Advances in management of Sepsis
Important randomized controlled trials in the last decade
Part - II

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Glucose control in Sepsis

- Hyperglycemia is common in critically ill patients and is associated with increased morbidity and mortality.

- Stress hyperglycemia is a physiologic response caused by insulin resistance, glycogenolysis, and increased hepatic gluconeogenesis from the release of catecholamines, cortisol, and glucagon.

- Long-term hyperglycemia is associated with complications that can be improved with better glycemic control.

- Observational studies demonstrate strong associations between hyperglycemia and poor clinical outcomes, but they do not demonstrate a cause–effect relationship.

- How to approach glycemic control in critically ill patients ????

INTENSIVE INSULIN THERAPY IN CRITICALLY ILL PATIENTS

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

- N=1548 , Leuven Belgium
- CSICU patients receiving mechanical ventilation.
- Randomized to IIT vs Conventional

VARIABLE	CONVENTIONAL TREATMENT (N=783)	INTENSIVE TREATMENT (N=765)	P VALUE*
Death during intensive care — no./total no. (%)	63/783 (8.0)	35/765 (4.6)	<0.04 (adjusted)
During first 5 days of intensive care	14/783 (1.8)	13/765 (1.7)	0.9
Among patients receiving intensive care for >5 days	49/243 (20.2)	22/208 (10.6)	0.005
Reason for intensive care			
Cardiac surgery	25/493 (5.1)	10/477 (2.1)	
Neurologic disease, cerebral trauma, or brain surgery	7/30 (23.3)	6/33 (18.2)	
Thoracic surgery, respiratory insufficiency, or both	10/56 (17.9)	5/66 (7.6)	
Abdominal surgery or peritonitis	9/58 (15.5)	6/45 (13.3)	
Vascular surgery	2/32 (6.2)	2/30 (6.7)	
Multiple trauma or severe burns	3/35 (8.6)	4/33 (12.1)	
Transplantation	1/44 (2.3)	2/46 (4.4)	
Other	6/35 (17.1)	0/35	
No history of diabetes	57/680 (8.4)	31/664 (4.7)	
No history of diabetes and >5 days of intensive care	45/218 (20.6)	20/187 (10.7)	
History of diabetes	6/103 (5.8)	4/101 (4.0)	
History of diabetes and >5 days of intensive care	4/25 (16.0)	2/21 (9.5)	
Cause of death — no.			0.02
Multiple-organ failure with proven septic focus	33	8	
Multiple-organ failure without detectable septic focus	18	14	
Severe brain damage	5	3	
Acute cardiovascular collapse	7	10	
In-hospital death — no./total no. (%)			
All patients	85/783 (10.9)	55/765 (7.2)	0.01
Patients receiving intensive care for >5 days	64/243 (26.3)	35/208 (16.8)	0.01

NNT=10

- The greatest reduction in mortality involved deaths due to multiple-organ failure with a proven septic focus.
- ↓ overall in-hospital mortality – 34 %
- ↓ Bloodstream infections - 46 %
- ↓ ARF requiring dialysis or hemofiltration – 41 %
- ↓ Median RBC transfusions – 50 %
- ↓ Critical-illness polyneuropathy - 44 %
- Patients receiving IIT were less likely to require prolonged mechanical ventilation and intensive care.
- IIT to keep blood glucose levels at or below 110 mg/dl reduces morbidity and mortality in surgical ICU patients.

UNSTOPPABLE “ IIT EXPRESS” STARTED ITS JOURNEY

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 2, 2006 VOL. 354 NO. 5

Intensive Insulin Therapy in the Medical ICU

Greet Van den Berghe, M.D., Ph.D., Alexander Wilmer, M.D., Ph.D., Greet Hermans, M.D., Wouter Meersseman, M.D., Pieter J. Wouters, M.Sc., Ilse Milants, R.N., Eric Van Wijngaerden, M.D., Ph.D., Herman Bobbaers, M.D., Ph.D., and Roger Bouillon, M.D., Ph.D.

- N=1200, 3 Medical ICU's.
- Patients with an expected ICU length of stay of 3 or more days.

