Sepsis Management at the Hospital Point of Care

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ABIM Board Certified in Pulmonary Diseases, Critical Care, and Internal Medicine

Goals

- **Define sepsis**
  - Incidence/prevalence
  - Manifestations
  - Pathophysiology
- **Surviving Sepsis Campaign**
- **Treatments**

Definitions

- Sterile
- Colonization
- Infection
- Inflammation
  - Local
  - Systemic

Bone RC, Balk RA, Cerra FB, *et al*. ACCP/SCCM Consensus Conference: Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Chest 1992; 101:1644-1655

Definitions

- Sterile
- Colonization
- Infection
- Inflammation
  - Local
  - Systemic

Absence of microorganisms

ACCP/SCCP Consensus Conference Definitions

Definitions

- Sterile
- Colonization
- Infection
- Inflammation
  - Local
  - Systemic

Small number of microorganisms and absence of significant inflammatory response to the presence of microorganisms

ACCP/SCCP Consensus Conference Definitions

Definitions

- Sterile
- Colonization
- Infection
- Inflammation
  - Local
  - Systemic

Inflammatory response to the presence of microorganisms or the invasion of normally sterile host tissue by those organisms

ACCP/SCCP Consensus Conference Definitions

Definitions

- Sterile
- Colonization
- Infection
- Inflammation
  - Local
  - Systemic

Calor

Dolor

Rubor

Tumor

ACCP/SCCP Consensus Conference Definitions

Definitions

How do you define "systemic" inflammation?

Systemic Inflammatory Response Syndrome (SIRS)

- **SIRS requires *two* of the following**
  - Temp < 36°C or > 38°C
    - < 96.8°F or >100.4°F
  - Heart rate > 90 beats/min
  - RR > 20 breaths/min *or* P_aCO_2 < 32 mm Hg
  - WBC > 12,000 or < 4,000/mm^3, or > 10% band forms

ACCP/SCCP Consensus Conference Definitions

ACCP/SCCM Definitions

- **Sepsis =** SIRS + *Infection*
  - The body's inflammatory response to infection

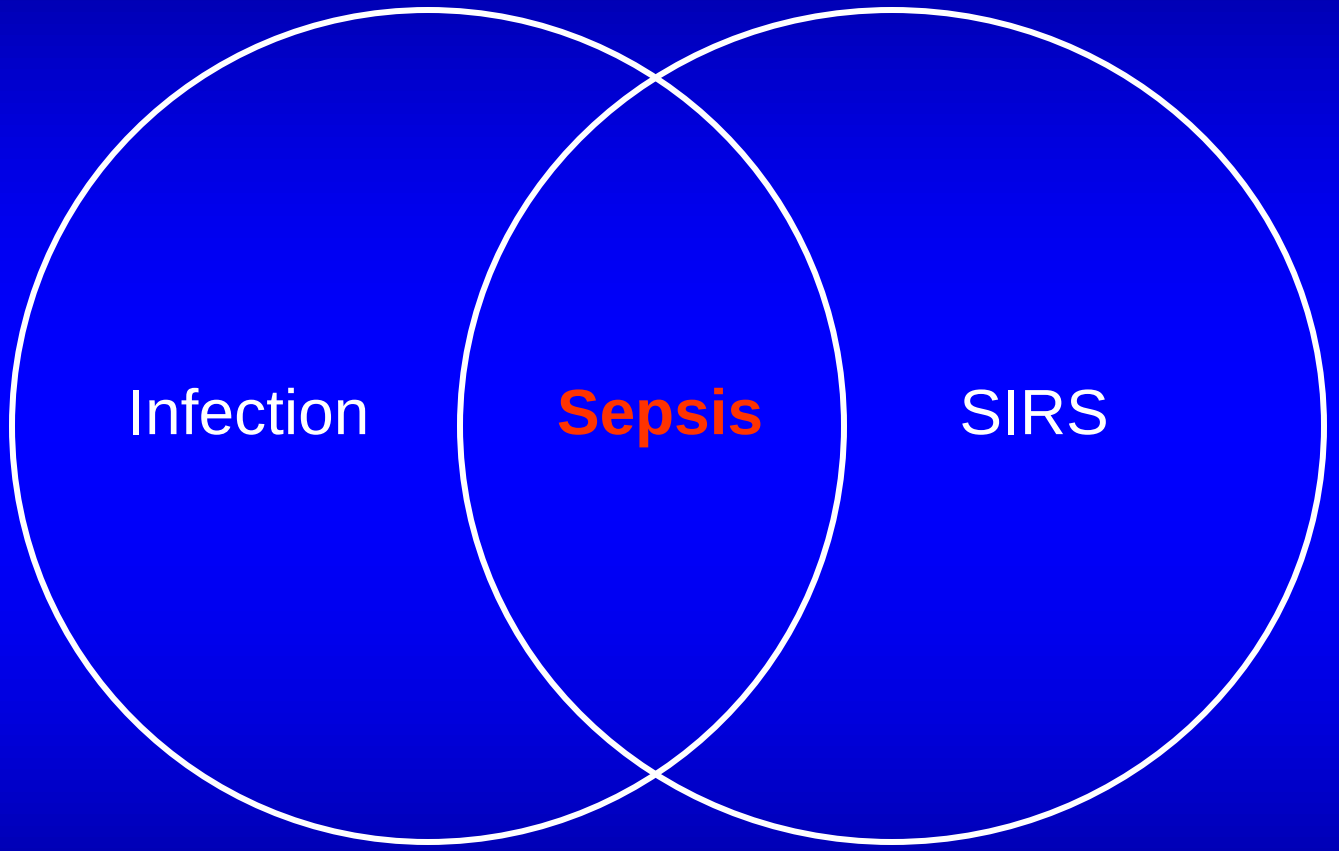
Diagnostic Criteria for Sepsis

Infection (documented or suspected) and some of the following

- **General variables**
  - SIRS criteria
  - Altered mental status
  - Significant edema or positive fluid balance
  - Hyperglycemia *in the absence of diabetes*
- **Inflammatory variables**
  - CRP > 2 SD above normal
  - PCT > 2 SD above normal
- **Hemodynamic variables**
  - SBP < 90 or MAP < 60
    - SBP decrease > 40 from baseline
  - S_{VO_2} > 70%
  - Cardiac index > 3.5L/min/m^2
- **Organ dysfunction variables**
  - Arterial hypoxemia
    - PaO_2/FiO_2 < 300 mm Hg
  - Acute oliguria
    - UOP < 0.5 ml/kg/hr $\underline{\geq}$ 2hrs
  - Creatinine increase > 0.5 mg/dl
  - Coagulation abnormalities
    - INR > 1.5 or aPTT > 60 sec
  - Ileus
  - Thrombocytopenia (<100K)
  - Hyperbilirubinemia (>4 mg/dl)
- **Tissue perfusion variables**
  - Hyperlactatemia
  - Decreased capillary refill or mottling

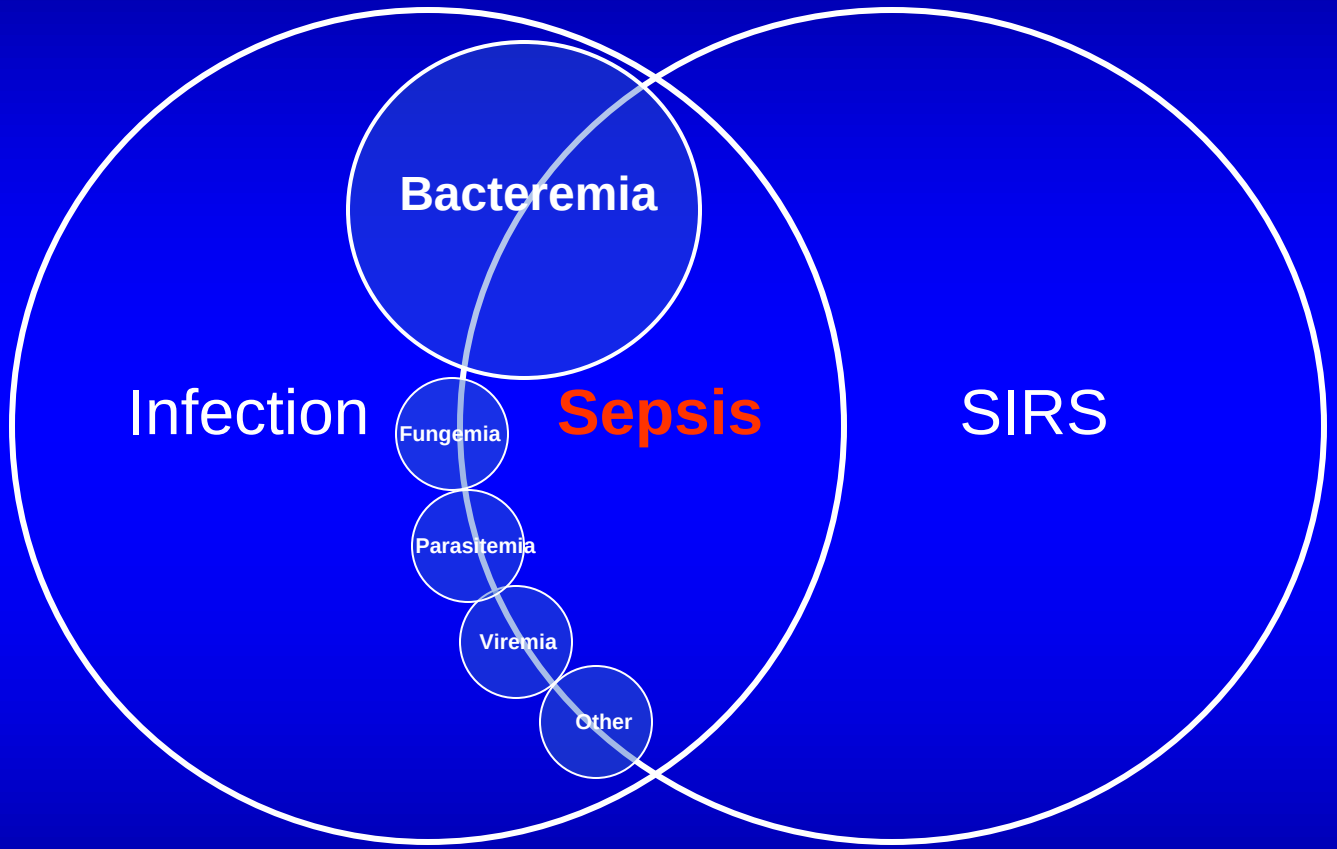
ACCP/SCCP Consensus Conference Definitions

ACCP/SCCM Definitions



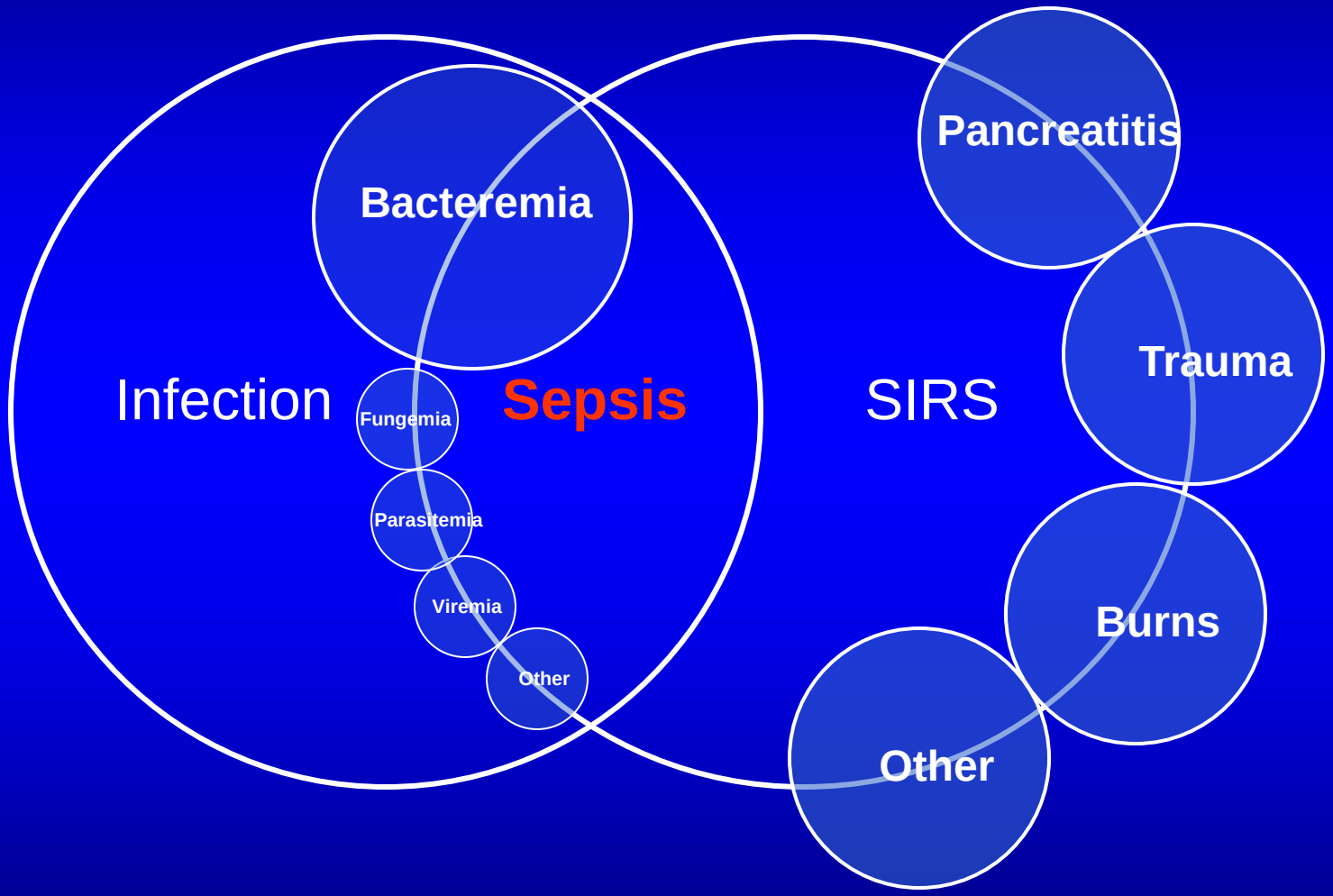
ACCP/SCCP Consensus Conference Definitions

ACCP/SCCM Definitions



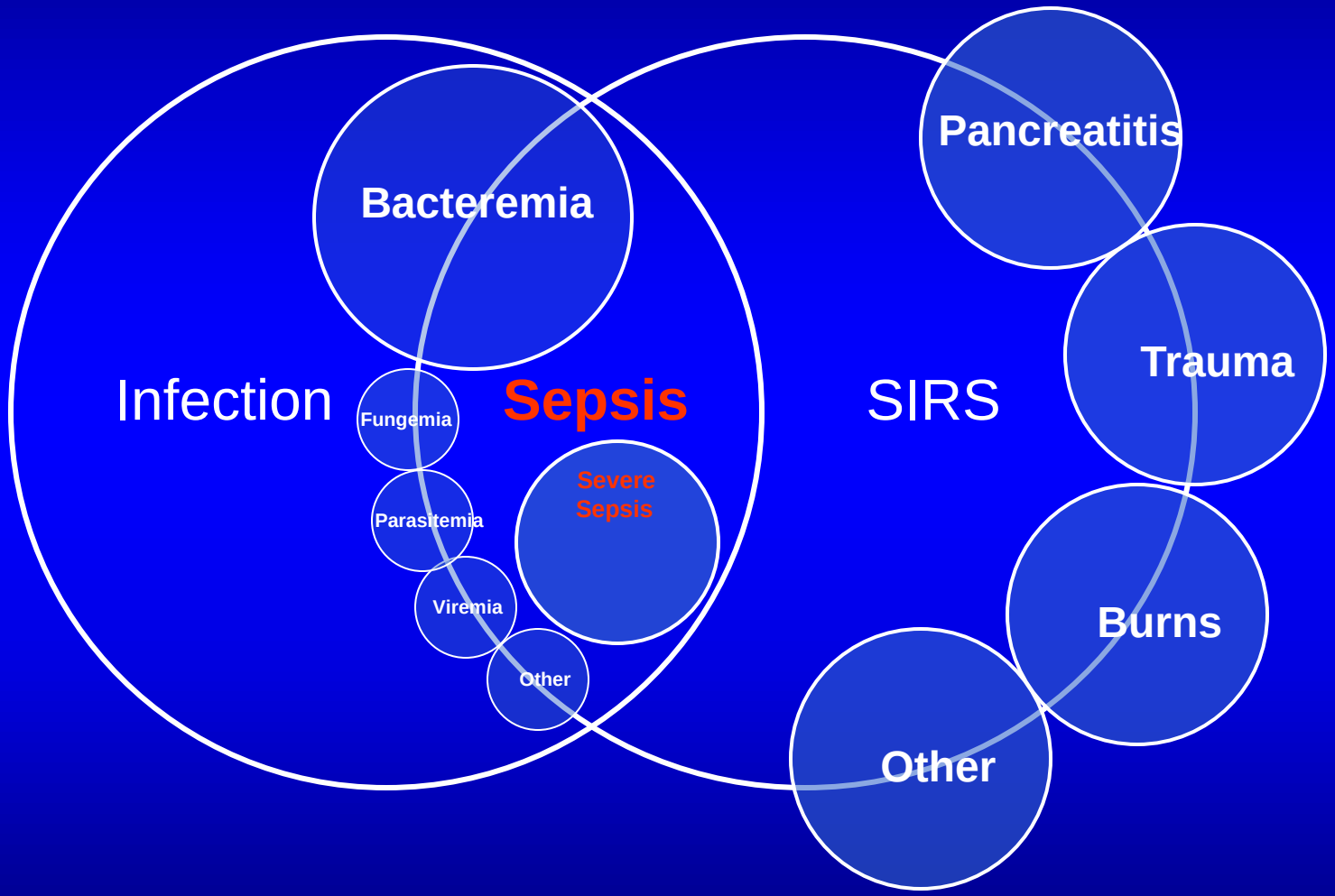
ACCP/SCCP Consensus Conference Definitions

ACCP/SCCM Definitions



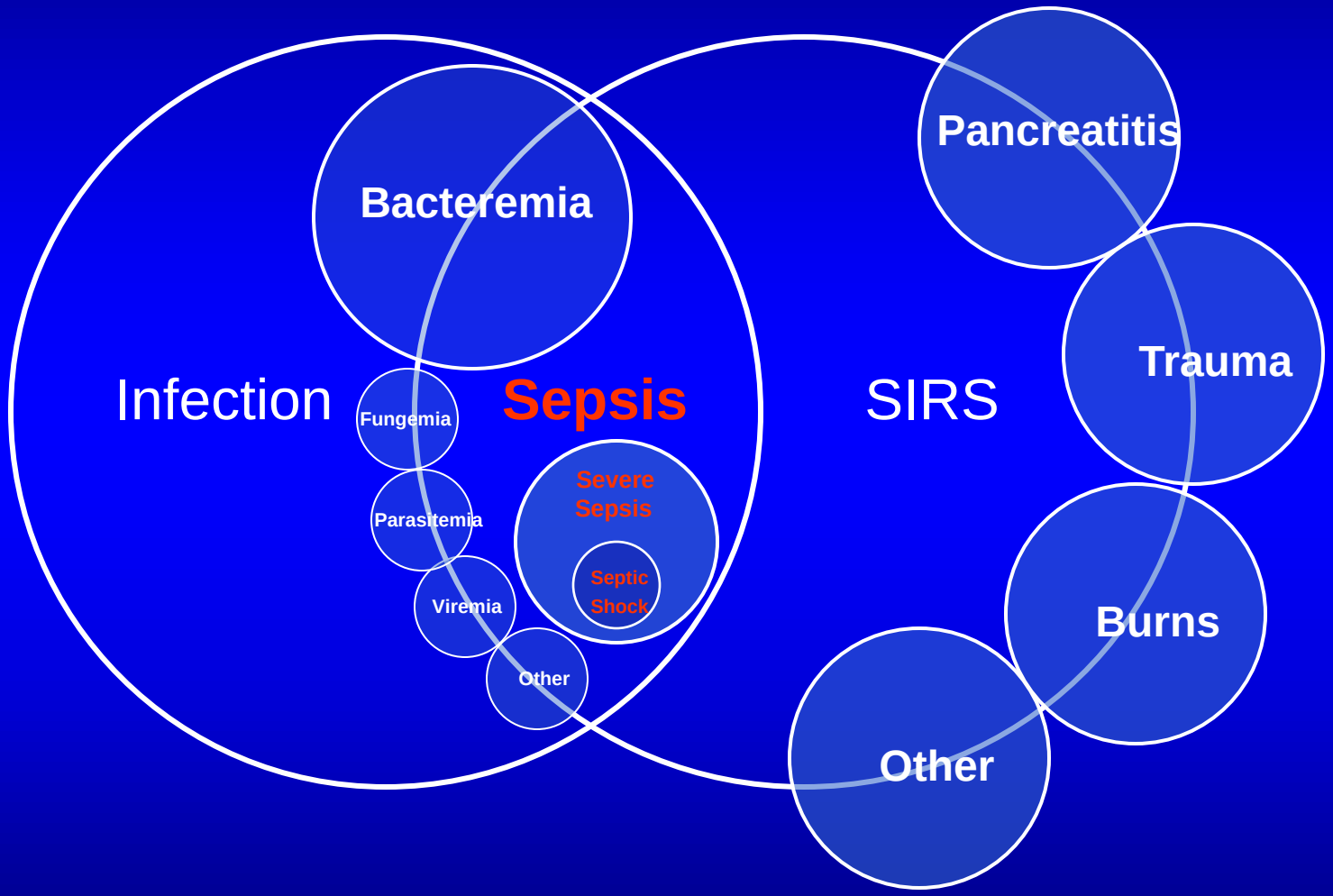
ACCP/SCCP Consensus Conference Definitions

ACCP/SCCM Definitions



ACCP/SCCP Consensus Conference Definitions

ACCP/SCCM Definitions



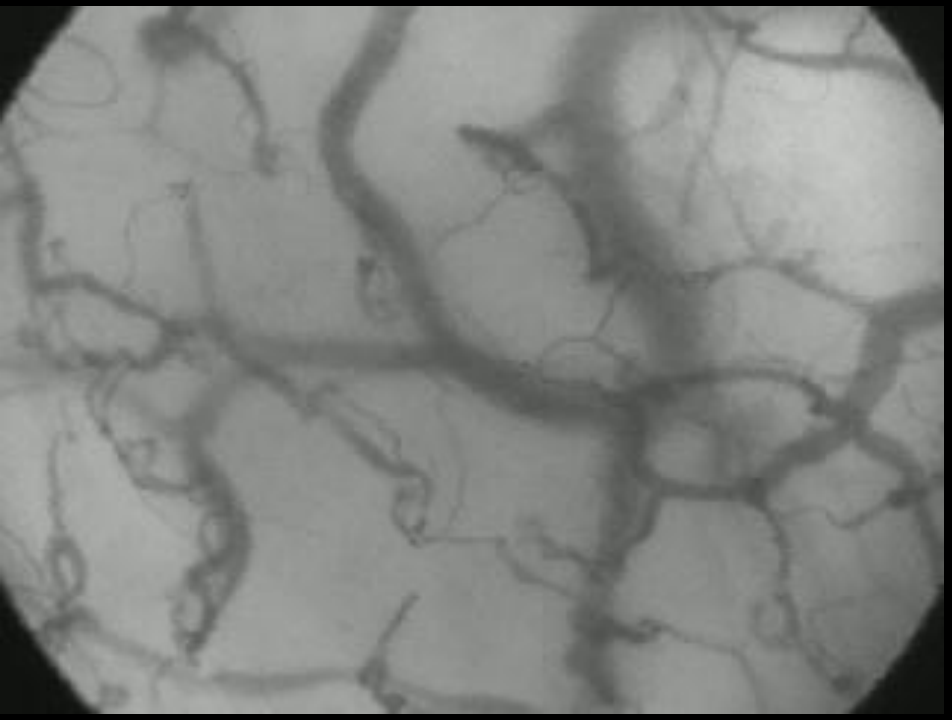
ACCP/SCCP Consensus Conference Definitions

ACCP/SCCM Definitions

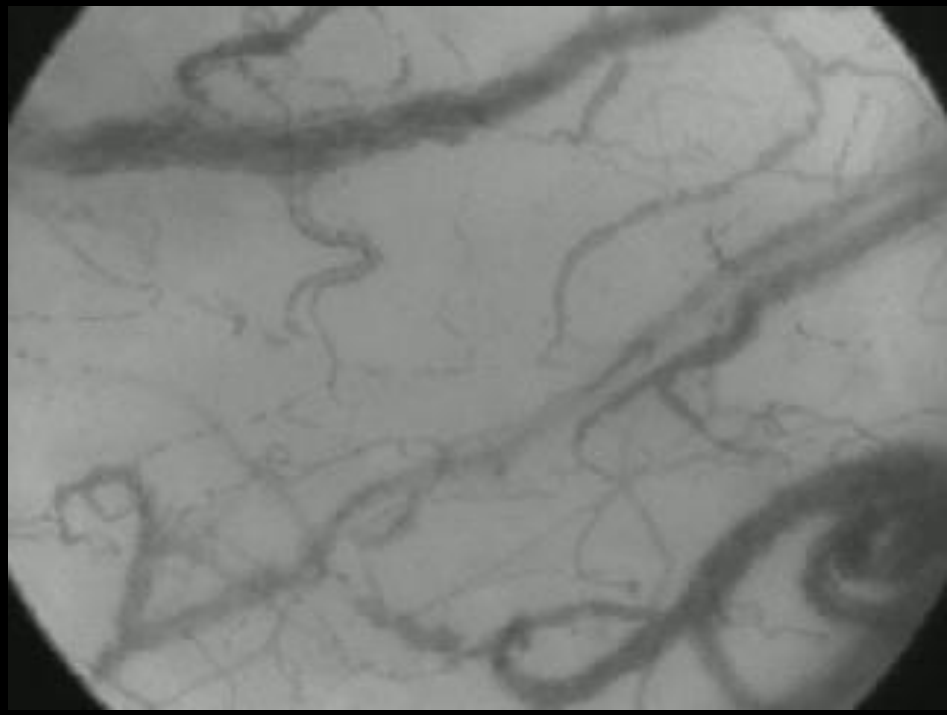
- **Severe sepsis – pathophysiology**
  - Endothelial dysfunction
  - Activation of coagulation cascade
  - Microvascular thrombosis
  - End-organ dysfunction

Sublingual Circulation

Normal subject



Septic shock



De Backer D, et al. *Am J Respir Crit Care Med* 2002; 106: 98-104

http://ajrccm.atsjournals.org/cgi/content/full/166/1/98/DC1

ACCP/SCCM Definitions

- **Severe sepsis – clinical manifestations**
  - Hypoperfusion
  - Hypotension
  - Organ dysfunction

