Special Article

# Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock: 2008

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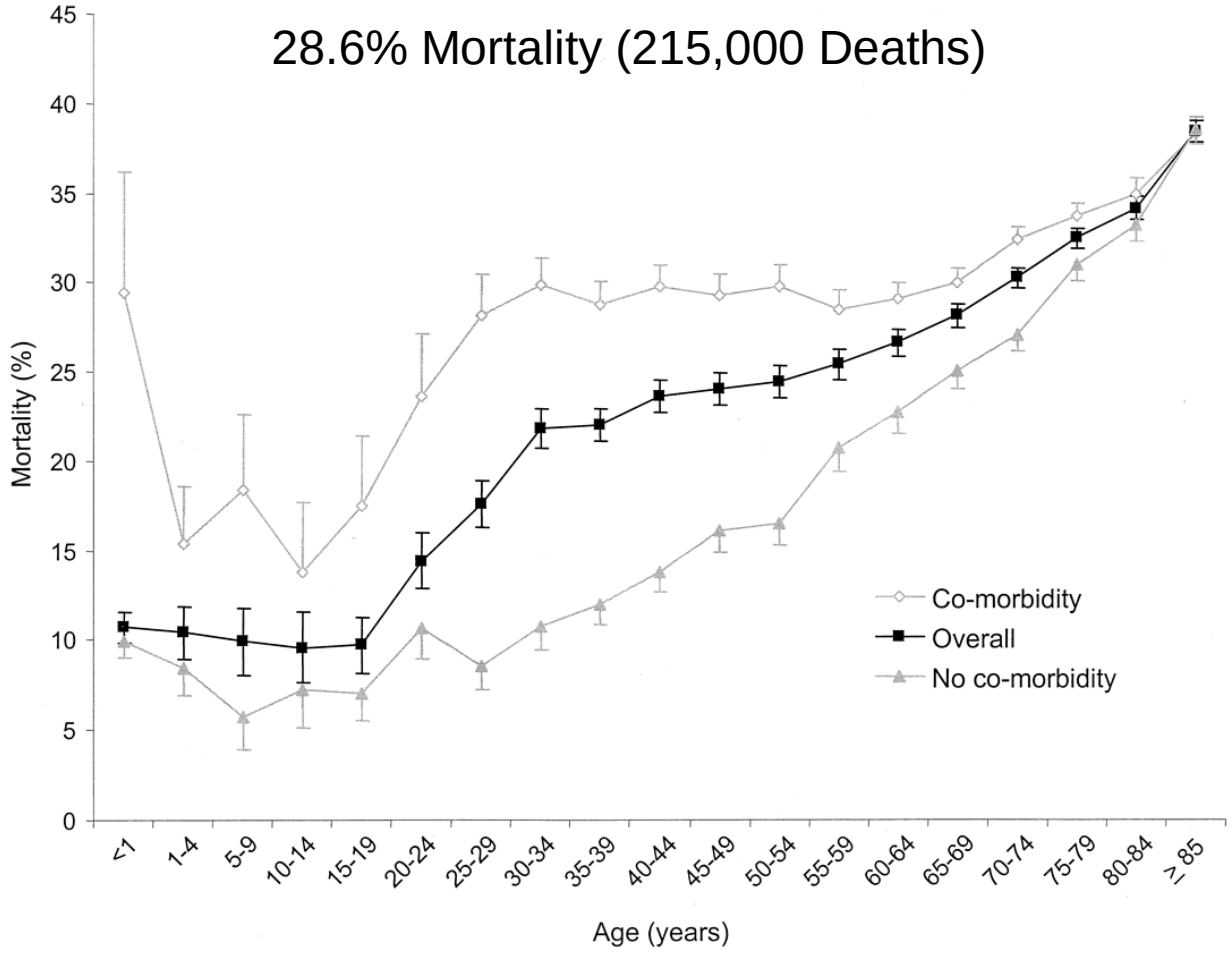
# Epidemiology of Severe Sepsis

- 1995 Hospital Discharges 6.6 million 7 large states
- Census, CDC, HCFA, AHA
- ICD-9 Sepsis
- Validation 5 hospitals

- 751,000 cases
- 3.0 / 1000 population
- 2.26 / 100 hospital discharges
- 161,000 (21%) surgery-related
- 51.1% ICU
- 17.3% IMCU / CCU

Angus Crit Care Med 2001

# Mortality Severe Sepsis




Angus Crit Care Med 2001

# SCCM Surviving Sepsis Campaign

*Crit Care Med 2008: 36: 296-327*

- A. Initial Resuscitation Goals at 6 hrs
  - Hypotension or elevated lactate
    - CVP 8-12 mm Hg
    - MAP $\geq$ 65 mm Hg
    - Urine $\geq$ 0.5 cc/kg/hr
    - Central vein (SVC) or mixed venous Saturation $\geq$70% or 65%

    Grade 1C
  - At 6 hrs $ScvO_2 \leq 70\%$ (or $SVO_2 < 65\%$) despite CVP 8-12 mmHg
    - Transfuse if Hct < 30%
    - Dobutamine 2.5-20mcg/kg/min

    Grade 2C

# Stop! What are these grades?

**Table 1.** Determination of the quality of evidence

- Underlying methodology
  - A. RCT
  - B. Downgraded RCT or upgraded observational studies
  - C. Well-done observational studies
  - D. Case series or expert opinion
- Factors that may decrease the strength of evidence
  1. Poor quality of planning and implementation of available RCTs, suggesting high likelihood of bias
  2. Inconsistency of results (including problems with subgroup analyses)
  3. Indirectness of evidence (differing population, intervention, control, outcomes, comparison)
  4. Imprecision of results
  5. High likelihood of reporting bias
- Main factors that may increase the strength of evidence
  1. Large magnitude of effect (direct evidence, RR >2 with no plausible confounders)
  2. Very large magnitude of effect with RR >5 and no threats to validity (by two levels)
  3. Dose-response gradient

RCT, randomized controlled trial; RR, relative risk.

**Sackett Chest 1989; 95: 2S-4S**

**Table 2.** Factors determining strong vs. weak recommendation

| What Should Be Considered | Recommended Process |
|---|---|
| Quality of evidence | The lower the quality of evidence, the less likely a strong recommendation |
| Relative importance of the outcomes | If values and preferences vary widely, a strong recommendation becomes less likely |
| Baseline risks of outcomes | The higher the risk, the greater the magnitude of benefit |
| Magnitude of relative risk, including benefits, harms, and burden | Larger relative risk reductions or larger increases in relative risk of harm make a strong recommendation more or less likely, respectively |
| Absolute magnitude of the effect | The larger the absolute benefits and harms, the greater or lesser likelihood, respectively, of a strong recommendation |
| Precision of the estimates of the effects | The greater the precision, the more likely a strong recommendation |
| Costs | The higher the cost of treatment, the less likely a strong recommendation |

# GRADE

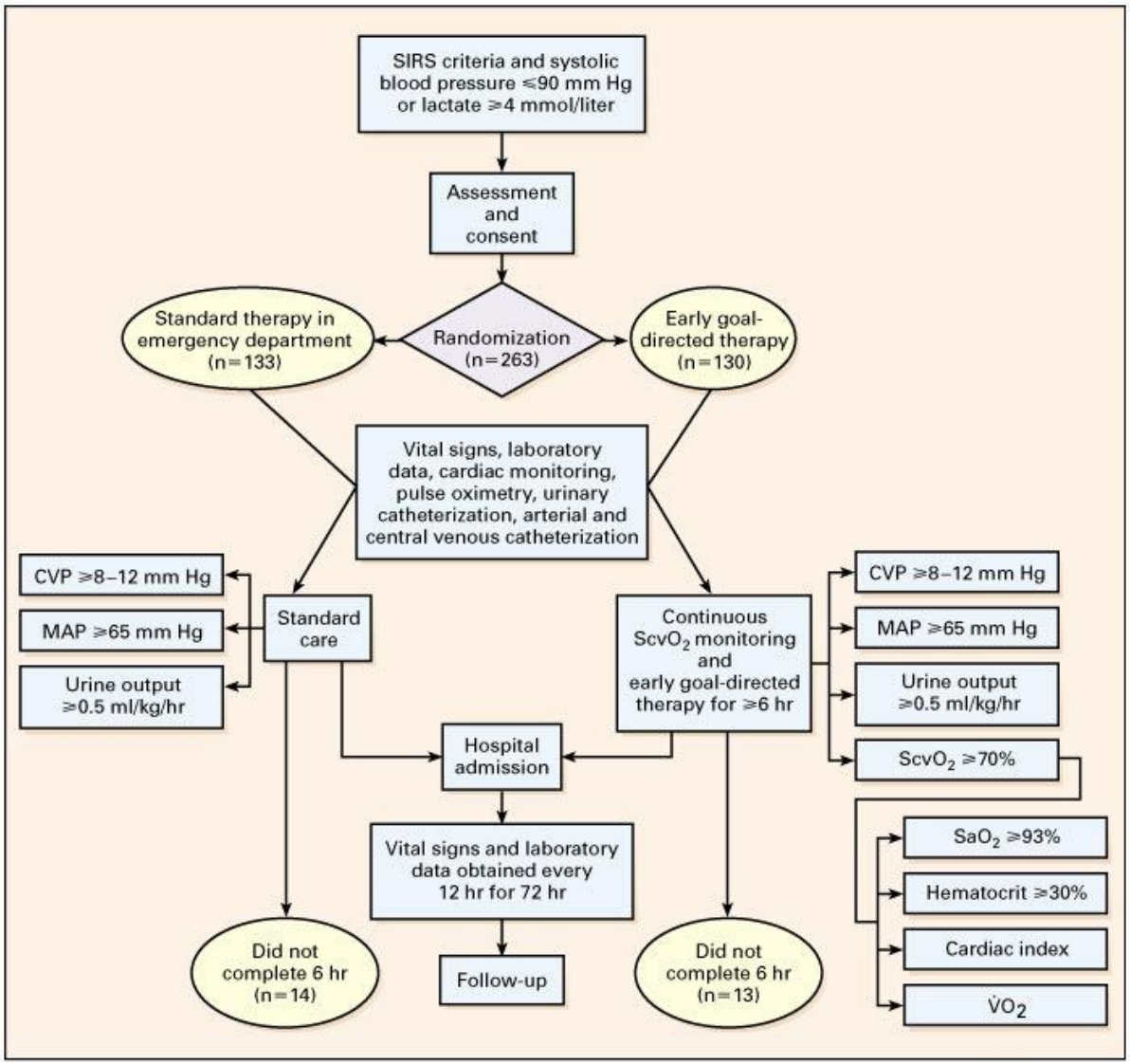
- Grade 1 strong
- Grade 2 weak

- Quality of evidence
  - A high
  - B moderate
  - C low
  - D very low

**GRADE working group 2004; 328: 1490-1498**

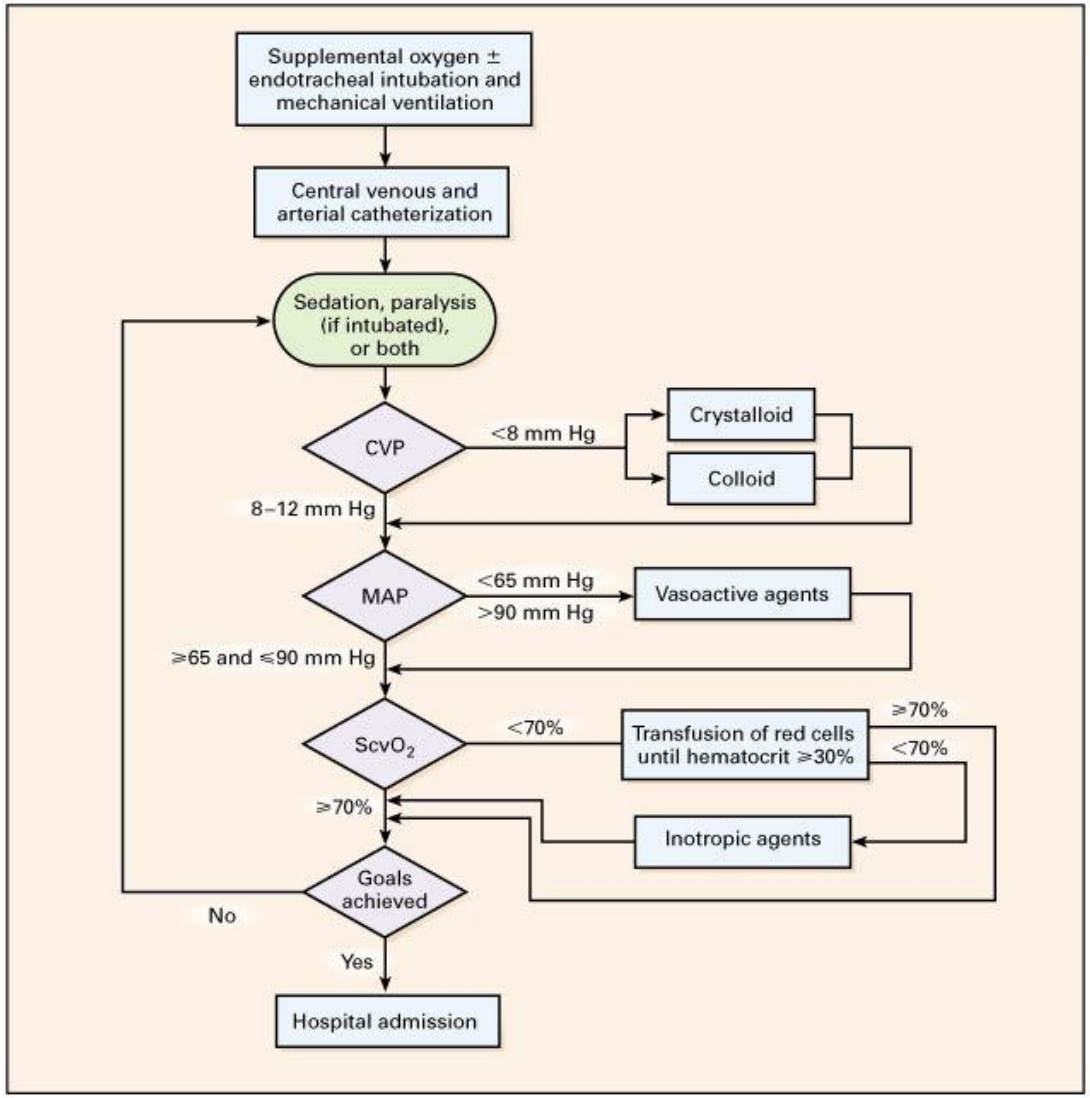
# Early Goal Directed Resuscitation

*Rivers et al New Engl J Med 2001*



# Early Goal Directed Resuscitation

*Rivers et al New Engl J Med 2001*



# Early Goal Directed Resuscitation

*Rivers et al New Engl J Med 2001*

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

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

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

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

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

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*Crit Care Med 2008: 36: 296-327*