Variable	Intention-to-Treat Group			Group in ICU for ≥3 Days		
	Conventional Treatment (N=605)	Intensive Treatment (N=595)	P Value	Conventional Treatment (N=381)	Intensive Treatment (N=386)	P Value
Total deaths during intensive care — no. (%)	162 (26.8)	144 (24.2)	0.31	145 (38.1)	121 (31.3)	0.05
Causes of death during intensive care — no. (% of patients in the category)			0.90			0.70
Persistent MOF after septic or SIRS-induced shock	59 (51.3)	56 (48.7)		55 (51.4)	52 (48.6)	
Respiratory failure	50 (54.3)	42 (45.7)		49 (55.7)	39 (44.3)	
Therapy-resistant septic shock	21 (50.0)	21 (50.0)		14 (53.8)	12 (46.2)	
Cardiovascular collapse	18 (54.5)	15 (45.5)		16 (66.7)	8 (33.3)	
Severe brain damage	14 (58.3)	10 (41.7)		11 (52.4)	10 (47.6)	
In-hospital deaths — no. (%)	242 (40.0)	222 (37.3)	0.33	200 (52.5)	166 (43.0)	0.009
Hazard ratio (95% CI)		0.94 (0.84–1.06)	0.31		0.84 (0.73–0.97)	0.02†

- Morbidity was significantly reduced.
- Prevention of newly acquired kidney injury.

- Accelerated weaning from mechanical ventilation

- Accelerated discharge from the ICU and the hospital

- 433 patients - ICU < days - Mortality was greater among those receiving IIT.
- 767 patients - ICU ≥ 3 or more days - In-hospital mortality in the 386 who received IIT was reduced.
- 52.5 vs 43.0 percent (P = 0.009).
- Intensive insulin therapy significantly reduced morbidity but not mortality among all patients in the medical ICU.
- Hypoglycemia more frequent with IIT
- Although the risk of subsequent death and disease was reduced in patients treated for three or more days, these patients could not be identified before therapy.
- Further studies are needed to confirm these preliminary data

ORIGINAL ARTICLE

Intensive Insulin Therapy and Pentastarch Resuscitation in Severe Sepsis

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

- **Multicenter, 2 X 2 factorial design**
- **Intensive vs Conventional glucose control.**
- **10 % Pentastarch vs Ringer's lactate**
- **Coprimary end points – 28 day mortality and mean SOFA score.**

- **Terminated early for safety reasons.**

- **At 28 days, no significant difference between the two groups in the rate of death or the mean score for organ failure.**

- **The rate of severe hypoglycemia & SAE's was higher in the IIT group.**

- **HES therapy was associated with higher rates of acute renal failure and renal-replacement therapy than was Ringer's lactate.**

Glucose control

- *Van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in the critically ill patients. N Engl J Med 2001;345(19):1359–67.*

- *Van den Berghe G, Wilmer A, Hermans G, et al. Intensive insulin therapy in the medical ICU. N Engl J Med 2006;354(5):449–61.*

- *Brunkhorst FM, Engel C, Bloos F, et al. Intensive insulin therapy and pentastarch resuscitation in severe sepsis. N Engl J Med 2008;358(2):125–39. Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis (VISEP) study.*

- Patients who will have a prolonged stay in the ICU cannot be identified with certainty on admission, adequately powered trials are needed.

- On the basis of our current data, such studies would require at least 5000 patients in the medical ICU.

Intensive versus Conventional Glucose Control in Critically Ill Patients

The NICE-SUGAR Study Investigators*

- N= 6104 (3054 – IIT , 3050 Conventional)
- Patients with expected ICU stay > 3 days.
- Randomly assigned to undergo either intensive glucose control, with a target blood glucose range of 81 to 108 mg/dl, or conventional glucose control, with a target of 180 mg or less/dl.
- Primary end point as death from any cause within 90 days after randomization.
- ANZICS Clinical Trials Group, the George Institute for International Health (University of Sydney), the Canadian Critical Care Trials Group, and the Vancouver Coastal Health Research Institute (University of British Columbia).

N Engl J Med 2009;360:1283-97.