ACCP/SCCM Definitions

- **Severe sepsis**
  - Hypoperfusion
  - Hypotension
  - Organ dysfunction

Altered mental status

Urine output < 0.5 cc/kg/hr

Lactic acid production

ACCP/SCCM Definitions

- **Severe sepsis**
  - Hypoperfusion
  - Hypotension
  - Organ dysfunction

Altered mental status

Urine output < 0.5 cc/kg/hr

Lactic acid production

SBP < 90 mm Hg

or decrease of $\geq$ 40 mm Hg from baseline

ACCP/SCCM Definitions

- **Severe sepsis**
  - Hypoperfusion
  - Hypotension
  - Organ dysfunction

Altered mental status

Urine output < 0.5 cc/kg/hr

Lactic acid production

SBP < 90 mm Hg

or decrease of ≥ 40 mm Hg from baseline

Alteration in function of any organ or system

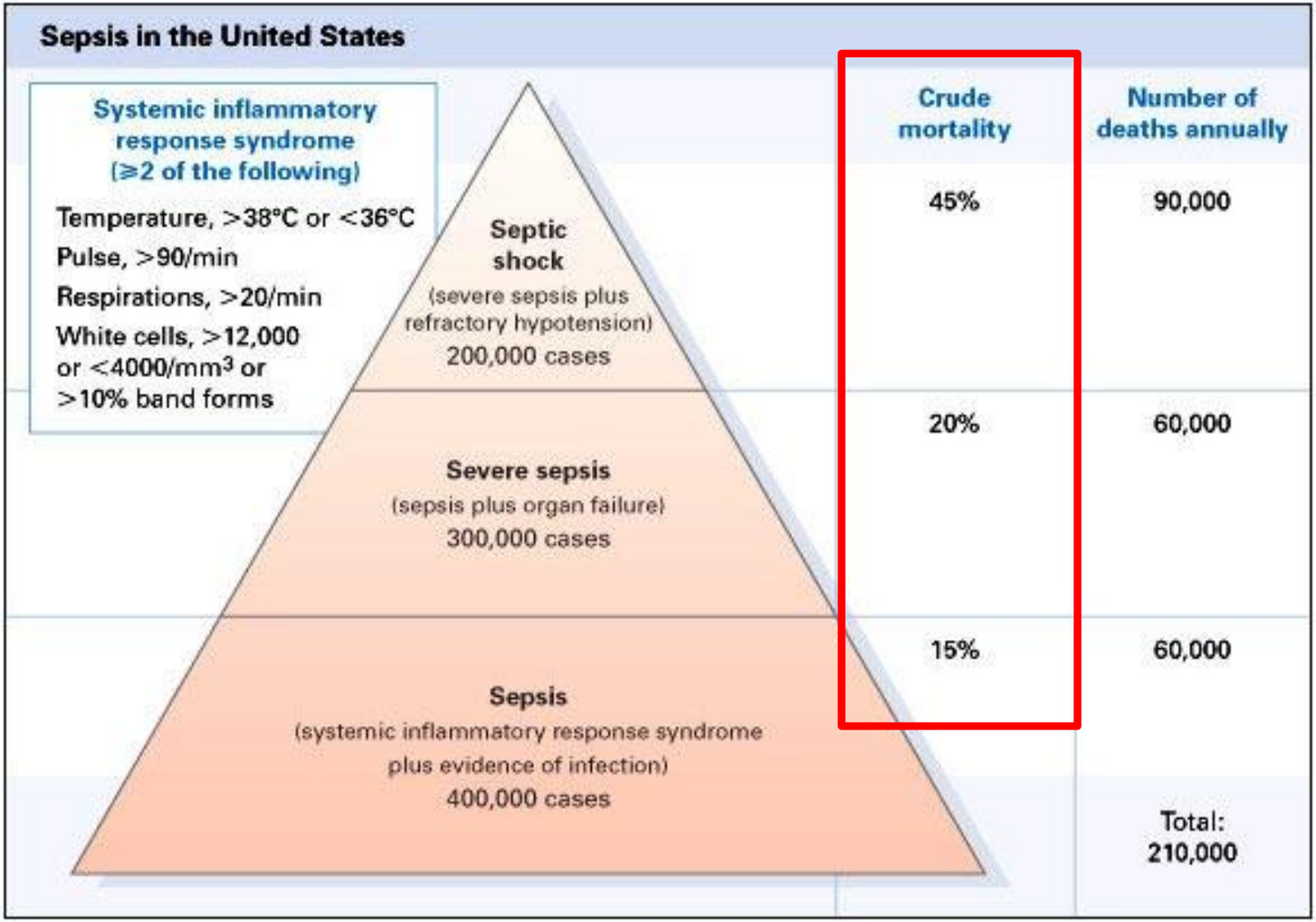
ACCP/SCCM Definitions

- **Septic Shock**
  - Sepsis-induced hypotension *despite adequate fluid resuscitation*
    - Perfusion abnormalities
      - Lactic acidosis
      - Oliguria
      - Acute alteration in mental status

ACCP/SCCM Definitions

- **Septic Shock**

Patients receiving inotropic or vasopressor agents may no longer be hypotensive by the time they manifest hypoperfusion abnormalities or organ dysfunction, yet they are *still considered to have septic shock*



Wenzel R. *N Engl J Med* 2002;347:966-967

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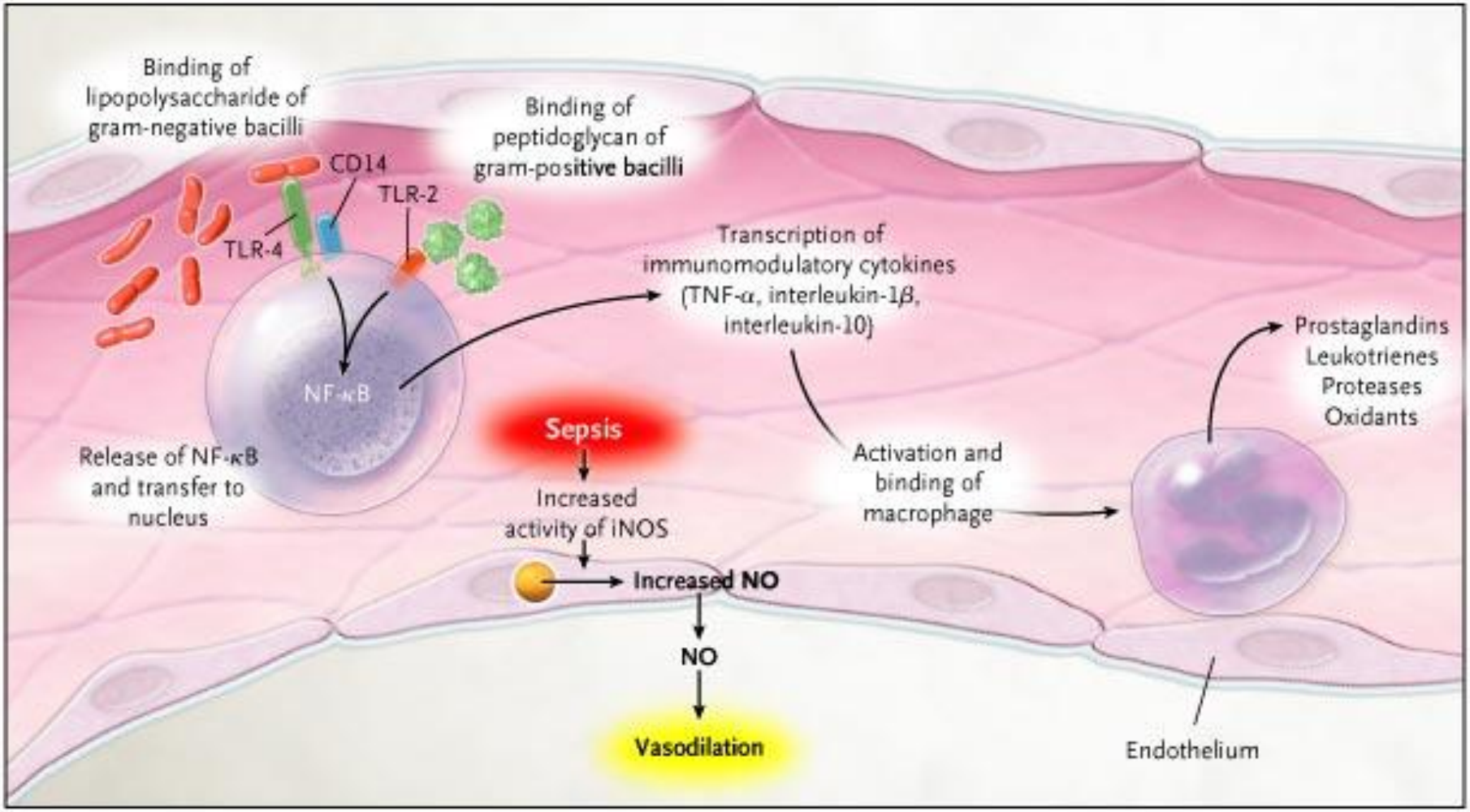
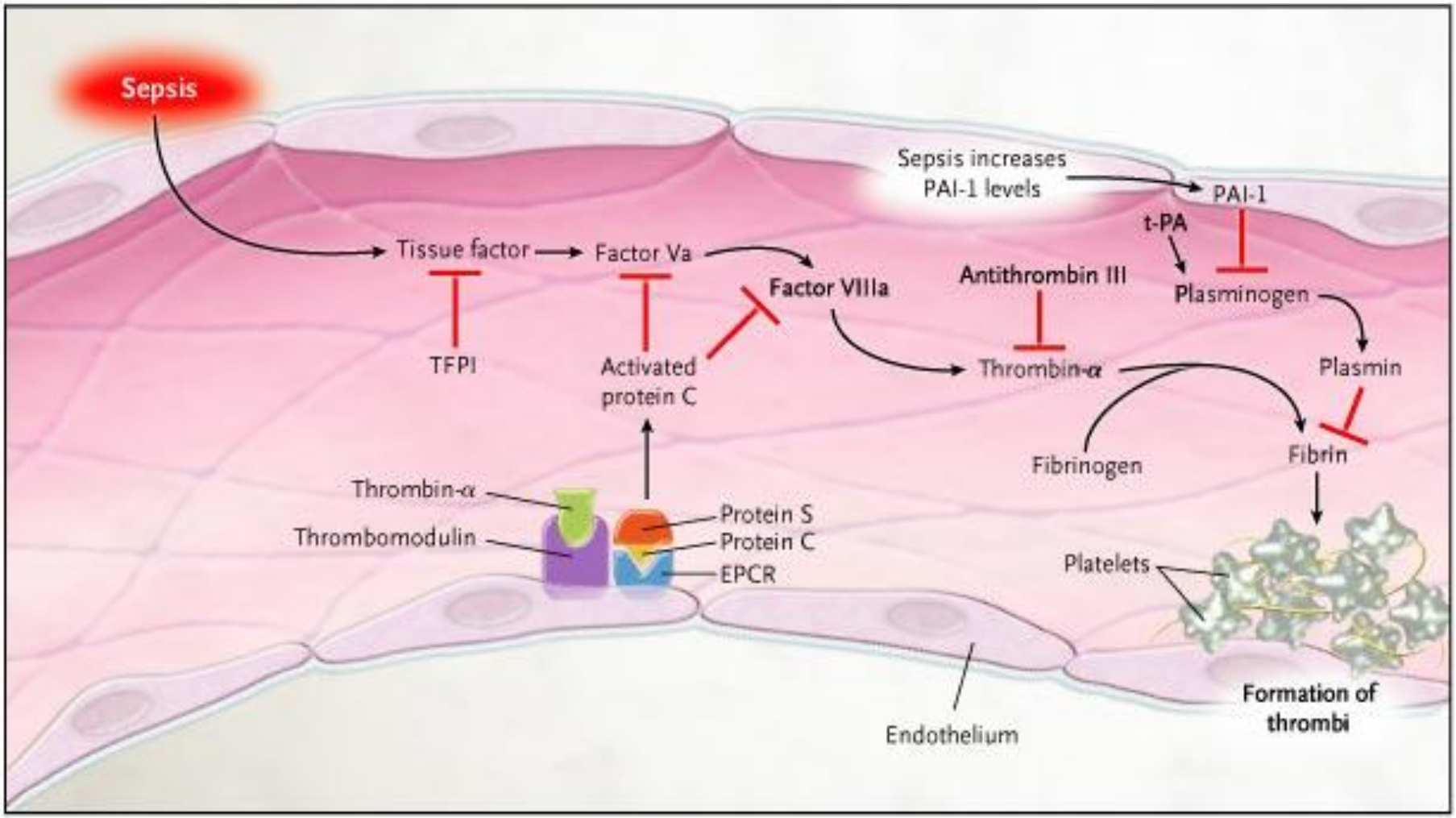
Pathophysiology of Sepsis

Inflammatory Responses to Sepsis



Russell J. *N Engl J Med* 2006;355:1699-1713

Procoagulant Response in Sepsis



Russell J. *N Engl J Med* 2006;355:1699-1713

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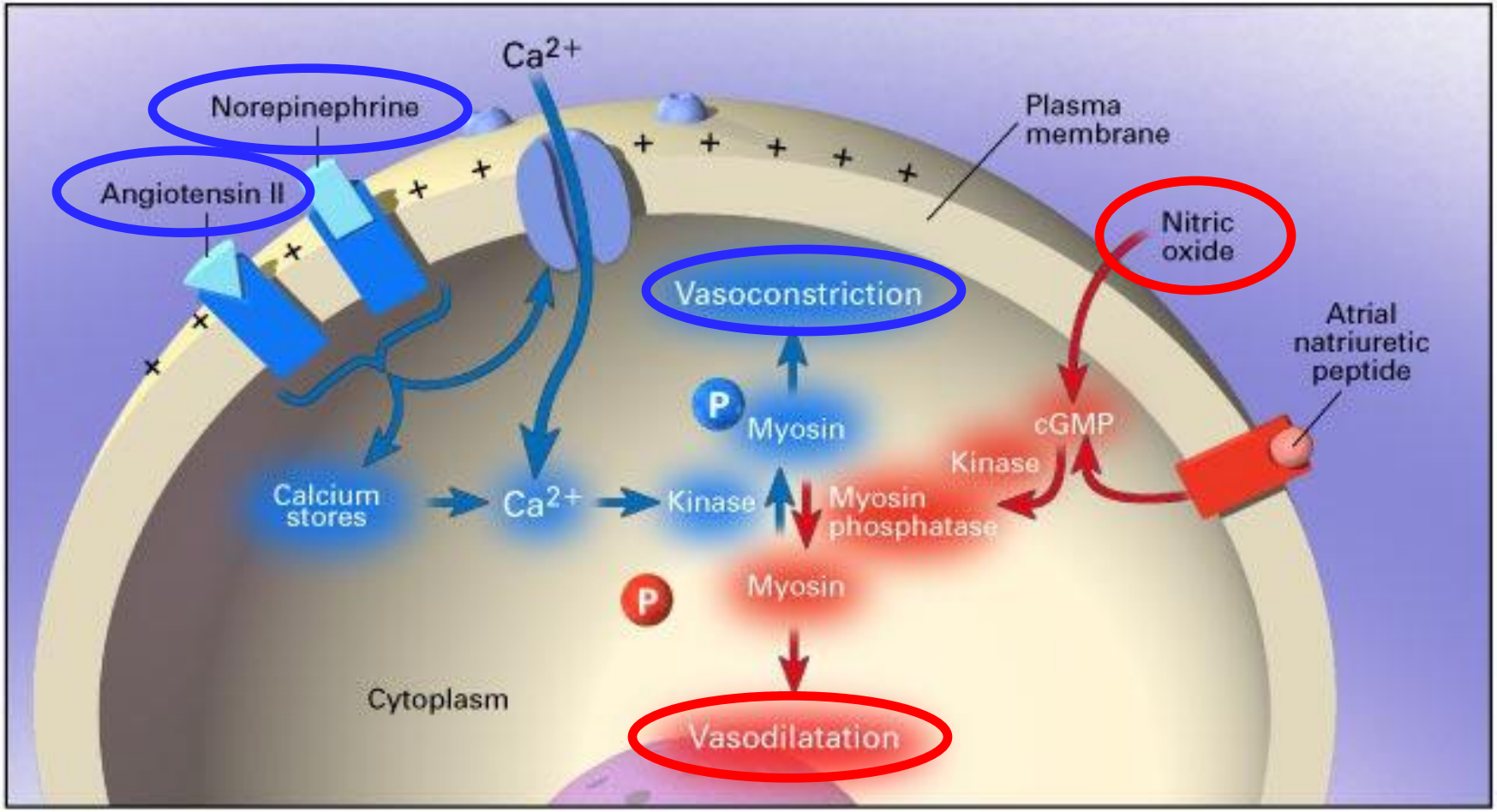
Regulation of Vascular Smooth-Muscle Tone



Landry D. *N Engl J Med* 2001;345:588-595

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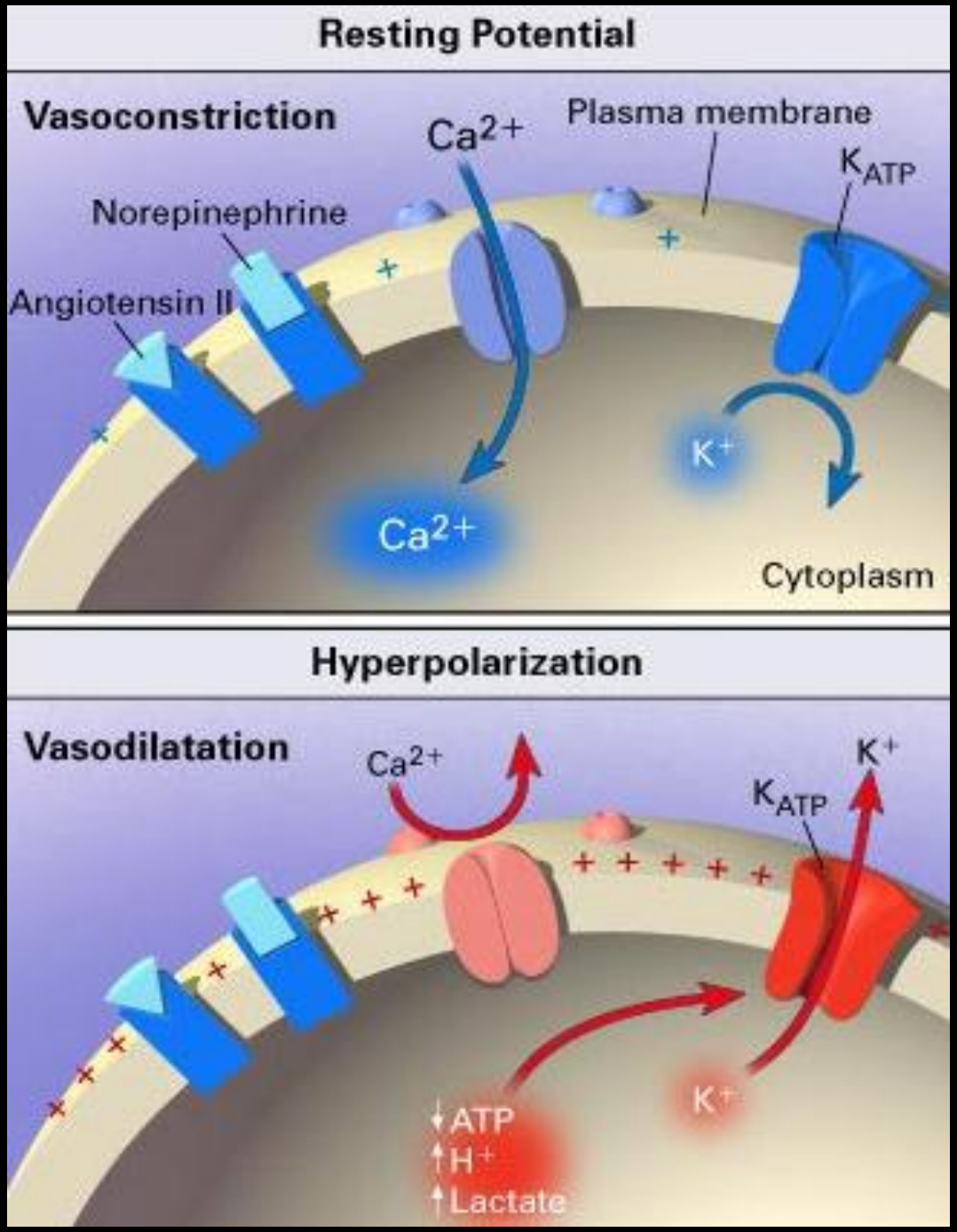

Effect of Membrane Potential on the Regulation of Vascular Tone

Effect of Lactic Acidosis on Vascular Tone

Landry D. *N Engl J Med* 2001;345:588-595

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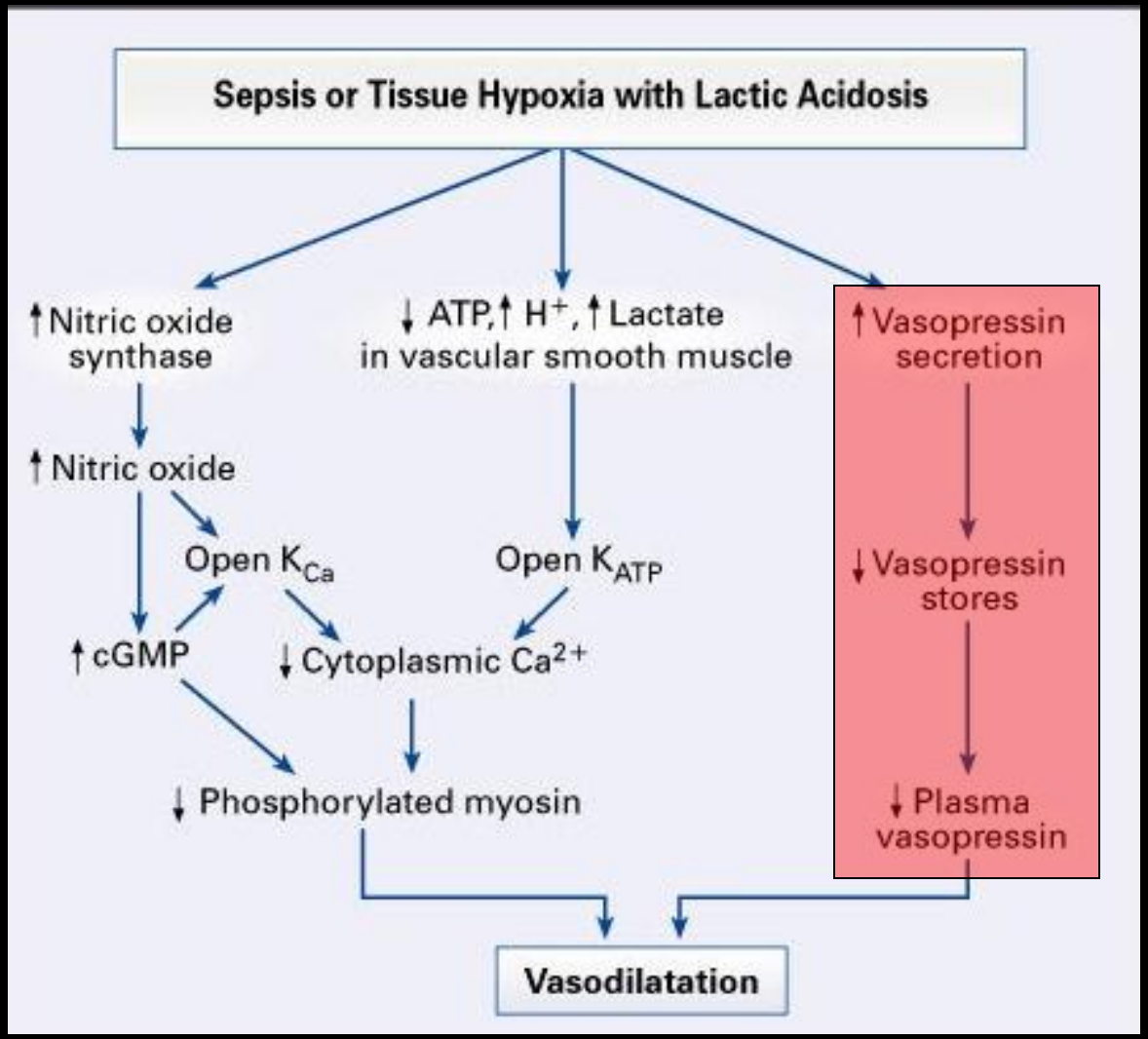
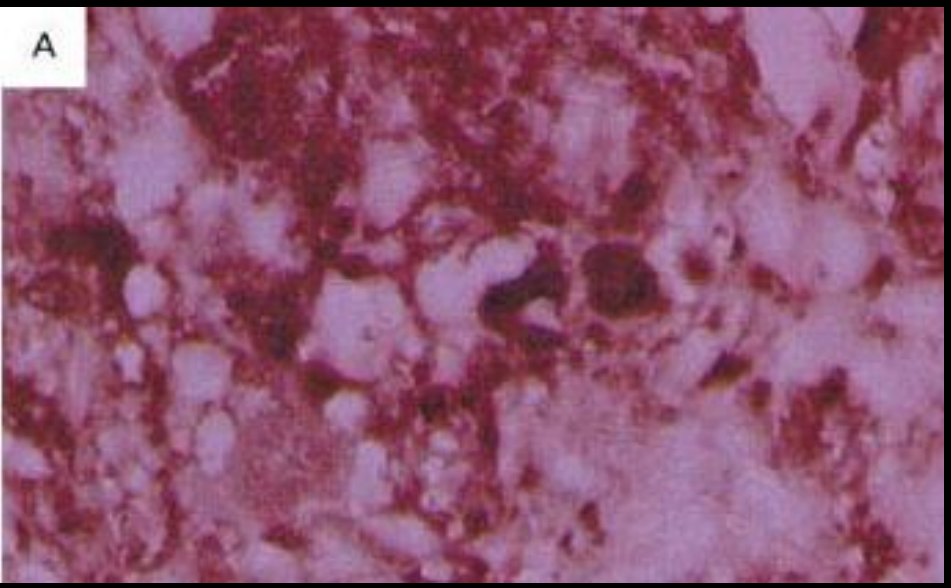
Mechanisms of Vasodilatory Shock

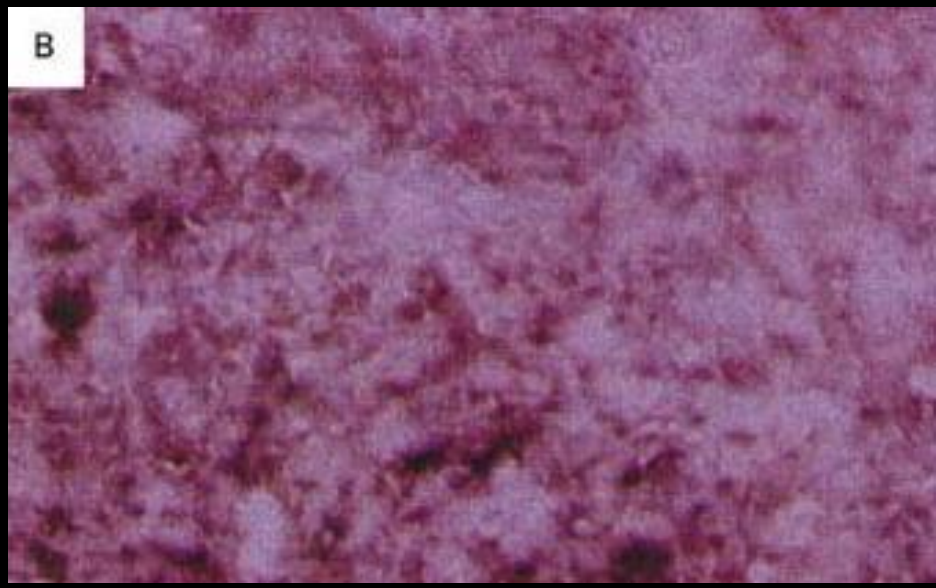


Landry D. *N Engl J Med* 2001;345:588-595

Vasopressin immunoreactivity in the neurohypophysis after severe hemorrhagic hypotension (MAP 40 mm Hg) for one hour



Normal Dog



After Shock for One Hour

Landry D. *N Engl J Med* 2001;345:588-595

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Stages of Sepsis

From tissue insult to SIRS to Sepsis to Severe Sepsis to MODS to Death

From the Dogs of War to the Doves of Peace

Compensatory Anti-Inflammatory Response Syndrome (CARS)

- **Follows SIRS; may be as large or larger**
  - **Downregulation of inflammatory cytokines**
    - TNF-γ and IL-2
  - **Upregulation of anti-inflammatory cytokines**
    - IL-4, 6, 10, 11, 13, TNF-α, IL-1 ra, TFG-β
  - **Impaired Antigen presenting activity**
    - Diminished MHC-2 expression
  - **HLA-DR monocyte expression reduced to < 30%**
    - Diminished ability to produce inflammatory cytokines