- B. Diagnosis
  - Culture before antibiotics
    - 2 blood
      - One via peripheral puncture
      - One via line
    - Other sites as appropriate

    Grade 1C
  - Diagnostic Studies
    - Imaging
    - Sample likely sources

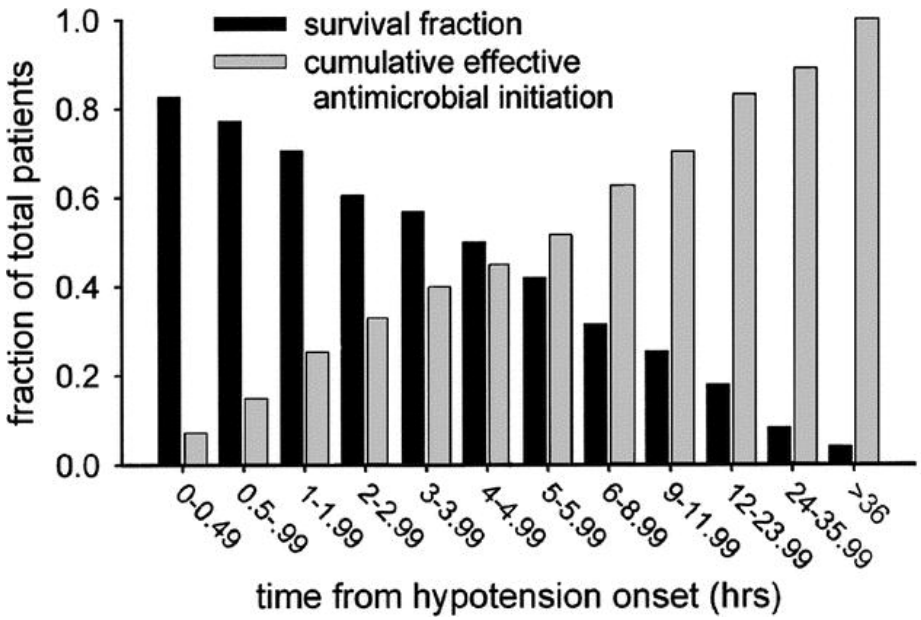
    Grade 1C

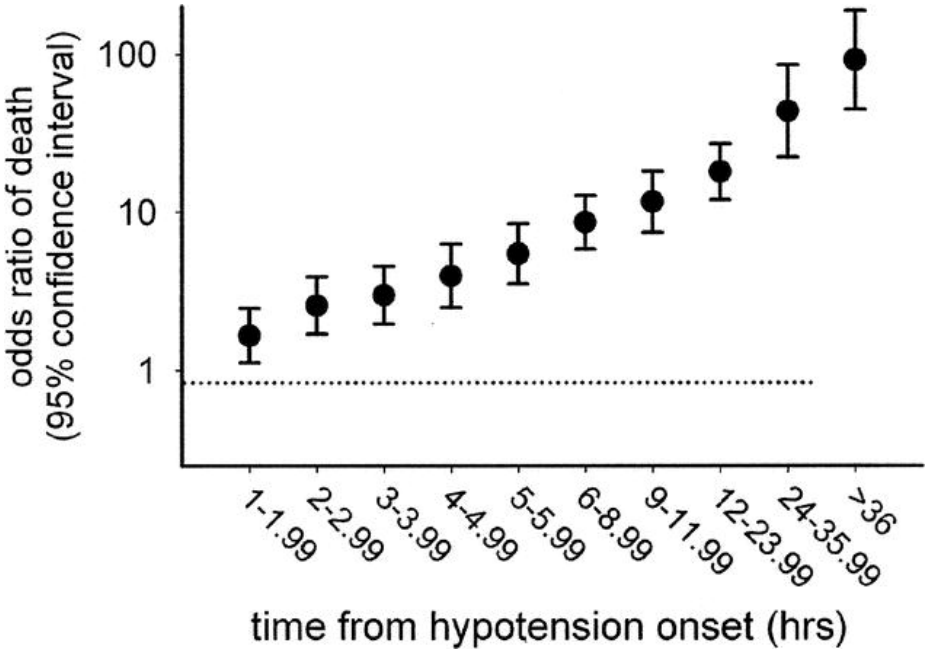
# SCCM Surviving Sepsis Campaign

*Crit Care Med 2008: 36: 296-327*

- C. Antibiotic Therapy
  - Start within 1 hr of recognizing severe sepsis (1D) and septic shock (1B)
  - One or more antibiotics with coverage for likely organisms **Grade 1C**
  - Reassess antibiotics at 48 hrs **Grade 1C**
  - Duration typically 7-10 days (longer if slow response, undrainable abscess, immunodeficiency) **Grade 1D**
  - If syndrome is due to noninfectious cause stop antibiotics **Grade 1D**

# Duration of hypotension and timing of antibiotics




2,731 adult patients with septic shock

Each hour of delay over 6 was associated with an average decrease in survival of 7.6%.

**In multivariate analysis (including APACHE II score and therapeutic variables), time to initiation of antimicrobial therapy was the single strongest predictor of outcome.**

**Kumar et al Crit Care Med 2006; 34: 1589-1596**

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*Crit Care Med 2008: 36: 296-327*

- D. Source Control
  - Make a specific diagnosis as rapidly as possible
  - Drain abscess
  - Remove infected devices

Grade 1C

# SCCM Surviving Sepsis Campaign

*Crit Care Med 2008: 36: 296-327*

- E. Fluid therapy
  - Crystalloid vs colloid. There is no evidence based support for one over the other

Grade 1B

# Crystalloid vs. colloid

## Meta-analyses

- Choi et al Crit Care Med 1999; 27: 200-210
- Cook et al Ann Int Med 2001; 135: 205-208
- Schierhout et al BMJ 1998; 316:961-964
- Perel and Roberts Cochrane Database Syst Rev 2007

# *Saline vs Albumin Fluid Evaluation Study (SAFE)*

- *New Eng J Med 2004*
- *6997 patients ANZICSCTG*
- Maintenance fluids, replacement fluids, nutrition, and blood products discretion of the clinicians.
- Patients require fluid administration to maintain or increase intravascular volume.
- 4 percent albumin (Albumex, CSL) or normal saline.

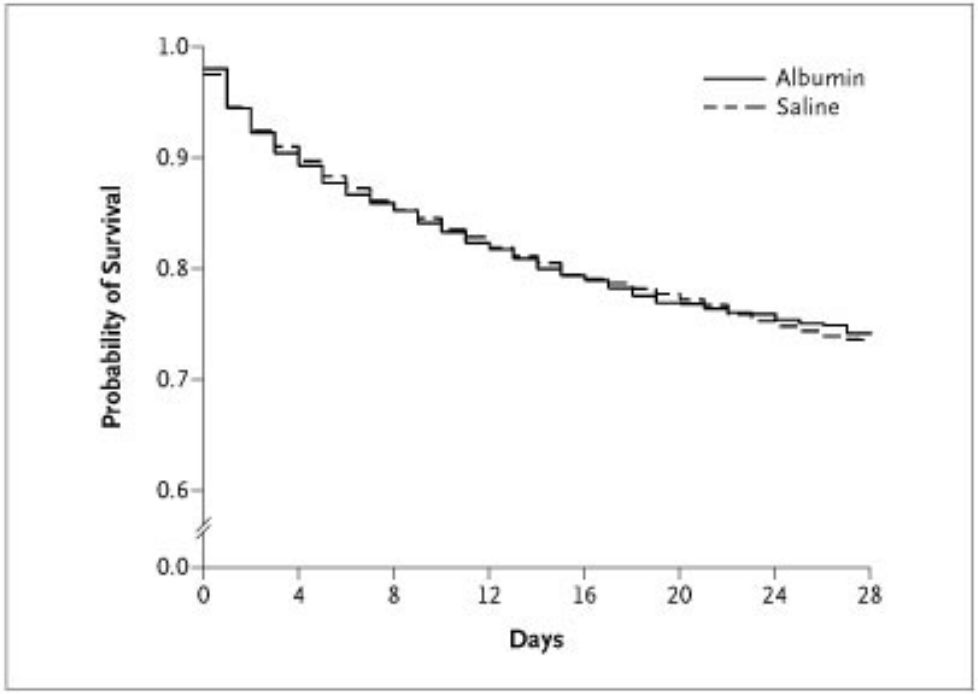
**Table 2. Fluids Administered and Physiological Effects of Treatment.***

| Variable | Albumin Group | | Saline Group | | P Value† |
|---|---|---|---|---|---|
| | No. of Patients | Value | No. of Patients | Value | |
| Study fluid (ml) | | | | | |
| Day 1 | 3410 | 1183.9±973.6 | 3418 | 1565.3±1536.1 | <0.001 |
| Day 2 | 3059 | 602.7±892.7 | 3068 | 954.0±1484.4 | <0.001 |
| Day 3 | 2210 | 268.0±554.5 | 2202 | 348.3±753.5 | 0.03 |
| Day 4 | 1686 | 192.3±427.0 | 1664 | 228.6±642.6 | 0.57 |
| Nonstudy fluid (ml) | | | | | |
| Day 1 | 3392 | 1459.4±1183.2 | 3405 | 1505.6±1254.3 | 0.30 |
| Day 2 | 3051 | 2615.9±1372.5 | 3057 | 2707.3±1435.7 | 0.009 |
| Day 3 | 2199 | 2618.5±1346.5 | 2191 | 2660.9±1319.3 | 0.15 |
| Day 4 | 1680 | 2691.5±1228.7 | 1656 | 2707.7±1255.4 | 0.36 |
| Packed red cells (ml) | | | | | |
| Day 1 | 3411 | 97.8±360.7 | 3415 | 71.7±296.8 | <0.001 |
| Day 2 | 3066 | 106.5±321.4 | 3074 | 61.1±235.2 | <0.001 |
| Day 3 | 2217 | 59.8±225.5 | 2210 | 49.5±190.8 | 0.30 |
| Day 4 | 1692 | 43.6±167.5 | 1668 | 46.0±189.0 | 0.77 |
| Net positive fluid balance (ml) | | | | | |
| Day 1 | 3363 | 1543.6±1619.7 | 3382 | 1990.5±2061.7 | <0.001 |
| Day 2 | 3044 | 1015.3±1826.9 | 3052 | 1505.1±2215.9 | <0.001 |
| Day 3 | 2190 | 422.1±1633.3 | 2182 | 553.0±1732.3 | 0.007 |
| Day 4 | 1671 | 137.2±1491.0 | 1649 | 155.7±1650.6 | 0.70 |
| Mean arterial pressure (mm Hg) | | | | | |
| Day 1 | 3406 | 81.4±14.4 | 3408 | 80.9±14.5 | 0.14 |
| Day 2 | 3068 | 84.4±15.1 | 3075 | 84.2±15.7 | 0.49 |
| Day 3 | 2215 | 87.2±15.3 | 2209 | 86.9±16.1 | 0.62 |
| Day 4 | 1688 | 88.3±15.9 | 1666 | 88.4±16.3 | 0.87 |
| Heart rate (beats/min) | | | | | |
| Day 1 | 3398 | 88.0±20.2 | 3406 | 89.7±20.8 | <0.001 |
| Day 3 | 3071 | 88.5±19.5 | 3075 | 89.5±19.2 | 0.06 |
| Day 3 | 2216 | 88.8±19.1 | 2213 | 89.7±18.8 | 0.10 |
| Day 4 | 1691 | 89.5±18.9 | 1668 | 89.9±18.5 | 0.52 |
| Central venous pressure (mm Hg) | | | | | |
| Day 1 | 2204 | 11.2±4.8 | 2270 | 10.0±4.5 | <0.001 |
| Day 2 | 2095 | 11.6±4.9 | 2135 | 10.4±4.3 | <0.001 |
| Day 3 | 1531 | 11.4±4.8 | 1589 | 10.7±4.4 | <0.001 |
| Day 4 | 1221 | 11.1±4.8 | 1230 | 10.5±4.4 | <0.001 |
| Serum albumin (g/liter) | | | | | |
| Day 1 | 2081 | 28.7±7.0 | 2061 | 24.7±6.5 | <0.001 |
| Day 2 | 2708 | 30.8±6.4 | 2703 | 24.5±5.9 | <0.001 |
| Day 3 | 1921 | 30.0±6.4 | 1905 | 23.6±5.6 | <0.001 |
| Day 4 | 1498 | 29.0±6.2 | 1478 | 23.1±5.5 | <0.001 |

* Plus–minus values are means ±SD.
† P values are for the comparison between the two means for each variable at each time point.

