr. Sousa), Salvador-Bahia, Brazil.

Results and Conclusions



The main result of the study was a strong, independent relationship of BP course to adverse outcome, *with an almost twofold increased risk of poor outcome for every 10% decrease in the SBP over the first 24 hours.*



The degree of SBP variation over the first 24 hours was unrelated to stroke severity but robustly related to stroke outcome.

Oliveira-Filho J, Neurology 2003;61:1047

Results and Conclusions

- **The degree of SBP reduction was unrelated to antihypertensive medication use (59% of patients), but related to higher admission BP.**

- **Even spontaneous decreases in BP may be harmful to ischemic brain tissue. Cannot rule out that further decreases with antihypertensive medications may further worsen outcome.**

- **Need for an acute intervention trial randomizing patients for predefined BP values.**

Oliveira-Filho J, Neurology 2003;61:1047

SUMMARY

NEW THERAPIES IN ICU PATIENTS ("Drivers" of Mortality)

- "Goal directed" early (ED) resuscitation
  - Rivers, NEJM 2001
  - 30.5% mortality versus 46.5% (NNT = 6)

- Intensive insulin therapy
  - Van den Berghe, NEJM 2001
  - 10.6% mortality versus 20.2% (NNT = 20)

- Low dose steroids in sepsis
  - Annane, JAMA 2002
  - 53% mortality versus 63% (NNT = 10)

NEW THERAPIES (cont)

- Low tidal volumes for ALI/ARDS
  - ARDS network, NEJM 2000
  - 31.0% mortality versus 39.8% (NNT = 11)
- “Appropriate” antibiotics
  - Kollef, Chest 1999
  - 12.2% mortality versus 52.1% (NNT = 2.5)
- “Invasive” strategy for VAP diagnosis
  - Fagon, Ann Int Med 2000
  - 16.2% mortality versus 25.8% (NNT = 10)

NEW THERAPIES (cont)

- Activate protein C (Xigris®) for sepsis
  - Bernard, NEJM 2001
  - 24.7% mortality versus 30.8% (NNT = 16)

- Intensivist led multidisciplinary ICU team
  - Young, Effective Clinical Practice 2000
  - Up to 60% reduction in mortality

LESS PROVEN THERAPIES (no good placebo controls)

- Transfusion practices
- Pulmonary artery catheters
  - Have not been shown to improve outcome
- Liberal versus conservative fluid strategy
- Prevent the "2nd hit" (DVT, VAP, GI bleeding)

Acknowledgements

Marie R. Baldisseri, MD