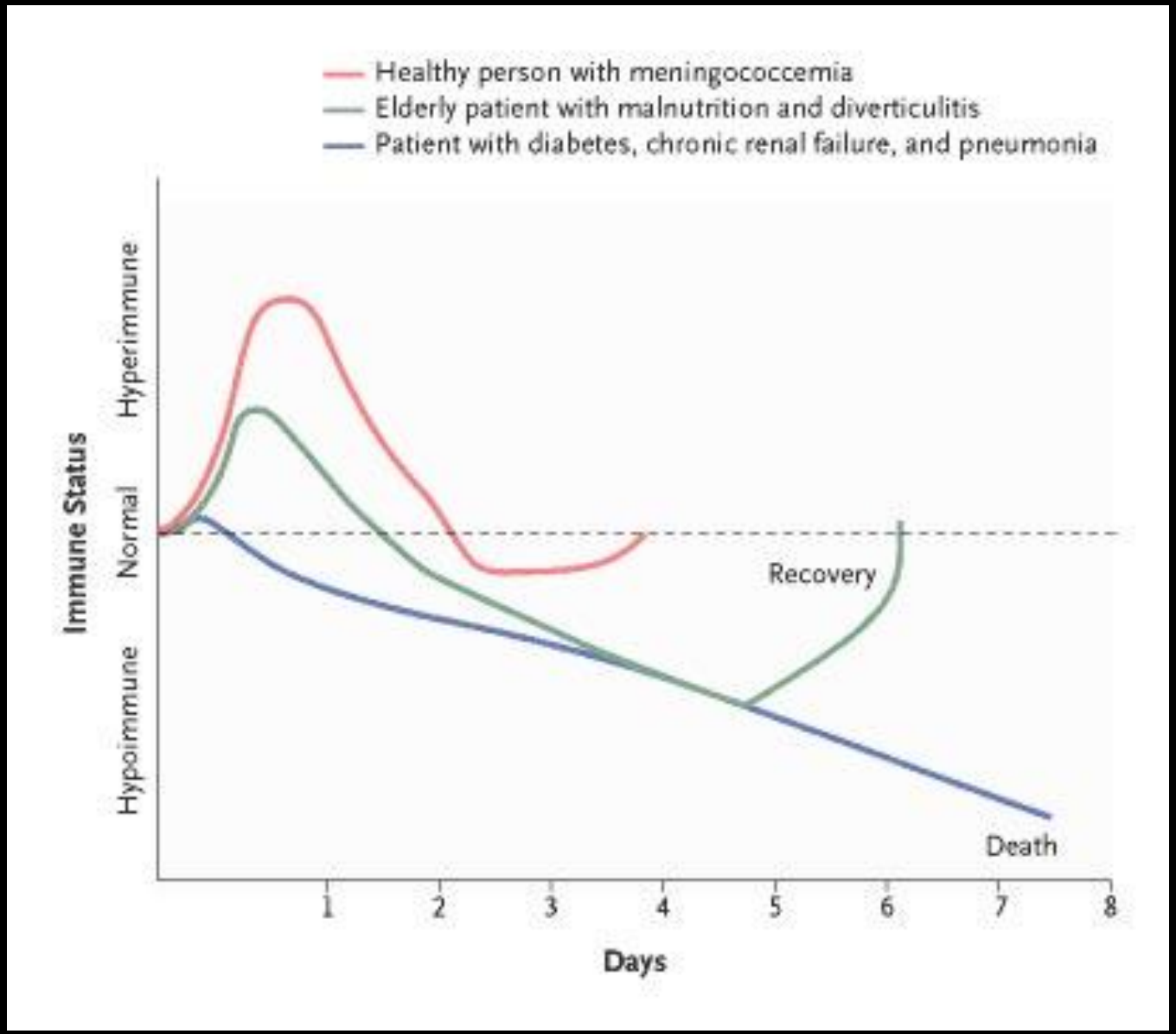
Bone RC. *Chest* 1997; 112:235-243
Fisher CJ. *Crit Care Med* 1993; 21:318-27

Stages after Initial Insult

- Local inflammation/CARS
- Systemic inflammation/CARS
- Loss of inflammatory regulation
- Excessive anti-inflammatory reaction
- Immunologic dissonance

Bone RC. *Chest* 1997; 112:235-43

Immunologic Response of Three Hypothetical Patients with Sepsis



Hotchkiss R and Karl I. N Engl J Med 2003;348:138-150

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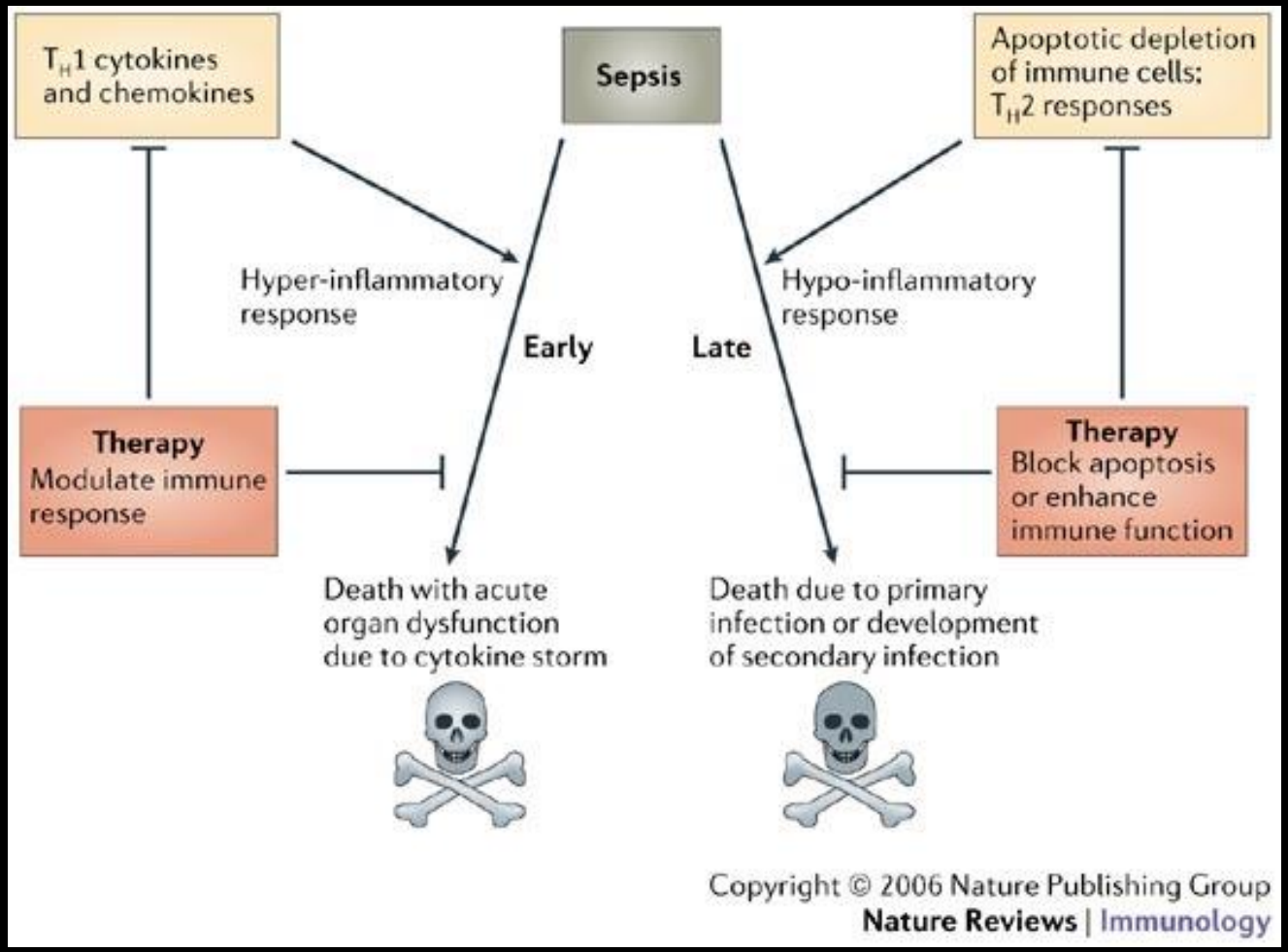
Apoptosis and caspases regulate death and inflammation in sepsis

Richard S. Hotchkiss and Donald W. Nicholson‡*



Hotchkiss *Nature Reviews Immunology* 2006; 6:813-22

nature REVIEWS IMMUNOLOGY

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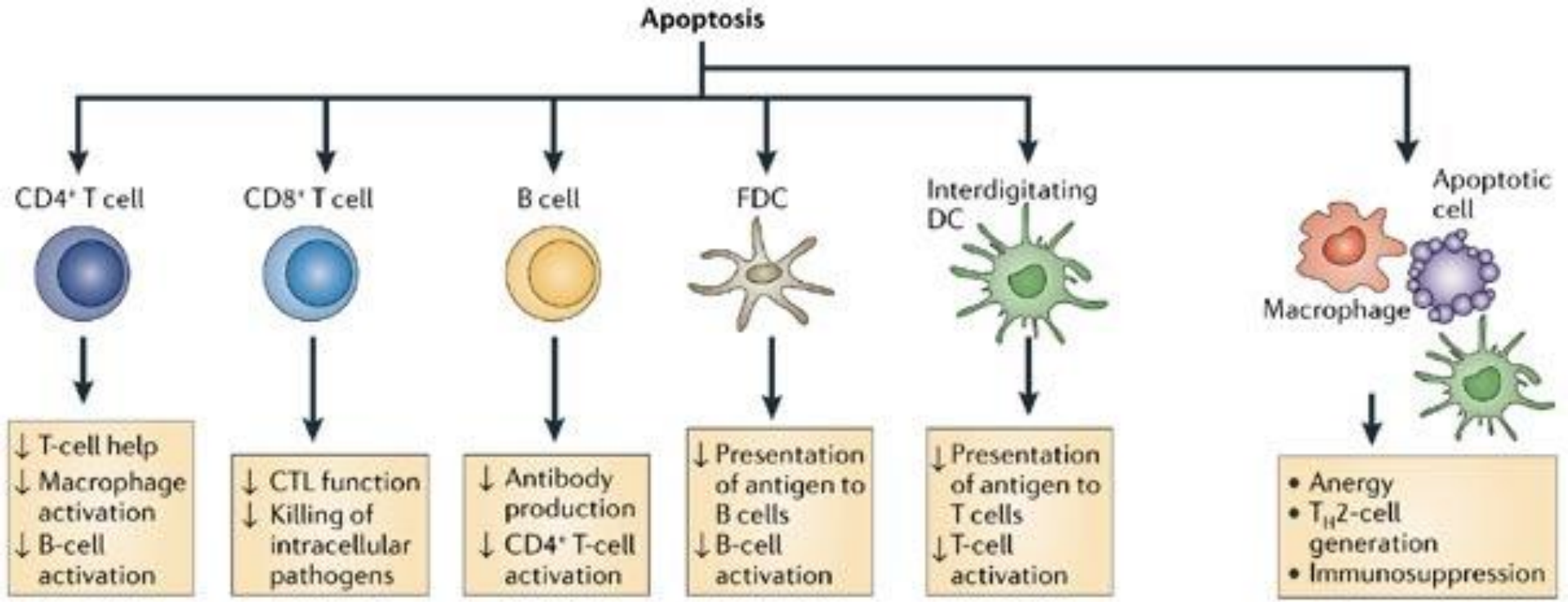

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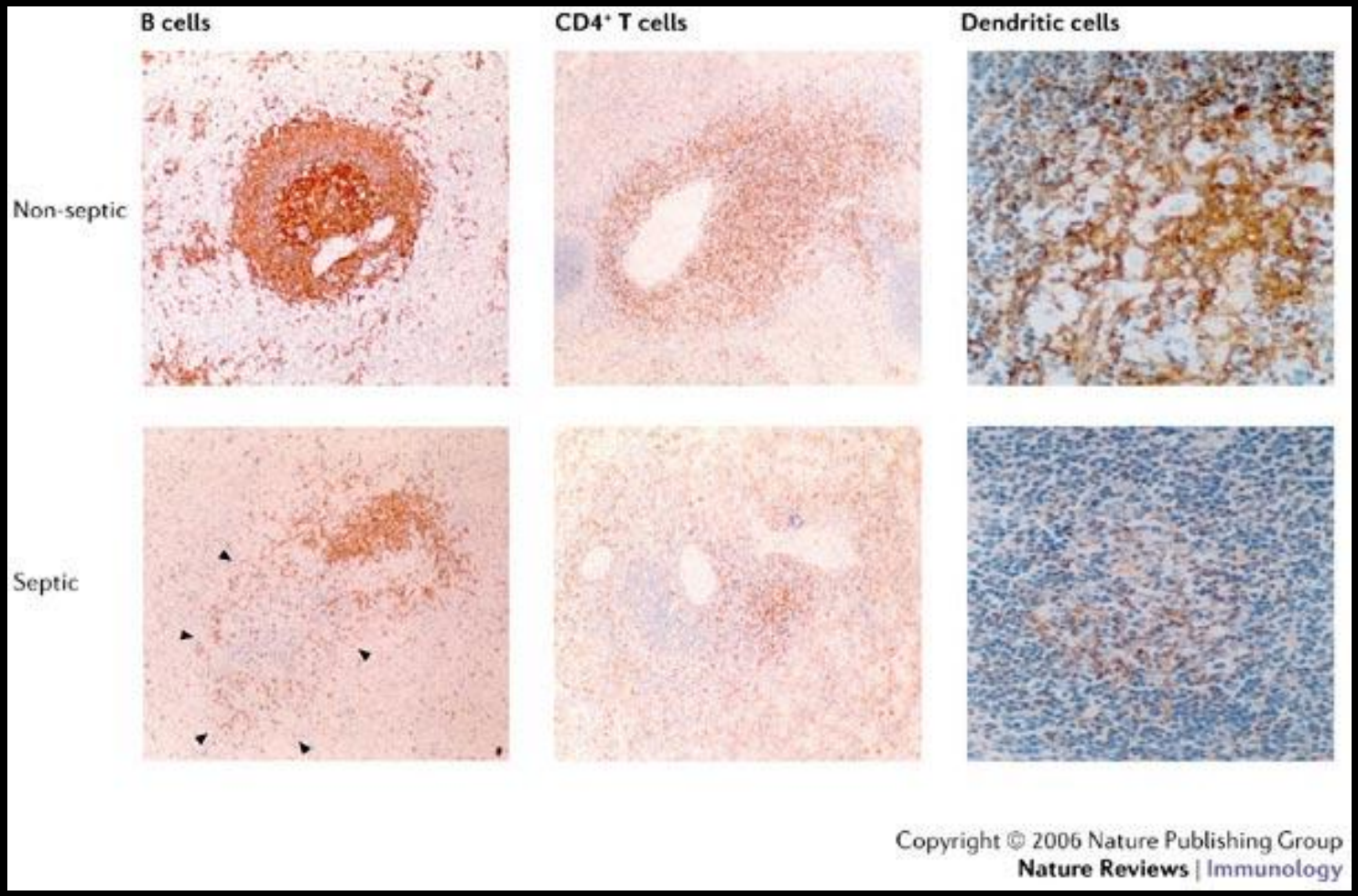

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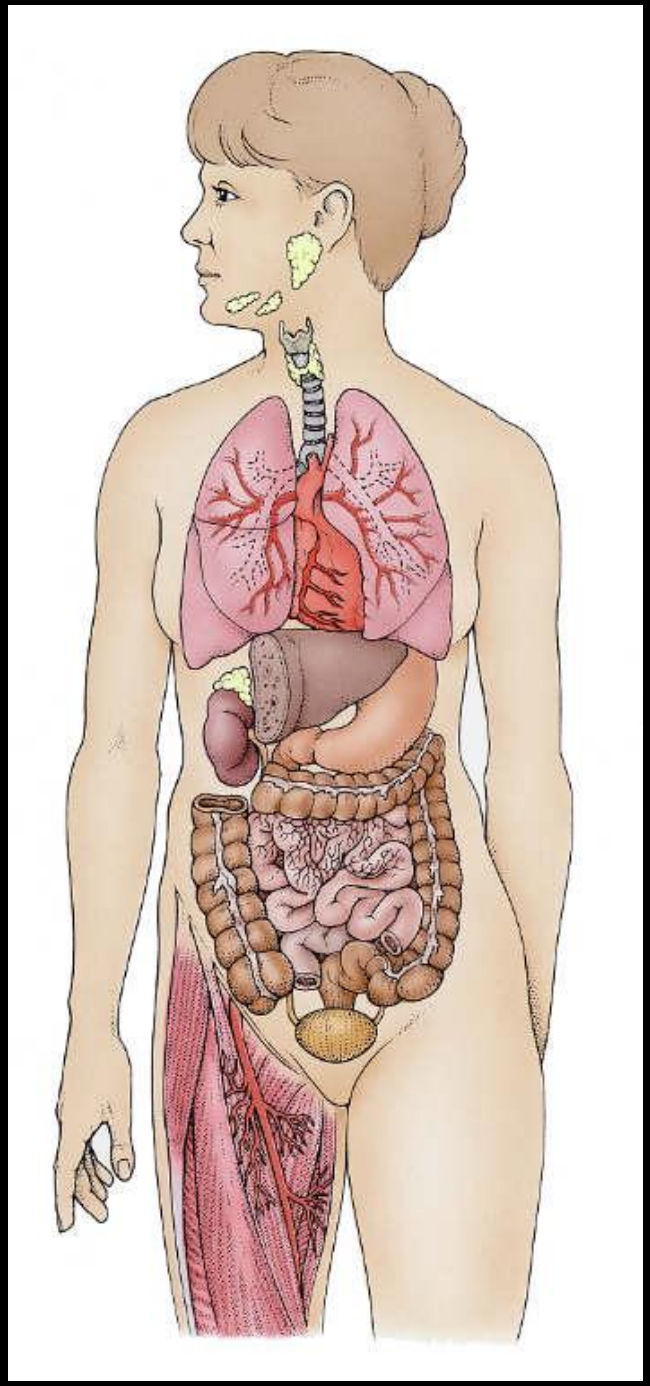
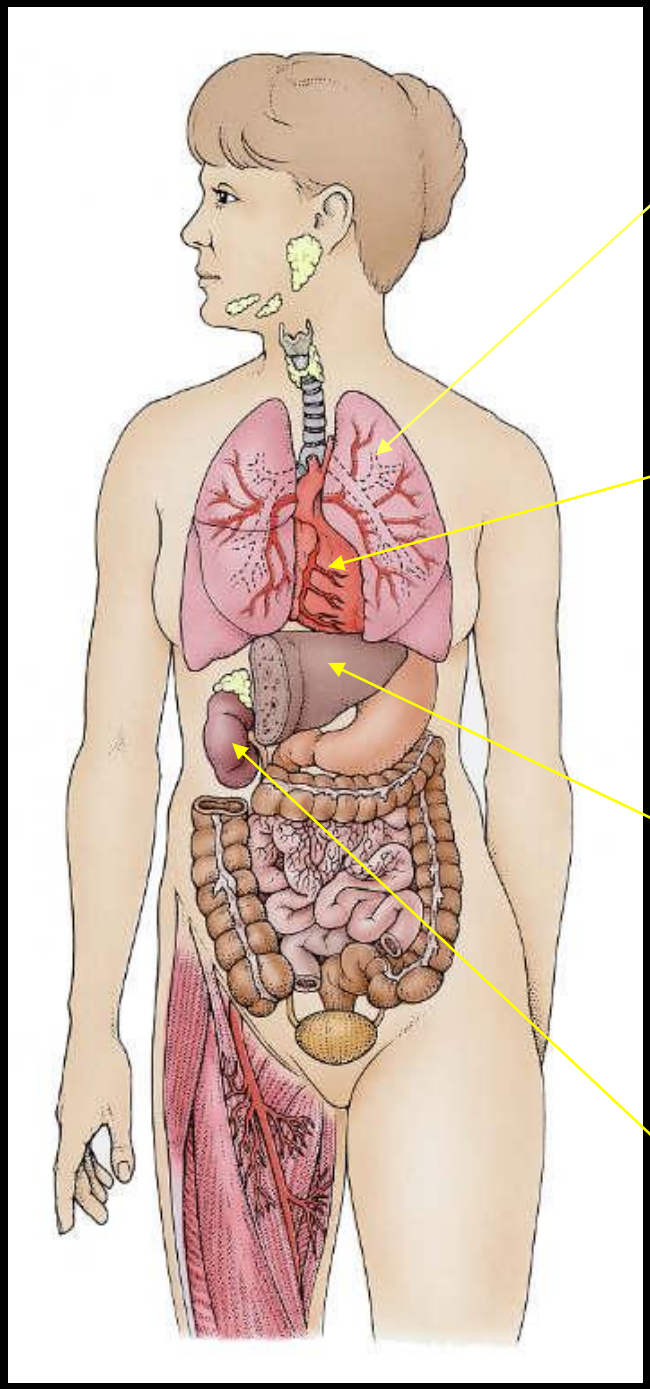
nature REVIEWS IMMUNOLOGY



All Organ Systems Can Be Affected in Severe Sepsis/Septic Shock



Respiratory Dysfunction

Failure of oxygenation

Need for Mechanical Ventilation

Neurologic Dysfunction

Altered mental status

Deceased GCS, delirium, obtundation, coma

Cardiovascular Dysfunction

Hypotension

Arrythmia

Use of inotropic or vasopressor support

Elevated CVP or PCWP

Changes in heart rate

Cardiac arrest

GI Dysfunction

GI Bleeding

Acalculous cholecystitis

Pancreatitis

Ileus

Intolerance of enteral nutrition

Intestinal ischemia or infarction

Development of GI perforation

Hepatic Dysfunction

Elvevated serum aminotransferases

Elevated LDH

Elevated alkaline phosphatase

Jaundice/hyperbilirubinemia

Hypoalbuminemia

Elevated Prothrombin time (PT)

Hematologic Dysfunction

Coagulopathy with high PT, PTT, DIC

Thrombocytopenia

Leukocytosis/leukopenia

Endocrine Dysfunction

Hyperglycemia (insulin resistance)

Thyroid dysfunction

Hypertriglyceridemia

Hypoalbuminemia

Hypercatabolism

Weight loss

Renal Dysfunction

Increased serum creatinine

Decreased urine output

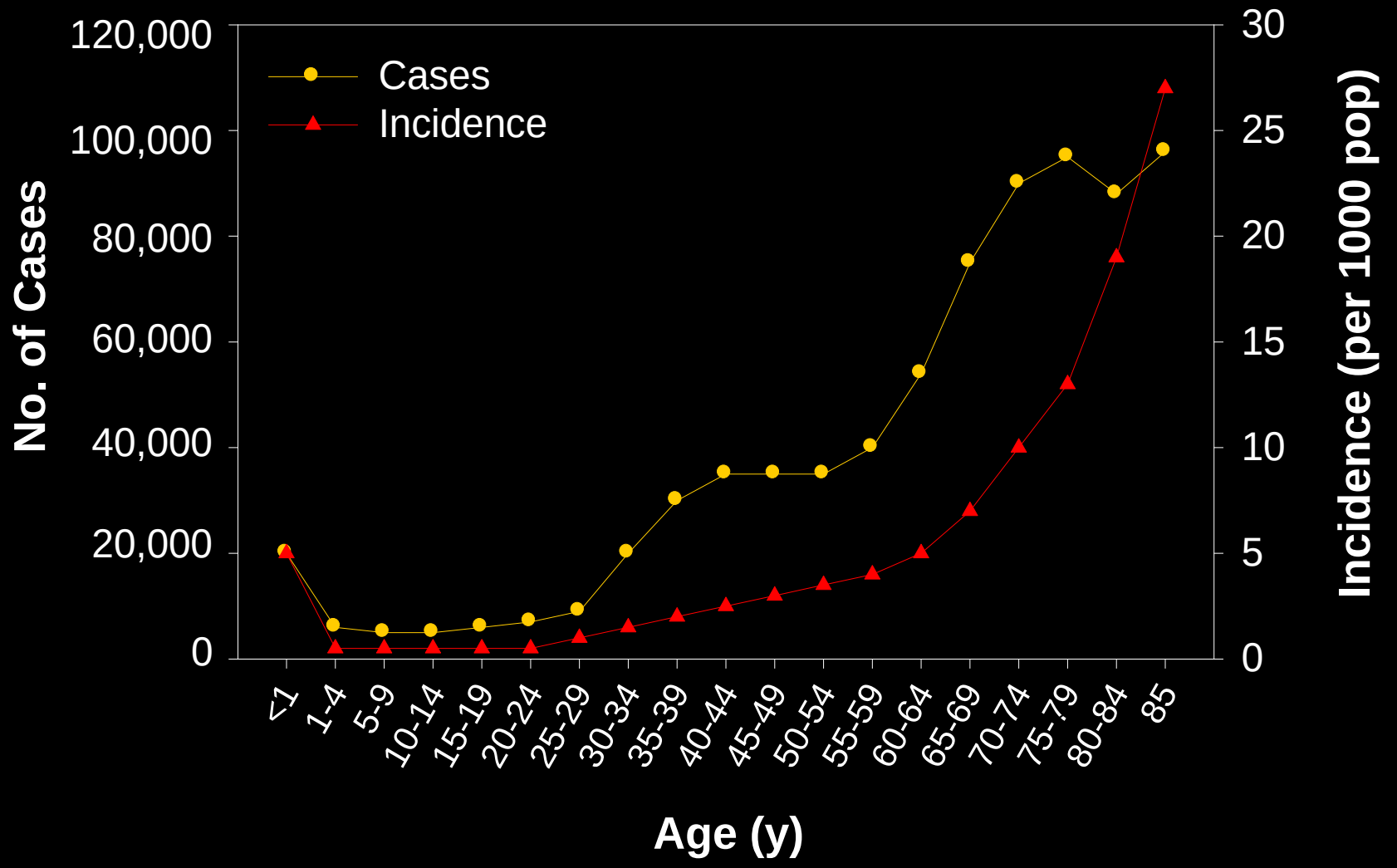
Need for renal replacement therapy

Immune System Dysfunction

Epidemiology of Sepsis

More cases, worse bugs

Age-Specific Number and Incidence of Severe Sepsis in the United States



Angus DC, et al. *Crit Care Med*. 2001.

