Surviving Sepsis

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Disclosures

- No conflicts of interest

Sepsis

- Principles of management of septic shock in the operating room
- "Surviving Sepsis" guidelines

Add-on Case for Your OR

- “Please call the front desk”
- Butt case
- Add-on from Hell

The Case from Hell

- 76 year old man for exploratory laparotomy.
- 100kg
- Acute peritonitis
- ARDS and septic shock
- On intermittent positive pressure ventilation
- On vasopressors
- ? paracolic abscess on CT scan

The Patient is on Some Drips

What is Sepsis?

Special Communication | Caring for the Critically Ill Patient FREE

February 23, 2016

The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)

Mervyn Singer, MD, FRCP[1]; Clifford S. Deutschman, MD, MS[2]; Christopher Warren Seymour, MD, MSc[3]; et al

» Author Affiliations | Article Information

JAMA. 2016;315(8):801-810. doi:10.1001/jama.2016.0287

Sepsis

- Life-threatening organ dysfunction caused by a dysregulated host response to infection
- Increased Sequential [Sepsis-related] Organ Failure Assessment (SOFA) score of 2+
- In-hospital mortality greater than 10%.

***Organ System,* Measurement**	**SOFA Score**				
	0	1	2	3	4
Respiration PaO_2/FiO_2, mmHg	Normal	<400	<300	<200 (with respiratory support)	<100 (with respiratory support)
Coagulation Platelets $x10^3/mm^3$	Normal	<150	<100	<50	<20
Liver Bilirubin, mg/dL (µmol/l)	Normal	1.2-1.9 (20-32)	2.0-5.9 (33-101)	6.0-11.9 (102-204)	>12.0 (<204)
Cardiovascular Hypotension	Normal	MAP<70 mmHg	Dopamine ≤5 or dobutamine (any dose)**	Dopamine >5 or epinephrine ≤0.1 or norepinephrine ≤0.1	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1
Central Nervous System Glasgow Coma Score	Normal	13-14	10-12	6-9	<6
Renal Creatinine, mg/dL (µmol/l) or Urine output	Normal	1.2-1.9 (110-170)	2.0-3.4 (171-299)	3.5-4.9 (300-440) or <500 mL/day	>5.0 (>440) or <200 mL/day

Septic Shock

- Subset of sepsis with profound circulatory, cellular, and metabolic abnormalities
- Associated with a greater risk of mortality than with sepsis alone
- Vasopressor to MAP > 65 mm Hg
- Lactate level > 2 mmol/L in the absence of hypovolemia
- Hospital mortality rates >40%

Rapid Identification

- Out-of-hospital, emergency department, or general hospital ward settings, adult patients with suspected infection
- quickSOFA (qSOFA)
  - Respiratory rate >22/min
  - Altered mentation
  - Systolic <100 mm Hg
- Score >= 2 indicates poor outcomes

The Case from Hell

- 76 year old man for exploratory laparotomy.
- 100kg
- Acute peritonitis
- ARDS and septic shock
- On intermittent positive pressure ventilation
- On vasopressors
- ? paracolic abscess on CT scan

Why Are We Doing This Case?

- He is too sick for the OR.
- Can’t they stabilize him before we take him?

Why?

- Recommend anatomic diagnosis of infection requiring emergent source control be identified
- Or excluded as rapidly as possible in patients with sepsis or septic shock
- Source control as soon as medically and logistically practical (Best Practice Statement)

What to Do?

- How should we manage the hemodynamic compromise?
- What fluids should we give?
- What is the best way to oxygenate this patient?
- Is there anything else we should give?
- What is the evidence for these maneuvers?

Can’t We Just Set Some Goals?

- Numbers to aim for to make management easier

Shoemaker's Goals of Therapy 1980s Supranormal Values

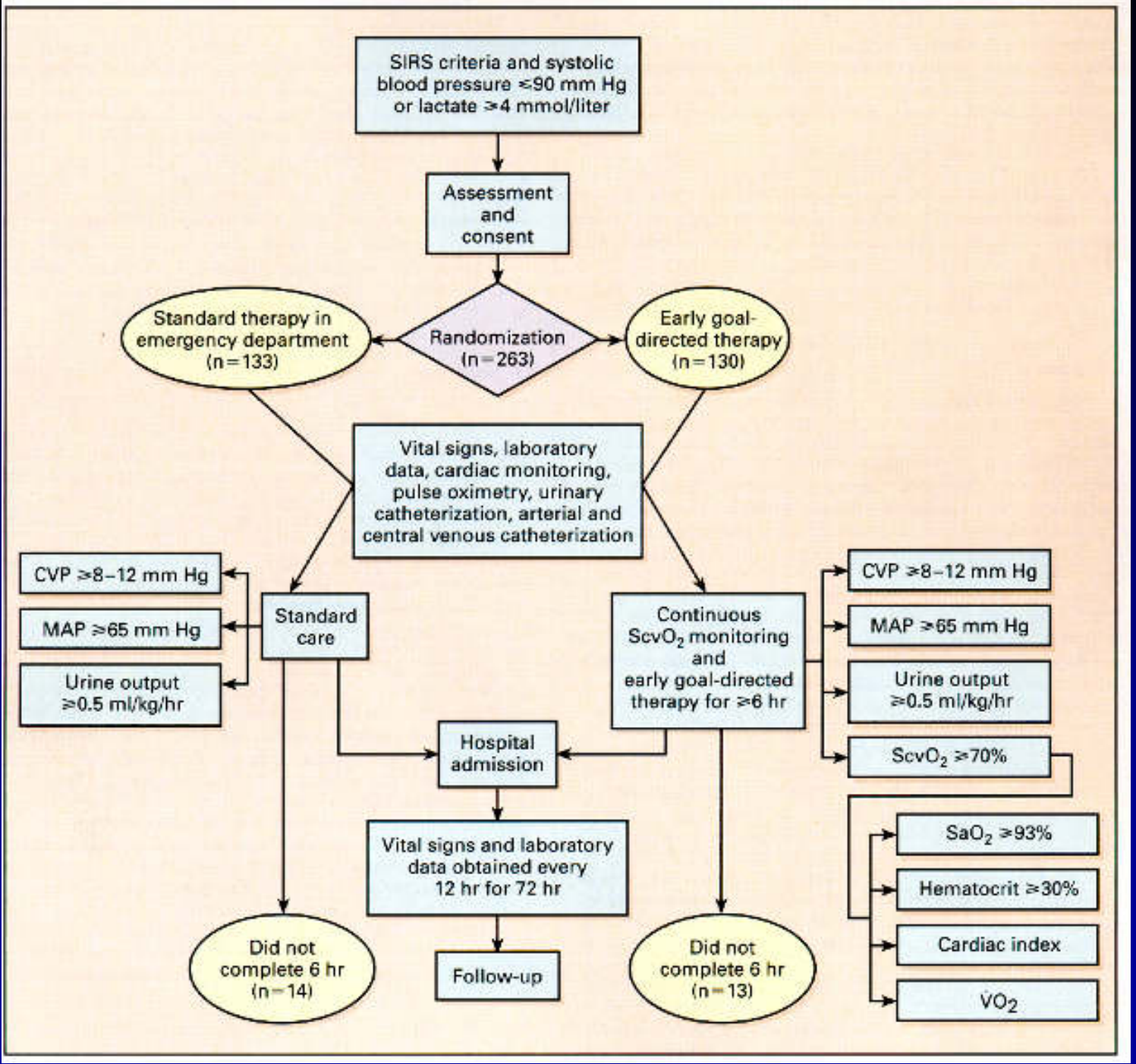
- Blood volume increased by 500ml
- Cardiac Index > 4.5 l/min/m^2
- Oxygen delivery > 600 ml/min/m^2
- Oxygen consumption > 170 ml/min/m^2