? Biologic significance

# SAFE Trial

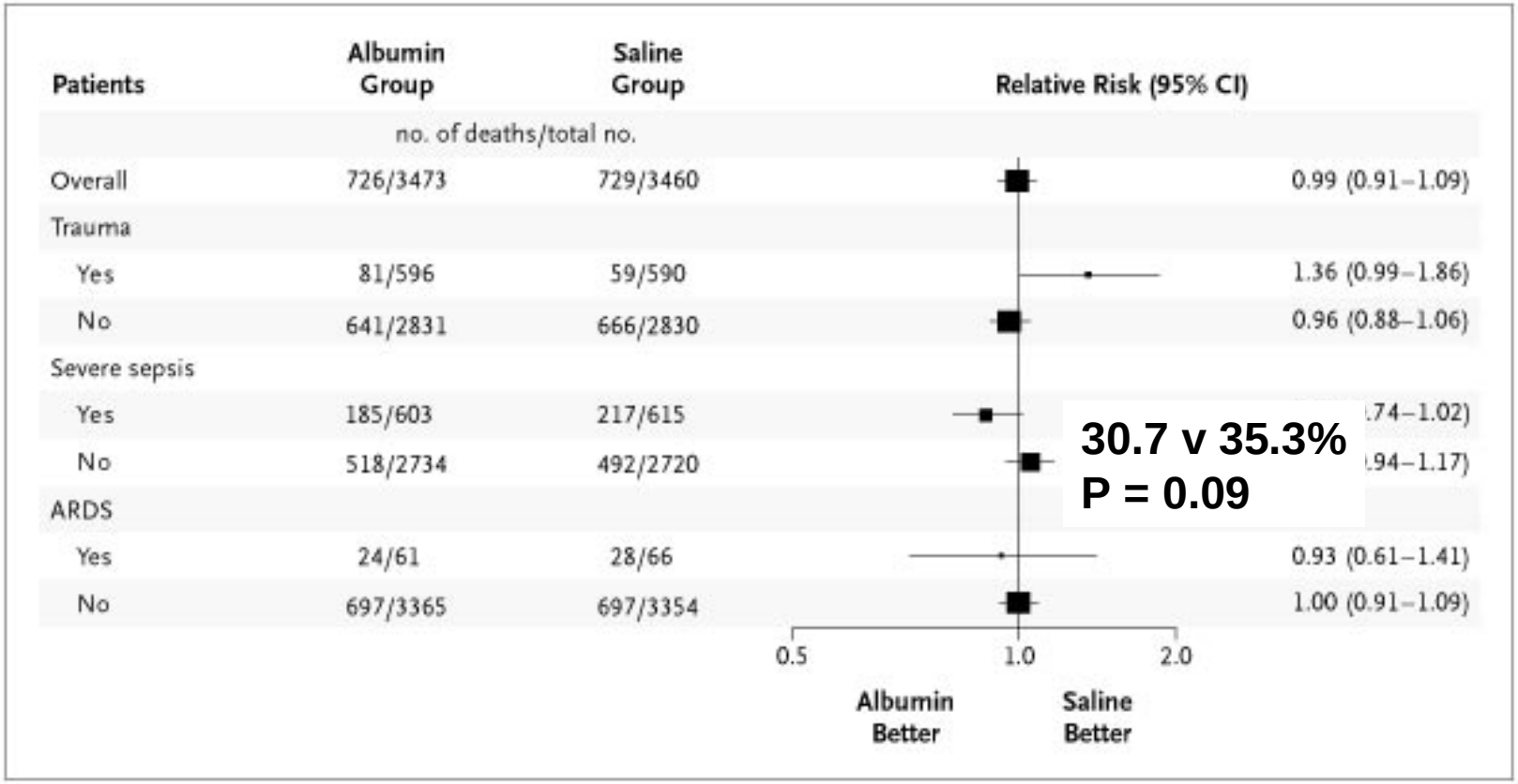



| | |
|---|---|
| Dead | 20.9% vs 21.1% |
| Alive is ICU | 3.2 vs. 2.5% |
| Alive in hospital | 22.8 vs. 24.5% |
| ICU LOS | 6.5 vs 6.2 d |
| Hosp LOS | 15.3 vs 15.6 d |
| Vent | 4.5 vs 4.3 d |
| New organ failure | 47.3 vs 46.7% |
| Death Trauma | 13.6 vs 10.0% |
| Death Sepsis | 30.7 vs 35.3% |
| Death ARDS | 39.3 vs 42.4% |

*(SAFE) New Eng J Med 2004*

# Relative Risk Death Any Cause

*Among 6 predefined subgroups*



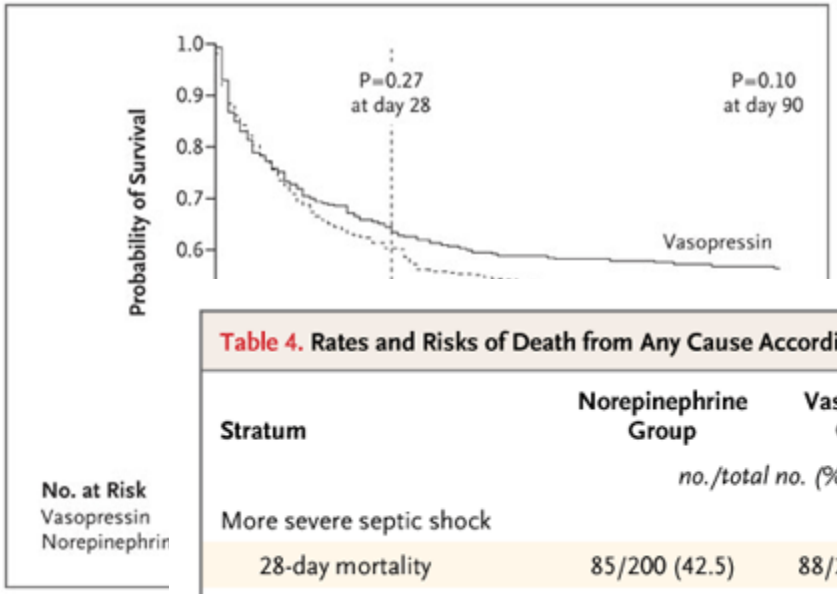

*(SAFE) New Eng J Med 2004*

# SCCM Surviving Sepsis Campaign

*Crit Care Med 2008: 36: 296-327*

- F. Vasopressors
  - MAP ≥ 65 **Grade 1C**
  - When appropriate fluid does not maintain pressure, use a vasopressor
  - Norepi or dopamine is first choice **Grade 1C**
  - Epi, phenylephrine and vasopressin are not first line
  - VP can be added to Norepi **Grade 2C**
  - Epi is the 1st choice of alternatives to Norepi or Dopa **Grade 2B**
  - Low dose dopa should not be used for renal protection **Grade 1A**
  - Arterial line **Grade 1D**

# Vasopressin versus Norepinephrine Infusion in Patients with Septic Shock




778 pts on > 5 mcg/min NE
- NE v VP

**Table 4. Rates and Risks of Death from Any Cause According to the Severity of Shock.***

| Stratum | Norepinephrine Group | Vasopressin Group | P Value† | Absolute Risk Reduction (95% CI) | Relative Risk (95% CI) |
|---|---|---|---|---|---|
| | *no./total no. (%)* | | | % | |
| More severe septic shock | | | | | |
| 28-day mortality | 85/200 (42.5) | 88/200 (44.0) | 0.76 | –1.5 (–11.2 to 8.2) | 1.04 (0.83 to 1.3) |
| 90-day mortality | 105/199 (52.8) | 103/199 (51.8) | 0.84 | 1.0 (–8.8 to 10.8) | 0.98 (0.81 to 1.18) |
| Less severe septic shock | | | | | |
| 28-day mortality | 65/182 (35.7) | 52/196 (26.5) | 0.05 | 9.2 (–0.1 to 18.5) | 0.74 (0.55 to 1.01) |
| 90-day mortality | 83/180 (46.1) | 69/193 (35.8) | 0.04 | 10.4 (0.4 to 20.3) | 0.78 (0.61 to 0.99) |

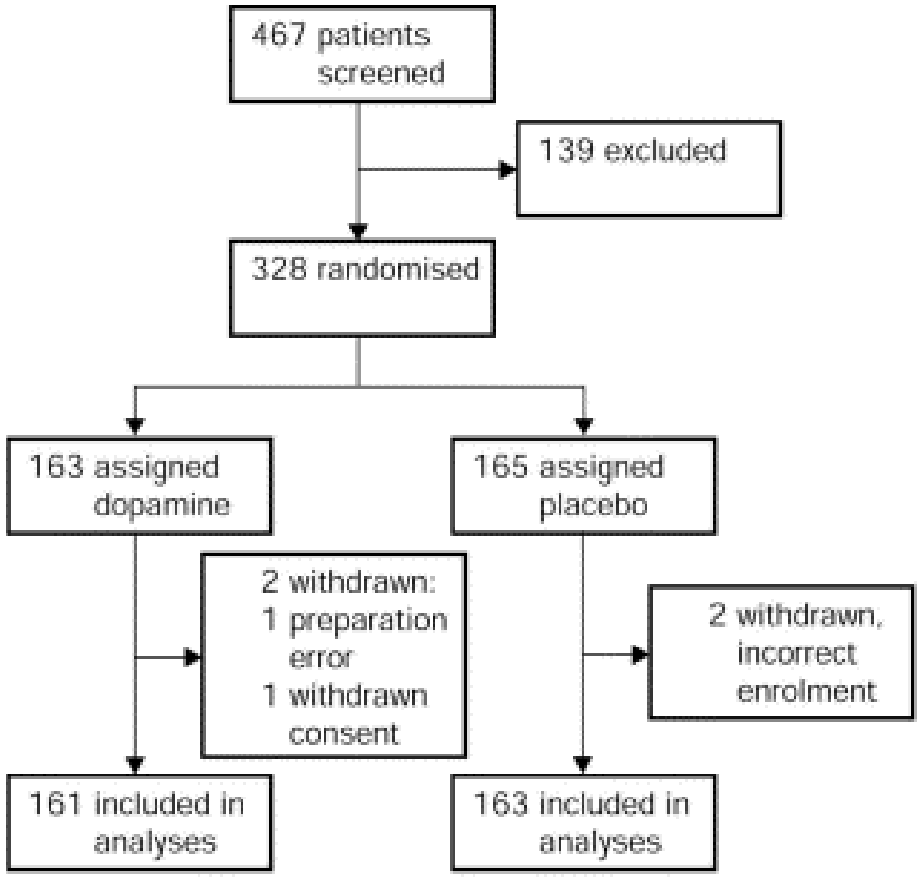
* Patients with more severe septic shock were defined as those who required at least 15 μg of norepinephrine per minute or the equivalent at the time of randomization. Those with less severe septic shock were defined as those who required 5 to 14 μg of norepinephrine per minute or the equivalent at the time of randomization.
† Two-sided P values are based on Pearson's chi-square test.

Severe ≥ 15 mcg/min NE (0.21mcg/kg/min-70kg)

**Russell et al New Eng J Med 2008 358: 877-887**

# Renal-dose Dopamine

- Low-dose dopamine in patients with early renal dysfunction: a placebo-controlled randomised trial. The Lancet 2000; 356: 2139-2143.
- Australian and New Zealand Intensive Care Society (ANZICS) Clinical Trials Group
- 23 ICUs




**Bellomo et al Lancet 2000; 356: 2139-2143**

| Characteristic | Dopamine (*n*=161) | Placebo (*n*=163) |
|---|---|---|
| Demography | | |
| Age (years)* | 63 (15) | 61 (17) |
| Male/female† | 94/67 | 102/61 |
| | | |
| Condition | | |
| Admission APACHE II score* | 21 (6) | 21 (8) |
| Admission SAPS II score* | 43 (14) | 45 (16) |
| APACHE II score at start of infusion* | 18 (7) | 18 (7) |
| SAPS II score at start of infusion* | 40 (15) | 41 (15) |
| Shock‡ at start of infusion† | 93 | 102 |
| On ventilator at start of infusion† | 138 | 141 |
| | | |
| Type of admission† | | |
| Respiratory, medical | 32 | 25 |
| General, surgical | 30 | 35 |
| Vascular, surgical | 19 | 16 |
| Cardiac, surgical | 12 | 12 |
| Multiple trauma | 8 | 14 |
| Cardiac, medical | 4 | 12 |
| General, medical | 13 | 6 |
| Haematology/oncology | 8 | 7 |
| Gastrointestinal, medical | 7 | 6 |
| Thoracic, surgical | 5 | 6 |
| Other, medical | 8 | 9 |
| Other, surgical | 15 | 15 |
| | | |
| Renal characteristics | | |
| Pre-renal renal dysfunction† | 152 | 154 |
| Nephrotoxic component† | 9 | 9 |
| Baseline creatinine (mmol/L)* | 183 (85) | 182 (81) |
| Baseline urea (mmol/L)* | 14·3 (7·5) | 14·4 (7·1) |
| Oliguria† | 109 | 113 |
| | | |
| Haemodynamics | | |
| Mean arterial pressure (mm Hg)* | 80 (15) | 80 (16) |
| Central venous pressure (mm Hg) | 14 (8) | 13 (7) |

Lancet 2000

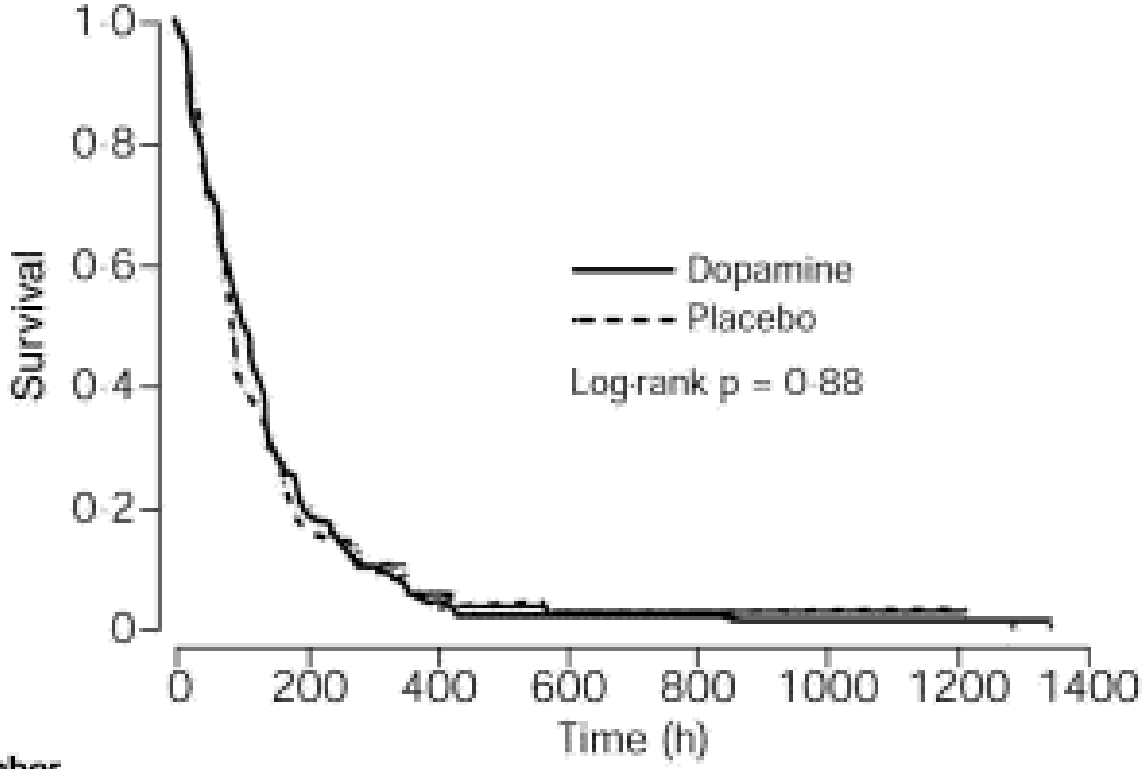
# Effect of Dopa on Markers of Renal Function

| | Dopamine ($n$=161) | Placebo ($n$=163) | Difference (95% CI) |
|---|---|---|---|
| Serum concentrations* | | | |
| Peak creatinine (µmol/L) | 245 (144) | 249 (147) | 4 (−28 *to* 36) |
| Peak urea (mmol/L) | 20 (10) | 23 (12) | 3 (−0 · 8 *to* 6 · 8) |
| Increase in creatinine (µmol/L) | 62 (107) | 66 (108) | 4 (−21 *to* 29) |
| Increase in urea (mmol/L) | 6 (8) | 7 (9) | 1 ((−1 *to* 3) |
| Number of patients with event | | | |
| Creatinine concentration >300 mmol/L | 56 | 56 | 0 (−16 *to* 16) |
| Renal replacement therapy | 35 | 40 | 5 (−10 *to* 20) |
| Urine output (mL/h)* | | | |
| Baseline | 37 (40) | 50 (59) | 13 (−21 *to* 27) |
| After 1 h | 71 (81) | 72 (77) | 1 (−20 *to* 22) |
| After 24 h | 96 (101)† | 92 (72)† | 4 (−19 *to* 27) |
| After 48 h | 99 (83)† | 109 (95)† | 10 (−11 *to* 31) |