Increasing Incidence of Sepsis

- **New cases increase by 1.5% per year**
  - More elderly
  - More invasive/diagnostic procedures
  - More immunocompromised patients
  - More immunosuppressive & cytotoxic therapy
  - More microorganism resistance
  - More awareness

Characteristics of Patients with Sepsis from 1979 - 2000

Table 1. Characteristics of Patients with Sepsis, According to Subperiod.*

Characteristic	1979–1984 (N=1,332,468)	1985–1989 (N=2,220,659)	1990–1994 (N=2,697,472)	1995–2000 (N=4,068,819)
Demographic characteristics				
Age — yr	57.4±28.9	59.3±22.9	60.8±16.2	60.8±13.7
Male sex — %	49.6	48.9	46.8	48.0
Race — no./100,000 population (% of patients)†				
White	92.1 (81.2)	166.4 (80.3)	167.8 (78.5)	186.3 (76.3)
Black	163.0 (15.2)	301.7 (16.0)	322.8 (17.2)	378.2 (17.7)
Other	187.3 (3.6)	298.0 (3.7)	300.6 (4.3)	370.5 (6.0)
Length of hospital stay — days	17.0±8.5	15.6±6.0	15.3±4.0	11.8±2.6
Coexisting conditions — % of patients				
Chronic obstructive pulmonary disease	5.7	7.3	9.3	12.1
Congestive heart failure	8.6	9.9	13.6	15.2
Cancer	17.1	17.9	18.0	14.5
HIV infection‡	—	1.0	2.1	2.0
Cirrhosis	2.4	2.5	2.2	2.3
Diabetes	12.2	14.5	16.9	18.7
Hypertension	7.0	9.2	13.6	18.6
Pregnancy	0.6	0.5	0.4	0.3
No. of organs with failure — % of patients				
0	83.2	78.1	74.0	66.4
1	13.6	17.9	20.1	24.6
2	2.7	3.5	4.8	7.1
≥3	0.5	0.5	1.1	1.9

Martin, G. et al. N Engl J Med 2003;348:1546-1554

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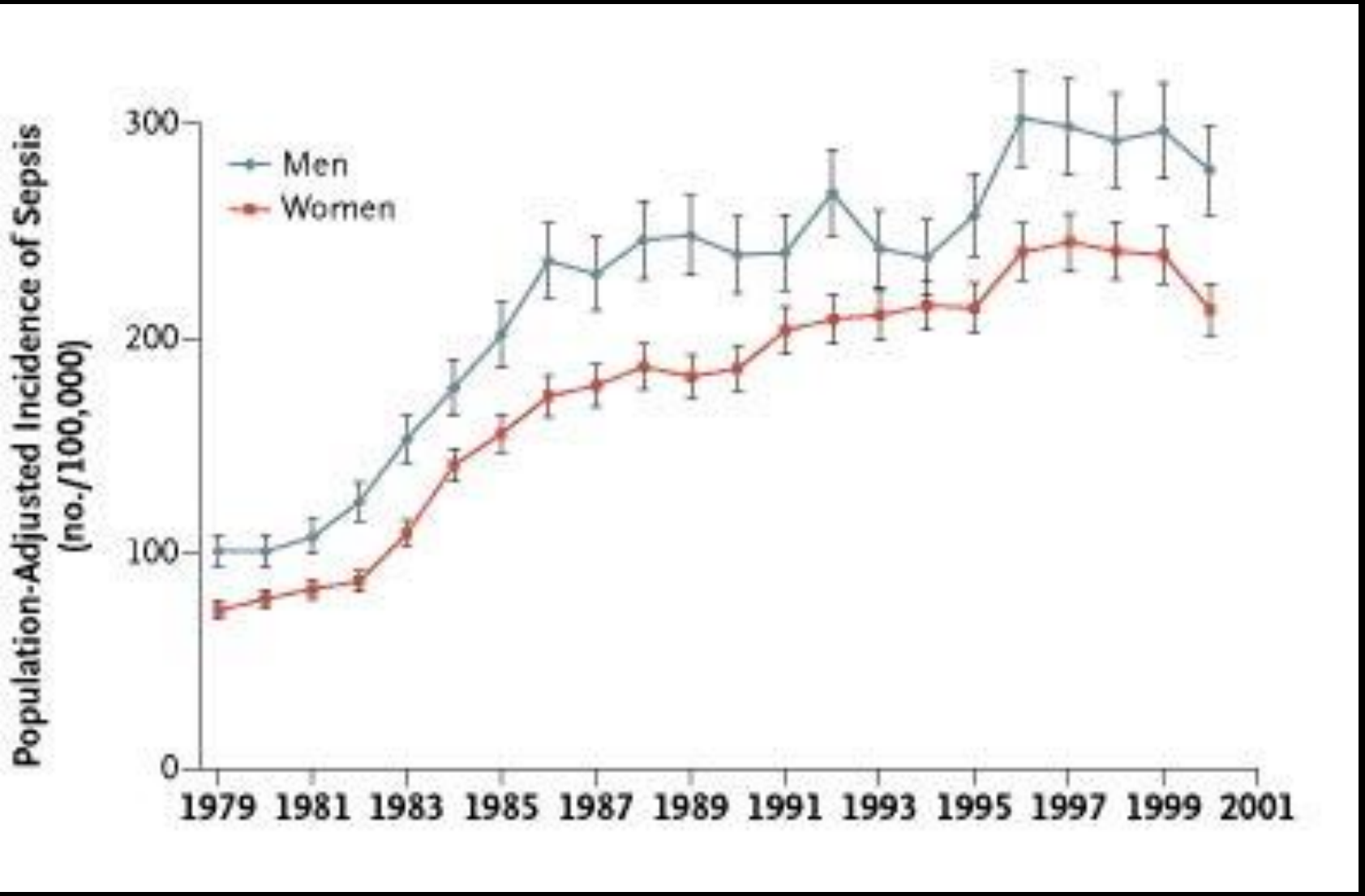
Population-Adjusted Incidence of Sepsis, According to Sex, 1979-2000



Martin, G. et al. N Engl J Med 2003;348:1546-1554

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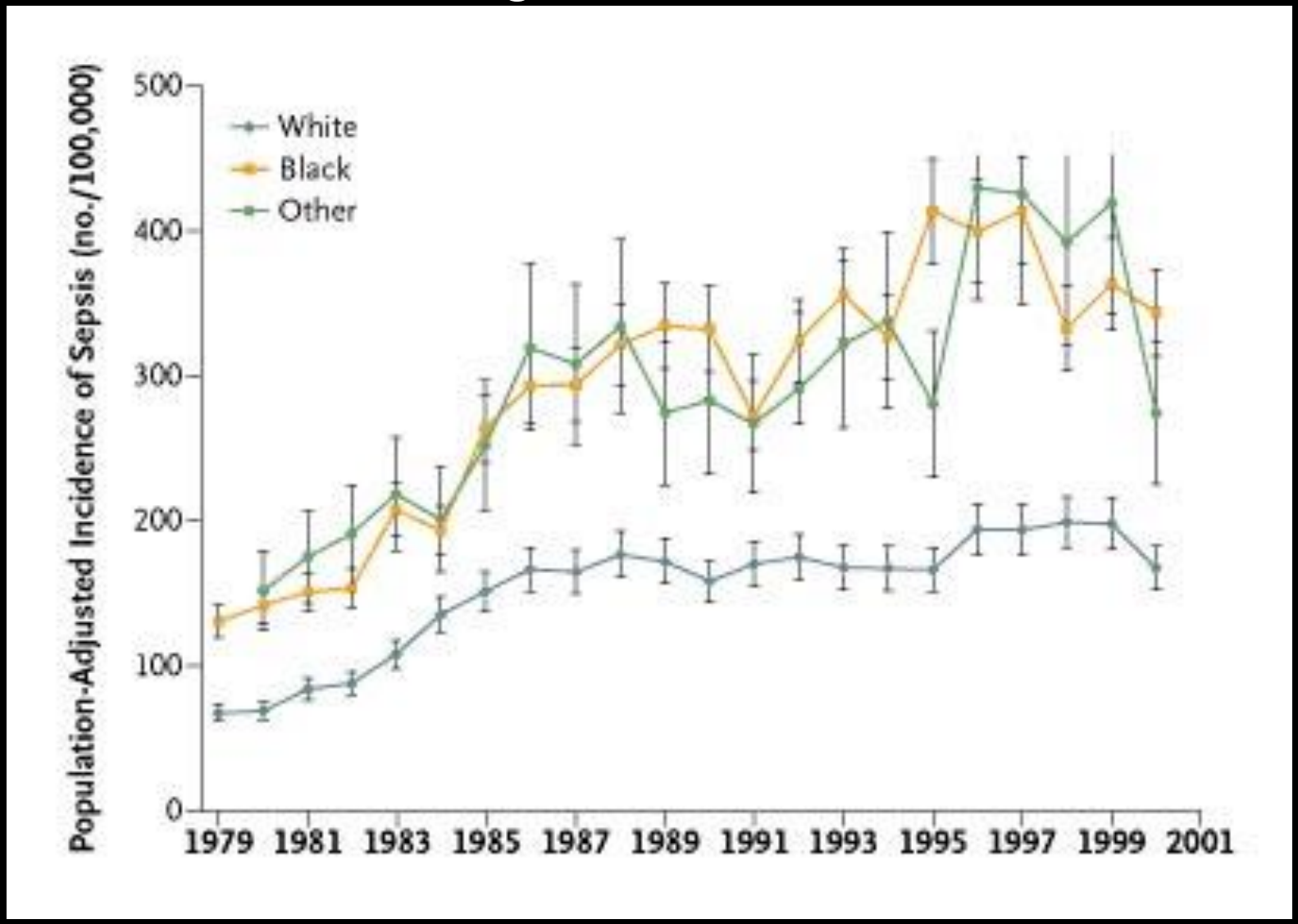
Population-Adjusted Incidence of Sepsis, According to Race, 1979-2000



Martin, G. et al. N Engl J Med 2003;348:1546-1554

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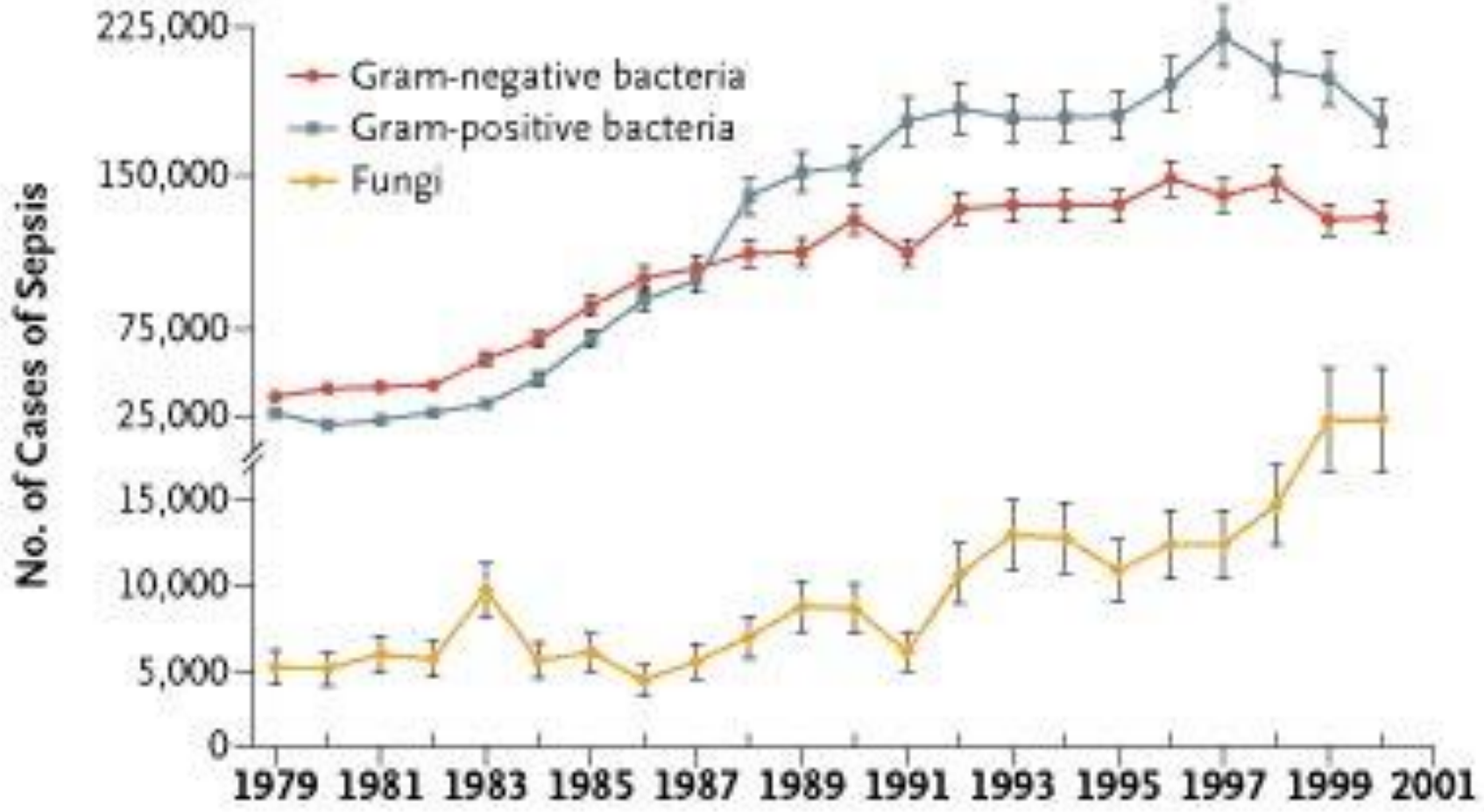
Numbers of Cases of Sepsis in the United States, According to the Causative Organism, 1979-2000



Martin, G. et al. N Engl J Med 2003;348:1546-1554

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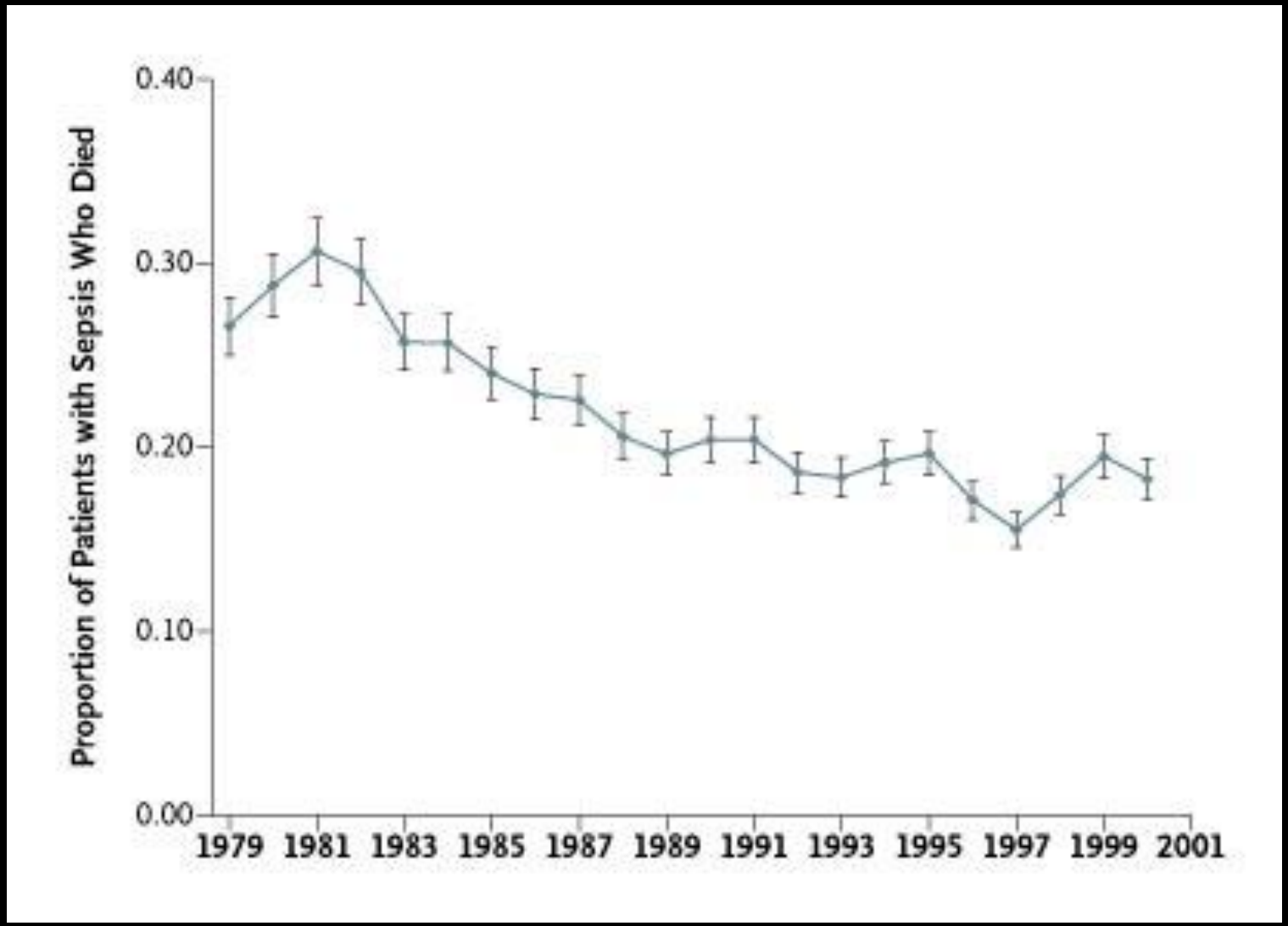
Overall In-Hospital Mortality Rate among Patients Hospitalized for Sepsis, 1979-2000



Martin, G. et al. N Engl J Med 2003;348:1546-1554

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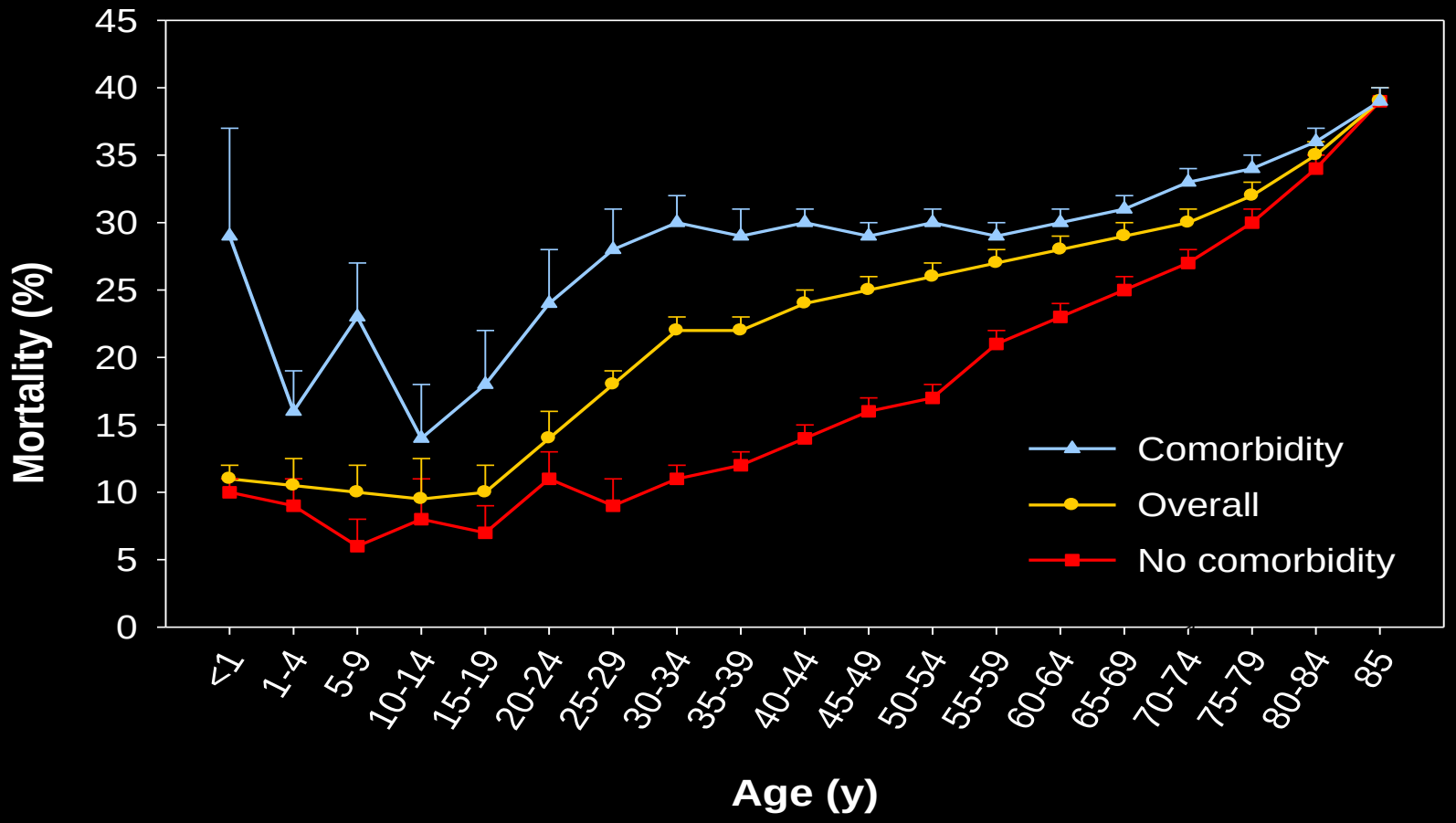
Age-Specific Mortality for Severe Sepsis in the United States



Angus DC, et al. *Crit Care Med*. 2001.

Fluid Management in Sepsis

A drop in the bucket

This is NOT a Good Idea

Excessive

Fluids

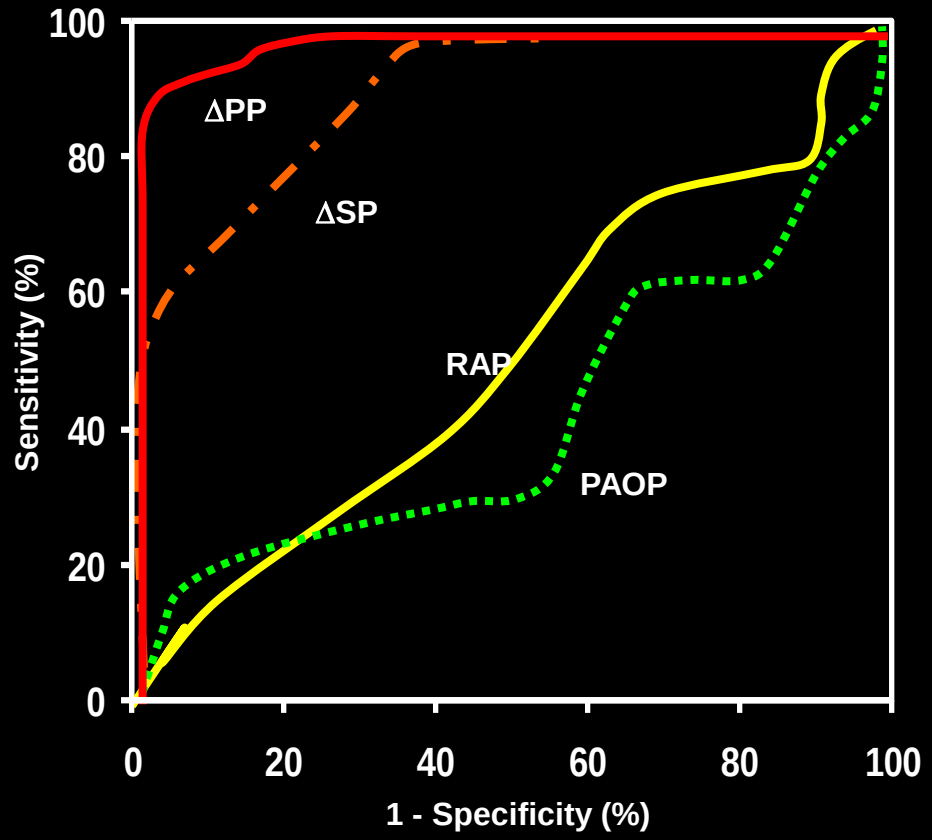
Fluids

Fluids

Positive Fluid Balance

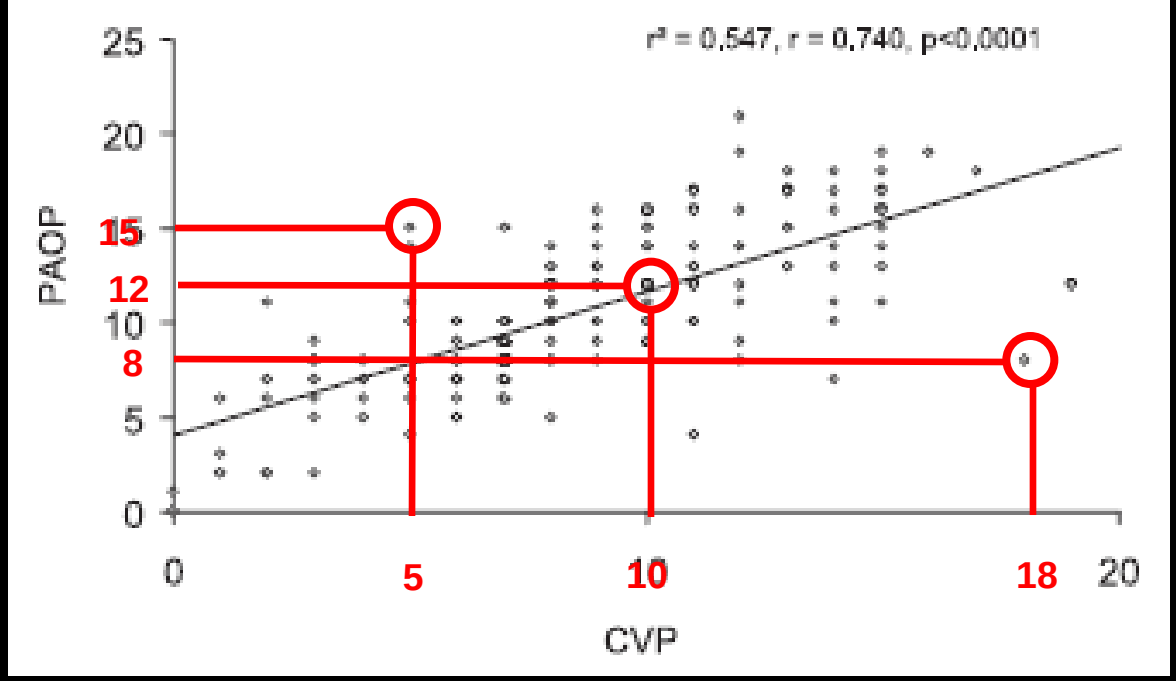
One of the strongest predictors of death

Comparing Methods of Determining Fluid Responsiveness

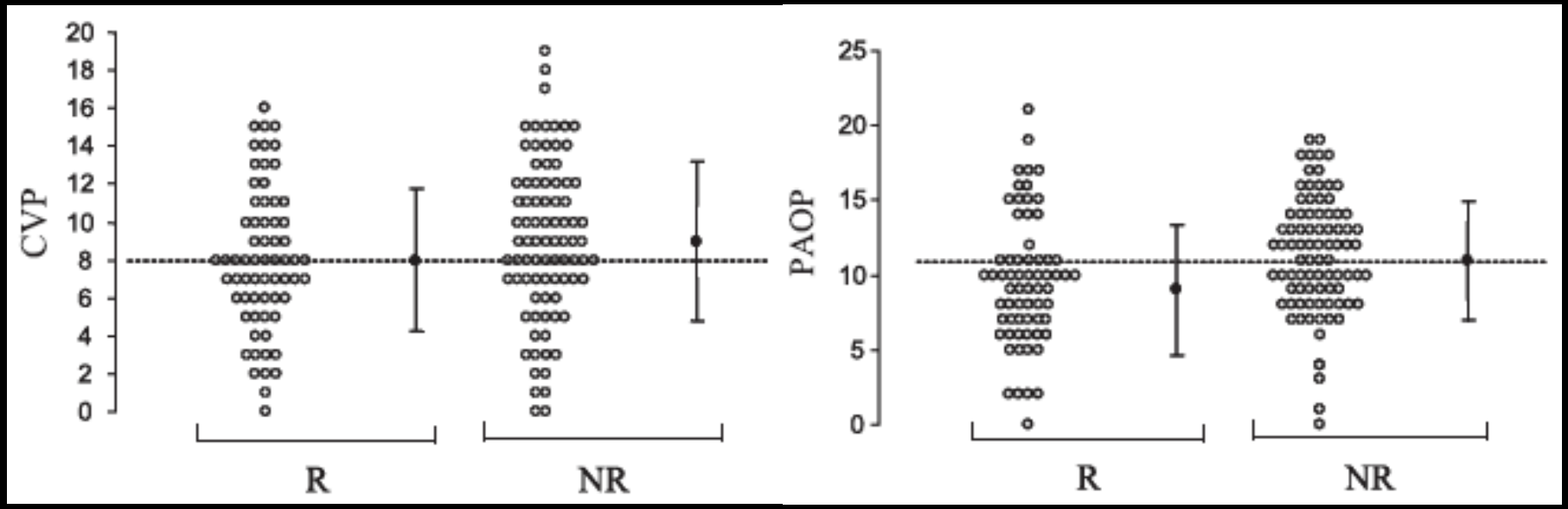


ROC curves comparing ΔPp, ΔPs, RAP, and PAOP to discriminate responders (CI increase ≥ 15%) and non-responders to volume expansion