Outcome Measure	Intensive Glucose Control	Conventional Glucose Control	Odds Ratio or Absolute Difference (95% CI)†	Statistical Test	P Value
Death — no. of patients/total no. (%)				Logistic regression	
At day 90	829/3010 (27.5)	751/3012 (24.9)	1.14 (1.02 to 1.28)		0.02
At day 28	670/3010 (22.3)	627/3012 (20.8)	1.09 (0.96 to 1.23)		0.17
Severe hypoglycemia — no. of patients/total no. (%)	206/3016 (6.8)	15/3014 (0.5)	14.7 (9.0 to 25.9)	Logistic regression	<0.001
Days in ICU — median (IQR)	6 (2 to 11)	6 (2 to 11)	0	Log-rank test	0.84
Days in hospital — median (IQR)	17 (8 to 35)	17 (8 to 35)	0	Log-rank test	0.86
Mechanical ventilation — no. of patients/total no. (%)	2894/3014 (96.0)	2872/3014 (95.3)	0.7 (−0.3 to 1.76)	Pearson's test	0.17
Days of mechanical ventilation	6.6±6.6	6.6±6.5	0	Wilcoxon rank-sum test	0.56
Renal-replacement therapy — no. of patients/total no. (%)	465/3014 (15.4)	438/3014 (14.5)	0.9 (−0.9 to 2.7)	Pearson's test	0.34
Days of renal-replacement therapy	0.8±2.6	0.8±2.8	0	Wilcoxon rank-sum test	0.39
No. of new organ failures — no. of patients/total no. (%)‡				Pearson's test	0.11
0	1571/2682 (58.6)	1536/2679 (57.3)			
1	790/2682 (29.5)	837/2679 (31.2)			
2	263/2682 (9.8)	257/2679 (9.6)			
3	44/2682 (1.6)	46/2679 (1.7)			
4	11/2682 (0.4)	2/2679 (0.1)			
5	3/2682 (0.1)	1/2679 (<0.1)			

Treatment effect did not differ significantly between surgical and medical patients

N Engl J Med 2009;360:1283-97.

Stop the “IIT EXPRESS”

Conclusions

- ***Surviving Sepsis 2008*** – Recommended a target blood glucose level of less than 150 mg/ dl.

- ***Surviving Sepsis Campaign Statement on Glucose Control in Severe Sepsis (June 2009)*** - Until additional information is available, teams seeking to implement glucose control should consider initiating insulin therapy when blood glucose levels exceed 180 mg/dL with a goal blood glucose approximating 150 mg/dl.

Fluid therapy – Colloids/ Crystalloids

- Conflicting reports of Meta-analysis.

Human albumin administration in critically ill patients: systematic review of randomised controlled trials

Cochrane Injuries Group Albumin Reviewers

24 studies, n= 1419

Pooled difference in the risk of death with albumin was 6% (95% confidence interval 3% to 9%) with a fixed effects model.

NNH= 17.

Strong suggestion that Albumin use may increase mortality.

Use of human albumin in critically ill patients should be urgently reviewed and that it should not be used outside the context of rigorously conducted, randomised controlled trials.

BMJ 1998;317:235–40

Patient Survival after Human Albumin Administration

A Meta-Analysis of Randomized, Controlled Trials

Mahlon M. Wilkes, PhD, and Roberta J. Navickis, PhD

- **55 Trials, N=3504.**
- **Albumin administration did not significantly affect mortality in any category of indications.**
- **For all trials, the relative risk for death was 1.11 (95% CI, 0.95 to 1.28).**
- **Relative risk was lower among trials with blinding (0.73 [CI, 0.48 to 1.12]; n= 7), mortality as an end point (1.00 [CI, 0.84 to 1.18]; n=17), no crossover (1.04 [CI, 0.89 to 1.22]; n=35), and 100 or more patients (0.94 [CI, 0.77 to 1.14]; n=10).**
- **Meta analysis supported the safety of albumin.**
- **The influence of methodologic quality on relative risk for death suggests the need for further well-designed clinical trials.**

Ann Intern Med. 2001;135:149-164.

Fluid therapy in Sepsis

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Comparison of Albumin and Saline for Fluid Resuscitation in the Intensive Care Unit