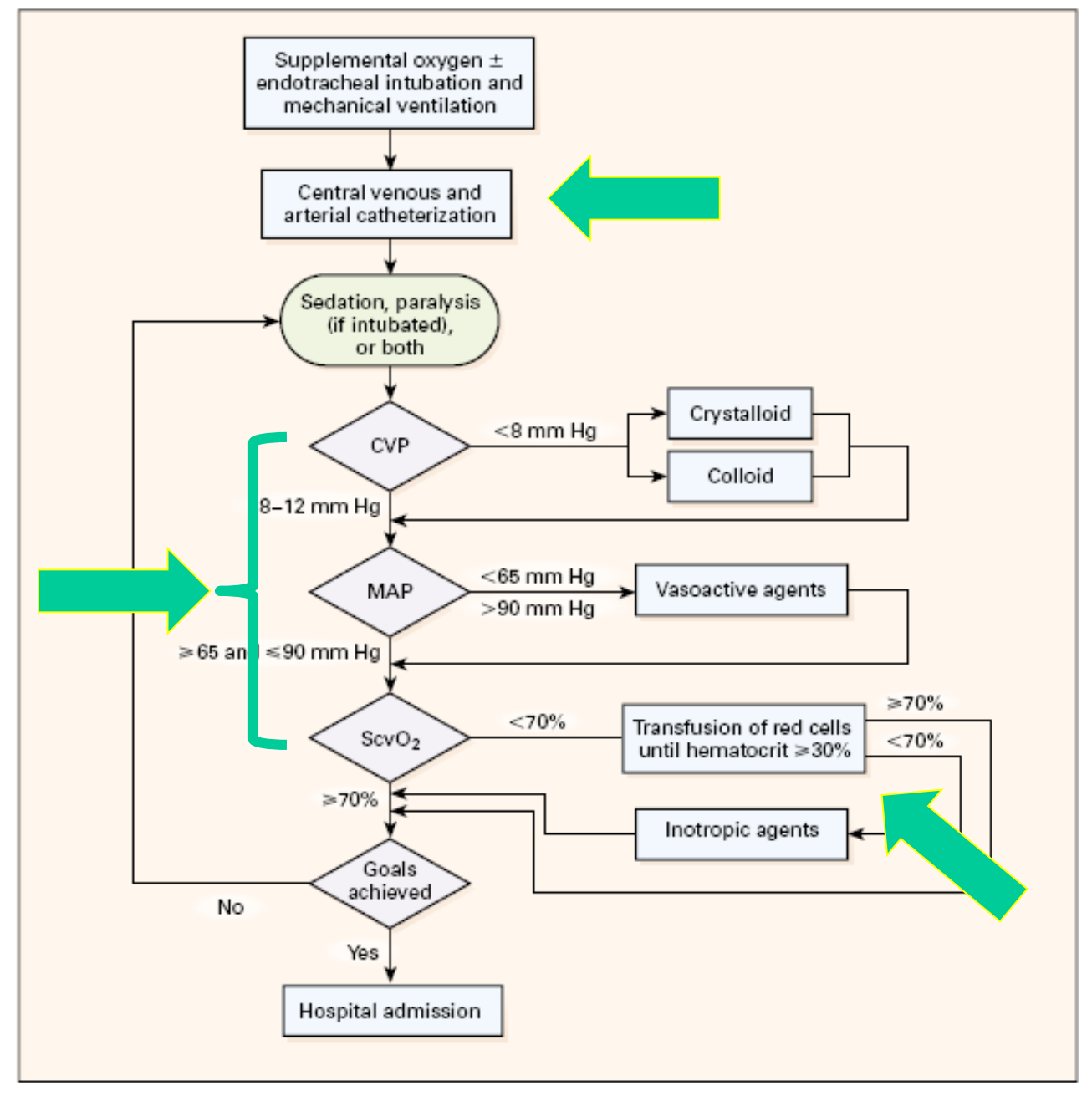
Goal Directed Therapy of Sepsis

- Elevation of systemic oxygen delivery in the treatment of critically ill patients. Hayes MA - *N Engl J Med* 1994
- A trial of goal-oriented hemodynamic therapy in critically ill patients. SvO2 Collaborative Group. Gattinoni L - *N Engl J Med* 1995

Early Goal-Directed Therapy

- Early goal-directed therapy in the treatment of severe sepsis and septic shock. Rivers E - *N Engl J Med* 2001
- 263 patients
- 130 randomized to early goal-directed therapy
- 133 randomized to standard therapy
- First 6 hours, prior to ICU admission


SIRS criteria and systolic blood pressure ≤90 mm Hg or lactate ≥4 mmol/liter
Assessment and consent
Standard therapy in emergency department (n=133)
Randomization (n=263)
Early goal-directed therapy (n=130)
Vital signs, laboratory data, cardiac monitoring, pulse oximetry, urinary catheterization, arterial and central venous catheterization
CVP ≥8–12 mm Hg
MAP ≥65 mm Hg
Urine output ≥0.5 ml/kg/hr
Standard care
Continuous ScvO2 monitoring and early goal-directed therapy for ≥6 hr
CVP ≥8–12 mm Hg
MAP ≥65 mm Hg
Urine output ≥0.5 ml/kg/hr
ScvO2 ≥70%
SaO2 ≥93%
Hematocrit ≥30%
Cardiac index
VO2
Hospital admission
Vital signs and laboratory data obtained every 12 hr for 72 hr
Follow-up
Did not complete 6 hr (n=14)
Did not complete 6 hr (n=13)


Supplemental oxygen ± endotracheal intubation and mechanical ventilation
Central venous and arterial catheterization
Sedation, paralysis (if intubated), or both
CVP
<8 mm Hg
Crystalloid
Colloid
8–12 mm Hg
MAP
<65 mm Hg
>90 mm Hg
Vasoactive agents
≥65 and ≤90 mm Hg
ScvO2
<70%
Transfusion of red cells until hematocrit ≥30%
≥70%
<70%
≥70%
Inotropic agents
Goals achieved
No
Yes
Hospital admission

Results

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.

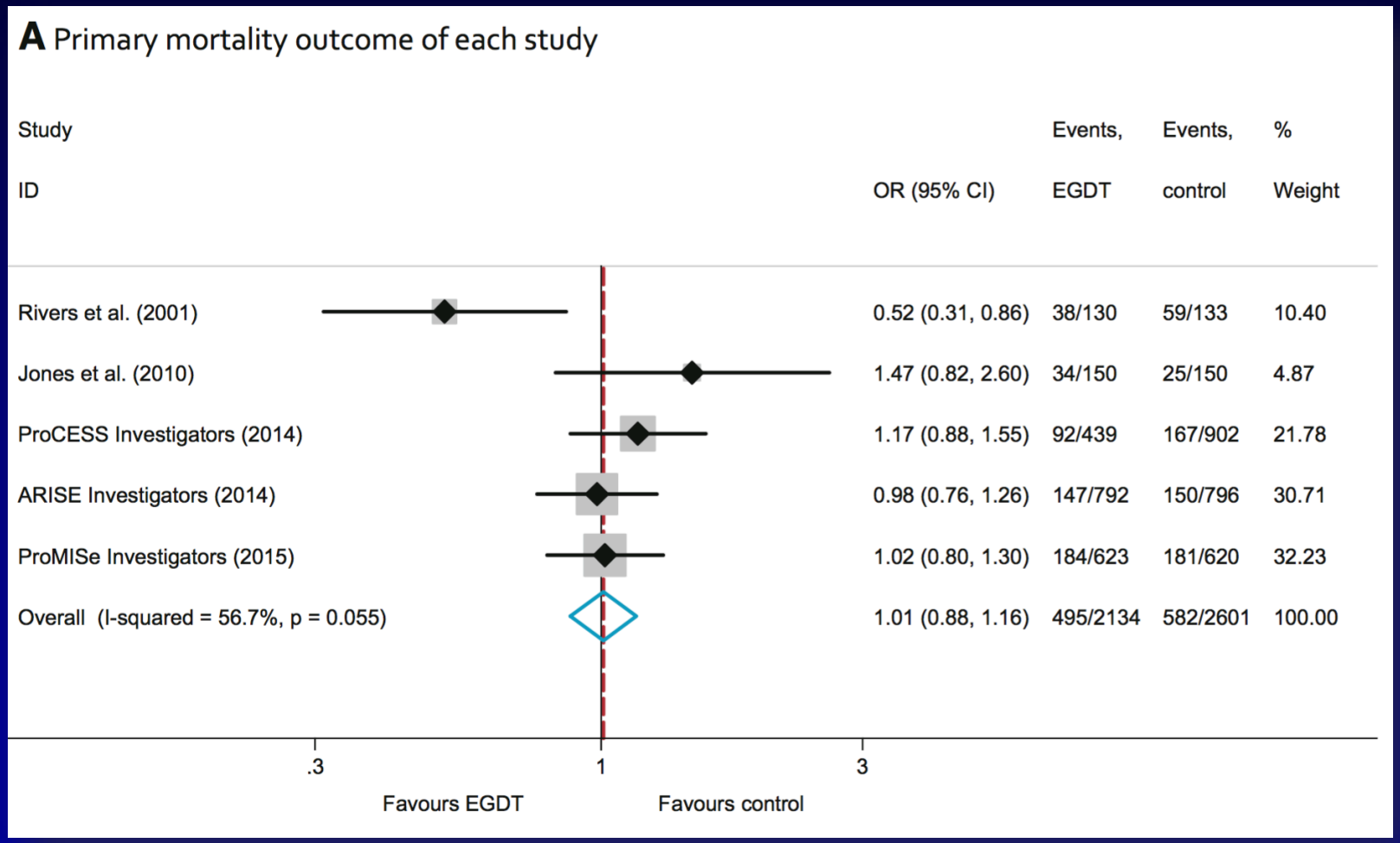
†Percentages were calculated by the Kaplan–Meier product-limit method.