Michard F. *Am J Respir Crit Care Med* 2000; 162:134-138

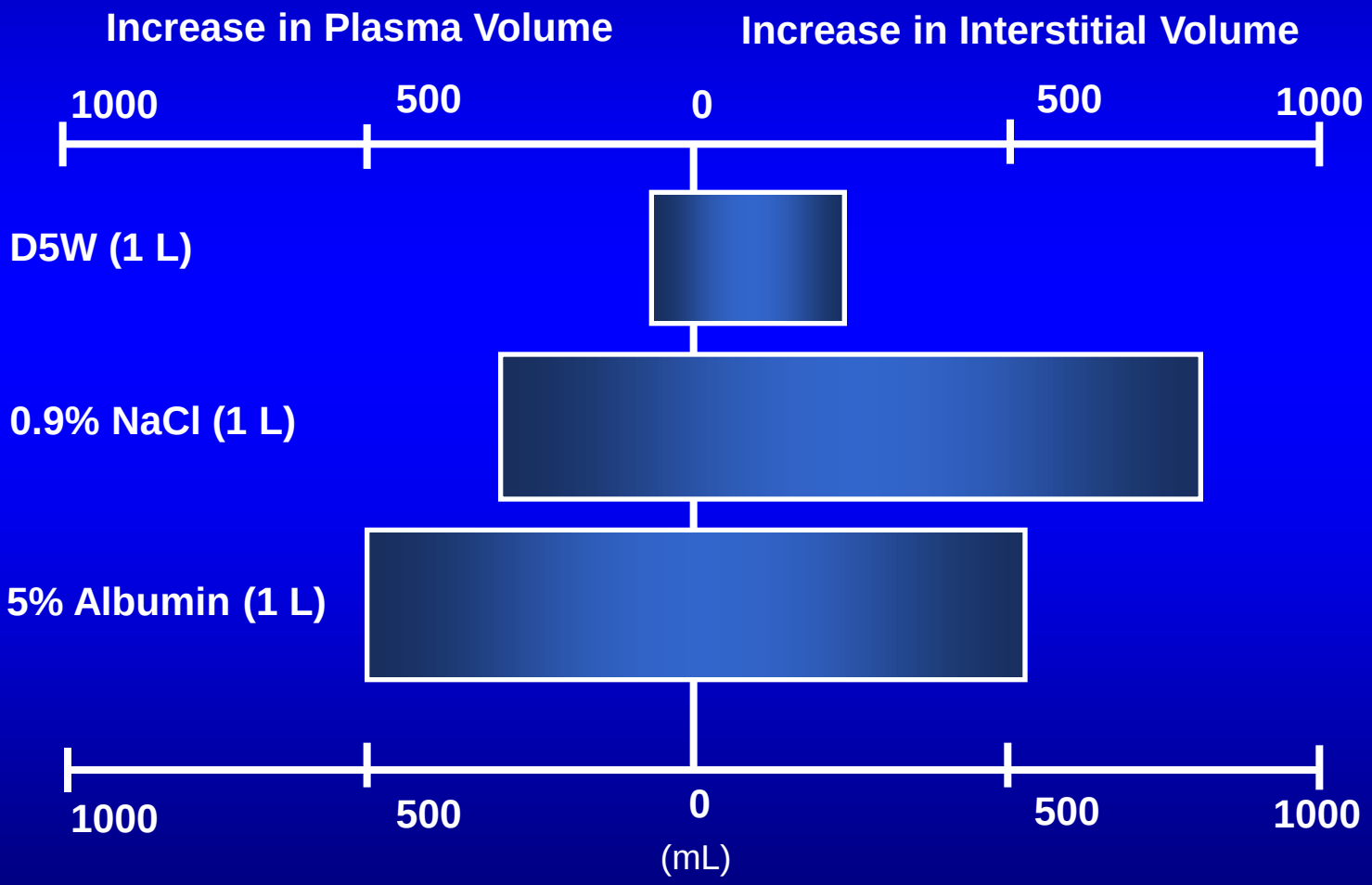


Relationship between CVP and PAOP before fluid loading in the overall population reveals a large overlap. Linear correlation $r^2 = 0.547$, $r = 0.740$, $p < 0.0001$



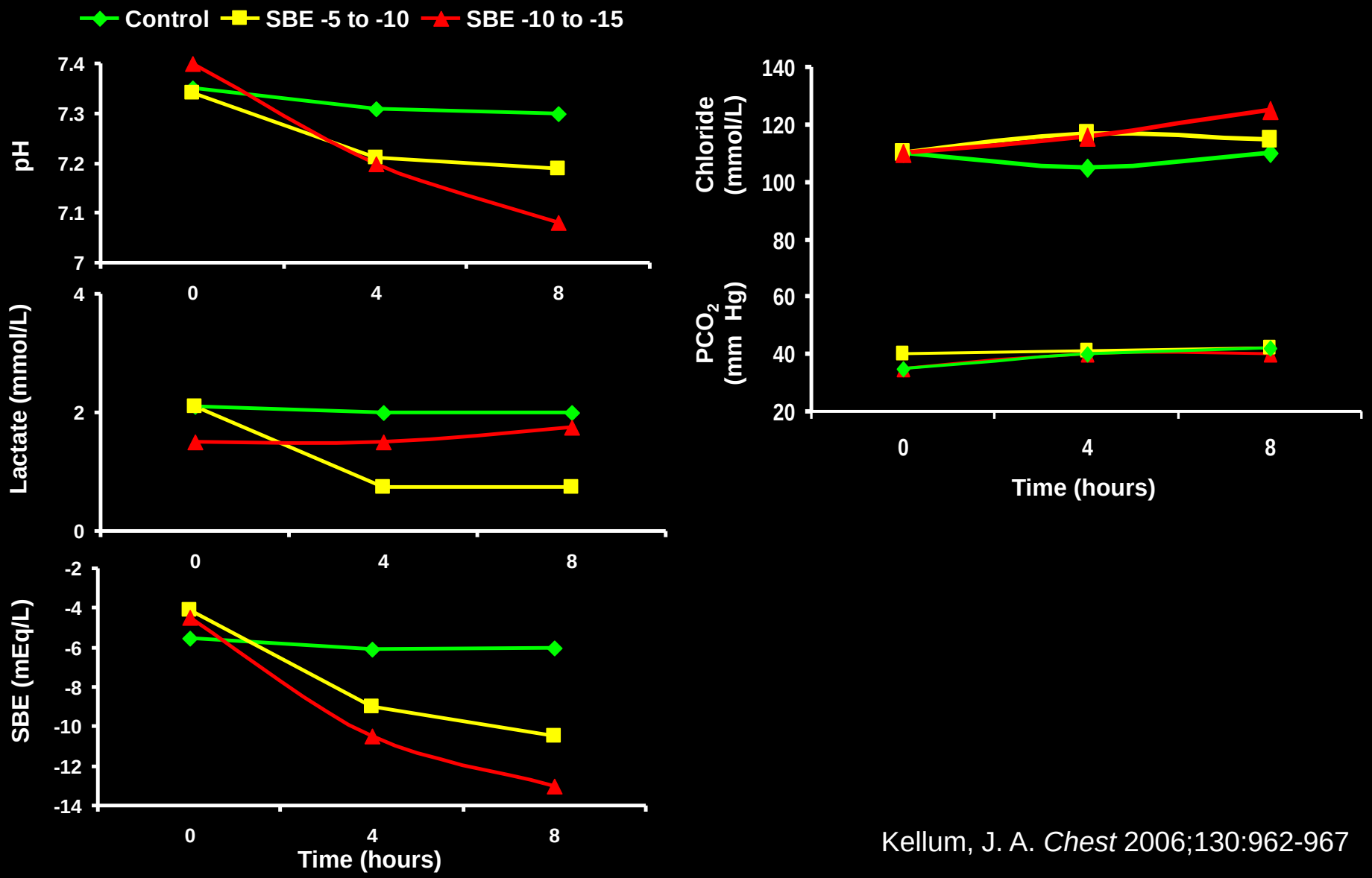
Individual values (open circles) and mean values ± SD (closed circles) of pre-infusion CVP and PAOP in responders (R) and nonresponders (NR)

Influence of Colloid and Crystalloid Fluids on Volume



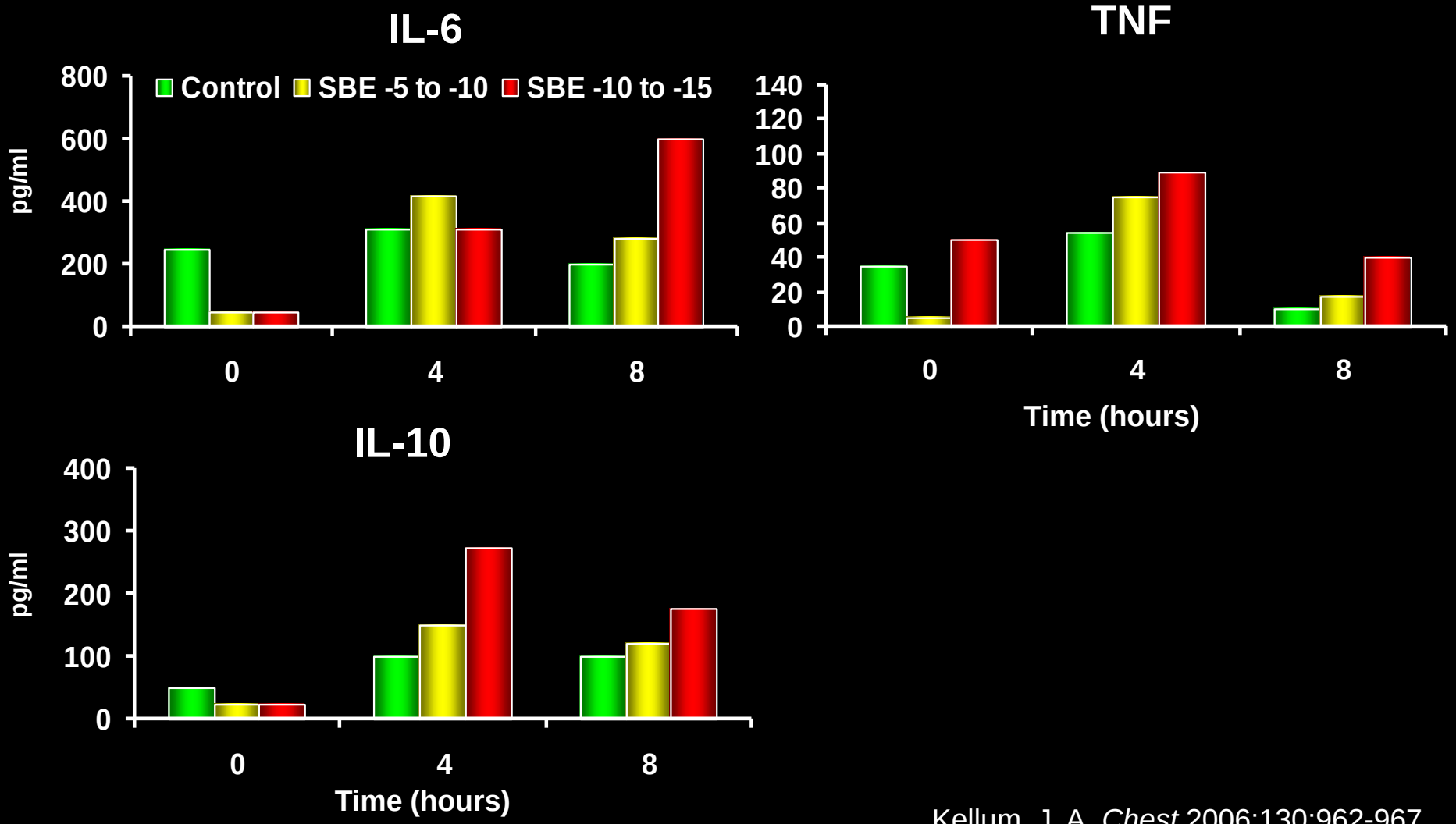
Imm A, Carlson RW. *Crit Care Clin* 1993; 9:313

Hyperchloremic Acidosis is Associated with Increased Serum Cytokine Levels



Kellum, J. A. *Chest* 2006;130:962-967

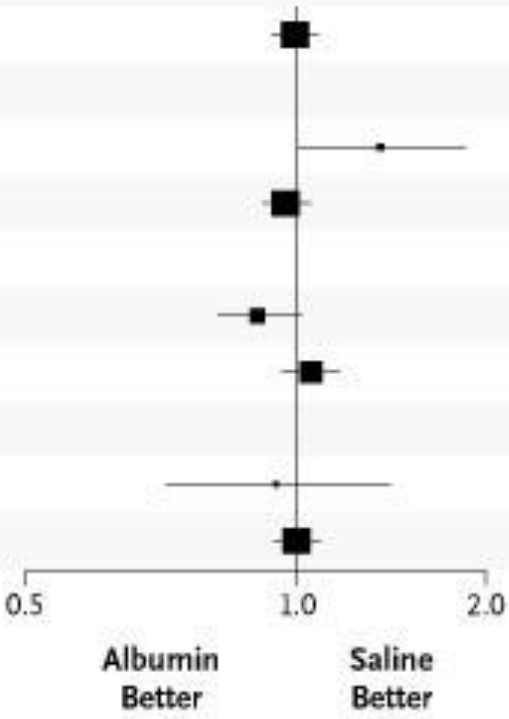
Hyperchloremic Acidosis induces changes in plasma IL-6, IL-10, and TNF



Kellum, J. A. *Chest* 2006;130:962-967

SAFE Study: Colloid vs. Crystalloid

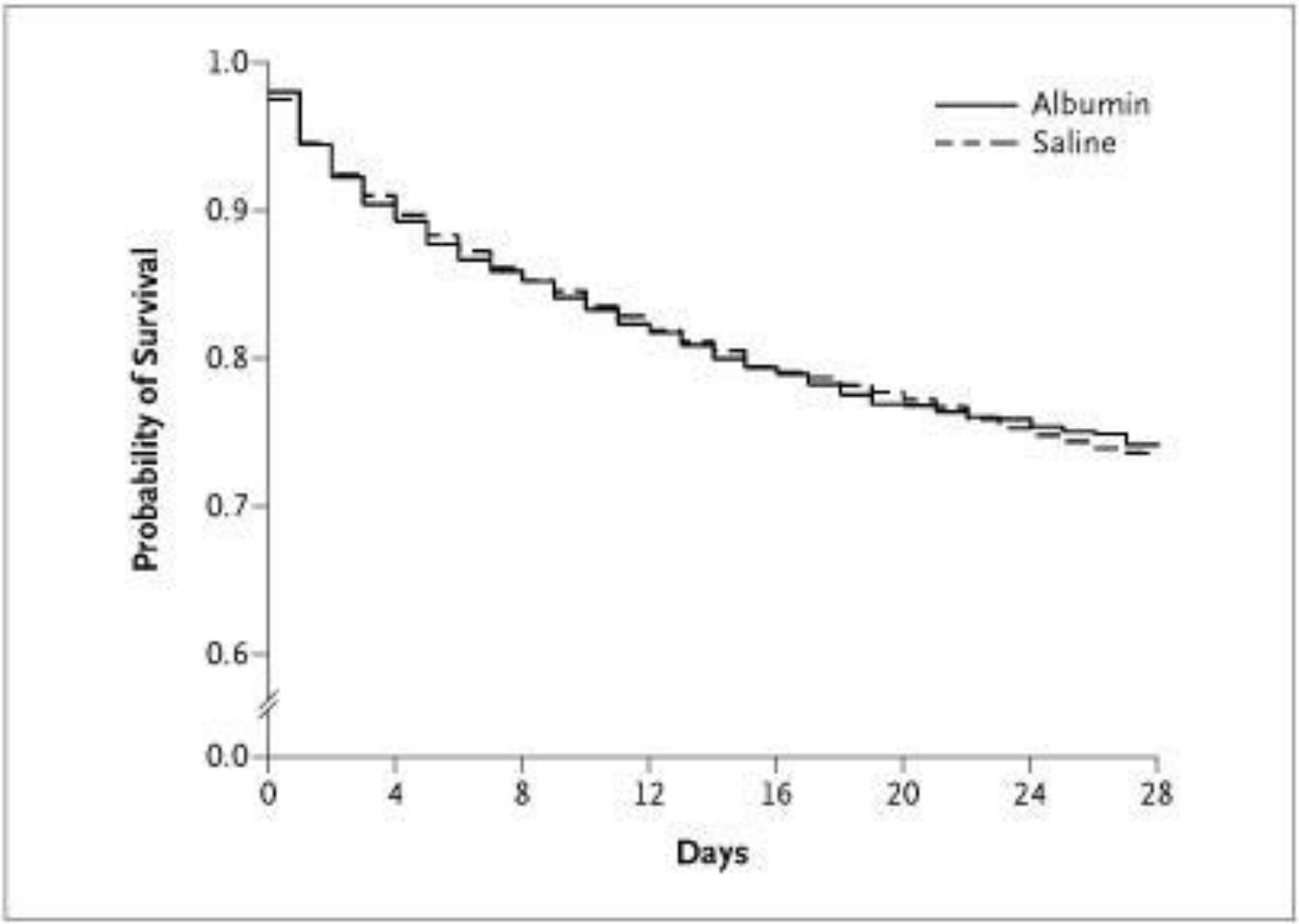
Patients	Albumin Group	Saline Group	Relative Risk (95% CI)
	no. of deaths/total no.		
Overall	726/3473	729/3460	0.99 (0.91–1.09)
Trauma			
Yes	81/596	59/590	1.36 (0.99–1.86)
No	641/2831	666/2830	0.96 (0.88–1.06)
Severe sepsis			
Yes	185/603	217/615	0.87 (0.74–1.02)
No	518/2734	492/2720	1.05 (0.94–1.17)
ARDS			
Yes	24/61	28/66	0.93 (0.61–1.41)
No	697/3365	697/3354	1.00 (0.91–1.09)



The SAFE Study Investigators. N Engl J Med 2004;350:2247-2256

The NEW ENGLAND JOURNAL of MEDICINE

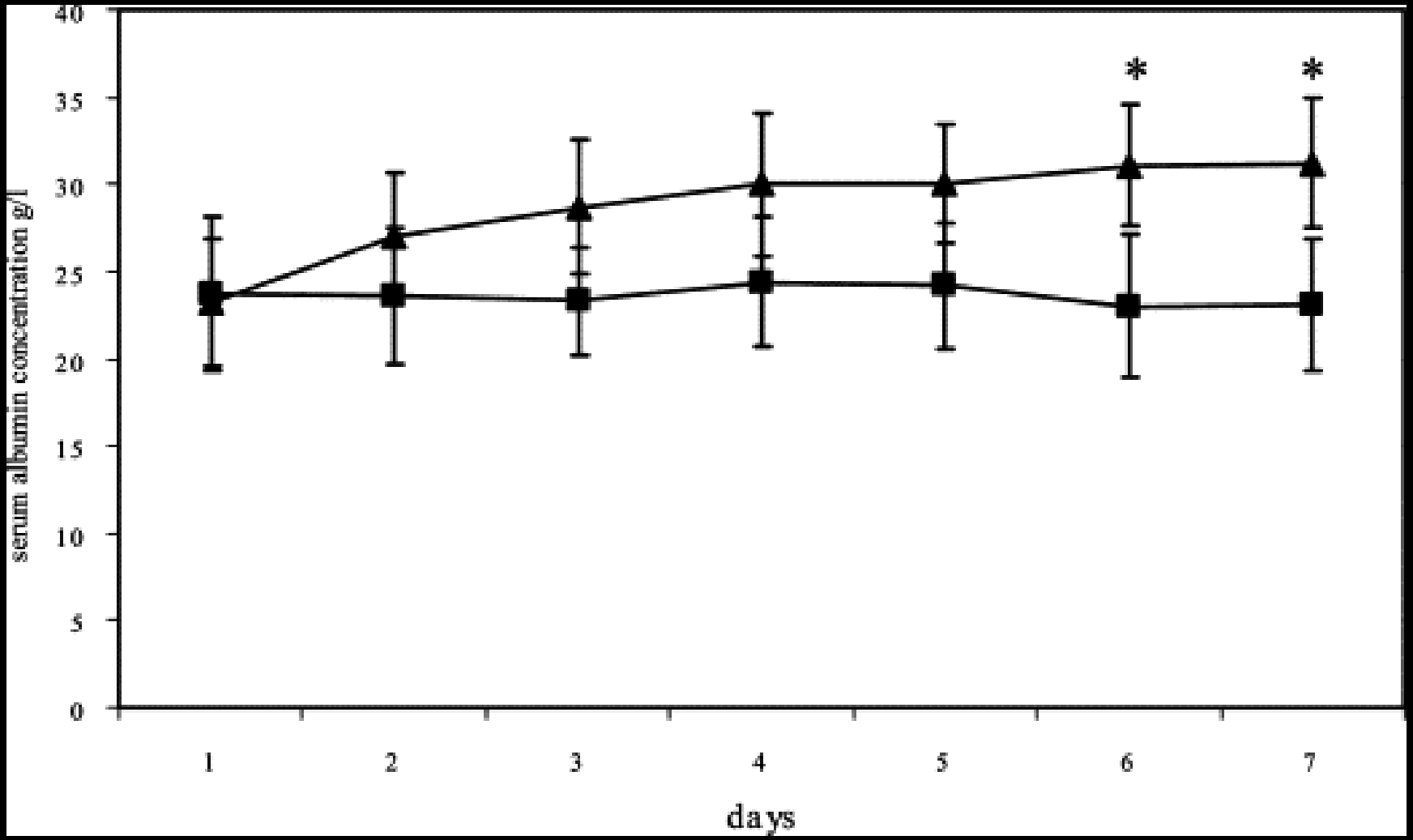
Kaplan-Meier Estimates of the Probability of Survival



The SAFE Study Investigators. *N Engl J Med* 2004;350:2247-2256

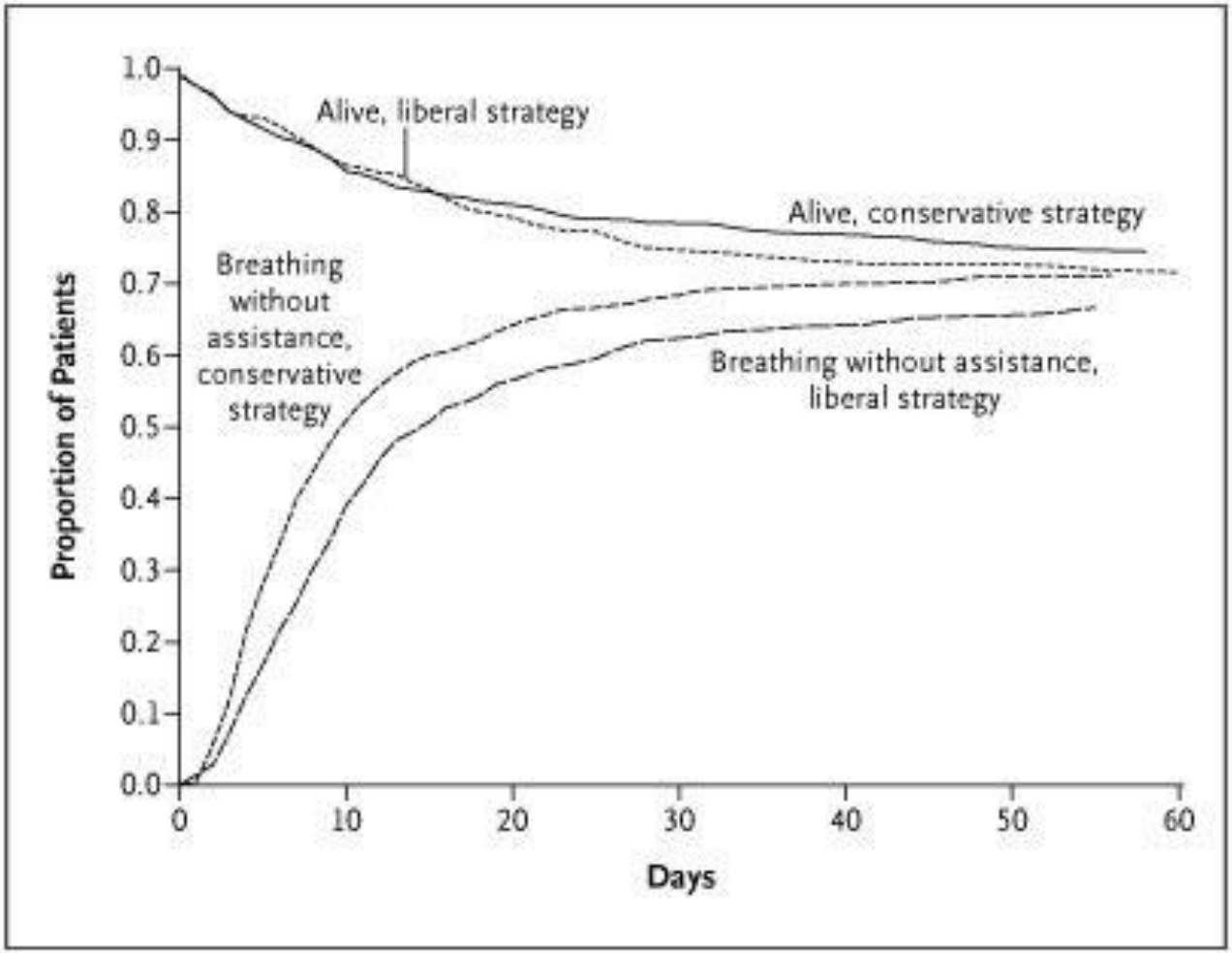
The NEW ENGLAND JOURNAL of MEDICINE

Albumin administration improves organ function in critically ill hypoalbuminemic patients



Critical Care Medicine - Volume 34, Issue 10 (October 2006)

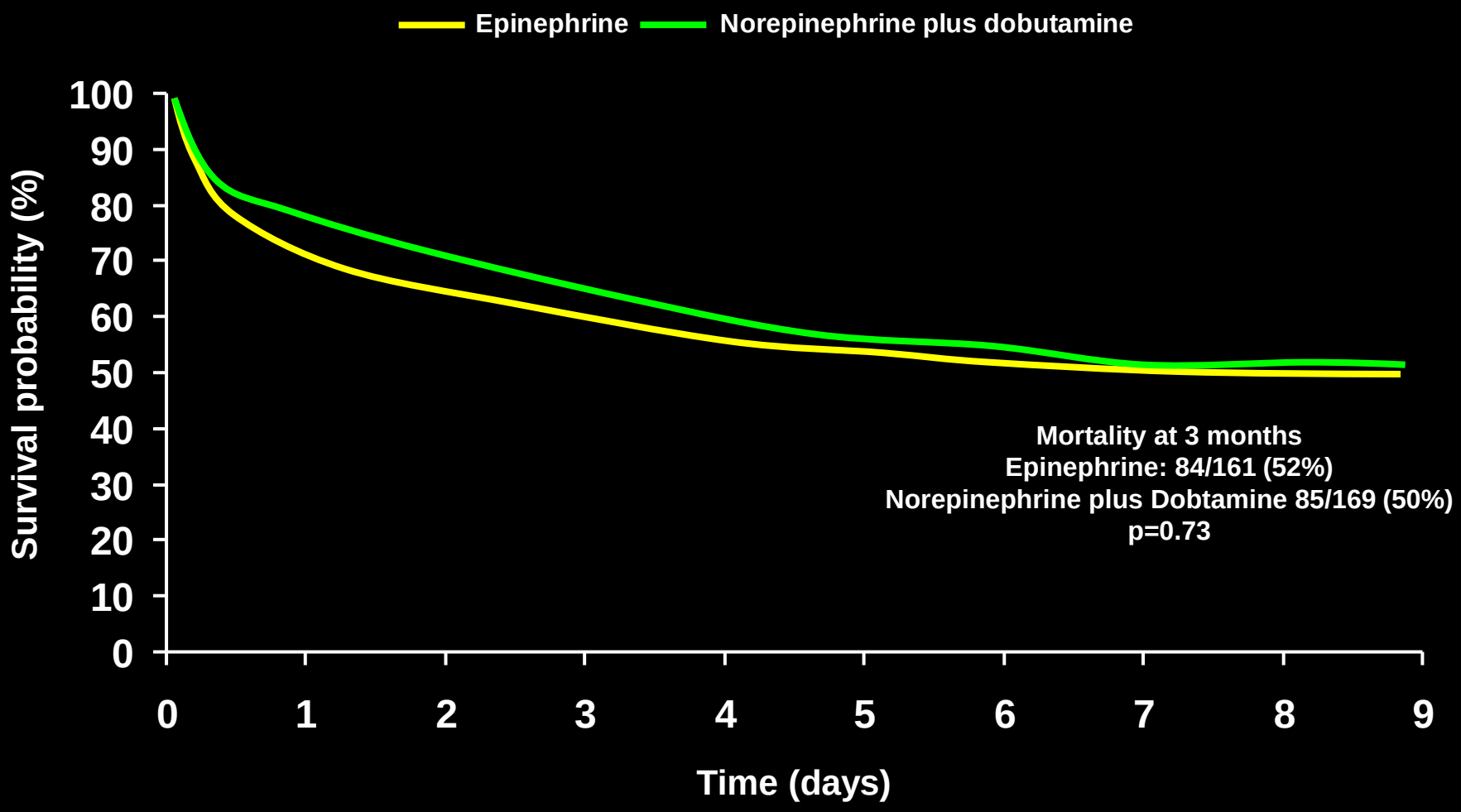
Mortality in ARDS with Liberal or Conservative Fluid Management



The National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network. N Engl J Med 2006;354:2564-2575

The NEW ENGLAND JOURNAL of MEDICINE

Norepinephrine plus Dobutamine versus Epinephrine for Management of Septic Shock



Annane D. *Lancet* 2007;370:676-684.