The SAFE Study Investigators*

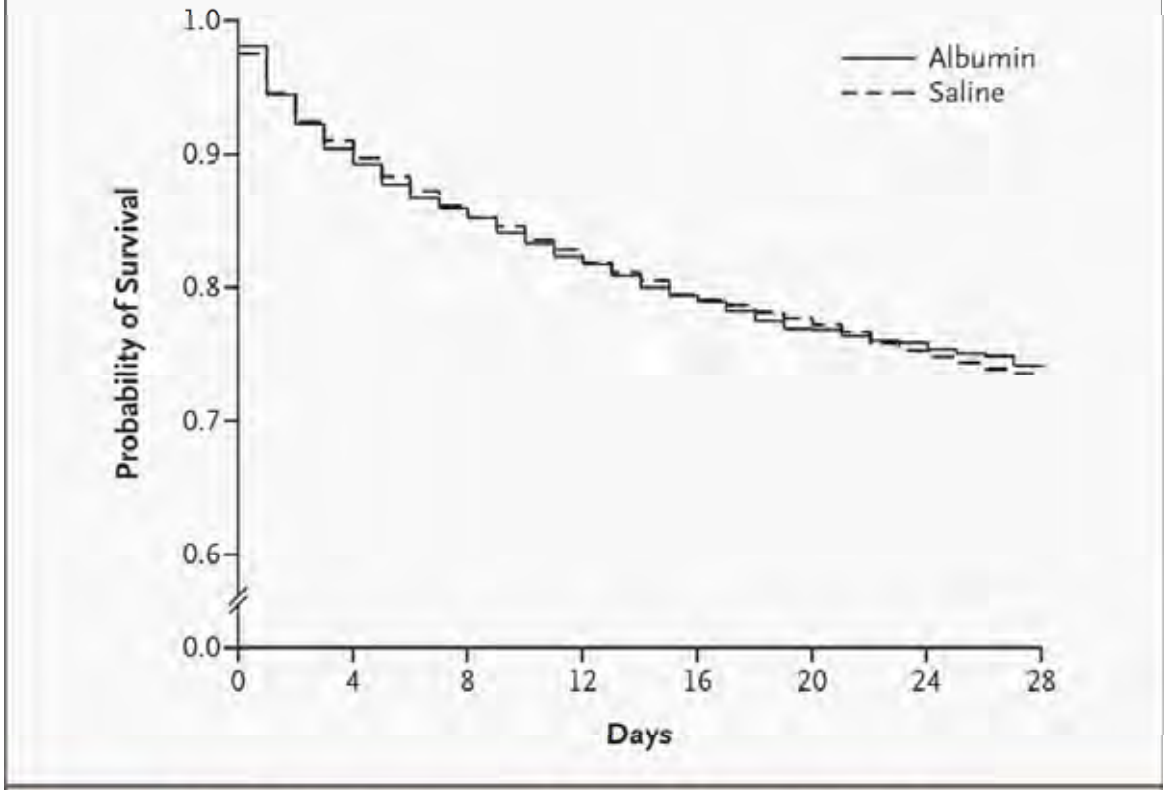


Figure 1. Kaplan–Meier Estimates of the Probability of Survival.

The Saline versus Albumin Fluid Evaluation (SAFE) Study

Multicenter, randomized, double-blind trial. N=6997

Heterogeneous population of patients in the ICU.

To compare 4 % albumin with Saline.