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

Results

- During the 1st 6 hours
- EGDT group received more
  - intravenous fluid (5.0 vs. 3.5 L, $p < 0.001$)
  - red cell transfusions ($p < 0.001$)
  - inotropic therapy ($p < 0.001$)
- During the subsequent 66 hrs
- Control group
  - More red cell transfusions ($p < 0.001$)
  - More vasopressors ($p = 0.03$)
  - More mechanical ventilation ($p < 0.001$)
  - More pulmonary artery catheterization ($p = 0.04$)

A systematic review and meta-analysis of early goal-directed therapy for septic shock: the ARISE, ProCESS and ProMISe Investigators



Angus, D.C., Barnato, A.E., Bell, D. et al. Intensive Care Med (2015) 41: 1549

Surviving Sepsis Campaign Guidelines Critical Care Medicine 2004-2016

- International effort to increase awareness and improve outcome in severe sepsis
- 55 Critical Care and ID experts from 25 international organizations
- Consensus conference
- Graded review of the literature
- Graded recommendations

TABLE 3. Comparison of 2016 Grading Terminology with Previous Alphanumeric Descriptors

	2016 Descriptor	2012 Descriptor
Strength	Strong	1
	Weak	2
Quality	High	A
	Moderate	B
	Low	C
	Very Low	D
Ungraded strong recommendation	Best Practice Statement	Ungraded

Initial Resuscitation

- At least 30 mL/kg of IV crystalloid fluid be given within the first 3 hours
  - (strong recommendation, low quality of evidence)
- Additional fluids be guided by frequent reassessment of hemodynamic status
  - (BPS)
- Assess cardiac function if the type of shock is not clear
  - (BPS)
- Use dynamic over static variables to predict fluid responsiveness
  - (weak recommendation, low quality of evidence)

Dynamic Variables to Predict Fluid Responsiveness

- Static variables
  - CVP, left or right heart pressures or volumes
- Dynamic variables
  - Passive leg raises
  - Fluid challenges against:
    - Stroke volume measurements
    - Variations in systolic pressure, pulse pressure, or stroke volume to changes in intrathoracic pressure induced by mechanical ventilation


PA
40
CVP
160
20
80
0
0
P1 Art
105
P2 not zeroe
SpO2
Naso
5.8
T2
°C
Blad
36.9
SPV & PPV
SPV
mmHg
PPV
%
18
28
SPV Manual
mmHg
NIBP
SYS
M
(81)
Alarm Setup
Monitor Setup
Procedures
Data & Pages
Trends
Print Waveforms
Freeze/ Snapshot
NIBP
NIBP Auto

Initial Resuscitation

- Target MAP of 65 mm Hg if using vasopressors
  - (strong recommendation, moderate quality of evidence).
- Guide resuscitation to normalize lactate, if elevated, as a marker of tissue hypoperfusion
  - (weak recommendation, low quality of evidence)

Fluid Therapy - Colloid or Crystalloid?

- Crystalloid 1st
  - (strong recommendation, moderate quality of evidence)
- Balanced crystalloids or saline acceptable
  - (weak recommendation, low quality of evidence)
- Albumin may be added if large amounts of crystalloid required
  - (weak recommendation, low quality of evidence)
- No hetastarch
  - (strong recommendation, high quality of evidence)

Safe Study

- Saline vs Albumin Fluid Evaluation
- ANZICS – 16 academic tertiary hospitals
- 3497 patients resuscitated with albumin
- 3500 patients resuscitated with saline

N Engl J Med 2004;350:2247-56.

SAFE Results

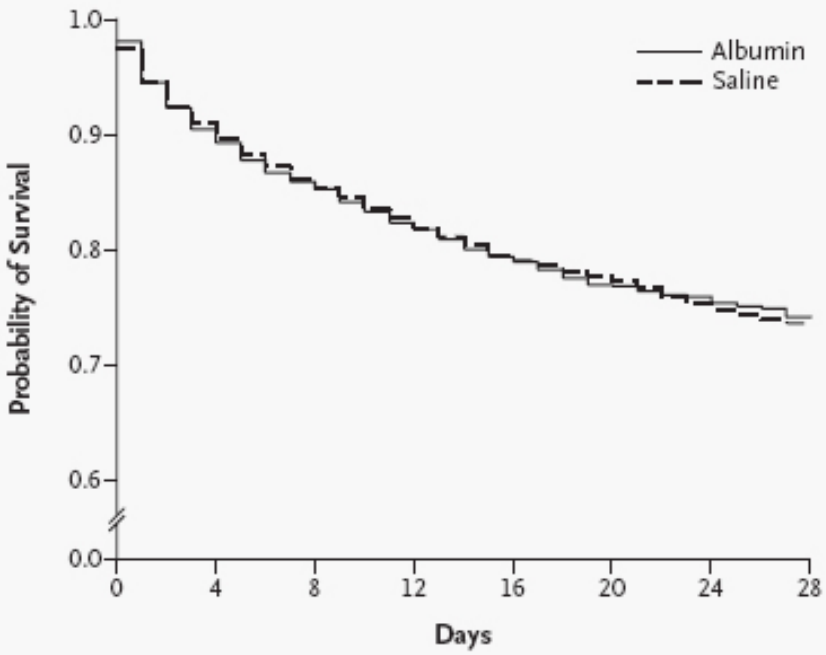


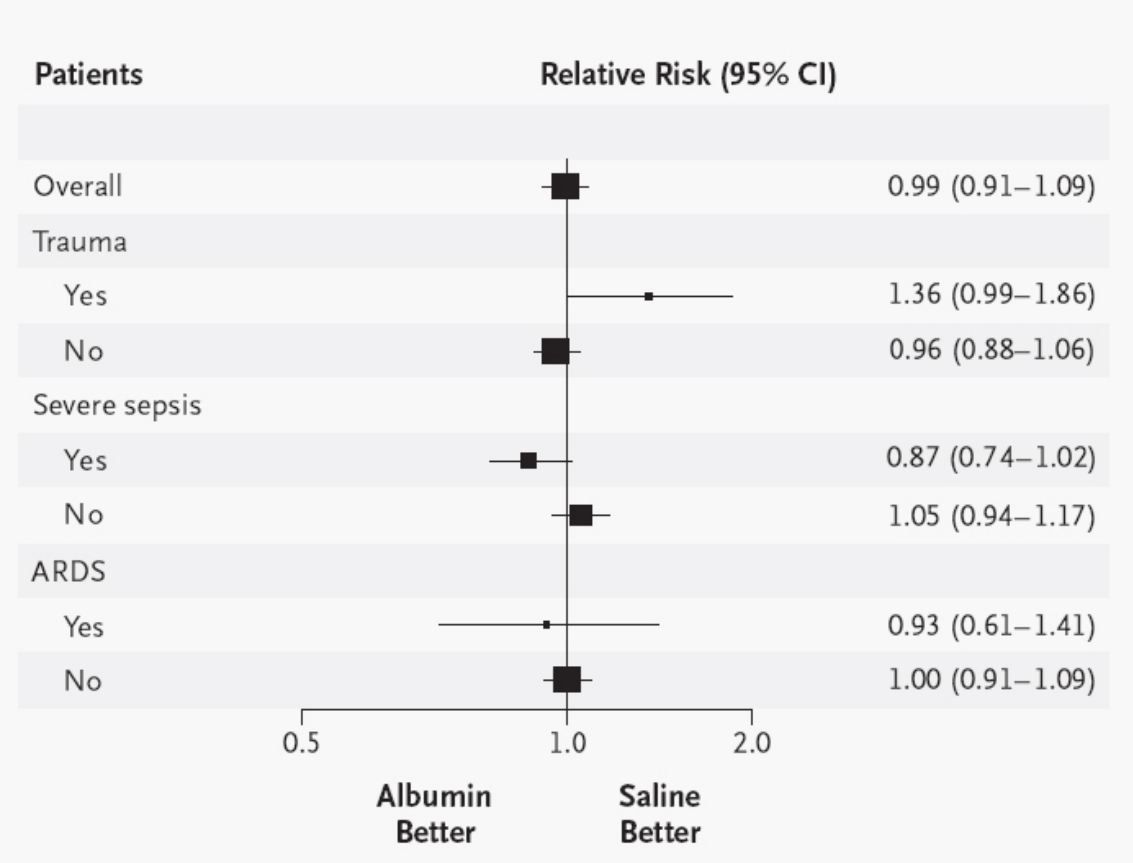
Figure 1. Kaplan–Meier Estimates of the Probability of Survival.
P=0.96 for the comparison between patients assigned to receive albumin and those assigned to receive saline.