Surviving Sepsis

www.survivingsepsis.org

What works?

Results of Positive RCTs

Table 2. Results of Positive Randomized, Controlled Trials.*

Group	Study	No. of Patients	Intervention Group	Control Group	Mortality Rate†		NNT‡	Level of Evidence
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					%			
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Russell J. N Engl J Med 2006;355:1699-1713

The NEW ENGLAND JOURNAL of MEDICINE

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

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

Treatment goal:
Optimize Oxygen Delivery (DO_2)

$$DO_2 = CO \times C_aO_2$$

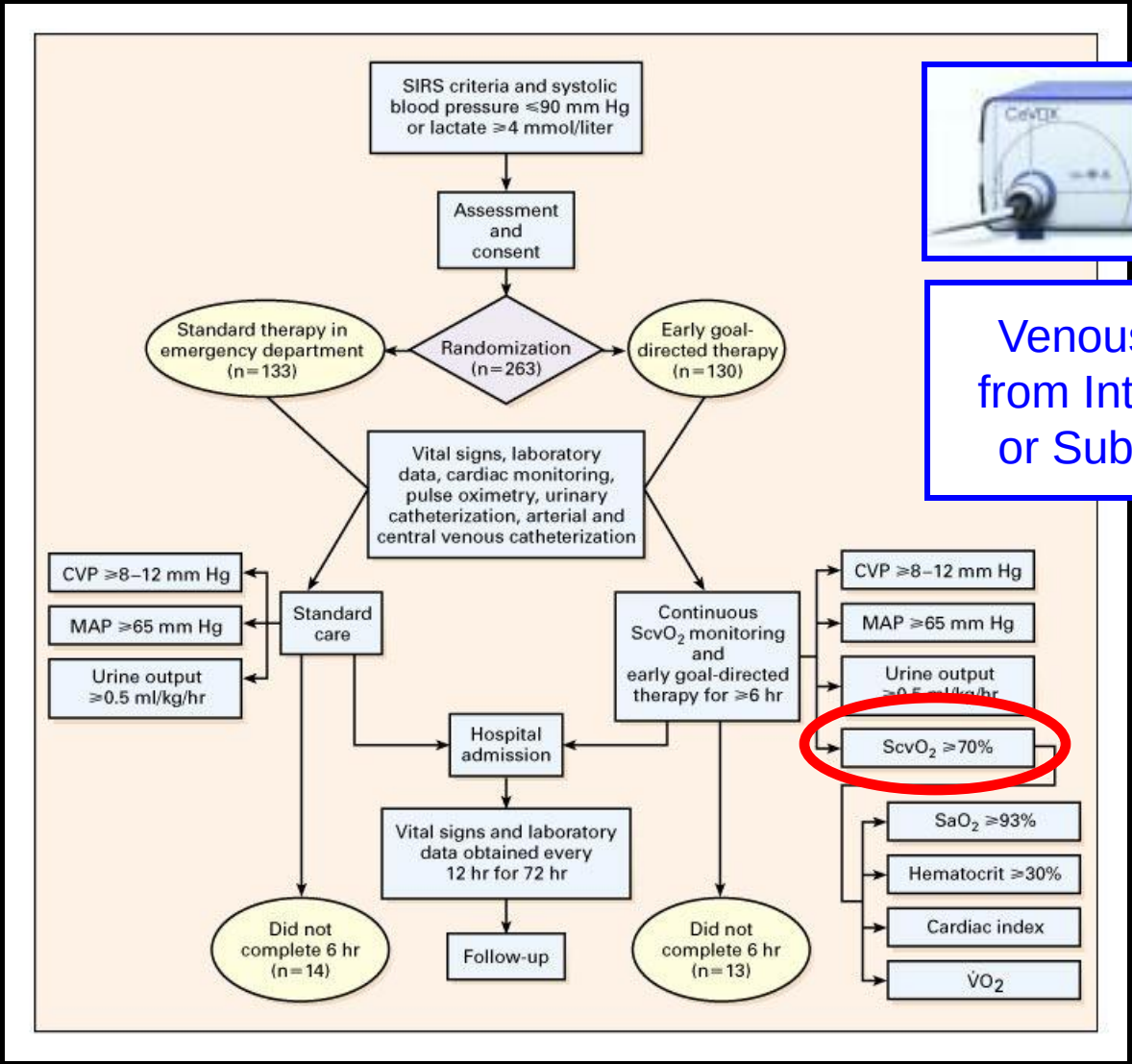
CO = SV x HR (or MAP ÷ SVR)

CaO_2 = Hb X 1.34 x S_aO_2

Rivers E , et al. *N Engl J Med* 2001;345:1368-1377

The NEW ENGLAND JOURNAL of MEDICINE

Early Goal Directed Therapy (EGDT) in Severe Sepsis and Septic Shock

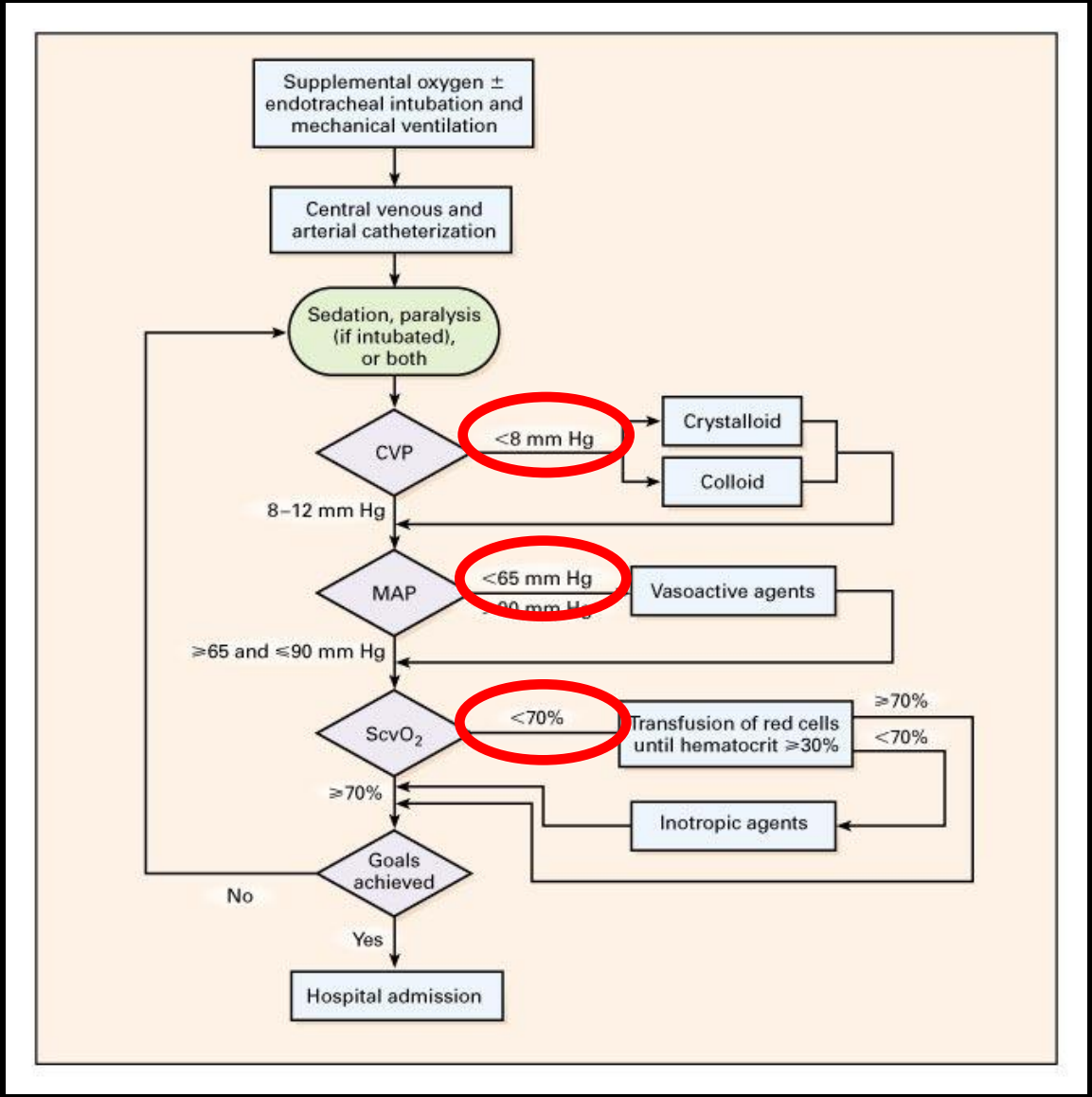


Venous Blood Gas from Internal Jugular or Subclavian Vein

Rivers E , et al. *N Engl J Med* 2001;345:1368-1377

The NEW ENGLAND JOURNAL of MEDICINE

Protocol for EGDT in Severe Sepsis and Septic Shock



Rivers E et al. *N Engl J Med* 2001;345:1368-1377

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Mortality and Causes of In-Hospital Death

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

VARIABLE	STANDARD THERAPY (N=133)	EARLY GOAL-DIRECTED THERAPY (N=130)	RELATIVE RISK (95% CI)	P VALUE
	no. (%)			
In-hospital mortality†				
All patients	59 (46.5)	38 (30.5)	0.58 (0.38–0.87)	0.009
Patients with severe sepsis	19 (30.0)	9 (14.9)	0.46 (0.21–1.03)	0.06
Patients with septic shock	40 (56.8)	29 (42.3)	0.60 (0.36–0.98)	0.04
Patients with sepsis syndrome	44 [illegible]	37 (35.1)	0.66 (0.42–1.04)	0.07
28-Day mortality†	[illegible]	[illegible] (33.3)	0.58 (0.39–0.87)	0.01
60-Day mortality†	70 [illegible]	[illegible] (44.3)	0.67 (0.46–0.96)	0.03
Causes of in-hospital death‡				
Sudden cardiovascular collapse	25/119 [illegible]	12/[illegible] [illegible].3)	—	0.02
Multiorgan failure	26/119 (21.8)	19/117 (16.2)	—	0.27

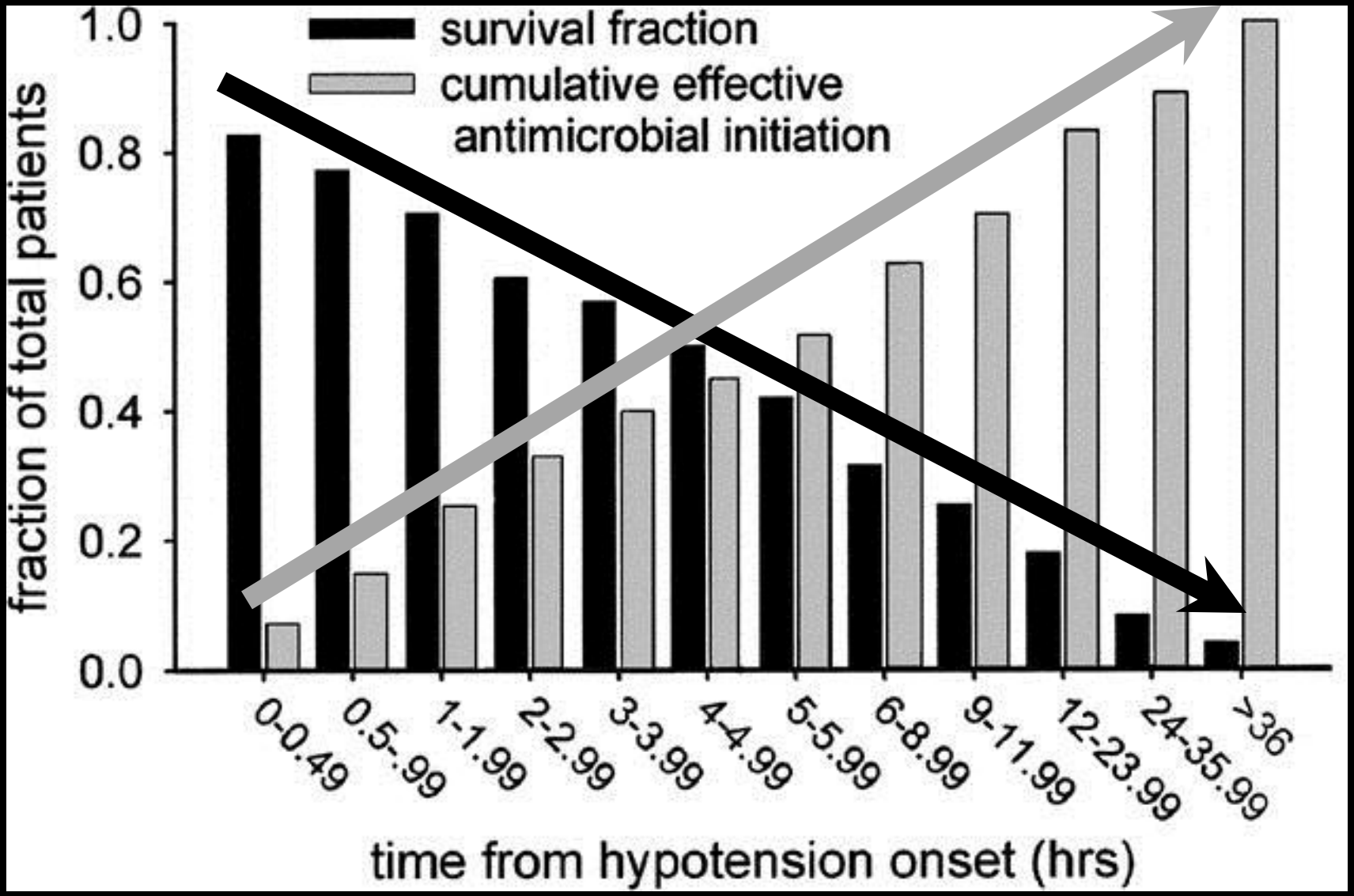
16%
Absolute Risk Reduction

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

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

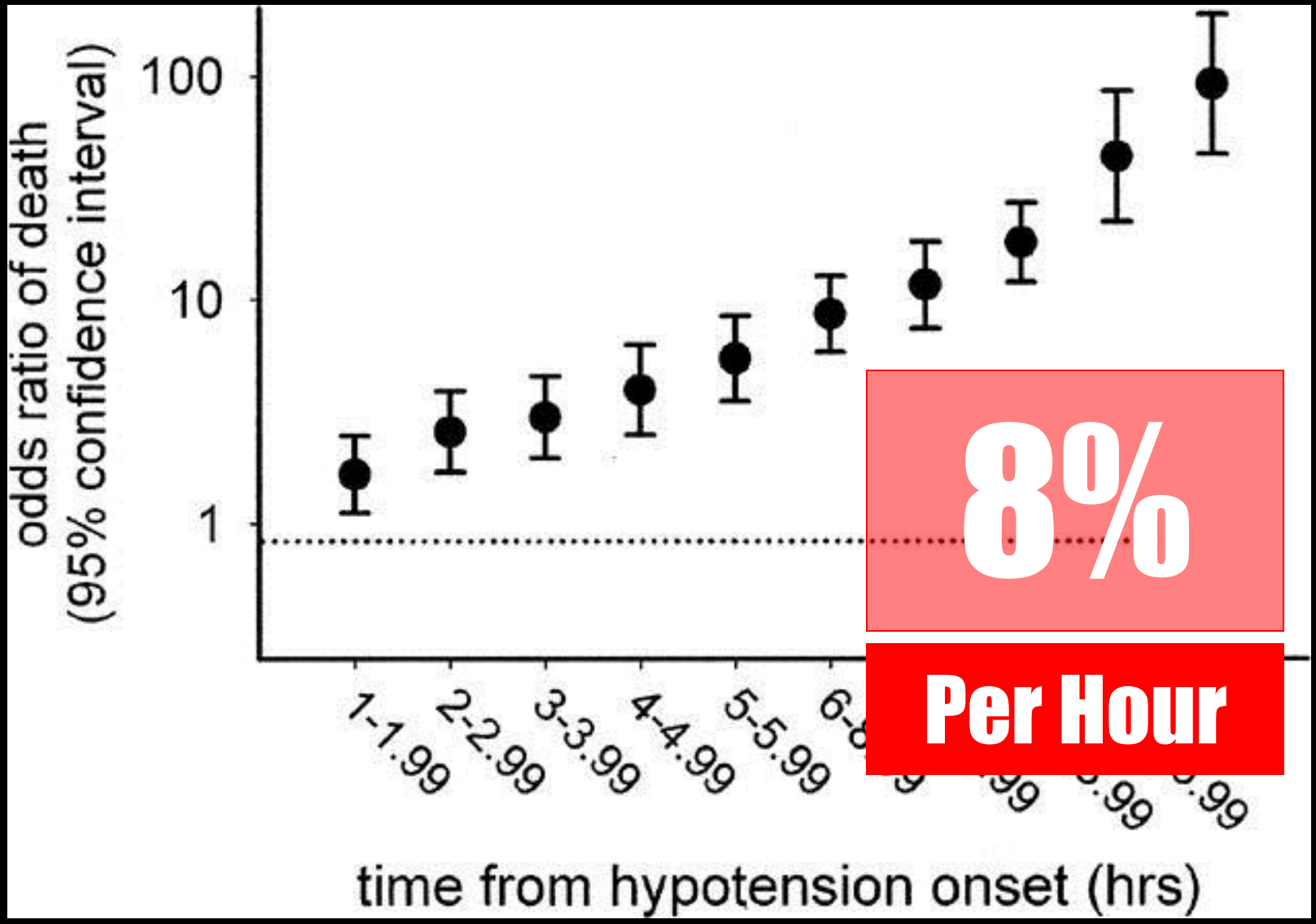
‡The denominators indicate the numbers of patients in each group who completed the initial six-hour study period.

Mortality increases proportionally to the delay in initiation of *effective* antimicrobial therapy



Kumar A. *Crit Care Med*, 2006; 34: 1589-1596

Mortality increases proportionally to the delay in initiation of *effective* antimicrobial therapy



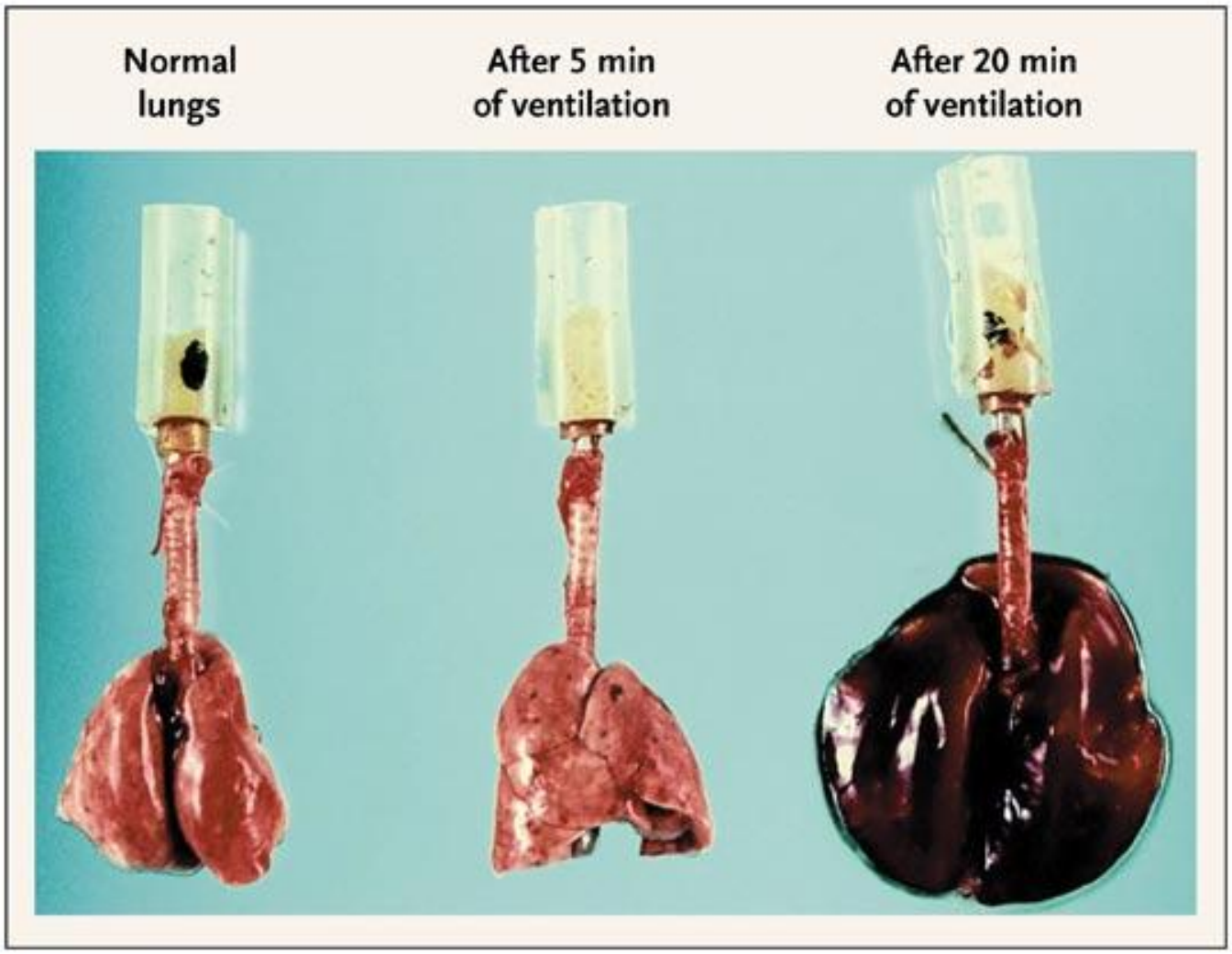
Kumar A: *Crit Care Med*, 2006; 34: 1589-1596

Acute Respiratory Distress Syndrome (ARDS)

Low Tidal Volumes

Corticosteroids

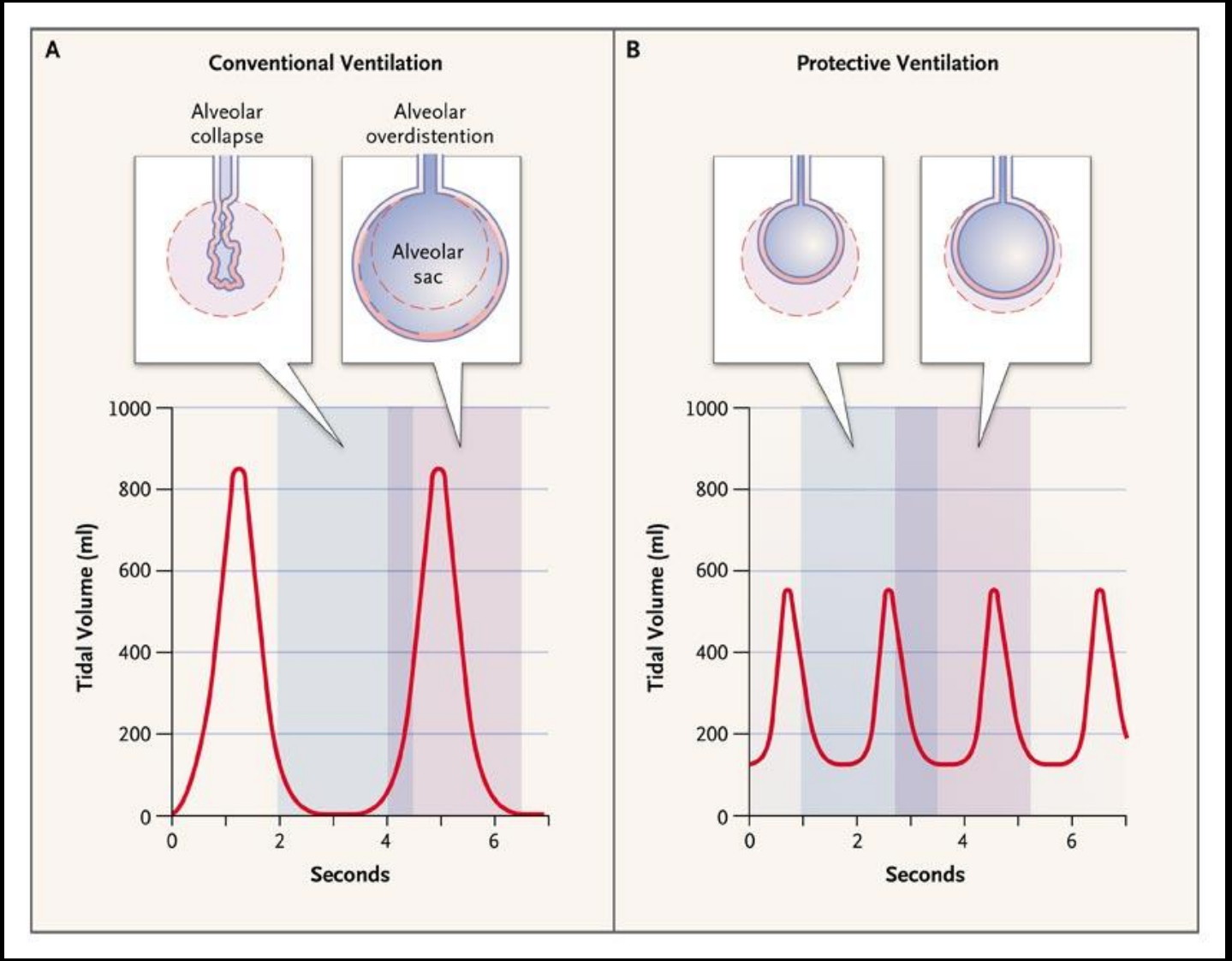
Lung Injury Induced by High-Pressure Mechanical Ventilation (Peak Airway Pressure of 45 cm H_2O)



Malhotra A. *N Engl J Med* 2007;357:1113-1120

The NEW ENGLAND JOURNAL of MEDICINE

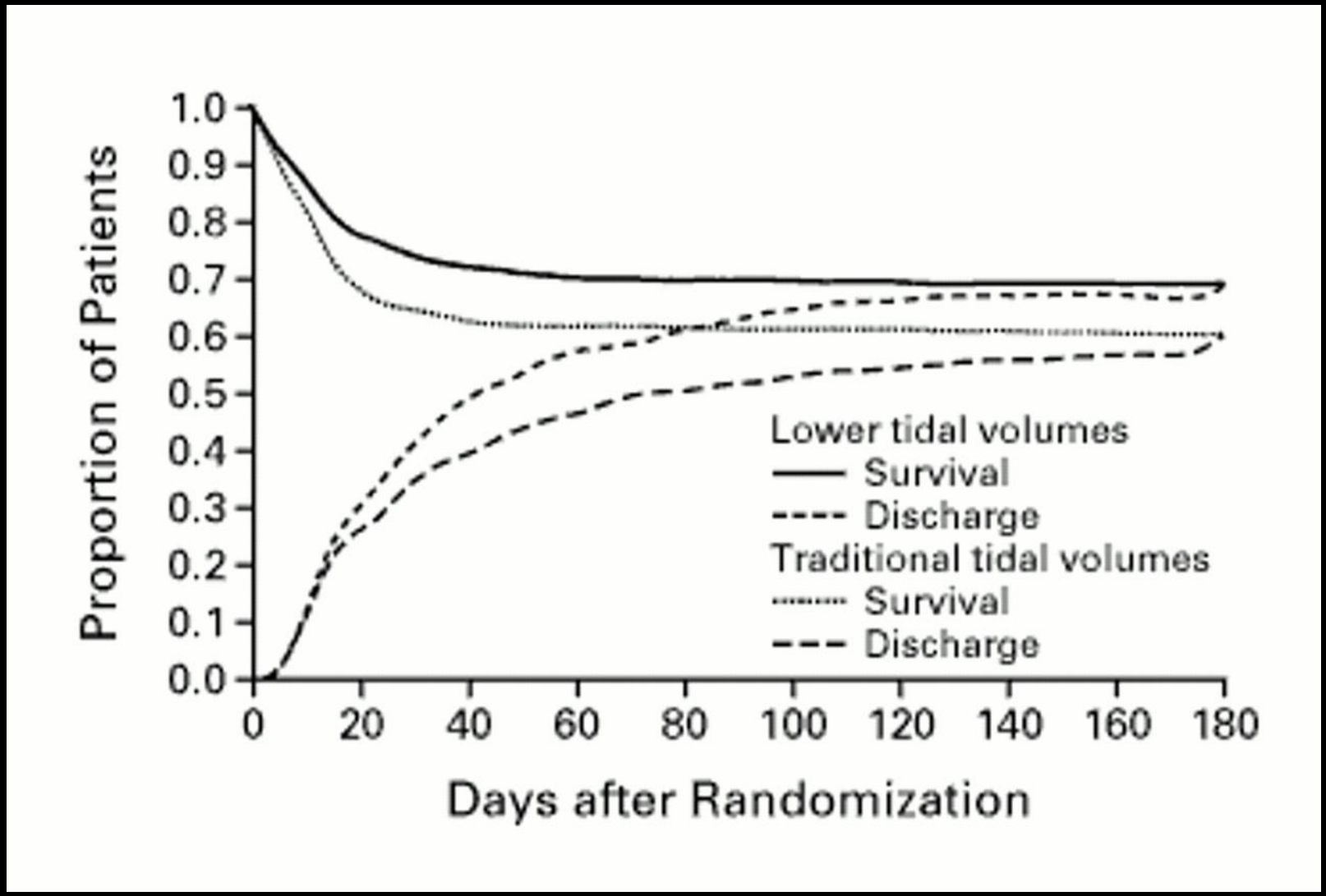
Conventional Ventilation (12 cc/kg of IBW) vs. Protective Lung Ventilation (6 cc/kg of IBW)