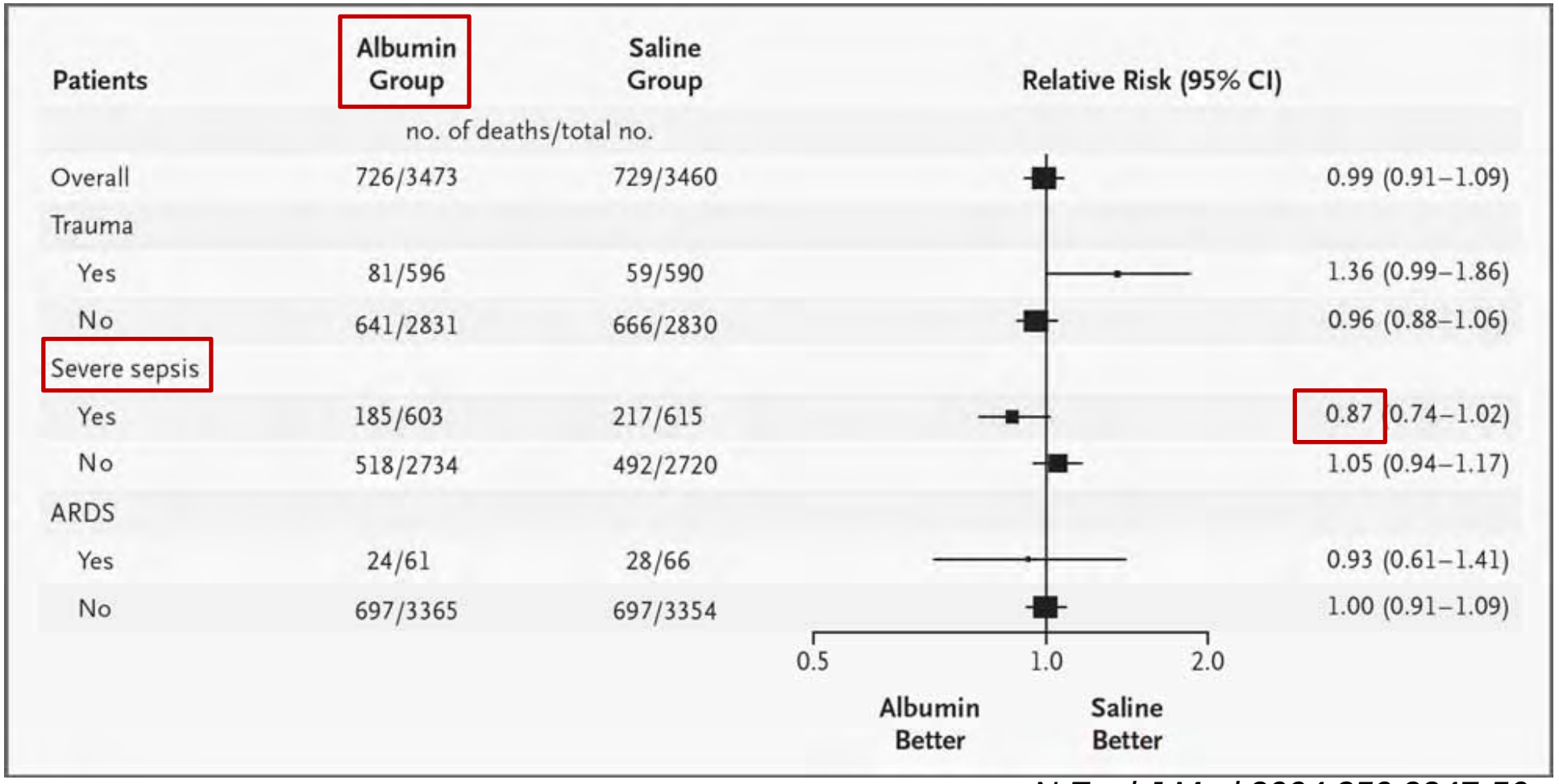
Primary outcome – Effect on 28 day mortality

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

Table 3. Primary and Secondary Outcomes.*

Outcome	Albumin Group	Saline Group	Relative Risk (95% CI)	Absolute Difference (95% CI)	P Value
Status at 28 days — no./total no. (%)					
Dead	726/3473 (20.9)	729/3460 (21.1)	0.99 (0.91 to 1.09)		0.87
Alive in ICU	111/3473 (3.2)	87/3460 (2.5)	1.27 (0.96 to 1.68)		0.09
Alive in hospital†	793/3473 (22.8)	848/3460 (24.5)	0.93 (0.86 to 1.01)		0.10
Length of stay in ICU — days	6.5±6.6	6.2±6.2		0.24 (–0.06 to 0.54)	0.44
Length of stay in hospital — days†	15.3±9.6	15.6±9.6		–0.24 (–0.70 to 0.21)	0.30
Duration of mechanical ventilation — days	4.5±6.1	4.3±5.7		0.19 (–0.08 to 0.47)	0.74
Duration of renal-replacement therapy — days	0.48±2.28	0.39±2.0		0.09 (–0.0 to 0.19)	0.41
New organ failure — no. (%)‡					0.85§
No failure	1397 (52.7)	1424 (53.3)			
1 organ	795 (30.0)	796 (29.8)			
2 organs	369 (13.9)	361 (13.5)			
3 organs	68 (2.6)	75 (2.8)			
4 organs	18 (0.7)	17 (0.6)			
5 organs	2 (0.1)	0			
Death within 28 days according to subgroup — no./total no. (%)					
Patients with trauma	81/596 (13.6)	59/590 (10.0)	1.36 (0.99 to 1.86)		0.06
Patients with severe sepsis	185/603 (30.7)	217/615 (35.3)	0.87 (0.74 to 1.02)		0.09
Patients with acute respiratory distress syndrome	24/61 (39.3)	28/66 (42.4)	0.93 (0.61 to 1.41)		0.72