726 deaths in the albumin group 729 deaths in the saline group

SAFE Results

- No significant differences
  - Days spent in the ICU (6.5 albumin and 6.2 saline group)
  - Days spent in the hospital (15.3 and 15.6)
  - Days of mechanical ventilation (4.5 and 4.3)
  - Days of renal-replacement therapy (0.5 and 0.4)

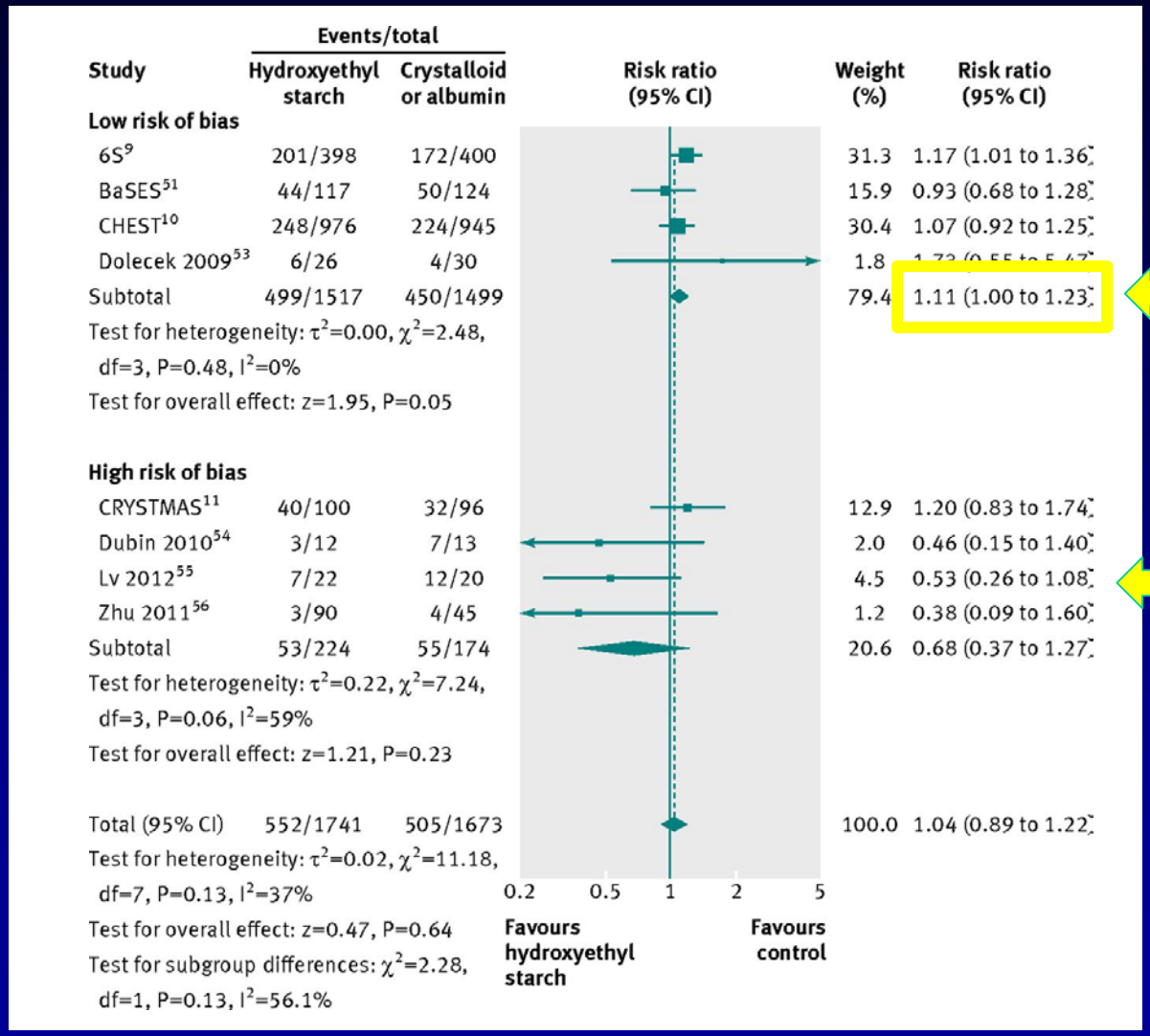
SAFE Results



TBI mortality: Albumin 24.5% vs Saline 15.1%, p=0.009

Severe sepsis: Albumin 30.7% vs Saline 35.3%, p=0.09

Hetastarch
Forest plot of all cause mortality in relation to risk of bias in trials



11% increased risk of mortality.
And higher risk of RRT (RR, 1.36; 95% CI, 1.08–1.72; (high-quality evidence)

Sponsored by industry, had potential academic bias, or lack of blinding.

Nicolai Haase et al. BMJ 2013;346:bmj.f839

Back to our Patient

- Fully fluid resuscitated
- Still hypotensive
- What vasopressors should we choose?

Vasopressors

- Norepinephrine is the first-choice vasopressor (strong recommendation, moderate quality of evidence).
- Add either vasopressin (up to 0.03 U/min) (weak recommendation, moderate quality of evidence) to norepinephrine to raise MAP
- Or add epinephrine (weak recommendation, low quality of evidence) to norepinephrine to raise MAP
- Or add vasopressin (up to 0.03 U/min) (weak recommendation, moderate quality of evidence) to decrease norepinephrine dosage

VASST

- Vasopressin in Septic Shock Trial
- 1º hypothesis - Low dose vasopressin – (0.03units/min) will decrease 28 day mortality from 60% to 50% in septic shock compared to norepinephrine alone
- 2º stratification
  - Severe septic shock norepinephrine dose > 15 mcg/min
  - Less severe septic shock = norepinephrne 5-14 mcg/min
- Resulted in 50% in each group

Russell JA, et al; VASST Investigators: Vasopressin versus norepinephrine infusion in patients with septic shock. *N Engl J Med* 2008; 358:877–887

VASST

- Inclusion
  - Severe septic shock
  - SIRS criteria 2/4
  - Infection
  - 1 organ dysfunction
- Exclusion
  - Septic shock > 24h
  - Unstable heart
  - Received any vasopressin
- Method
  - Blinded infusion of vasopressin 0.01units/min or norepinephrine 5mcg/min
  - Titrated to MAP 65-75 mmHg
  - If vasopressin reached 0.03units/min or norepi 15mcg/min then other pressors were added

VASST

28 day mortality	Norepi	Vasopressin	p value
Total	39.3%	35.4%	0.26
More severe sepsis	42.5%	44%	0.84
Less severe sepsis	35.7%	26.5%	0.04

- Bottom line; mortality decreased with low dose vasopressin only in patients with less severe sepsis

Dopamine?