Loop diuretics administered to 90 pts in each group
Furosemide Dose 192 mg Dopa vs 268 mg Placebo

Lancet 2000

# Time to Recovery of Renal Function




**Number at risk**

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Dopamine | 97 | 16 | 4 | 2 | 2 | 1 | 1 | 0 |
| Placebo | 87 | 16 | 5 | 2 | 2 | 2 | 2 | 0 |

No difference in secondary outcome: Survival, Ventilation, arrythmias, LOS

Lancet 2000

# SCCM Surviving Sepsis Campaign

*Crit Care Med 2008: 36: 296-327*

- G. Inotropic Therapy
  - Low cardiac output despite adequate fluid administration treat with Dobutamine. If hypotensive combine with vasopressor

**Grade 1C**

  - A strategy to reach a predefined cardiac output is not recommended.

**Grade 1B**

# Prospective Trials Supranormal Resuscitation

| Author | Patients | Time Course | N | Mortality | |
|---|---|---|---|---|---|
| | | | | Control | Supranormal |
| Shoemaker, 1988 | Surgical | Early | 88 | 36 | 4 |
| Tuhschmidt, 1989 | Sepsis | Late | 51 | 72 | 50 |
| Gutierrez, 1992 | Critical Ill, | | | | |
| | Nl pHi | Early | 141 | 58 | 42 |
| | LowpHi | Late | 119 | 63 | 64 |
| Flemming, 1992 | Trauma | Early | 67 | 44 | 24 |
| Boyd, 1993 | Surgical | Early | 107 | 22 | 6 |
| Yu, 1993 | Critical Ill | Late | 67 | 34 | 34 |
| Hayes, 1994 | Critical Ill | Late | 100 | 30 | 50 |
| Bishop, 1995 | Trauma | Early | 115 | 37 | 18 |
| Gattinoni, 1995 | Critical Ill | Late | 505 | 48 | 49 |
| Yu, 1998 | Surgery, Sepsis | Late | | | |
| | 50-75 yrs | | 66 | 52 | 21 |
| | > 75 yrs | | 39 | 61 | 57 |
| McKinley, 2002 | Trauma | Early | 36 | 89 | 72 |

# SCCM Surviving Sepsis Campaign

*Crit Care Med 2008: 36: 296-327*

- H. Steroids
  - IV hydrocortisone should be given only to adult septic shock patients after it has been confirmed that their blood pressure is poorly responsive to fluid resuscitation and vasopressor therapy

    **Grade 2C**
  - We suggest that the ACTH stimulation test not be used to identify the subset of adults with septic shock who should receive hydrocortisone

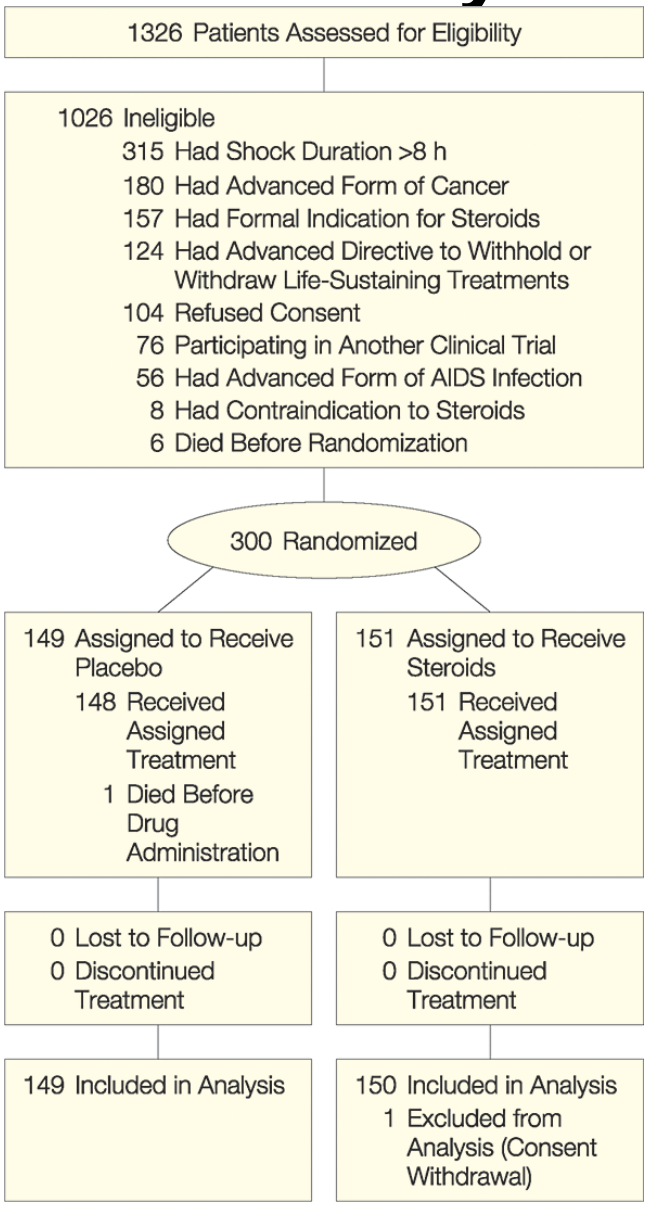
    **Grade 2B**

# Effect of Low Doses of Hydrocortisone and Fludrocortisone on Mortality in Septic Shock

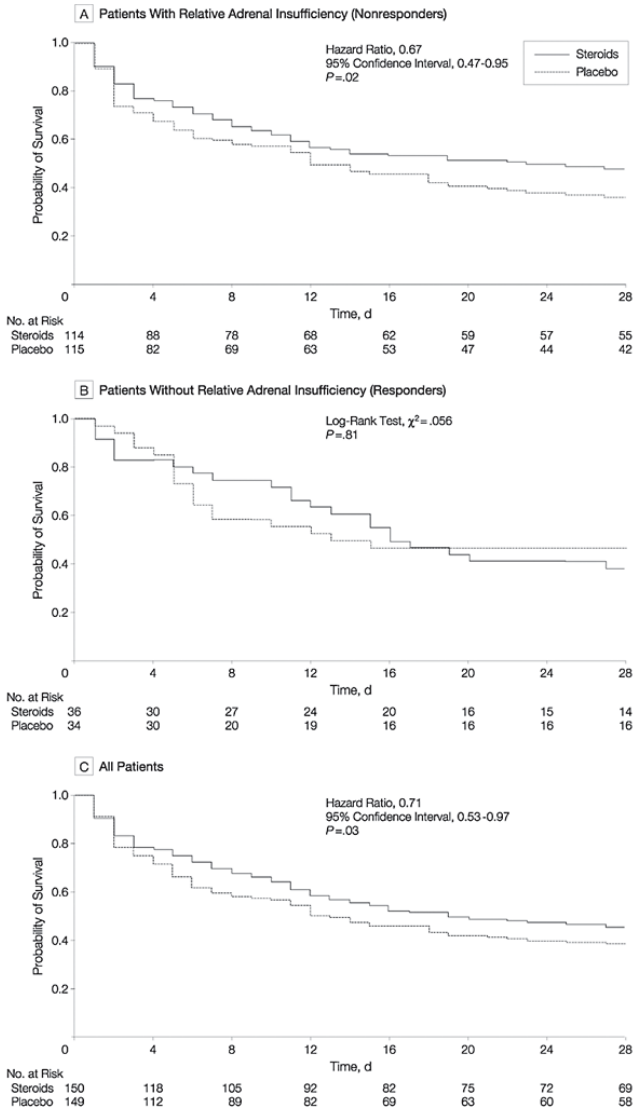
***Annane JAMA 2002***

Hydrocortisone 50 mg q 6 hrs +
Fludrocortisone 50 μg q d
7 days

Responders ACTH stim
Cortisol > 9 (70)
Nonresponders < 9 (229)



# Steroids and Mortality in Septic Shock
## *Annane JAMA 2002*




| *Mortality%* *(28 day)* | Placebo | Steroids | p |
|---|---|---|---|
| Responders | 53 | 61 | .96 |
| Nonresponders | 63 | 53 | .04 |
| All patients | 61 | 55 | .09 |

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# Hydrocortisone Therapy for Patients with Septic Shock

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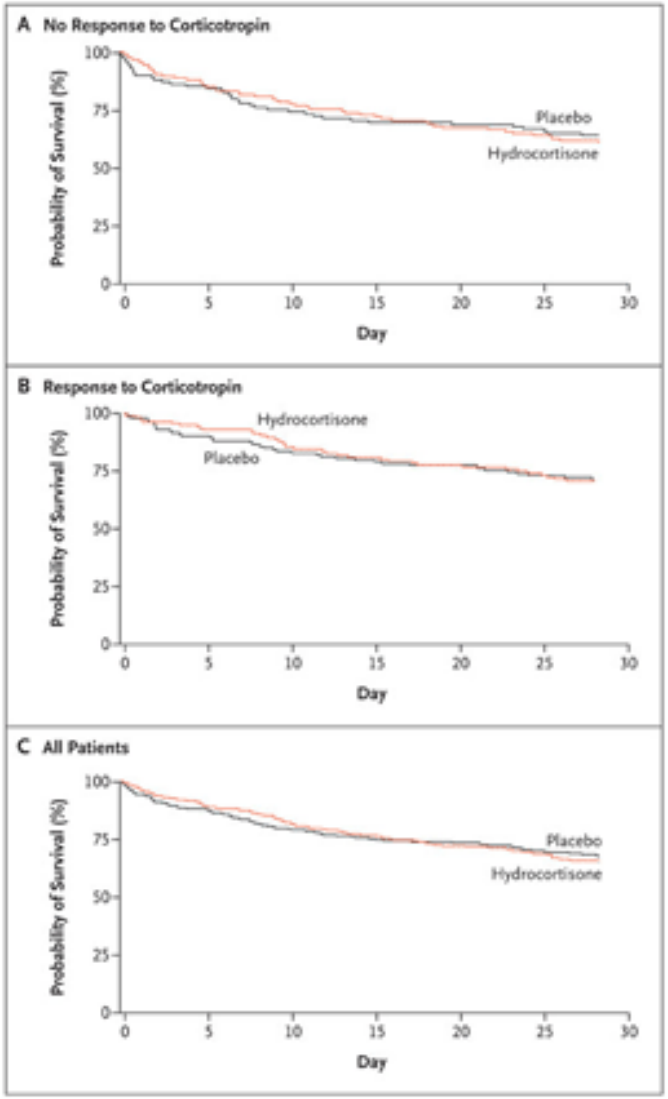


# SCCM Surviving Sepsis Campaign

*Crit Care Med 2008: 36: 296-327*

- H. Steroids
  - Patients with septic shock should not receive dexamethasone if hydrocortisone is available (**grade 2B**).
  - Daily addition of oral fludrocortisone (50 μg) if hydrocortisone is not available and the steroid that is substituted has no significant mineralocorticoid activity. Fludrocortisone is considered optional if hydrocortisone is used (**grade 2C**).
  - Wean the patient from steroid therapy when vasopressors are no longer required (**grade 2D**).
  - Doses of corticosteroids comparable to >300 mg of hydrocortisone daily should not be used in severe sepsis or septic shock for the purpose of treating septic shock (**grade 1A**).