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



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

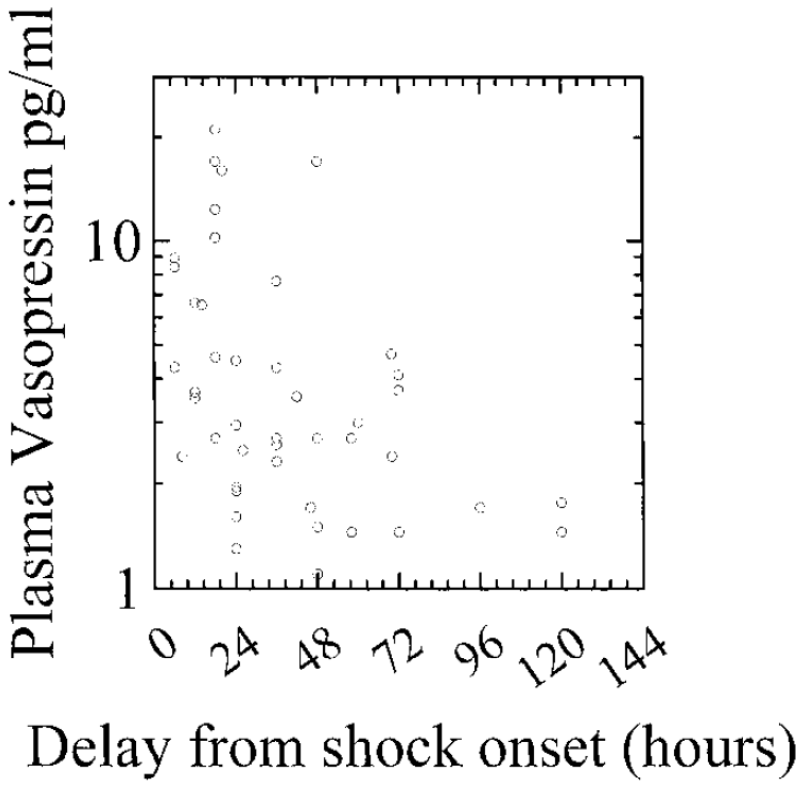
- Such differences between subgroups frequently occur by chance and that only specifically designed and appropriately powered studies can determine whether any such treatment effects are real.

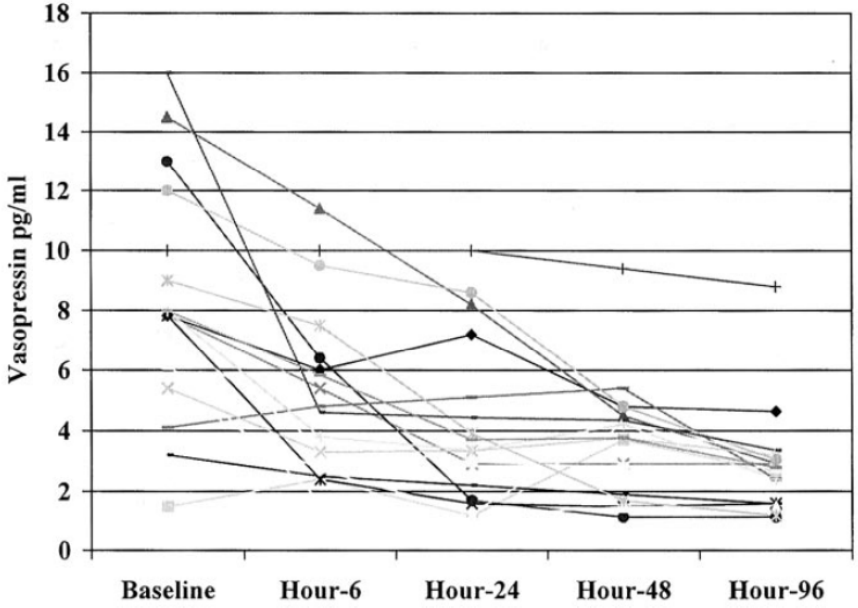
- SSC - recommend fluid resuscitation with either natural/artificial colloids or crystalloids. There is no evidence based support for one type of fluid over another (grade 1B).