- Dopamine as an alternative agent to norepinephrine only in patients with low risk of tachyarrhythmias, who are bradycardic (weak recommendation, low quality of evidence)
- No low-dose dopamine for renal protection (strong recommendation, high quality of evidence).

Inotropes

- Dobutamine in patients with persistent hypoperfusion despite adequate fluid loading and the use of vasopressor agents
  - (weak recommendation, low quality of evidence)
- Dobutamine titrated to an end point reflecting perfusion
- Reduced or discontinued if worsening hypotension or arrhythmias

Back to the OR

- Oxygen saturation is falling
- Volume control ventilation
- Vt 600ml (pt. weighs 100kg)
- Rate 14
- Plateau pressure 35cm H2O
- FiO2 = 1
- PEEP 5cm H2O
- ABG pH 7.32, pO2 50, pCO2 48, SO2 83%

Mechanical Ventilation of Sepsis-Induced Acute Lung Injury

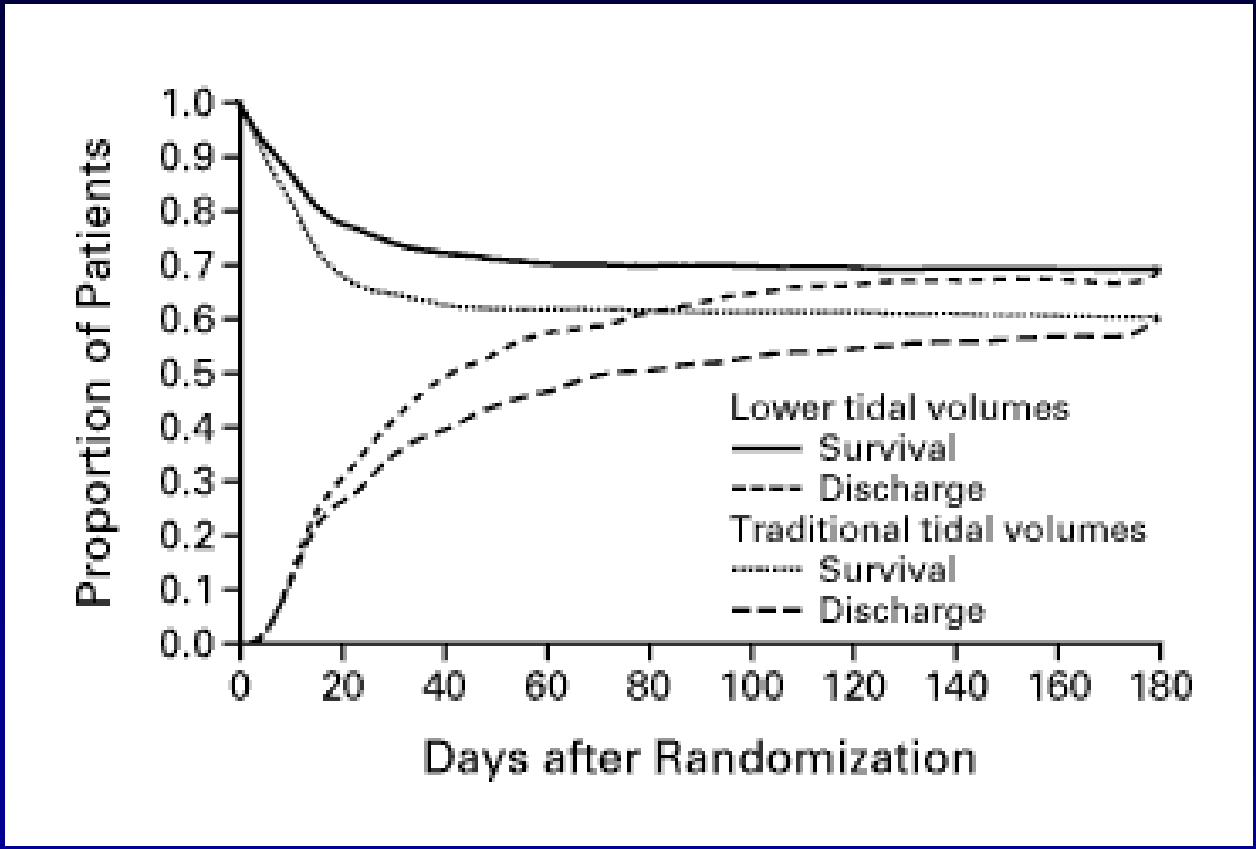
- **Lung protective ventilation**
  - **(strong recommendation, high quality of evidence)**
  - **“Low” tidal volume - 6 mL/kg**
  - **End-inspiratory plateau pressures <30 cm H2 O**

- **Based on ARDSNet trial NEJM 2000 ; 342 : 1301–1308**

ARDSNet – Low Tidal Volumes

- 861 pts with acute lung injury
- Volume assist control mode
- Low tidal volume 6 ml/kg
  - Predicted body weight
  - Plateau pressure 30 cmH2O or less
- High tidal volume 12 ml/kg
  - Plateau pressure 50 cmH2O or less

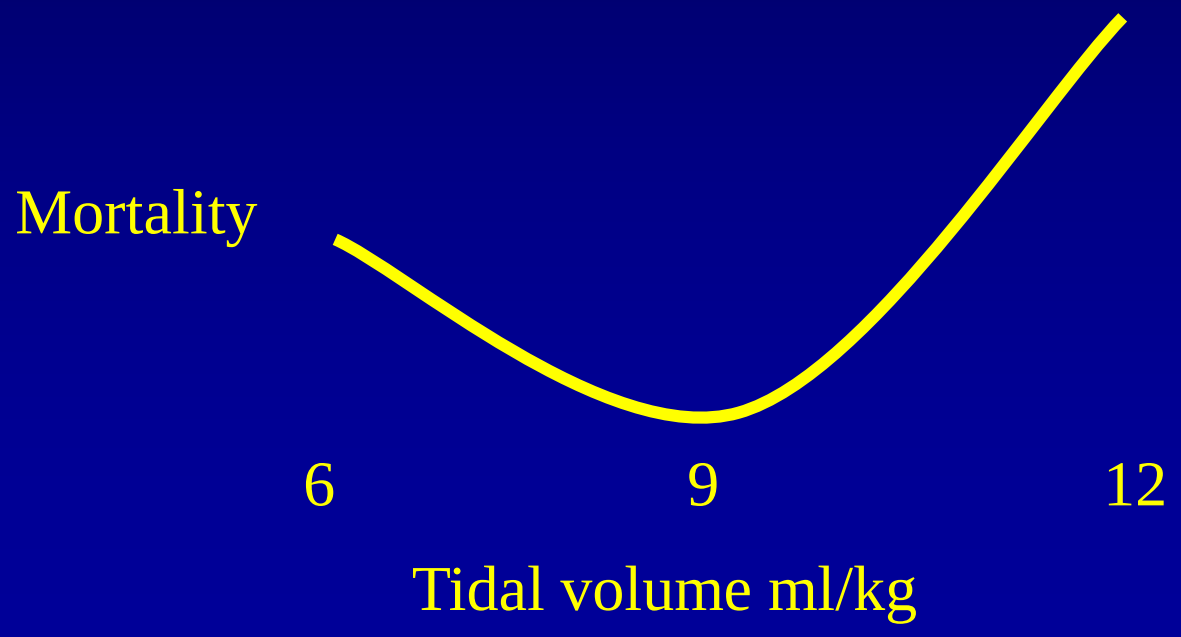
ARDSNet



Mortality 31.0 % (Low Vt) vs 39.8 % (High Vt) P=0.007

ARDSNet Criticisms

- 12ml/kg is too much
  - Nobody uses it
- U shaped dose response curve?