# SCCM Surviving Sepsis Campaign

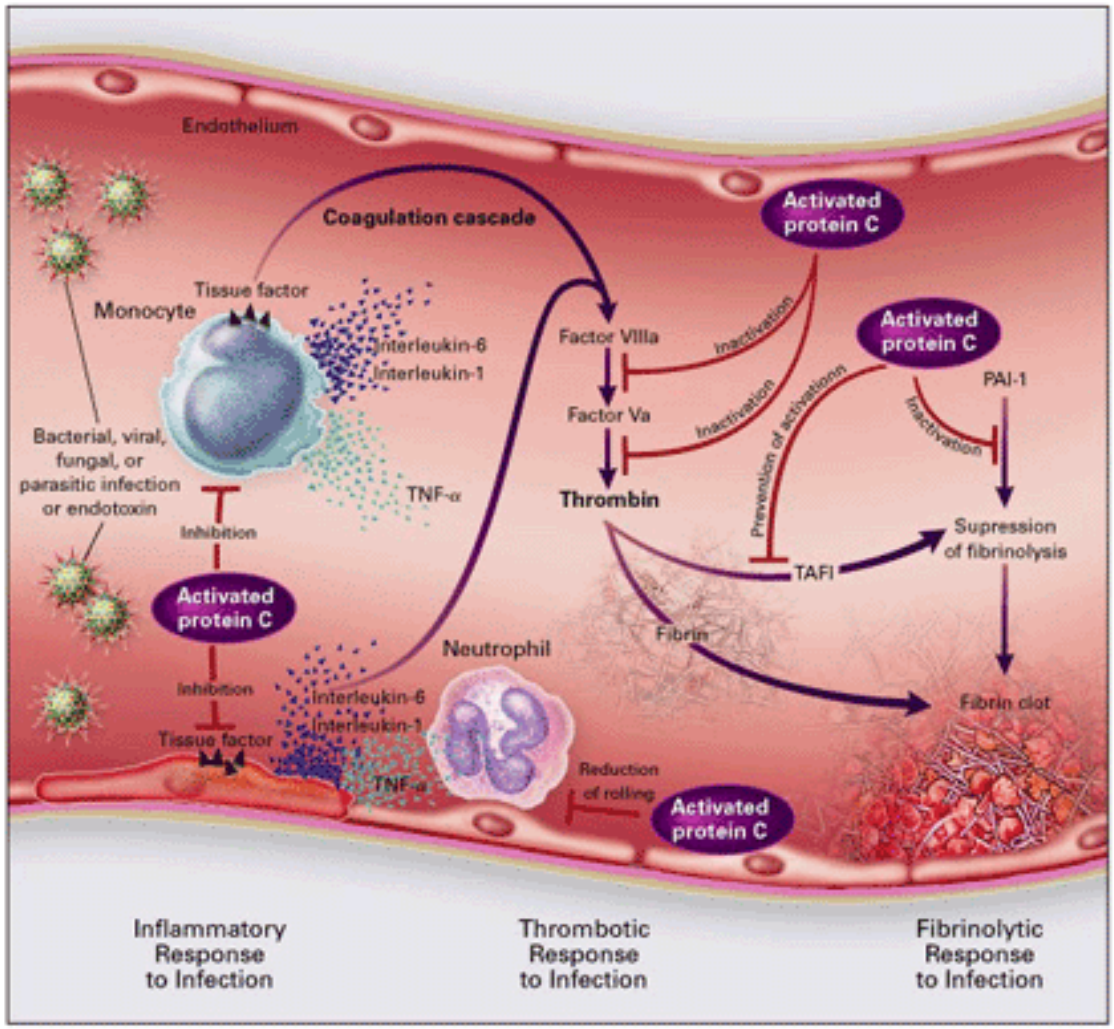
*Crit Care Med 2008: 36: 296-327*

- I. Recombinant Human Activated Protein C (rhAPC)
  - Sepsis-induced organ dysfunction associated with high risk of death, **APACHE II ≥ 25**, or MOF (grade 2B except for patients within 30 days of surgery, for whom it is grade 2C).
  - No bleeding risk that outweighs benefit of rhAPC
  - Severe sepsis and low risk of death, APACHE II <20 or one organ failure, should not receive rhAPC (grade 1A).

**PROWESS, ADDRESS, ENHANCE**

# Recombinant Human Activated Protein C for Severe Sepsis

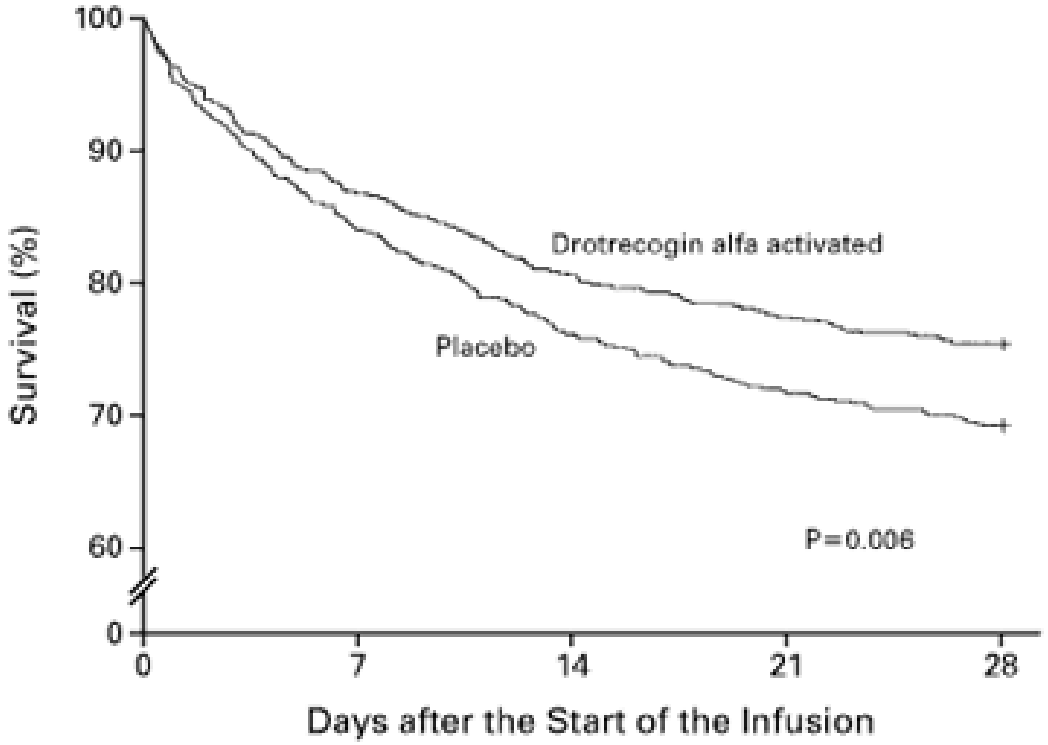
*Bernard New Eng J Med 2001*




Inflammation
Thrombosis
Fibrinolysis

# Recombinant Human Activated Protein C for Severe Sepsis (PROWESS)

*Bernard New Eng J Med 2001*

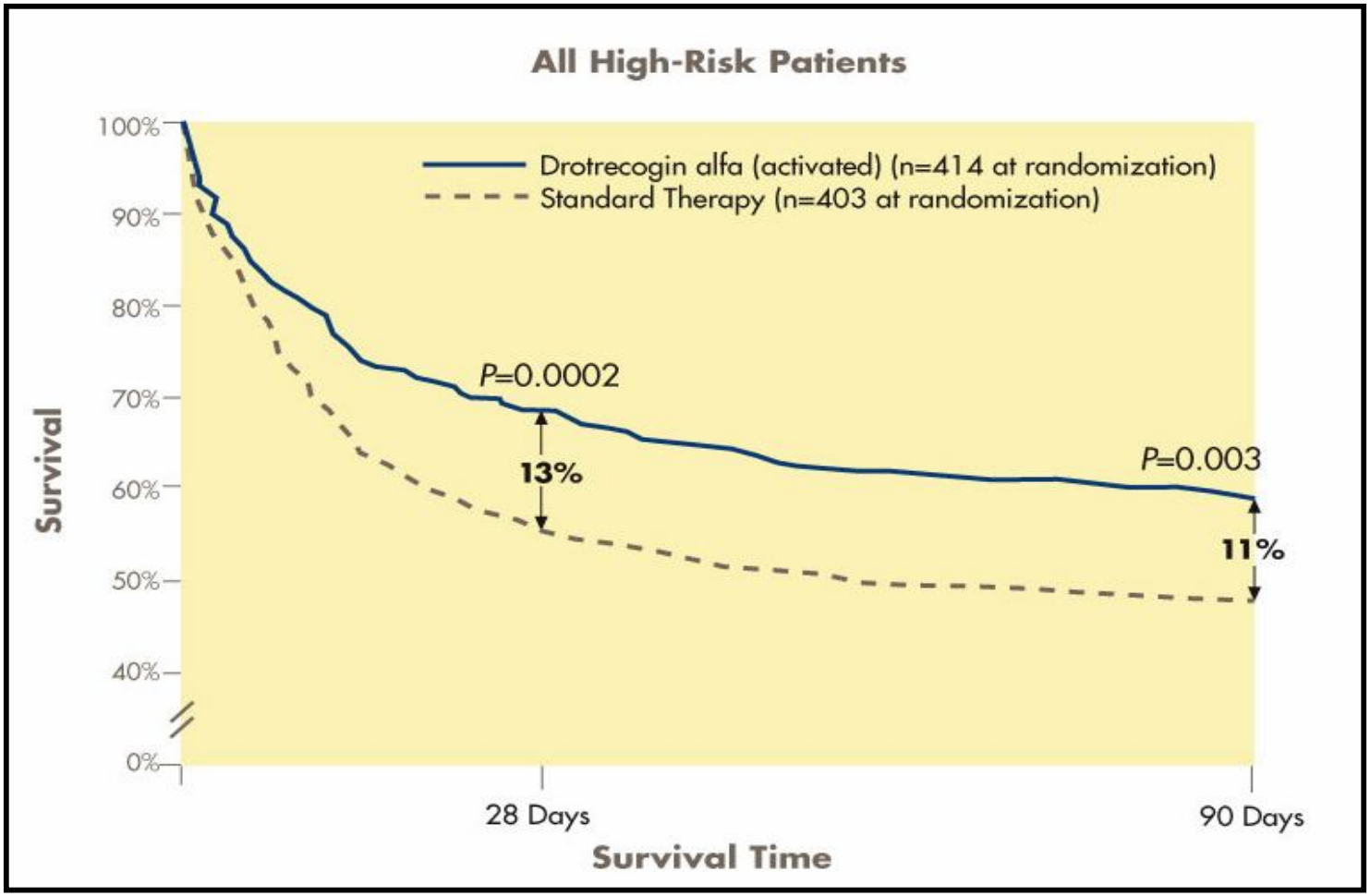



No. at Risk

| | | | | | |
|---|---|---|---|---|---|
| Drotrecogin alfa activated | 850 | 737 | 684 | 657 | 640 |
| Placebo | 840 | 705 | 639 | 602 | 581 |

# rhAPC in Patients at High Risk of Death

*Apache II > 25 or Vasopressors*



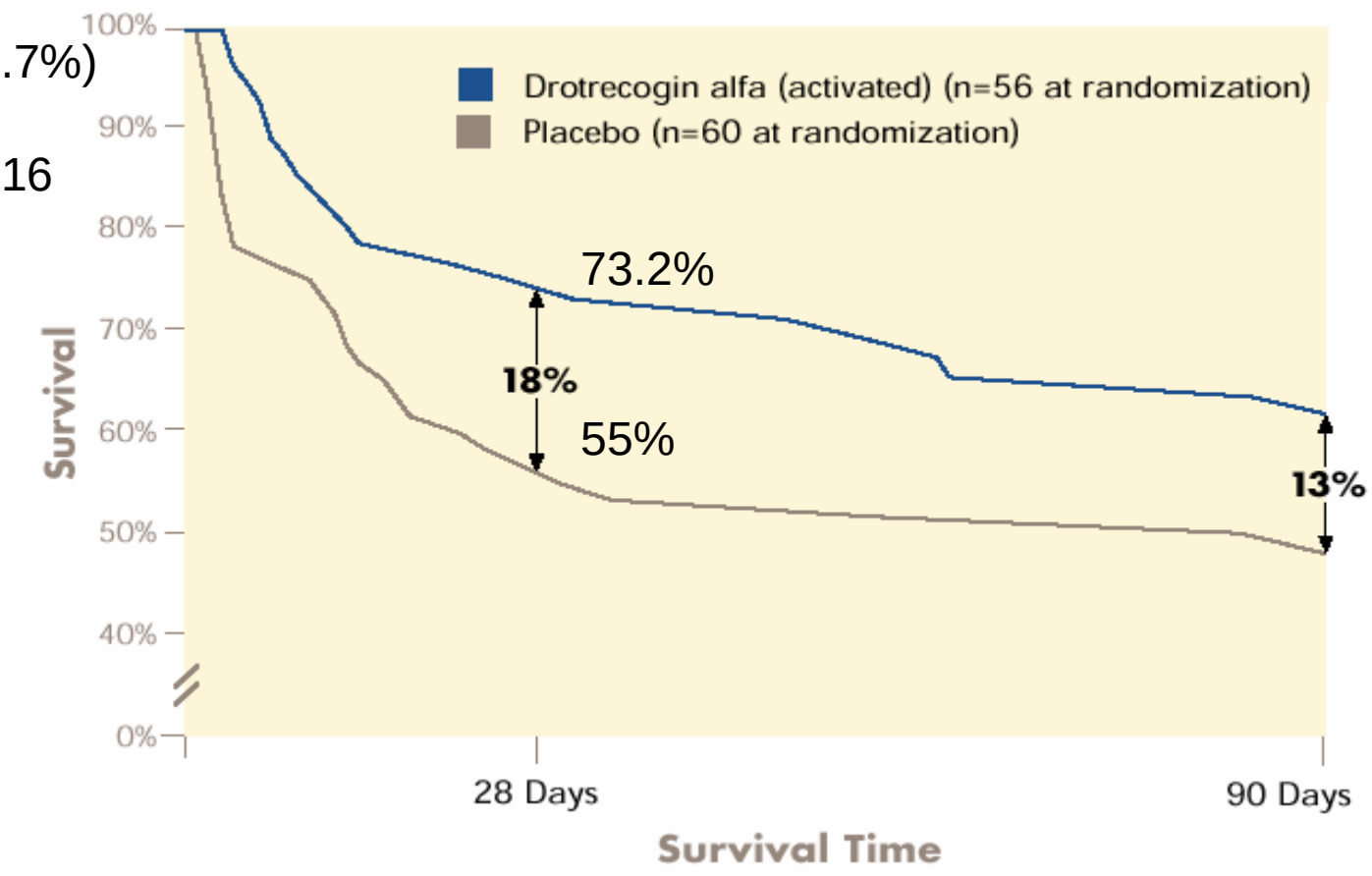

**44%**

**31%**

*Bernard New Eng J Med 2001*

# rhAPC Intra-Abdominal Surgery Patients

*Prowess*
N=1690
Surgery = 502 (29.7%)
Intra-abd = 315
Intra-abd AII>25 116




*Bernard New Eng J Med 2001*

# Bleeding Events

- All high risk patients
  - 2.2 vs 0.7%
- All intra-abdominal surgery patients
  - 2.5 vs 0%
- ICH
  - 0.2 vs 0.1%

**Bernard New Eng J Med 2001**

# Intra-cranial Hemorrhage

- PROWESS 0.1 vs 0.2%
- ADDRESS 0.4 vs 0.5%
- ENHANCE 1.5%

# Managing rhAPC in Surgery Patients

- T1/2 = 13 minutes
  - 80% eliminated in 30 minutes
- Discontinue 2 hrs prior to invasive procedure
- Resume 12 hrs after surgery

*Bernard New Eng J Med 2001*

# rhAPC

## *Contraindications*

**Appendix B.** Contraindications to use of recombinant human activated protein C (rhAPC)[a]

rhAPC increases the risk of bleeding. rhAPC is contraindicated in patients with the following clinical situations in which bleeding could be associated with a high risk of death or significant morbidity.