Malhotra A. *N Engl J Med* 2007;357:1113-1120

The NEW ENGLAND JOURNAL of MEDICINE

Lung Protective Strategy Improves Survival and Probability of Being Discharged Home and Breathing without Assistance



The Acute Respiratory Distress Syndrome Network. *N Engl J Med* 2000;342:1301-1308

The NEW ENGLAND JOURNAL of MEDICINE

Main Outcome Variables

TABLE 4. MAIN OUTCOME VARIABLES.*

VARIABLE	GROUP RECEIVING LOWER TIDAL VOLUMES	GROUP RECEIVING TRADITIONAL TIDAL VOLUMES	P VALUE
Death before discharge home and breathing without assistance (%)	31.0	39.8	0.007
Breathing without assistance by day 28 (%)			<0.001
No. of ventilator-free days, days 1 to 28			0.007
Barotrauma, days 1 to 28 (%)			0.43
No. of days without failure of nonpulmonary organs or systems, days 1 to 28			0.006

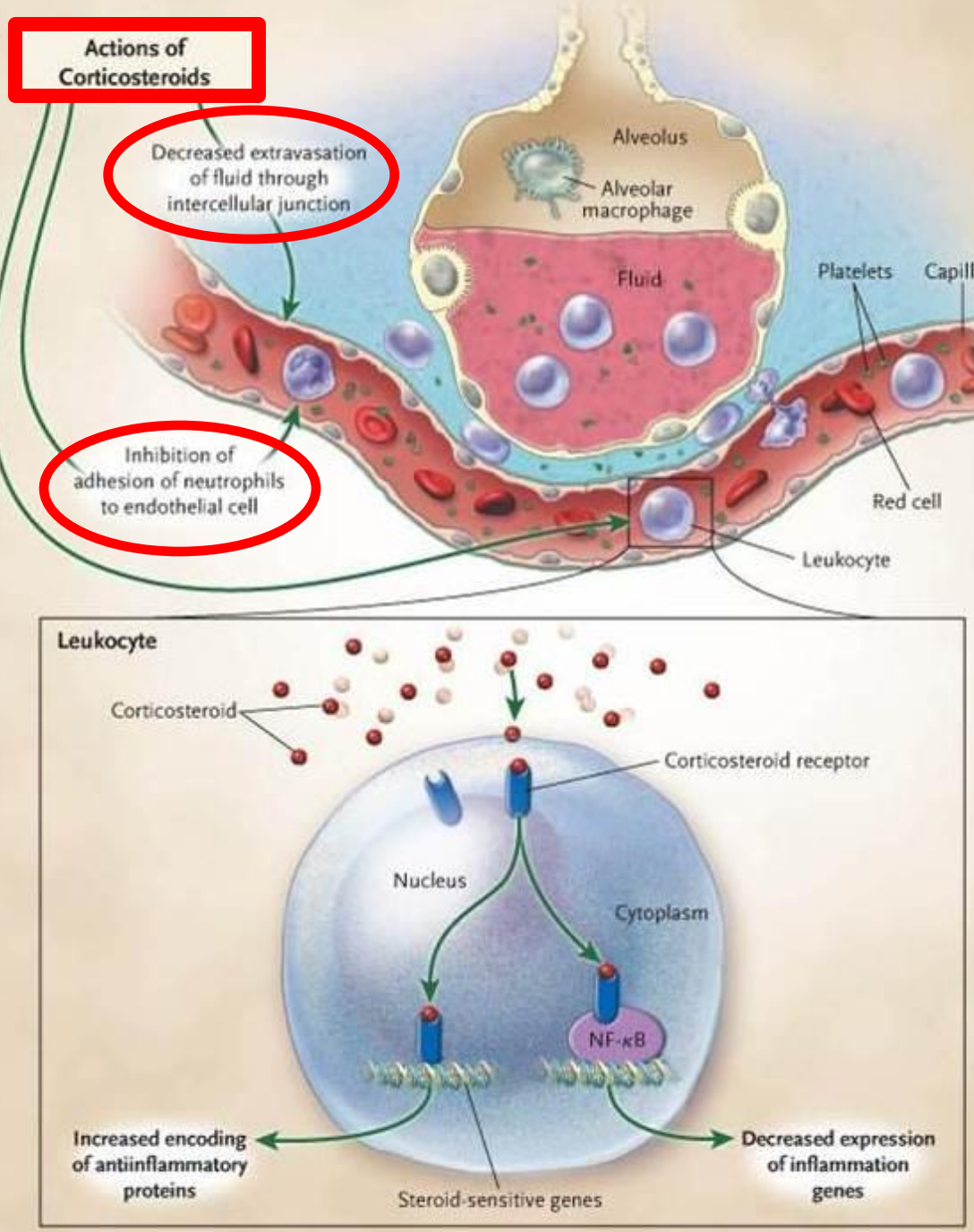
9% ARR

*Plus–minus values are means ±SD. The number of ventilator-free days is the mean number of days from day 1 to day 28 on which the patient had been breathing without assistance for at least 48 consecutive hours. Barotrauma was defined as any new pneumothorax, pneumomediastinum, or subcutaneous emphysema, or a pneumatocele that was more than 2 cm in diameter. Organ and system failures were defined as described in the Methods section.

The Acute Respiratory Distress Syndrome Network. *N Engl J Med* 2000;342:1301-1308

The NEW ENGLAND JOURNAL of MEDICINE

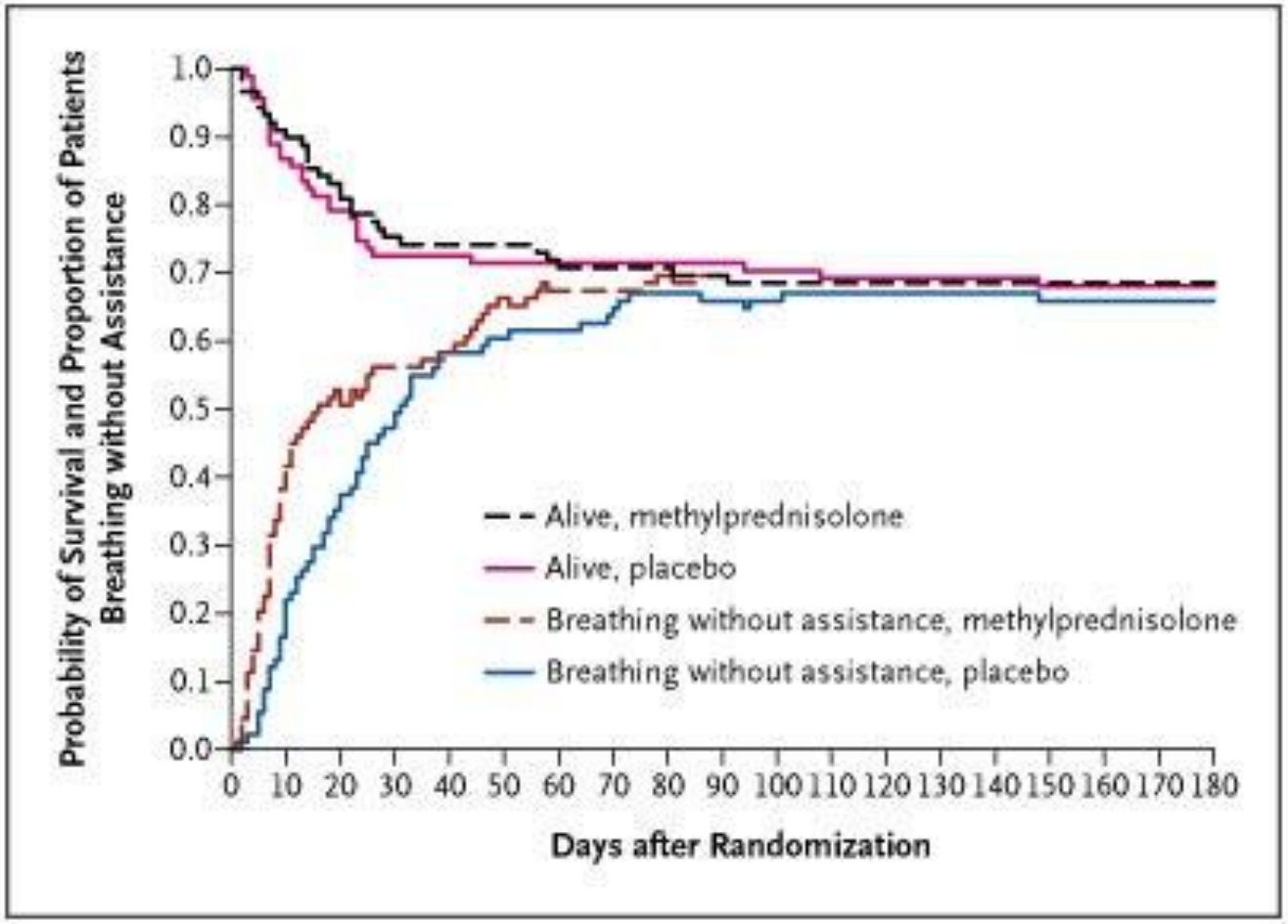
Pathways of the Inhibition of Inflammation by Corticosteroids in ARDS



Suter P. *N Engl J Med* 2006;354:1739-1742

The NEW ENGLAND JOURNAL of MEDICINE

In persistent ARDS, corticosteroid therapy started 2 weeks after refractory hypoxia did not improve outcomes



The National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network. *N Engl J Med* 2006;354:1671-1684

The NEW ENGLAND JOURNAL of MEDICINE

Low Dose Corticosteroids in Early ARDS

- **Action at low doses**
  - Anti-inflammatory without immune suppression
- **Duration**
  - Lower doses over longer time are superior to higher doses for shorter periods of time
  - *Early withdrawal negates effect!!!*
- **Dosing of methylprednisolone**
  - 2 weeks: 1 mg/kg
  - 1 week: 0.5 mg/kg
  - ½ week: 0.25 mg/kg
  - ½ week: 0.125 mg/kg

Meduri GU. *Chest* 2007; 132:1097-1100

Low Dose Corticosteroids in Early ARDS

Table 2—*Per-Protocol Analysis, Outcome Measures on or by Study Day 7

Variables	Methylprednisolone (n = 55)	Placebo (n = 24)	p Value
Extubated or with a ≥ 1-point reduction in LIS†	41 (74.6)	9 (37.5)	0.002
Patients breathing without assistance	32 (58.2)	7 (29.2)	0.02
LIS‡	2.03 ± 1.3	2.72 ± 0.1	< 0.001
PaO_2/FIO_2‡	268.6 ± 21	179.8 ± 21	0.003
Mechanical ventilation-free days‡	2.11 ± 2.0	0.96 ± 1.3	0.009
Multiple organ dysfunction syndrome score	0.69 ± 0.9	1.71 ± 1.3	0.02
C-reactive protein level, mg/dL	2.7 ± 0.8	13.4 ± 0.8	< 0.001
Patients with new infection§	9 (16.4)	8 (33.3)	0.09
Patients with ventilator-associated pneumonia	3 (5.5)	5 (20.8)	0.051
Survivors	52 (94.5)	20 (83.3)	0.19
Patients with unresolving ARDS treated with open-label methylprednisolone (2 mg/kg/d)†	4 (7.3)	10 (41.7)	< 0.001

*Data are presented as No. (%) or mean ± SEM.
†The proportion of patients alive and improved for methylprednisolone vs placebo: 87% vs 42% ($p < 0.001$).
‡Lung injury score and in PaO_2/FIO_2 values obtained in patients remaining on mechanical ventilation.

Meduri GU. *Chest* 2007; 132:1097-1100

Results of Positive RCTs

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Russell J. N Engl J Med 2006;355:1699-1713

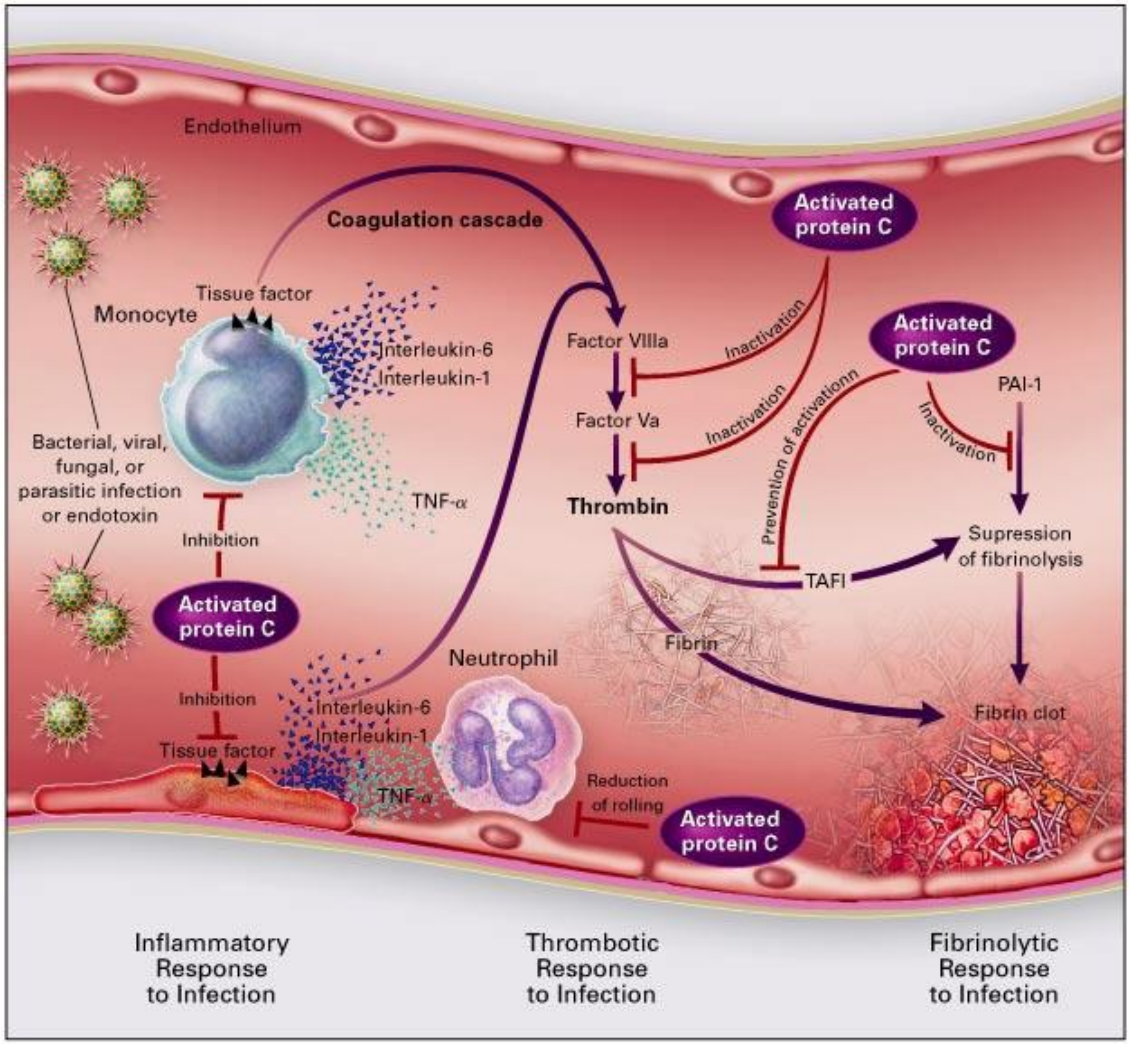
The NEW ENGLAND JOURNAL of MEDICINE

Proposed Actions of Activated Protein C

Anti-inflammatory:

Inhibits production of TNF-α, IL-1, and IL-6

Limits rolling of macrophages and PMNs



Limits thrombin generation:

Inactivates Factors Va and VIIIa

Increases fibrinolytic activity:

Inhibits PAI

Bernard G. *N Engl J Med* 2001;344:699-709

The NEW ENGLAND JOURNAL of MEDICINE

Dretrocogin Alpha
rhAPC

- **PROWESS**
  - Severe sepsis
  - High risk of death
    - APACHE > 25 *or*
    - Multiorgan failure
- **ADDRESS**
  - Severe sepsis
  - Low risk of death
    - APACHE < 25
    - Single organ failure

Bernard G et al. *N Engl J Med* 2001;344:699-709
Abraham E et al. *N Engl J Med* 2005;353:1332-1341

Incidence of Serious Adverse Events

PROWESS

TABLE 5. INCIDENCE OF SERIOUS ADVERSE EVENTS.

VARIABLE	PLACEBO GROUP (N=840)	DROTRECOGIN ALFA ACTIVATED GROUP (N=850)	P VALUE
	no. of patients (%)		
At least one serious adverse event	102 (12.1)	106 (12.5)	0.84
Serious bleeding event*	17 (2.0)	30 (3.5)	0.06
Gastrointestinal	9 (1.1)	9 (1.1)	
Intraabdominal	4 (0.5)	3 (0.4)	
Intrathoracic	1 (0.1)	6 (0.7)	
Retroperitoneal	0	4 (0.5)	
Intracranial	1 (0.1)	2 (0.2)	
Skin or soft tissue	0	2 (0.2)	
Genitourinary	0	2 (0.2)	
Source unidentified†	2 (0.2)	2 (0.2)	
Thrombotic events	25 (3.0)	17 (2.0)	0.20

*A serious bleeding event was defined as any intracranial hemorrhage, any life-threatening bleeding, any bleeding event classified as serious by the investigator, or any bleeding that required the administration of 3 units of packed red cells on two consecutive days.

†These patients received 3 units of packed red cells on two consecutive days but had no identifiable source of bleeding.

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

ADDRESS

Table 3. Adverse Events.*

Event	Placebo (N=1293)	DrotAA (N=1317)	P Value
	no. (%)		
Days 0–6 (infusion period)			
Any serious adverse event	78 (6.0)	75 (5.7)	0.71
Serious bleeding events	15 (1.2)	31 (2.4)	0.02
Bleeding involving the central nervous system	3 (0.2)	4 (0.3)	0.72
Serious nonbleeding events	66 (5.1)	46 (3.5)	0.04
Days 0–28			
Any serious adverse event	183 (14.2)	182 (13.8)	0.81
Serious bleeding events	28 (2.2)	51 (3.9)	0.01
Bleeding involving the central nervous system	5 (0.4)	6 (0.5)	0.79
Any bleeding event leading to transfusion	44 (3.4)	90 (6.8)	<0.001
Serious nonbleeding events	168 (13.0)	143 (10.9)	0.09

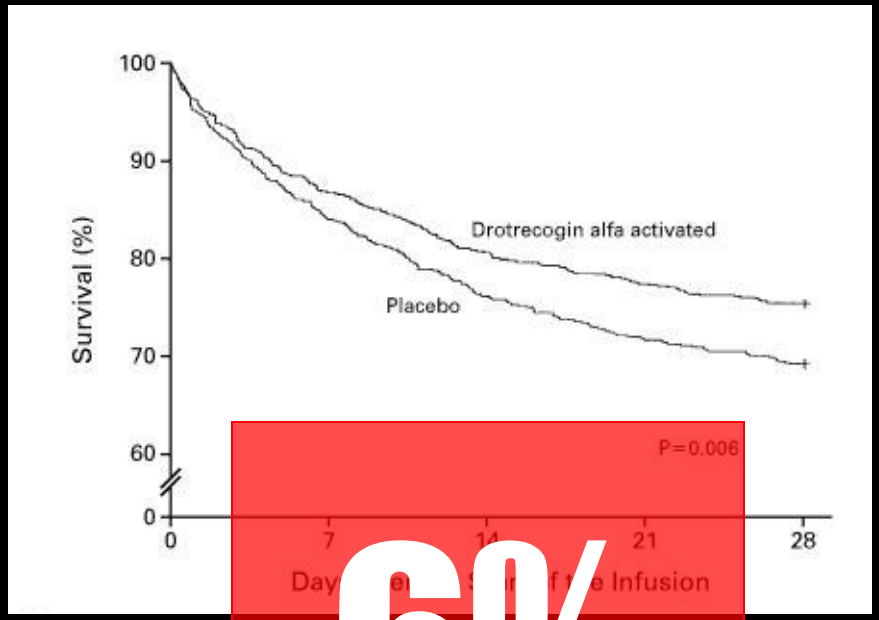
* DrotAA denotes drotrecogin alfa (activated). Only patients who received the assigned study drug are included in this analysis.

Abraham E et al. *N Engl J Med* 2005;353:1332-1341

The NEW ENGLAND JOURNAL of MEDICINE

Survival vs. Placebo

PROWESS

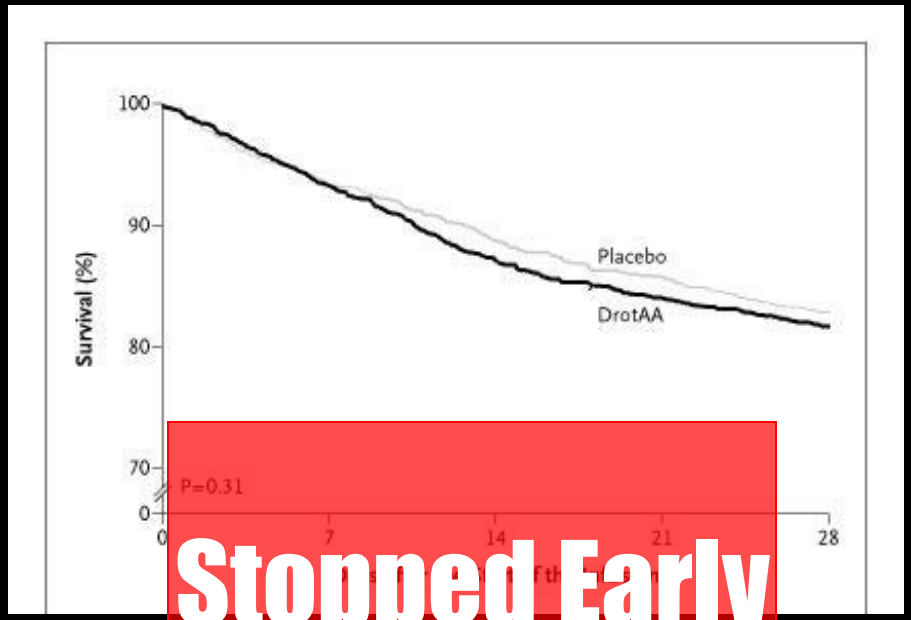


Bernard G et al. *N Engl J Med* 2001;344:699-709

6%

Absolute risk reduction

ADDRESS



Abraham E et al. *N Engl J Med* 2005;353:1332-1341

Stopped Early

No Difference

Current Recommendations for rhAPC

- **Severe sepsis with high risk of death**
  - **APACHE II score > 25**
  - Sepsis-induced multi-organ failure
  - Septic shock
  - Sepsis-induced ARDS
  - No absolute contraindications related to bleeding risk
  - No relative contraindication that outweighs potential benefit

Dellinger RP, et al. Surviving Sepsis Campaign Guidelines. *Crit Care Med* 2004; 32:858873

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Critically ill surgical patients	Van den Berghe et al.[31]	1548	Intensive insulin (to maintain glucose level of 4.4–6.1 mmol/liter)	Usual insulin (to maintain glucose level of 10–11.1 mmol/liter)	4.6	8	29	I
Patients in medical ICU††	Van den Berghe et al.[30]	1200	Intensive insulin (to maintain glucose level of 4.4–6.1 mmol/liter)	Usual insulin (to maintain glucose level of 10–11.1 mmol/liter)	37	40	NA	I

Russell J. N Engl J Med 2006;355:1699-1713

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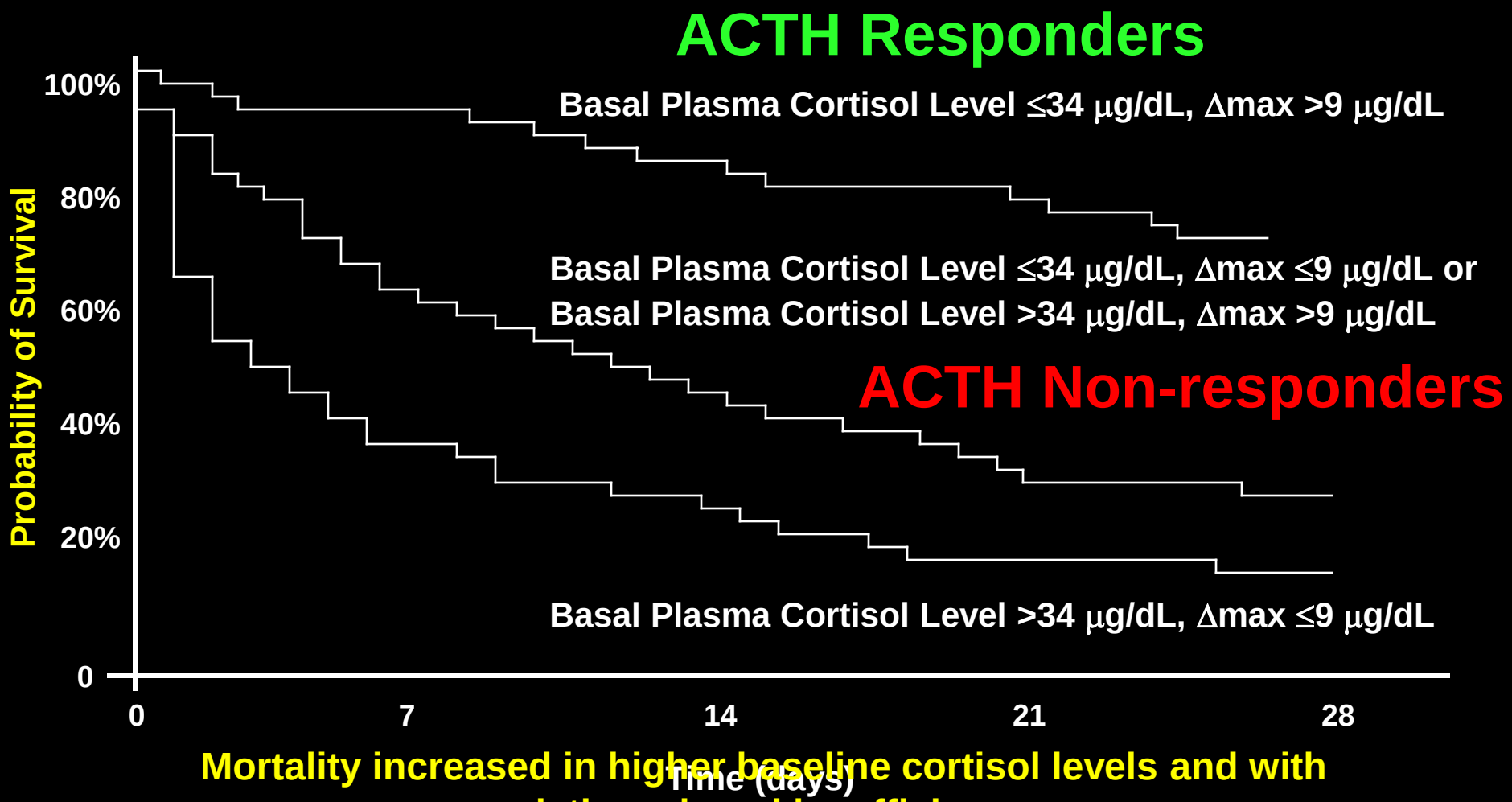
Survival in Severe Sepsis and Septic Shock
Baseline Cortisol and Post-ACTH