Back to the OR

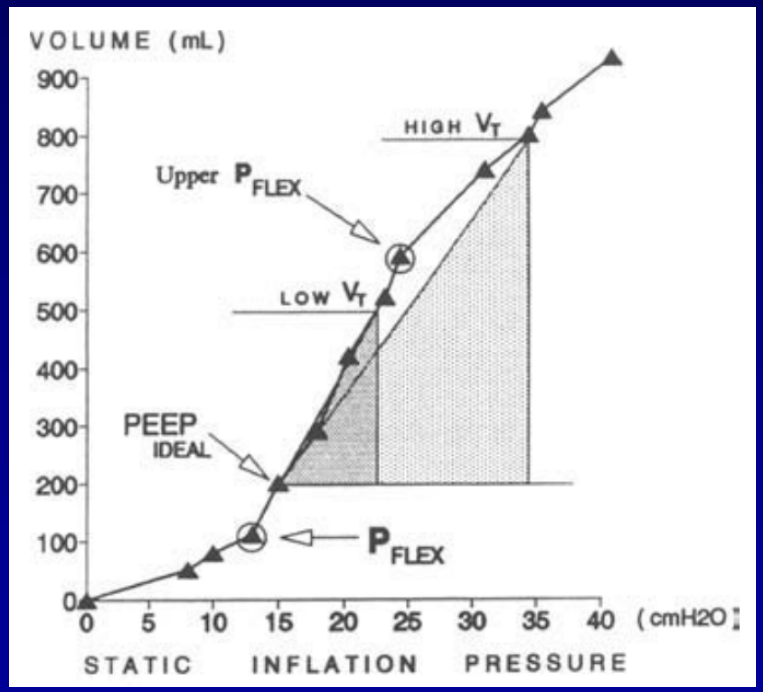
- Oxygen saturation is falling
- Volume control ventilation
- Vt 600ml (pt. weighs 100kg) Ht is 5’4”; PBW is 60kg
- Rate 14
- Plateau pressure 35cm H2O
- FiO2 = 1
- PEEP 5cm H2O
- ABG pH 7.32, pO2 50, pCO2 48, SO2 83%

Mechanical Ventilation of Sepsis-Induced Acute Lung Injury

- Higher PEEP vs lower PEEP (weak recommendation, moderate quality of evidence)
- Recruitment maneuvers in severe ARDS (weak recommendation, moderate quality of evidence)
- Pronation in ARDS and a Pao2/Fio2 ratio < 150 (strong recommendation, moderate quality of evidence)

Methods to “Ideal” PEEP

- Titrate PEEP according to bedside measurements of thoraco-pulmonary compliance



Methods to “Ideal” PEEP

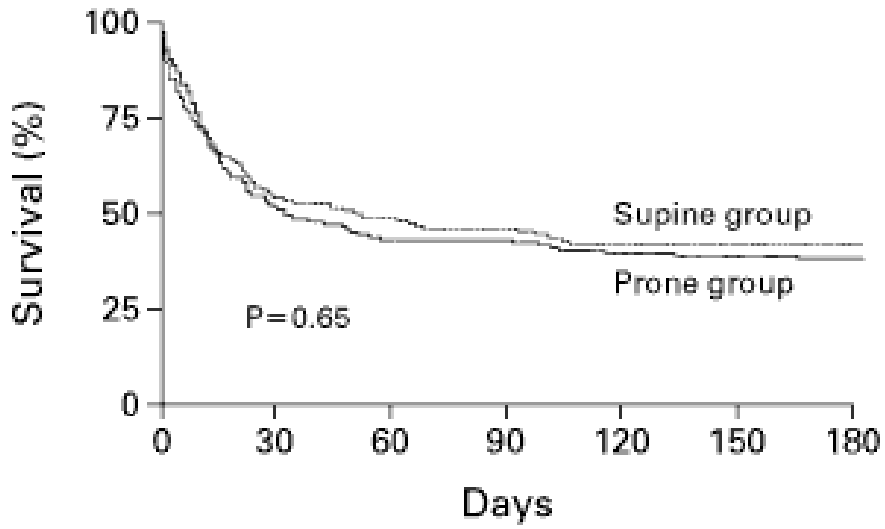
- Titrate PEEP upward on a tidal volume of 6 mL/kg PBW until the plateau airway pressure is 28-30 cm H2O

- Use a PEEP/Fio2 titration table that titrates PEEP based on the combination of Fio2 and PEEP required to maintain adequate oxygenation

	Fraction of Inspired Oxygen (FIO_2)							
	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1.0
PEEP ranges, cm H_2O	5	5-8	8-10	10	10-14	14	14-18	18-24

Pronation

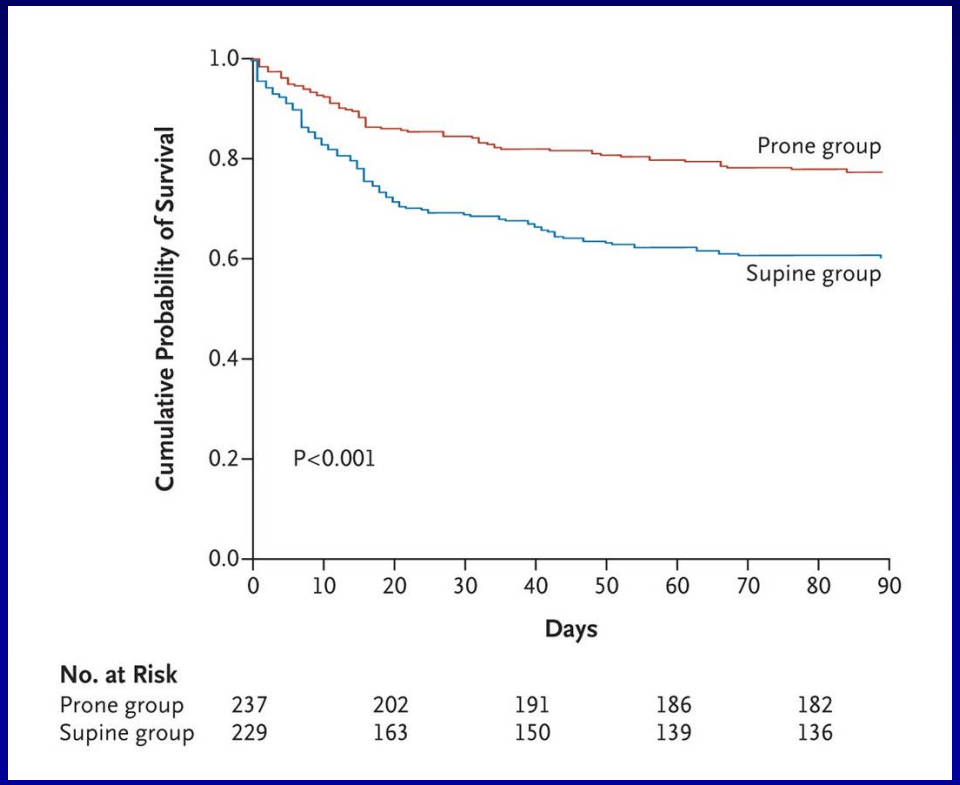
- Gattinoni NEJM (2001) 345 : 568-573
- Significant improvement in oxygenation



No. at Risk							
Supine group	152	82	72	68	62	62	62
Prone group	152	78	63	63	58	57	56

Pronation

- Proseva Group, N Engl J Med 2013; 368:2159-2168
- PaO_2:FiO_2 ratio of <150 mm Hg
- Proned for 16 hours per day



ICU Strategies for Acute Lung Injury

- No high-frequency oscillatory ventilation in ARDS (strong recommendation, moderate quality of evidence)
- No recommendation for noninvasive ventilation in ARDS
- NMBs for ≤ 48 hours in ARDS and a Pao2/Fio2 ratio < 150 mm Hg (weak recommendation, moderate quality of evidence)

ICU Strategies

- Conservative fluid strategy for ARDS without tissue hypoperfusion (strong recommendation, moderate quality of evidence)
- No ß-2 agonists unless bronchospasm (strong recommendation, moderate quality of evidence)
- No pulmonary artery catheter for ARDS (strong recommendation, high quality of evidence)
- Lower tidal volumes over higher tidal volumes without ARDS (weak recommendation, low quality of evidence)
- Head of the bed elevated between 30 and 45 degrees to limit aspiration and ventilator-associated pneumonia (strong recommendation, low quality of evidence)

ICU Strategies

- Spontaneous breathing trials in ventilated patients ready for weaning (strong recommendation, high quality of evidence)
- Weaning protocol in ventilated patients when tolerated (strong recommendation, moderate quality of evidence)

Steroids

- High dose corticosteroids are ineffective or harmful - Grade A (2012)