- Active internal bleeding
- Recent (within 3 months) hemorrhagic stroke
- Recent (within 2 months) intracranial or intraspinal surgery, or severe head trauma
- Trauma with an increased risk of life-threatening bleeding
- Presence of an epidural catheter
- Intracranial neoplasm or mass lesion or evidence of cerebral herniation

See labeling instructions for relative contraindications.

[a]The committee recommends that platelet count be maintained at ≥30,000 during infusion of rhAPC.

*Physicians' Desk Reference*. 57th Edition. Montvale, NJ, Thompson PDR, 2003, pp 1875–1876.

*Bernard New Eng J Med 2001*

# rhAPC

## *Relative Contraindications*

- INR > 3.0
- GI Bleeding within 6 weeks
- Thrombolytics within 3 days
- Oral anticoagulants or GPIIb/IIIA inhibitors within 7 days
- ASA within 7 days
- Ischemic stroke with 3 months
- AVM or aneurysm
- Bleeding diathesis
- Chronic liver disease

*Bernard New Eng J Med 2001*

# SCCM Surviving Sepsis Campaign

*Crit Care Med 2008: 36: 296-327*

- J. Blood products
  - Once hypoperfusion is resolved limit transfusion to pts with Hg < 7 g/dl **Grade 1B**
  - EPO is not indicated for anemia except in renal failure pts. **Grade 1B**

# Canadian Critical Care Trial Group

*Herbet New Eng J Med 1999*

- 838 critically ill patients with euvolemia after initial treatment
- 418 patients restrictive strategy
  - Hg below 7.0 g per deciliter
  - Hg maintained at 7.0 to 9.0 g per deciliter
- 420 patients liberal strategy
  - Hg below 10.0 g per deciliter
  - Hg maintained at 10.0 to 12.0 g per deciliter.

**TABLE 2.** OUTCOMES.*

| OUTCOME MEASURE | RESTRICTIVE-TRANSFUSION STRATEGY (N=418) | LIBERAL-TRANSFUSION STRATEGY (N=420) | ABSOLUTE DIFFERENCE BETWEEN GROUPS | 95% CONFIDENCE INTERVAL | P VALUE |
|---|---|---|---|---|---|
| | | | percent | | |
| Death — no. (%) | | | | | |
| 30-day | 78 (18.7) | 98 (23.3) | 4.7 | −0.84 to 10.2 | 0.11 |
| 60-day† | 95 (22.7) | 111 (26.5) | 3.7 | −2.1 to 9.5 | 0.23 |
| ICU | 56 (13.4) | 68 (16.2) | 2.3 | −2.0 to 7.6 | 0.29 |
| Hospital | 93 (22.2) | 118 (28.1) | 5.8 | −0.3 to 11.7 | 0.05 |
| Multiple-organ-dysfunction score | | | | | |
| Unadjusted score | 8.3±4.6 | 8.8±4.4 | 0.5 | −0.1 to 1.1 | 0.10 |
| Adjusted score‡ | 10.7±7.5 | 11.8±7.7 | 1.1 | 0.8 to 2.2 | 0.03 |
| Change from base-line score§ | 3.2±7.0 | 4.2±7.4 | 1.0 | 0.1 to 2.0 | 0.04 |
| No. of organs failing — no. (%) | | | | | |
| 0 | 100 (23.9) | 82 (19.5) | | | |
| 1 | 136 (32.5) | 149 (35.5) | | | |
| 2 | 109 (26.1) | 108 (26.0) | | | |
| 3 | 51 (12.2) | 63 (15.0) | | | |
| >3 | 22 (5.3) | 18 (4.3) | 1.8¶ | −3.4 to 7.1¶ | 0.53¶ |
| Length of stay — days | | | | | |
| ICU | 11.0±10.7 | 11.5±11.3 | 0.5 | −1.0 to 2.1 | 0.53 |
| Hospital | 34.8±19.5 | 35.5±19.4 | 0.7 | −1.9 to 3.4 | 0.58 |

*Plus–minus values are means ±SD. ICU denotes intensive care unit. Because of rounding, percentages may not total 100.

†Three patients were lost to follow-up at 60 days: two in the restrictive-strategy group and one in the liberal-strategy group.

‡All patients who died were given a score of 24 (the highest score).

§Adjusted scores were used.

¶The comparison is between three or more organ failures and fewer than three organ failures.

Subgroup Analysis

Primary or secondary diagnosis cardiac disease

Mortality

20.5 (R) vs 22.9% (S)

*Herbet New Eng J Med 1999*

**TABLE 3.** COMPLICATIONS THAT OCCURRED DURING THE PATIENTS' STAYS IN THE INTENSIVE CARE UNIT.

| COMPLICATION* | RESTRICTIVE-TRANSFUSION STRATEGY (N=418) | LIBERAL-TRANSFUSION STRATEGY (N=420) | ABSOLUTE DIFFERENCE BETWEEN GROUPS | 95% CONFIDENCE INTERVAL† | P VALUE |
|---|---|---|---|---|---|
| | no. (%) | | percent | | |
| Cardiac | 55 (13.2) | 88 (21.0) | 7.8 | 2.7 to 12.9 | <0.01 |
| Myocardial infarction | 3 (0.7) | 12 (2.9) | 2.1 | — | 0.02 |
| Pulmonary edema | 22 (5.3) | 45 (10.7) | 5.5 | 1.8 to 9.1 | <0.01 |
| Angina | 5 (1.2) | 9 (2.1) | 0.9 | — | 0.28 |
| Cardiac arrest | 29 (6.9) | 33 (7.9) | 0.9 | −2.6 to 4.5 | 0.60 |
| Pulmonary | 106 (25.4) | 122 (29.0) | 3.7 | −2.3 to 9.7 | 0.22 |
| ARDS | 32 (7.7) | 48 (11.4) | 3.8 | −0.2 to 7.8 | 0.06 |
| Pneumonia | 87 (20.8) | 86 (20.5) | −0.3 | −5.8 to 5.1 | 0.92 |
| Infectious | 42 (10.0) | 50 (11.9) | 1.9 | −2.4 to 6.1 | 0.38 |
| Bacteremia | 30 (7.2) | 40 (9.5) | 2.3 | −1.4 to 6.1 | 0.22 |
| Catheter-related sepsis | 21 (5.0) | 17 (4.0) | −1.0 | −3.8 to 1.8 | 0.50 |
| Septic shock | 41 (9.8) | 29 (6.9) | −2.9 | −6.7 to 0.8 | 0.13 |
| Hematologic‡ | 10 (2.4) | 10 (2.4) | 0 | −2.1 to 2.1 | 1.00 |
| Gastrointestinal§ | 13 (3.1) | 19 (4.5) | 1.4 | −1.2 to 4.0 | 0.28 |
| Neurologic¶ | 25 (6.0) | 33 (7.9) | 1.9 | −1.6 to 5.3 | 0.28 |
| Shock‖ | 67 (16.0) | 55 (13.1) | −2.9 | −7.7 to 1.8 | 0.23 |
| Any complication | 205 (49.0) | 228 (54.3) | 5.2 | −1.5 to 12.0 | 0.12 |

*Patients may have had more than one type of complication. ARDS denotes acute respiratory distress syndrome.

†In some cases, the number of patients in a group was too small to allow calculation of the 95 percent confidence interval.

‡This category includes transfusion reactions, hemolytic anemia, disseminated intravascular coagulation, and other blood dyscrasias.

§This category includes gastrointestinal bleeding, bowel perforation, and ischemic bowel syndrome.

¶This category includes cerebrovascular accidents and encephalopathies.

‖This category includes hypovolemic shock, cardiogenic shock, and all other types of shock except septic shock.

*New Eng J Med 1999*

# SCCM Surviving Sepsis Campaign

*Crit Care Med 2008: 36: 296-327*

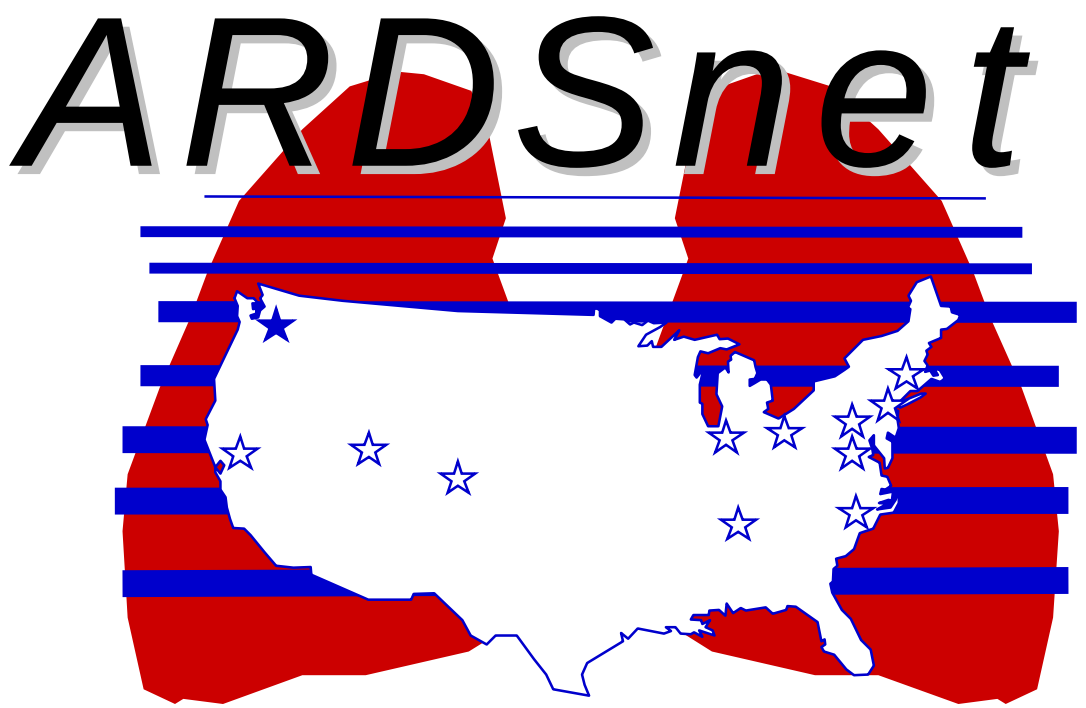
- FFP not indicated in patients without bleeding **Grade 2D**
- Antithrombin therapy not indicated **Grade 1B**
- Plts should be administered for Plts < 5,000 regardless of bleeding
- If risk of bleeding is high plts for counts 5,000-30,000
- Plts>50,000 required for surgery

**Grade 2D**

# SCCM Surviving Sepsis Campaign

*Crit Care Med 2008: 36: 296-327*

- K. Mechanical Ventilation
  - Lung protective ventilation
    - Vt 6 ml/kg **Grade 1B**
    - Pplat ≤ 30 **Grade 1C**
  - Hypercapnia can be tolerated **Grade 1C**
  - PEEP to avoid lung collapse **Grade 1C**
  - Consider prone position **Grade 2C**
  - Elevated HOB 45º **Grade 1B**
  - NIV **Grade 2B**
  - Weaning Protocol **Grade 1A**




**NIH NHLBI ARDS Clinical Trials Network**

# NIH NHLBI ARDS Network

Prospective, Randomized, Multi-Center Trial of 12 ml/kg Vs 6 ml/kg Tidal Volume Positive Pressure Ventilation for Treatment of Acute Lung Injury and Acute Respiratory Distress Syndrome

- **Mode: Volume Assist / Control**
- **Rate: Set rate < 35; adjust for pH goal = 7.30-7.45**
- **Oxygenation**
  **$PaO_2$ = 55-80 mmHg**
  **$SaO_2$ = 88-95%**
- **PEEP 5 5 8 8 10 10 10 .... 20**
  **$FiO_2$ .3 .4 .4 .5 .5 .6 .7 .... 1.0**
- **I:E = 1:1.8-1.3**
- **Weaning by Pressure Support when PEEP/FiO2 ≤ 8/.40**

**New Engl J Med 2000; 342: 1301-1308**

# Ventilator Procedures

## 12 ml/kg Group

- Initial Vt = 12 ml/kg IBW
- If Pplat > 50 cmH20, reduce Vt by 1 ml/kg.
- Minimum Vt = 4 ml/kg
- If Pplat < 45 cmH20 and Vt ≤ 11 ml/kg, increase Vt by 1 ml/kg.

## 6 ml/kg Group

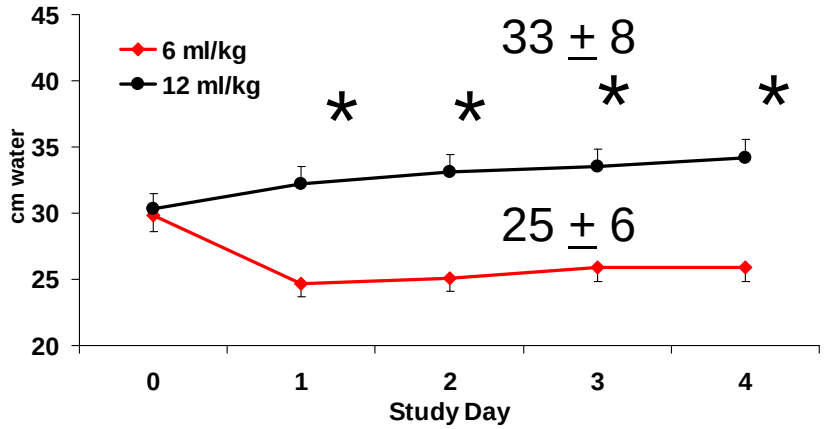
- Initial Vt = 6 ml/kg IBW.
- If Pplat > 30 cmH20, reduce Vt by 1 ml/kg.
- Minimum Vt = 4 ml/kg.
- If Pplat < 25 cmH20 and Vt ≤ 5 ml/kg, increase Vt by 1 ml/kg.