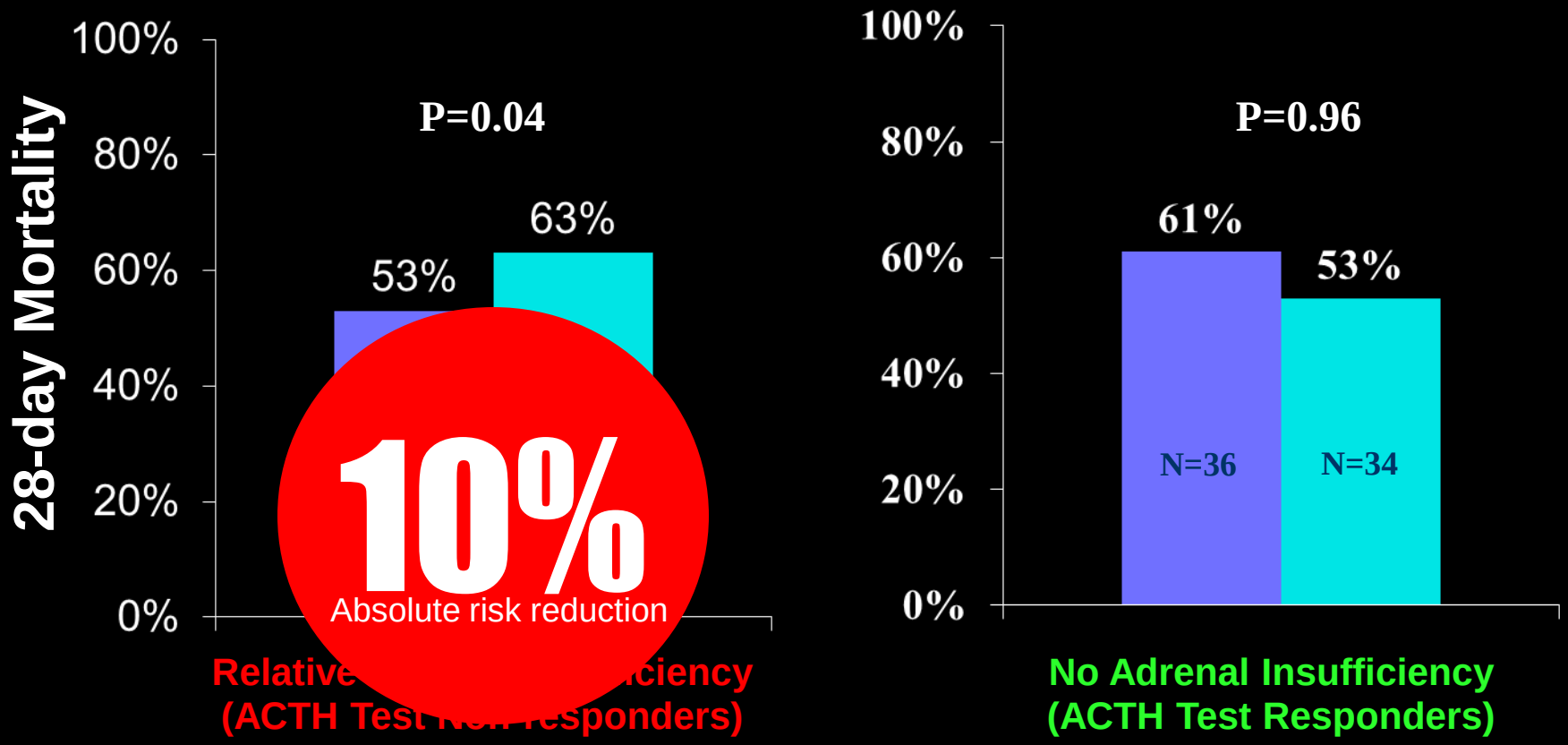


Mortality increased in higher baseline cortisol levels and with relative adrenal insufficiency

Annane D. *JAMA* 2000;283:1038-45.

JAMA

Low Dose Steroid Treatment in Septic Shock:
28 Day Mortality (Non-responders vs. Responders)



Annane, D. *JAMA*, 2002; 288: 868.

JAMA

Results of Positive RCTs

Table 2. Results of Positive Randomized, Controlled Trials.*

Group	Study	No. of Patients	Intervention Group	Control Group	Mortality Rate†		NNT‡	Level of Evidence
					Intervention Group	Control Group		
					%			
Patients with acute lung injury and ARDS§	ARDS Clinical Trials Network[1]	861	Low tidal volume (6 ml/kg of ideal body weight)	High tidal volume (12 ml/kg of ideal body weight)	31	40	11	I
Patients with severe sepsis and septic shock	Rivers et al.[2]	263	Early, goal-directed therapy	Usual therapy	33	49	6	I
Patients with severe sepsis and septic shock	Bernard et al.[5]	1690	Activated protein C	Placebo	25	31	16	I
Patients with severe sepsis and septic shock, at increased risk for death¶	Bernard et al.[5]	817	Activated protein C	Placebo	31	44	7.7	I
Patients in septic shock	Annane et al.[28]	299	Hydrocortisone + fludrocortisone	Placebo	55	61	NA	I–II
Patients in septic shock**	Annane et al.[28]	229	Hydrocortisone + fludrocortisone	Placebo	53	63	10	I–II
Critically ill surgical patients	Van den Berghe et al.[31]	1548	Intensive insulin (to maintain glucose level of 4.4–6.1 mmol/liter)	Usual insulin (to maintain glucose level of 10–11.1 mmol/liter)	4.6	8	29	I
Patients in medical ICU††	Van den Berghe et al.[30]	1200	Intensive insulin (to maintain glucose level of 4.4–6.1 mmol/liter)	Usual insulin (to maintain glucose level of 10–11.1 mmol/liter)	37	40	NA	I

Russell J. N Engl J Med 2006;355:1699-1713

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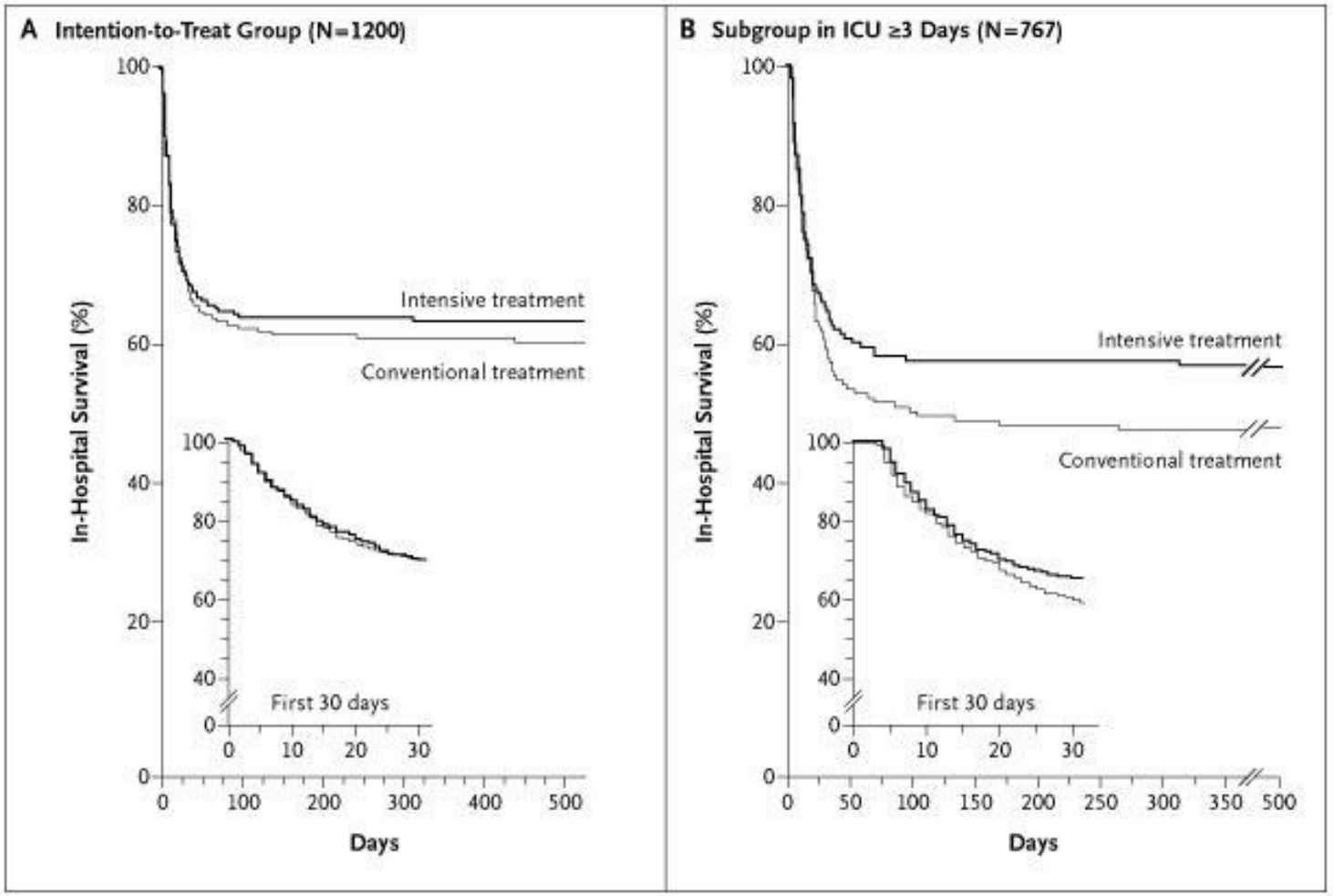
Intensive Insulin Treatment Improved Mortality in Surgical ICU Patients



Van den Berghe G et al. *N Engl J Med* 2006;354:449-461

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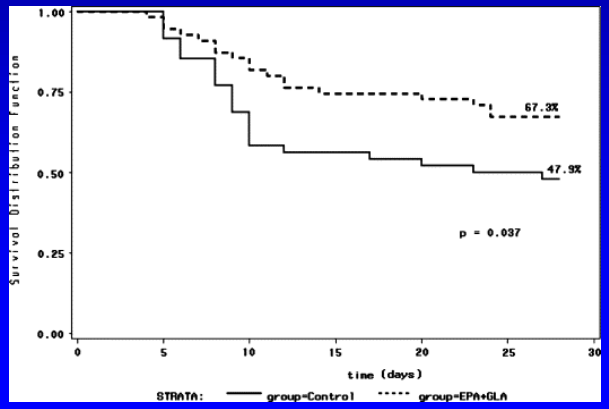
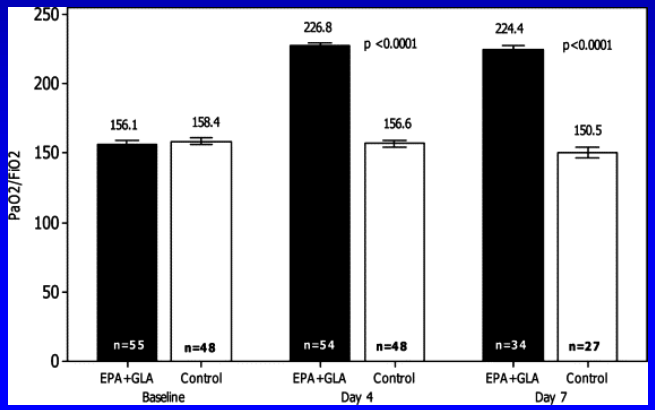
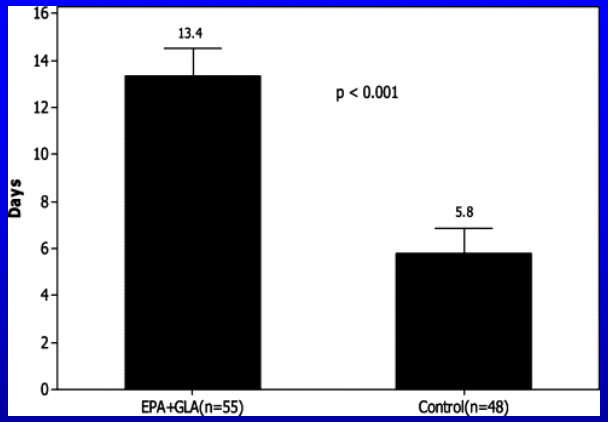
Enteral Feeding with Eicosapentanoic Acid, γ-linolenic acid, and Antioxidants in Mechanically Ventilated Patients with Severe Sepsis and Septic Shock



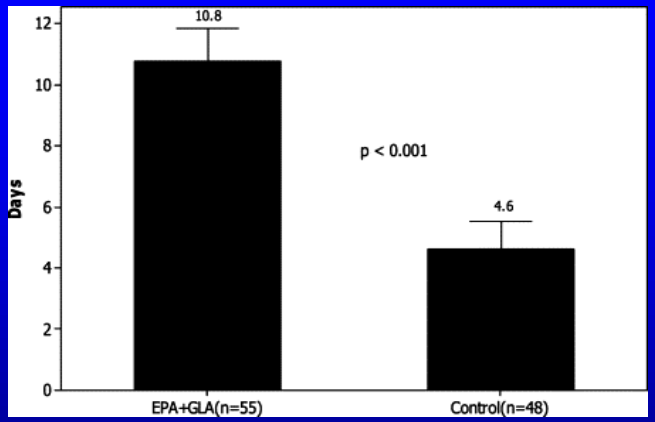
Improvement in Mortality



Improvement in Oxygenation



7.6 more ventilator-free days
(*p* < .001)



6.2 more ICU-free days
(*p* < .001)

Pontes-Arruda A. *Crit Care Med* 2006;34:2325-2333

Enteral Feeding with Eicosapentanoic Acid, γ-linolenic acid, and Antioxidants in Mechanically Ventilated Patients with Severe Sepsis and Septic Shock

Table 7. Development of new organ dysfunction

New Organ Failures	Control Diet (n = 48)	EPA + GLA Diet (n = 55)	*p* Value
Total	81 (39)	38 (21)	<.001
Cardiovascular	67 (32)	22 (12)	<.001
Renal	38 (18)	20 (11)	.049
Hematologic	27 (13)	9 (5)	.016
Metabolic	27 (13)	11 (65)	.035
Neurologic	19 (9)	5 (3)	.036
Gastrointestinal	15 (7)	4 (2)	.078[a]
Hepatic	12 (6)	4 (2)	.141[a]
Respiratory	10 (5)	9 (5)	.0.72[a]

EPA, eicosapentaenoic acid; GLA, γ-linolenic acid.

Less organ dysfunction

Pontes-Arruda A. *Crit Care Med* 2006;34:2325-2333

Efficacy and Safety of Epoetin Alfa in Critically Ill Patients

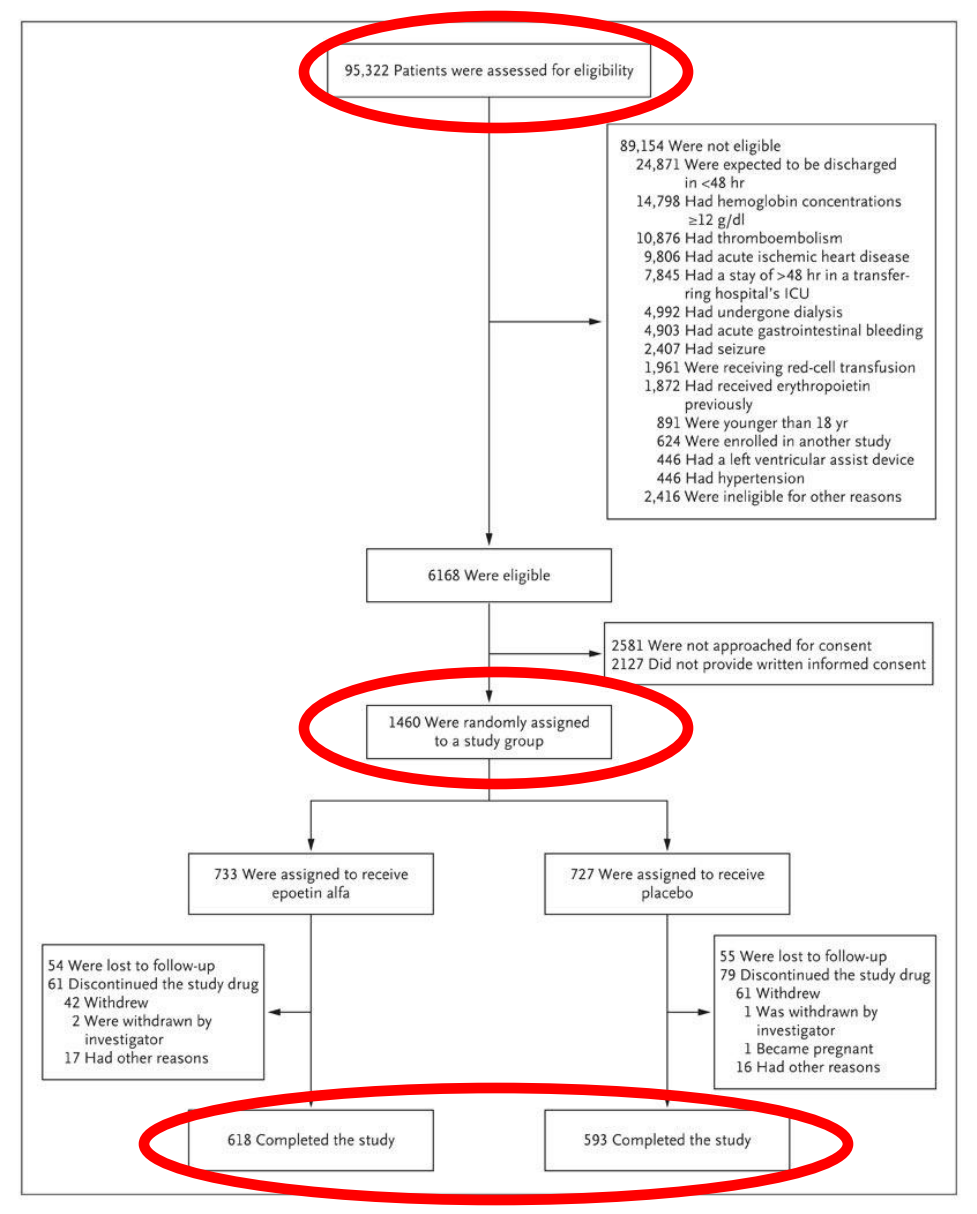


Table 4. Serious Adverse Events.*

Event	Epoetin Alfa (N=728)	Placebo (N=720)	P Value
	no. of patients (%)		
Any	320 (44.0)	313 (43.5)	0.87
Respiratory-system disorders			
Respiratory insufficiency	20 (2.7)	37 (5.1)	0.02
Dyspnea	12 (1.6)	15 (2.1)	0.57
Resistance-mechanism disorders			
Sepsis	47 (6.5)	50 (6.9)	0.67
Abscess	20 (2.7)	13 (1.8)	0.29
Multiple-organ failure	18 (2.5)	16 (2.2)	0.86
Clinically relevant thrombotic vascular event	120 (16.5)	83 (11.5)	0.008
Pulmonary embolism	16 (2.2)	12 (1.7)	0.57
Deep venous thrombosis	63 (8.7)	42 (5.8)	0.04
Cerebrovascular event	14 (1.9)	16 (2.2)	0.72
Myocardial infarction	15 (2.1)	6 (0.8)	0.08
Cardiac arrest or ventricular fibrillation	15 (2.1)	12 (1.7)	0.69

* The serious adverse events listed are those that occurred in more than 2% of patients in either study group. One patient in the epoetin alfa group who had received one dose had a positive scheduled mammogram at the day-140 visit. Biopsy of the lesion showed ductal carcinoma.

Corwin H et al. *N Engl J Med* 2007;357:965-976

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Table 2. Summary of Data on Red-Cell Transfusion.*

Variable	Epoetin Alfa (N=733)	Placebo (N=727)	Relative Risk (95% CI)	P Value
Patients receiving a transfusion — no. (%)	337 (46.0)	351 (48.3)	0.95 (0.85–1.06)	0.34
Admission group — no./total no. (%)				
Trauma				
Surgical,				
Medical,				
Units transfused per patient				
Mean	4.5±4.6	4.3±4.8		0.42
Median	3.0	3.0		0.69†
Total no. of days alive	10,073	10,879		
Total no. of units transfused	1525	1530		
Transfusion rate‡	0.15±0.09	0.14±0.18		0.36§

No Difference

* Plus–minus values are means ±SD.
† The P value was calculated with the use of the Wilcoxon–Mann–Whitney test.
‡ Transfusion rate was defined as the total number of units transfused divided by the total number of days alive.
§ The P value was calculated with the use of the t-test.

Process of Care Order Sets For Septic Shock

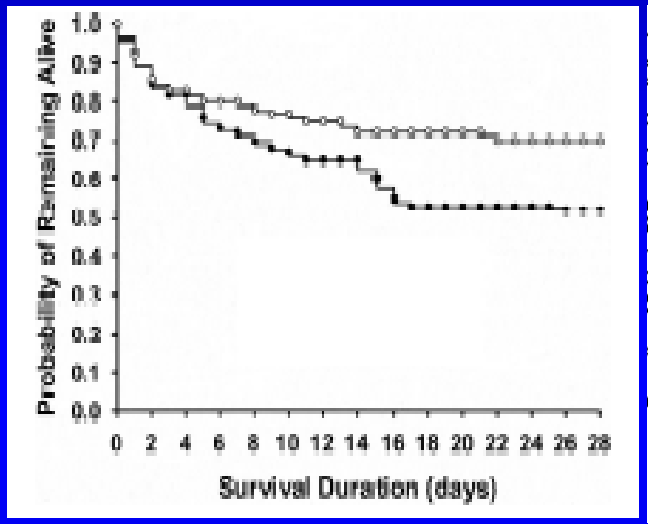
Table 2. Processes of medical care

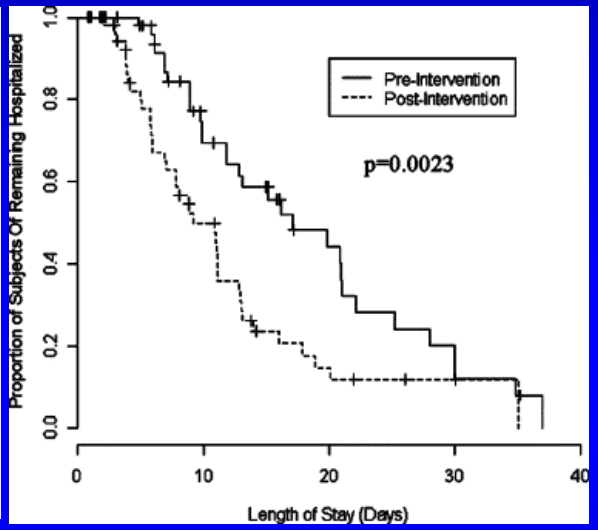
Variable	Before Group (n = 60)	After Group (n = 60)	p Value
Antibiotic administration within 3 hrs of ED arrival, n (%)	36 (60.0)	52 (86.7)	.001
Appropriate initial antibiotic treatment, n (%)	43 (71.7)	52 (86.7)	.043
Blood cultures obtained before antibiotic administration, n (%)	47 (78.3)	51 (85.0)	.345
Intravenous fluids administered in ED, mL	2825 ± 1624	3789 ± 1730	.002
Intravenous fluids administered before vasopressors, mL	1740 ± 1267	2771 ± 1242	<.001
Achieved 20 mL/kg intravenous fluids before vasopressors, n (%)	35 (58.3)	53 (88.3)	<.001
Transfused RBC units, n (%)	4 (6.7)	12 (20.0)	.032
ED length of stay, hrs	5.8 ± 3.6	7.3 ± 4.0	.015
Serum lactate measurement, n (%)	10 (16.7)	47 (78.3)	<.001
Documented central venous pressure of >8 mm Hg in ED, n (%)	3 (5.0)	29 (48.3)	<.001
Central venous oxygen saturation assessment in the ED, n (%)	1 (1.7)	29 (48.3)	<.001
Vasopressor administration[a], n (%)	60 (100.00)	43 (71.7)	<.001
Corticosteroid administration, n (%)	30 (50.0)	13 (21.7)	.001
Drotrecogin alfa (activated) administration, n (%)	7 (11.7)	2 (3.3)	.083

Micek ST. et al. *Crit Care Med* 2006;34:2707-2713.

Evidence-based sepsis protocols

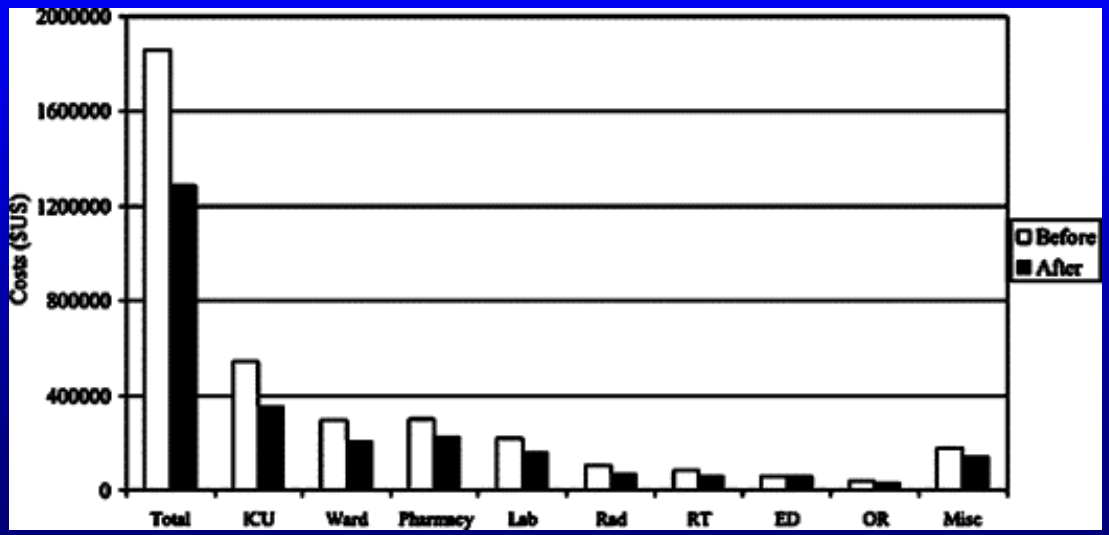
Before & After study of 120 ER Septic Shock Patients





Protocol Use:

- ↑ Survival (70% vs. 50%)
- ↓ LOS by 5 days
- ↓ Cost ($16K vs. $22K)



Shorr AF. *Crit Care Med* 2007;35:1257-1262.

Sepsis Bundles Save Lives

Prospective,observational study in 101 consecutive adult pts with severe se… …K hospitals.

Retros… …efore and af…

Sta… …APC

[R… …]

Up to 30% Reduction in Mortality!

Gao et al. *Crit Care Med* 2005; 9:R764

Kortgen et al *Crit Care Med* 2006;34:943-949.

Bang For The Buck

Absolute Risk Reduction in Mortality by Intervention

Early Goal Directed Therapy (EGDT)	16%
Low Tidal Volume Ventilation	9%
Corticosteroids for Early ARDS*	≤ 10%
Corticosteroids for Adrenal Insufficiency	10%
Intensive Insulin Therapy	10%
rhAPC in high risk of death	6%
Tube feeds with Eicosapentanoic Acid, γ-linolenic acid, and Antioxidants	20%
Sepsis bundles	≤ 30%

**Requires further studies*

Improving Mortality with POC Testing

- **Arterial Blood Gas (ABG)**
  - pH, PCO_2, PO_2
  - Electrolytes (Potassium, Chloride, HCO_3^-)
  - Renal function: BUN, Creatinine
  - Lactate
- **Venous Blood Gas (VBG)**
  - pH, PCO2, PO2
  - $ScvO_2$ (central venous O_2 saturation)
- **Blood Glucometer**
  - Glucose measurement

Thank You

- Questions