- 1980s: Dexamethasone Shok-Pak: ?1g

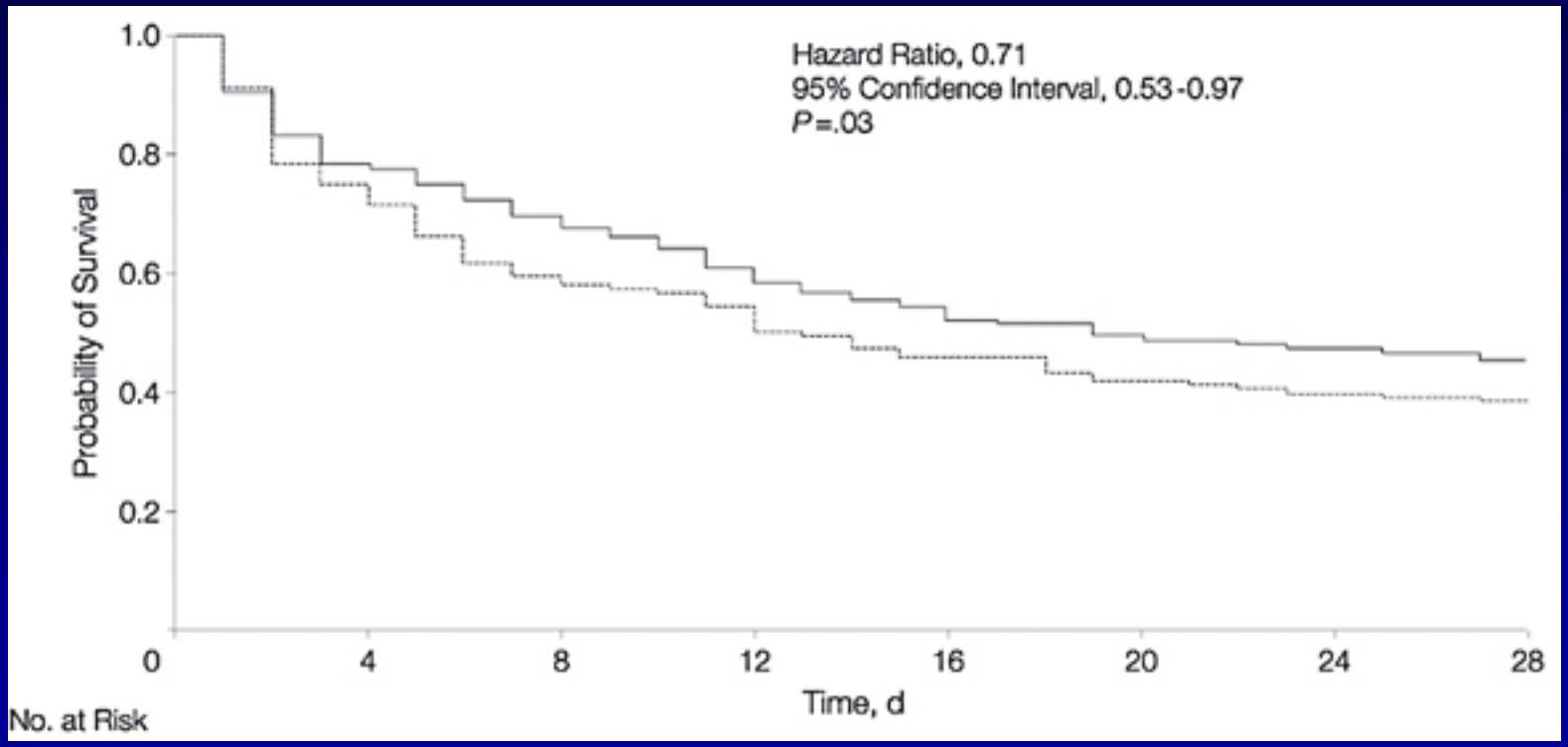
- Bone NEJM 317:653-658, 1987
- Mortality 59% vs 29%

Steroids

- Against using IV hydrocortisone to treat septic shock patients if adequate fluid resuscitation and vasopressor therapy are able to restore hemodynamic stability
- If this is not achievable, we suggest IV hydrocortisone at a dose of 200 mg per day
  - (weak recommendation, low quality of evidence).

Low Dose Steroids

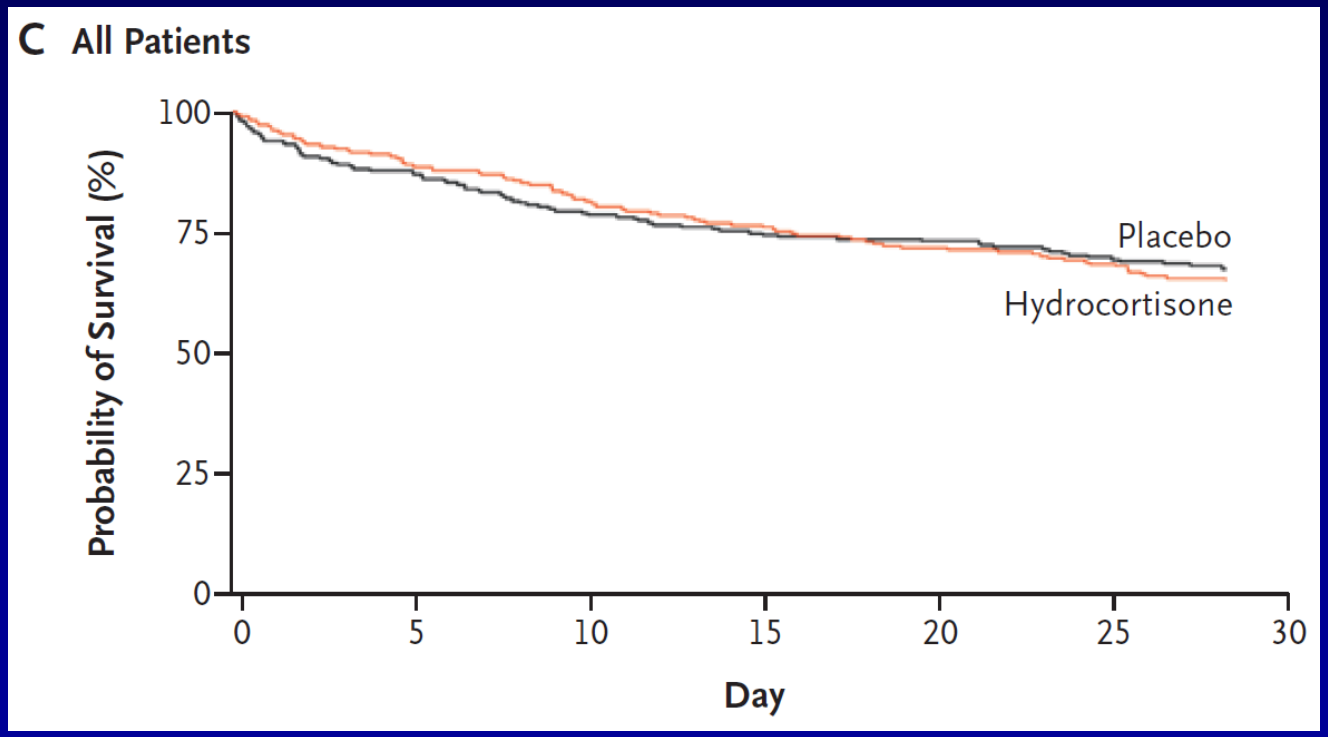
All Patients



Annane D – Low Dose Steroids in Septic Shock – JAMA 2002

CORTICUS

- 500 pateinets



CORTICUS

- Hydrocortisone does not decrease mortality in septic shock
- Does not increase reversal of shock but shock reverses quicker
- No polyneuropathy increase
- More superinfection
- ACTH is test not useful
- Hydrocortisone should not be routinely used in septic shock
- There may be a role in those still hypotensive after 1 hour