New Engl J Med 2000; 342: 1301-1308

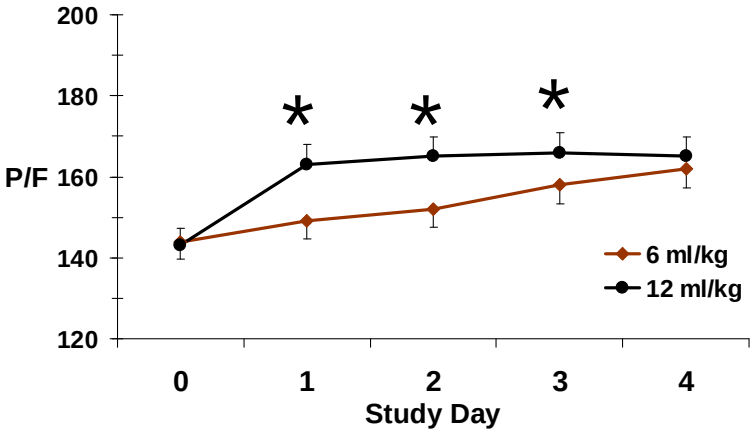
# NIH NHLBI ARDS Network

Prospective, Randomized, Multi-Center Trial of 12 ml/kg Vs 6 ml/kg Tidal Volume Positive Pressure Ventilation for Treatment of Acute Lung Injury and Acute Respiratory Distress Syndrome

## Plateau Pressure

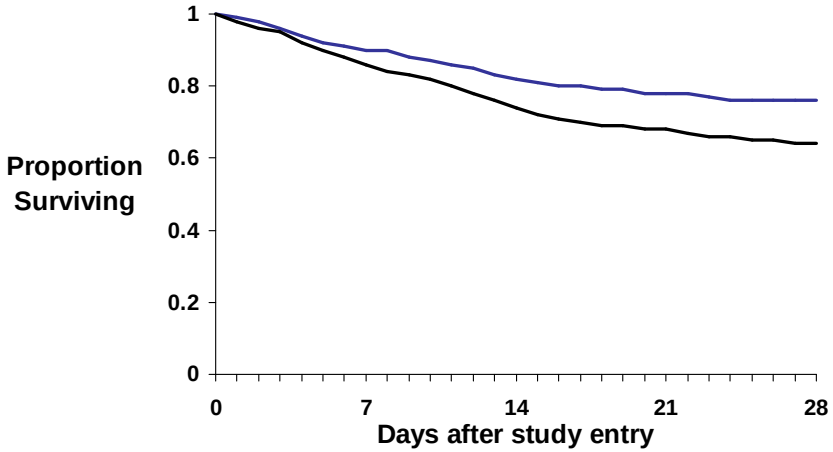


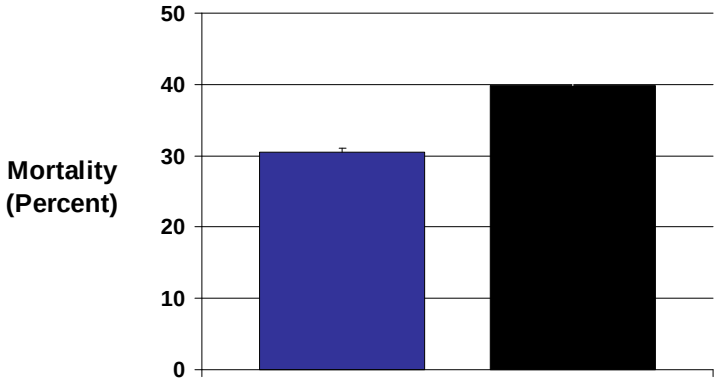

## Oxygenation




New Engl J Med 2000; 342: 1301-1308

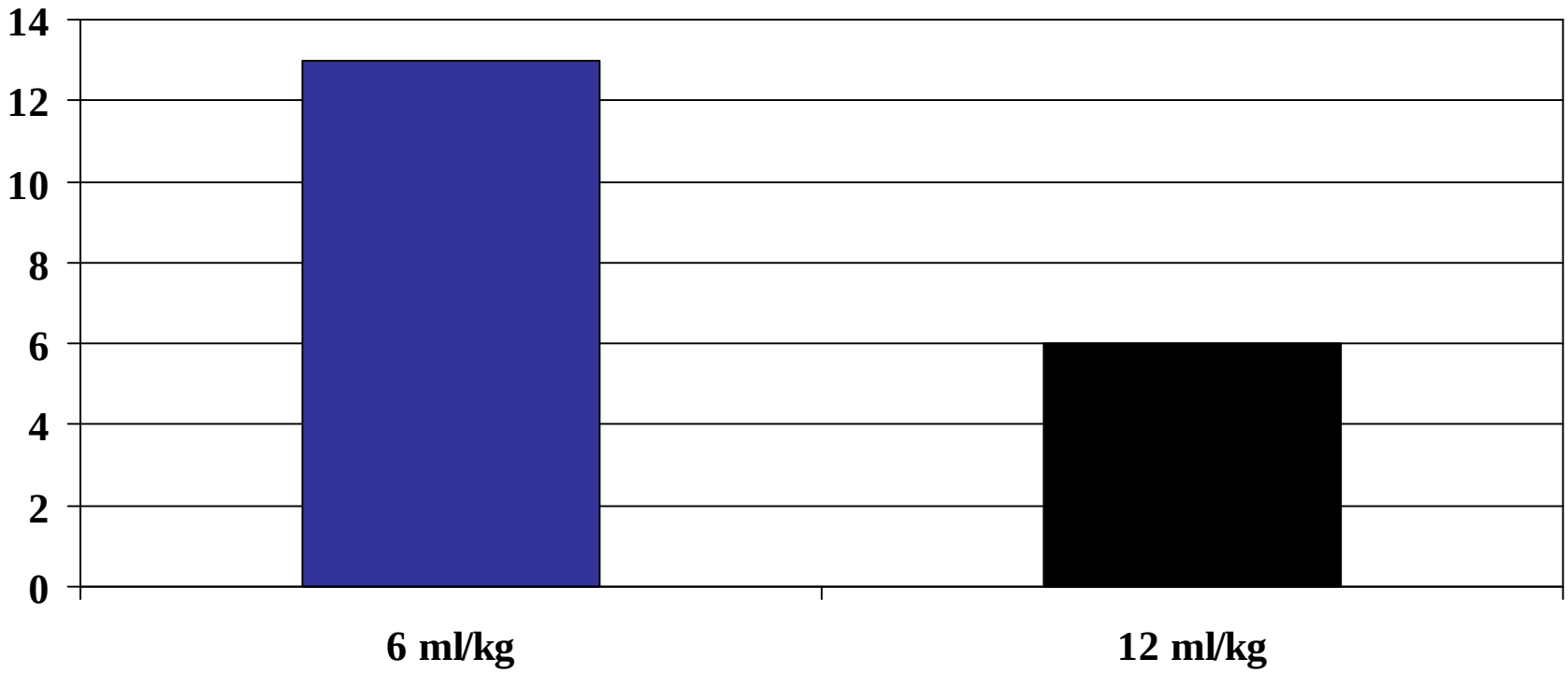
# 28 Day Survival



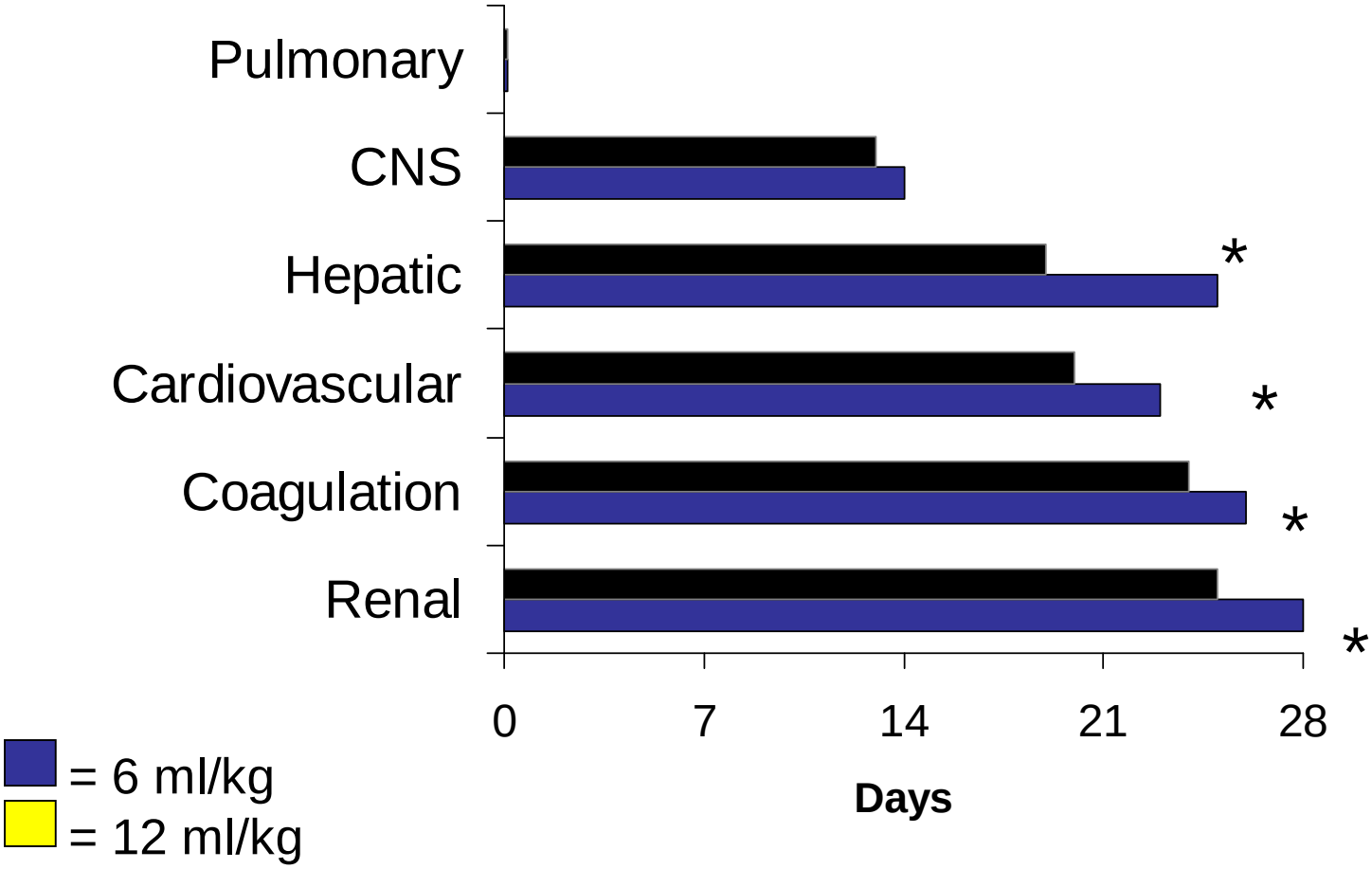

New Engl J Med 2000; 342: 1301-1308

# Median # Ventilator-Free Days




New Engl J Med 2000; 342: 1301-1308

# Median Organ Failure Free Days




New Engl J Med 2000; 342: 1301-1308

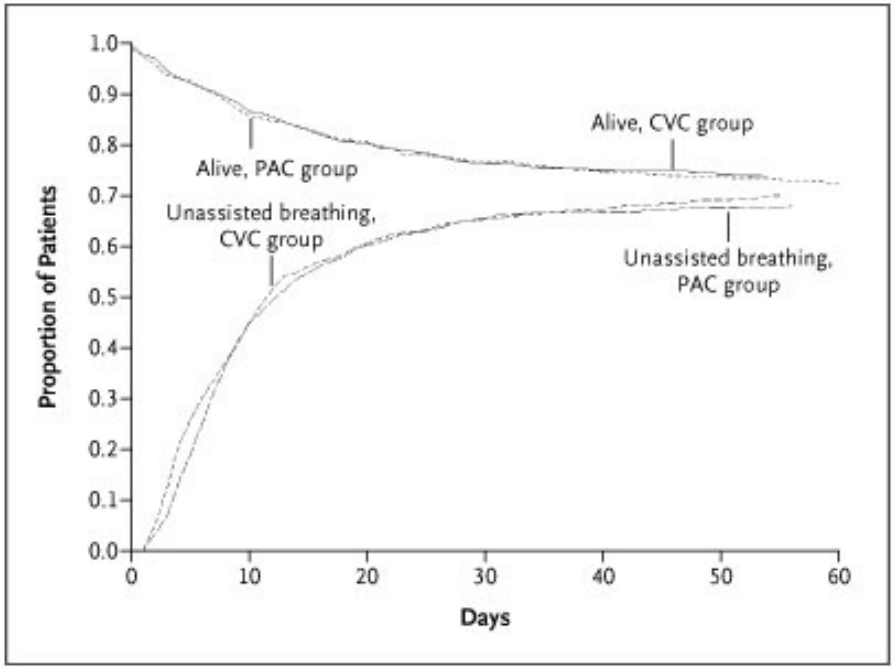
# SCCM Surviving Sepsis Campaign
*Crit Care Med 2008: 36: 296-327*

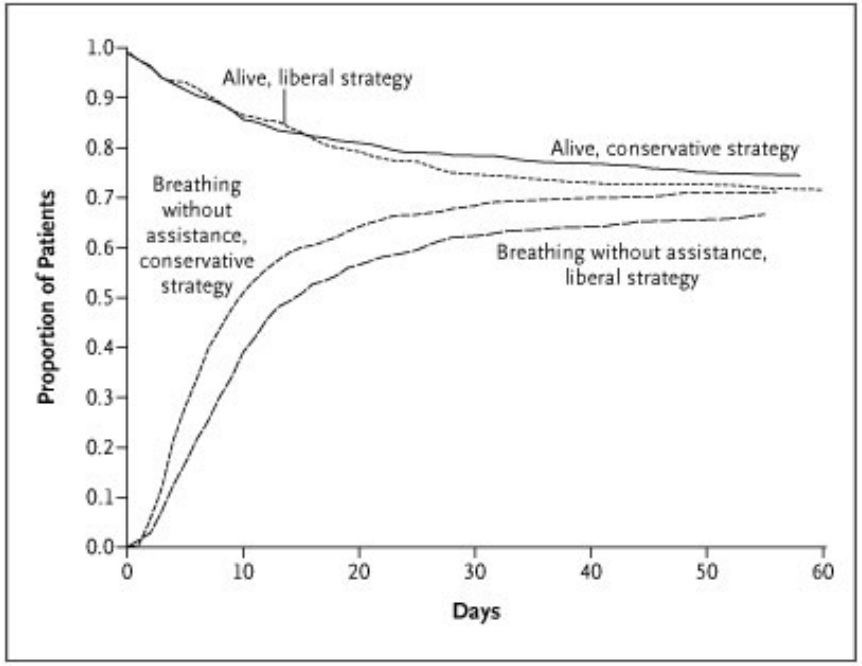
- K. Mechanical Ventilation
  - We recommend against the routine use of the pulmonary artery catheter for patients with ALI/ARDS (**grade 1A**).
  - To decrease days of mechanical ventilation and ICU length of stay we recommend a conservative fluid strategy for patients with established acute lung injury who do not have evidence of tissue hypoperfusion (**grade 1C**).