Glucose Control

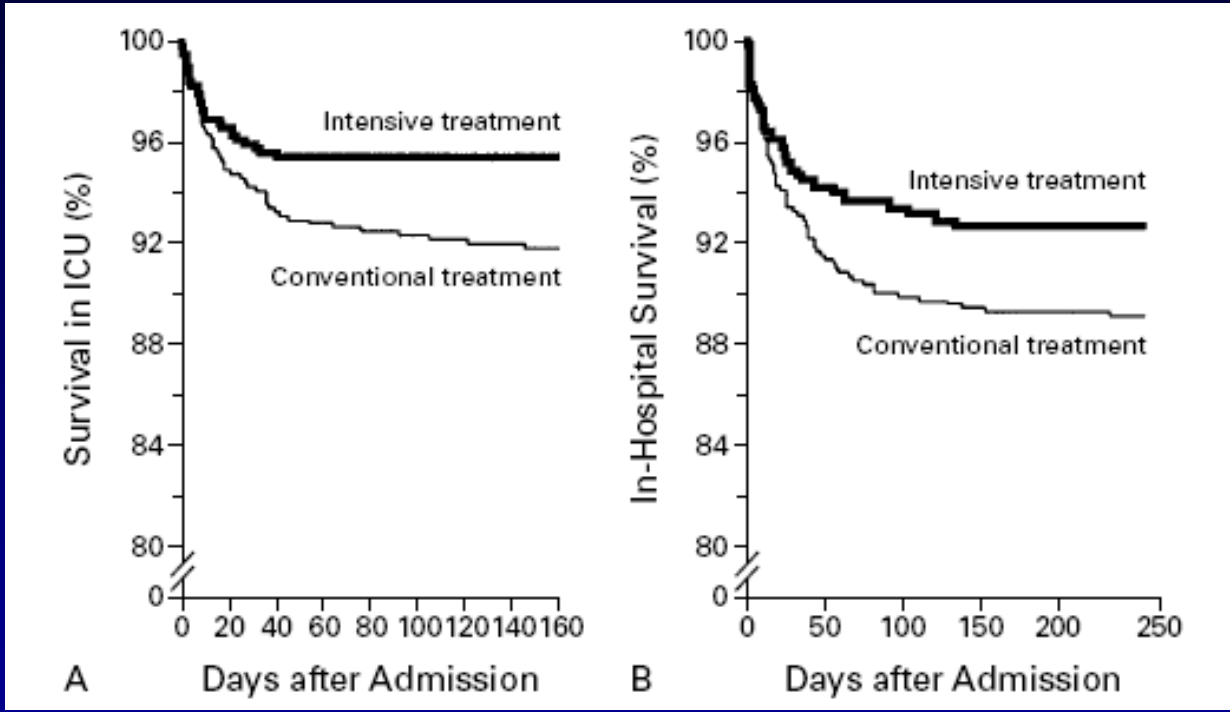
- Protocolize treatment
- Start insulin when two blood glucose levels are > 180 mg/dL.
- Target an upper blood glucose level ≤180 mg/dL rather than ≤ 110 mg/dL
  - (strong recommendation, high quality of evidence)

Tight Blood Glucose Control in ICU

- Prospective, randomized, controlled study
- 1548 patients
- Surgical intensive care unit – 60% cardiac surgery
- On mechanical ventilation
- Conventional management
  - Target BS 180 to 200
  - Insulin IVI started for BS > 215
- Or Insulin IVI
  - Target BS 80 to 110

Van Den Berghe G. NEJM 2001, 345; 1359-1367

Survival

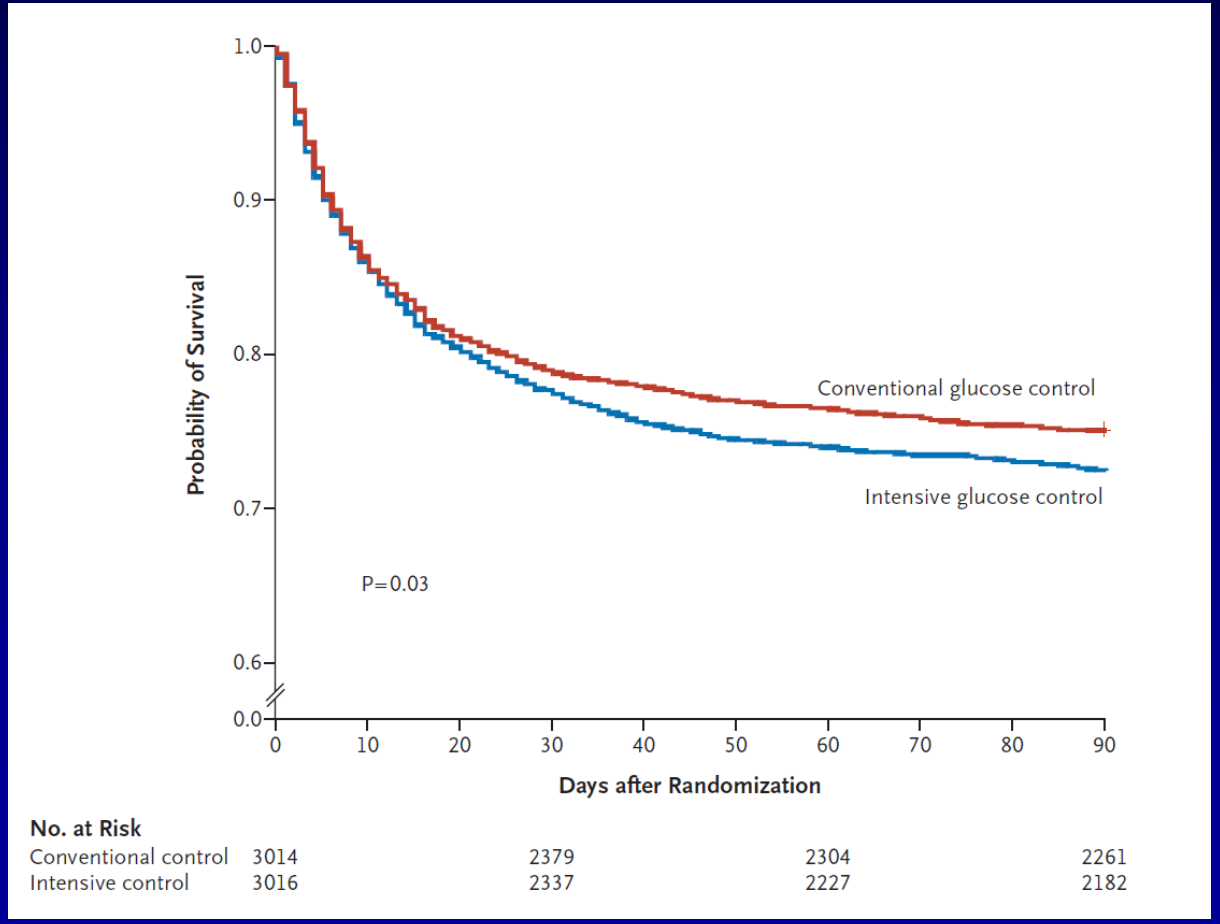


ICU Mortality 8% vs 4.6% $p<0.04$
In-hospital mortality reduced by 34 percent

Van Den Berghe G. NEJM 2001, 345; 1359-1367

NICE-SUGAR Study

- 6104 patients randomized to tight (81-108) or loose (<180). ANZICS/Canada



Glucontrol

- ECCRN and ESICM sponsored, PRBCT, 21 ICUs across Europe
- At 1st interim analysis the study was stopped
  - increased hypoglycemia
  - increased mortality in tight Group
  - increased protocol violations
- Other studies showed severe hypoglycemia (<40) in 6-29% with tight control

Blood Products

- Red cells Hb< 7 g/dL in the absence of myocardial ischemia, severe hypoxemia, or acute hemorrhage (strong recommendation, high quality of evidence)
- Erythropoietin: Not recommended (strong recommendation, moderate quality of evidence)
- FFP: Not recommended to correct PT/PTT, unless there is bleeding or a planned invasive procedures. (weak recommendation, very low quality of evidence).
- Platelets
  - Prophylactic,in the absence of bleeding if < 10,000/mm3
  - Significant risk of bleeding if < 20,000/mm3
  - Active bleeding, surgery, or invasive procedures if < 50,000/mm3 (weak recommendation, very low quality of evidence)

Take Home Points

- Septic shock continues to have very high mortality
- Patients may presentto us in a very unstable state but still require surgery to treat the underlying cause of their sepsis
- Surviving Sepsis Campaign Guidelines
  - Useful algorithm
  - Based on the best available evidence