# ARDS Network: FACTT

## *Fluids and Catheter Treatment Trial*

## *PAC vs. CVP*




**N Engl J Med 2006; 354:2213**

# SCCM Surviving Sepsis Campaign

*Crit Care Med 2008: 36: 296-327*

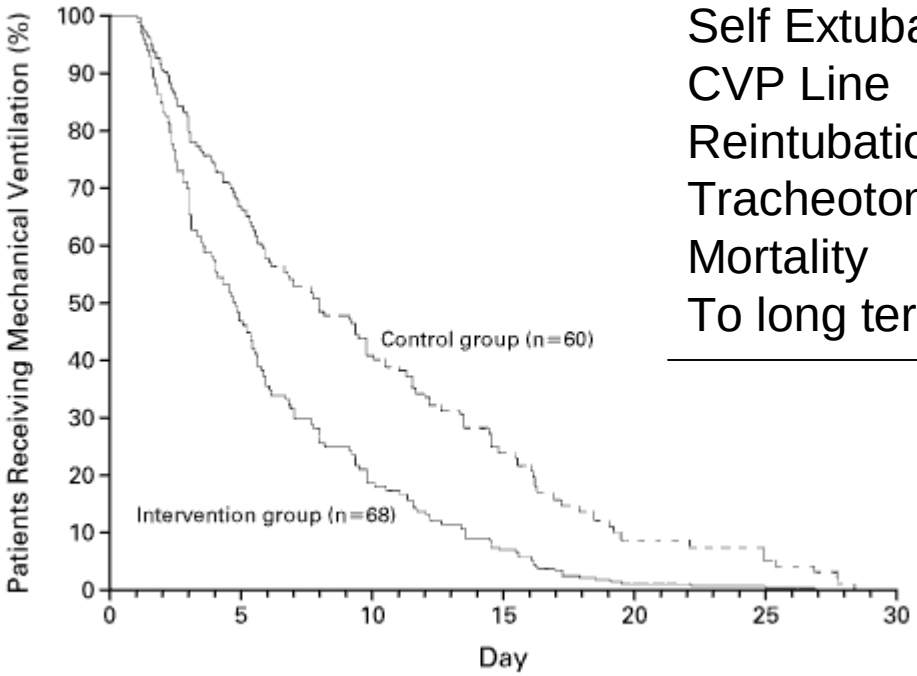
- L. Sedation, Analgesia, Neuromuscular Blockade
  - Protocols **Grade 1B**
  - Daily interruptions **Grade 1B**
  - Avoid neuromuscular blockade **Grade 1B**

# Daily Interruption of Sedative Infusions

*Kress New Eng J Med 2000*

- 128 adult patients who were receiving mechanical ventilation and continuous infusions of sedative drugs in a MICU
- Intervention group: sedatives interrupted until the patients were awake, on a **daily** basis
- Control group, the infusions were interrupted only at the discretion of the clinicians in the intensive care unit.

# Length of Ventilation




| *Variable* | Intervention | Control |
|---|---|---|
| Self Extubation | 2 | 4 |
| CVP Line | 1 | 0 |
| Reintubation | 12 | 18 |
| Tracheotomy | 12 | 16 |
| Mortality | 36 | 46.7 |
| To long term | 9 | 12 |

**Kress New Eng J Med 2000**

# SCCM Surviving Sepsis Campaign

*Crit Care Med 2008: 36: 296-327*

- M. Glucose Control
  - Following stabalization, use protocol to maintain glucose < 150 mg/dl **Grade 2C**
  - All patients on iv insulin should be receiving glucose **Grade 1C**

# Intensive Insulin Therapy in Critically Ill Patients

*Greet Van den Berghe*
*New Engl J Med 2001*

| *Characteristic* | Conventional N=783 | Intensive N=765 |
|---|---|---|
| Male | 71% | 71% |
| Age | 62.2% | 63.4% |
| BMI | 25.8% | 26.2% |
| Cardiac Surgery | 493 (63) | 477 (62) |
| Neurologic Disease | 290 (37) | 288 (38) |
| Cerebral Trauma | | |
| Thoracic Surgery | 56 (7) | 66 (9) |
| Abd Surgery | 58 (7) | 45 (6) |
| Vasc Surgery | 32 (4) | 30 (4) |
| Muti-trauma | 35 (4) | 33 (4) |
| Transplant | 44 (6) | 46 (6) |
| Other | 35 (4) | 35 (5) |
| Diabetes | 103 (13) | 101 (13) |
| Insulin | 33 (4) | 39 (5) |
| Oral | 70 (9) | 62 (8) |

# Intensive Insulin Therapy in Critically Ill Patients

*Greet Van den Berghe New Engl J Med 2001*

**TABLE 2.** INSULIN THERAPY AND CONTROL OF BLOOD GLUCOSE LEVELS.*

| VARIABLE | CONVENTIONAL TREATMENT (N=783) | INTENSIVE TREATMENT (N=765) | P VALUE† |
|---|---|---|---|
| Administration of insulin — no. (%) | 307 (39.2) | 755 (98.7) | <0.001 |
| Insulin dose — IU/day‡ | | | |
| Median | 33 | 71 | |
| Interquartile range | 17–56 | 48–100 | <0.001 |
| Duration of insulin use — % of ICU stay | | | |
| Median | 67 | 100 | <0.001 |
| Interquartile range | 40–100 | | |
| Morning blood glucose — mg/dl§ | | | |
| All patients | 153±33 | 103±19 | <0.001 |
| Patients receiving insulin | 173±33 | 103±18 | <0.001 |

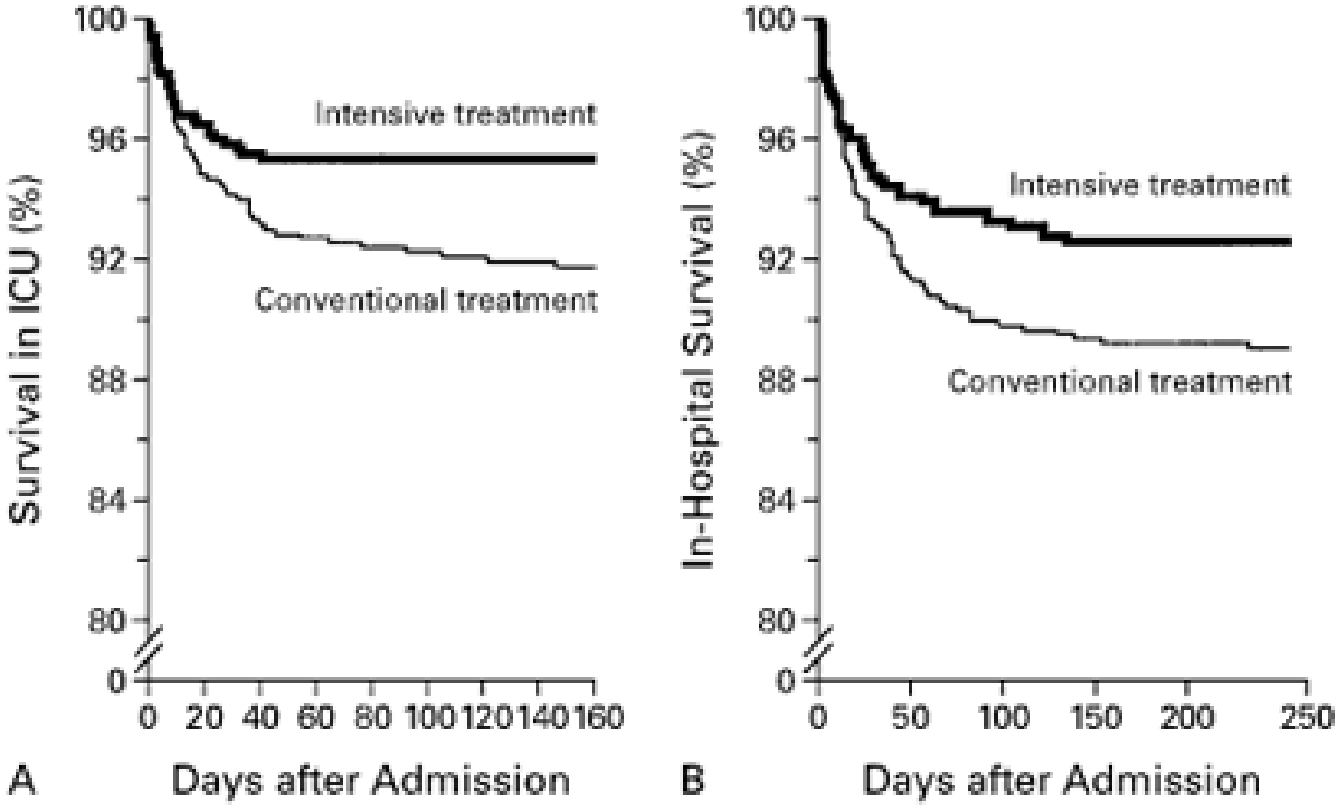
*Plus–minus values are means ±SD. ICU denotes intensive care unit.

†P values were determined with the use of Student's t-test, the Mann–Whitney U test, or the chi-square test, as appropriate.

‡Values were calculated only for days on which insulin was given.

§To convert the values for glucose to millimoles per liter, multiply by 0.05551.

# Mortality




**Greet Van den Berghe New Engl J Med 2001**

# Morbidity

| *Variable* | Conventional<br>783 | Intensive<br>765 | p |
|---|---|---|---|
| ICU LOS | | | |
| Median (d) | 3 | 3 | 0.2 |
| Patient > 14 d | 123 15 | 87 11.4 | 0.01 |
| Vent (d) | | | |
| Median | 2 | 2 | 0.06 |
| >14 d Vent | 93 11.9 | 57 7.5 | 0.003 |
| Renal Insufficiency | | | |
| Cr > 2.5 | 96 12.3 | 69 9.0 | 0.04 |
| BUN > 54 | 88 11.2 | 59 7.7 | 0.02 |
| RRT | 64 8.2 | 37 4.8 | 0.007 |
| Bili > 2 | 209 26.7 | 171 22.4 | 0.04 |
| Septicemia | 61 7.8 | 32 4.2 | 0.003 |

**Greet Van den Berghe New Engl J Med 2001**

# SCCM Surviving Sepsis Campaign

*Crit Care Med 2008: 36: 296-327*

- N. Renal Replacement
  - In the absence of hemodynamic instablity, CVVH and Intermittent Hemodialysis are equivalent. **Grade 2B**
  - CVVH is easier in hemodynamic unstable patients. **Grade 2D**

Intensive Care Med (2002) 28:29–37
DOI 10.1007/s00134-001-1159-4

ORIGINAL

John A. Kellum
Derek C. Angus
John P. Johnson
Martine Leblanc
Martin Griffin
Nagarajan Ramakrishnan
Walter T. Linde-Zwirble

# Continuous versus intermittent renal replacement therapy: a meta-analysis

Intermittent versus continuous renal replacement therapy for acute renal failure in adults (Review)

Rabindranath KS, Adams J, MacLeod AM, Muirhead N

THE COCHRANE COLLABORATION®

# SCCM Surviving Sepsis Campaign

*Crit Care Med 2008: 36: 296-327*

- O. Bicarbonate Therapy
  - Not recommended for the purpose of improving hemodynamics or decreasing need for vasopressors in hypoperfusion induced lactic acidosis with pH ≥7.15

**Grade 1B**

# SCCM Surviving Sepsis Campaign

*Crit Care Med 2008: 36: 296-327*

- P. DVT Prophylaxis
  - UFH or LMWH **Grade 1A**
  - Mechanical devices for pts with contraindications
  - Very high risk pts should receive both
  - In high risk pateints LMWH is preferred to UFH **Grade 2C**

# SCCM Surviving Sepsis Campaign

*Crit Care Med 2008: 36: 296-327*

- Q. Stress Ulcer Prophylaxis
  - $H_2RA$ **Grade 1A**
  - PPI **Grade 1B**

# SCCM Surviving Sepsis Campaign

*Crit Care Med 2008: 36: 296-327*

- R. Selective Digestive Tract Decontamination
  - The guidelines group was evenly split on the issue of SDD, with equal numbers weakly in favor and against recommending the use of SDD. The committee therefore chose not to make a recommendation for the use of SDD specifically in severe sepsis at this time.

# SCCM Surviving Sepsis Campaign

*Crit Care Med 2008: 36: 296-327*

- S. Consideration for limitation of support
  - Discussions with patients and family: likely outcome and realistic goals.

**Grade 1D**

# Institute Healthcare Improvement

## *Bundles*

- *Ventilator*
  - HOB > 30$^{o}$
  - DVT prophylaxis
  - PUD Prophylaxis
  - Daily interruption of sedative infusions
  - Intensive insulin therapy
  - Daily screening for weaning trials

# Institute Healthcare Improvement
## *Severe Sepsis Bundle (without shock)*

- 4-hour bundle
  - Presumptive diagnosis in 2 hours
  - Measure lactate
  - Antibiotics within 1 hour of diagnosis
- 24-hour bundle
  - Glucose control (<150)
  - Pplat < 30 for vent pts
  - Drotrrecogin alfa considered

# Institute Healthcare Improvement
## *Septic Shock Bundle*

- 4-hour bundle
  - Immediate fluid resuscitation
  - Antibiotics within 1 hour of diagnosis
  - CVP for pts unresponsive to fluid or lactate > 2
  - Vasopressors for MAP < 65 despite fluid
  - Inotropes and/or PRBCs for $SvcO_2$ <70% after fluid
- 24-hour bundle
  - Glucose control (<150)
  - Pplat < 30 for vent pts
  - Drotrrecogin alfa considered
  - Steroids for septic shock requiring vasopressors