Vasopressors in Sepsis

Circulating vasopressin levels in septic shock

Tarek Sharshar, MD; Anne Blanchard, MD, PhD; Michel Paillard, MD; Jean Claude Raphael, MD; Philippe Gajdos, MD; Djillali Annane, MD, PhD





Relative vasopressin deficiency is seen in approximately one-third of late septic shock patients.

Crit Care Med 2003; 31:1752–1758

Table 2. Clinical studies of vasopressin infusion in vasodilatory and septic shock

Authors	Ref. No.	Year	Study Type	No.	Condition Studied	Vasopressin Dose (Units/Min)	Significant Effects
Landry et al.	12	1997	Case series	5	Septic shock	0.03–0.05	A, B, C
Landry et al.	5	1997	Matched cohort	19	Septic shock	0.01–0.04	A, B, D in septic group
				12	Cardiogenic shock		
Argenziano et al.	11	1997	RCT Placebo: NS	10	Vasodilatory shock Post-LVAD implant	0.1	A, B in treatment arm D in all
Argenziano et al.	13	1998	Retrospective Case series	40	Postbypass Vasodilatory shock	0.1	A, B, D
Malay et al.	10	1999	RCT Placebo: NS	10	Septic shock—trauma	0.04	A, B in treatment arm
Chen et al.	17	1999	Case series	10	Organ donors with vasodilatory shock	0.04–0.1	A, D
Argenziano et al.	14	1999	Case series	20	Vasodilatory shock Post-cardiac transplant	0.1 U	A, B
Rosenzweig et al.	15	1999	Case series	11	Pediatric—vasodilatory Shock post-bypass	0.0003 to 0.002 U/kg/min	A, B, D
Morales et al.	16	2000	Retrospective Case series	50	Vasodilatory shock Post-LVAD implantation	0.09 +/− 0.05	A, B
Gold et al.	66	2000	Case series	7	Milrinone—hypotension	0.03–0.07	A, B, C
Holmes et al.	6	2001	Retrospective	50	Septic shock	0.01–0.6	A, B, C
Dünser et al.	70	2001	Retrospective	35	Septic shock	0.06–0.1	A, B
				25	Postcardiotomy shock		A, B
Dünser et al.	71	2002	Retrospective	41	Postcardiotomy shock	0.06–0.1	A, B
Patel et al.	7	2002	RCT	24	Septic shock	0.01–0.08	B, C, in treatment arm

RCT, randomized, controlled trial; A, increase in blood pressure; B, decrease or discontinuation of catecholamines; C, increase in urine output; D, inappropriately low plasma vasopressin levels in subjects; NS, not significant; LVAD, left ventricular assist device.

- **Potential benefits and adverse effects of vasopressin in septic shock.**
- **No large, multicenter, adequately powered RCT'S of vasopressin vs. norepinephrine in septic shock. Effect on mortality unknown.**

James A. Russell Crit Care Med 2007 Vol. 35, No. 9 (Suppl.)

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 28, 2008 VOL. 358 NO. 9

Vasopressin versus Norepinephrine Infusion in Patients with Septic Shock

James A. Russell, M.D., Keith R. Walley, M.D., Joel Singer, Ph.D., Anthony C. Gordon, M.B., B.S., M.D., Paul C. Hébert, M.D., D. James Cooper, B.M., B.S., M.D., Cheryl L. Holmes, M.D., Sangeeta Mehta, M.D., John T. Granton, M.D., Michelle M. Storms, B.Sc.N., Deborah J. Cook, M.D., Jeffrey J. Presneill, M.B., B.S., Ph.D., and Dieter Ayers, M.Sc., for the VASST Investigators*

- Hypothesis - Low-dose vasopressin as compared with norepinephrine would decrease mortality among patients with septic shock.
- Multicenter, randomized, double-blind trial. N=778
- Assigned patients who had septic shock and were receiving a minimum of 5 µg of norepinephrine per minute to receive either low-dose vasopressin or norepinephrine in addition to open-label vasopressors.
- Primary end point - Mortality rate 28 days after the start of infusions.

Table 2. Analysis of the Rates and Risks of Death from Any Cause and Secondary Outcomes.*

Variable	Norepinephrine Group (N=382)	Vasopressin Group (N=396)	P Value†	Absolute Risk Reduction (95% CI)‡	Relative Risk (95% CI)§	Adjusted Odds Ratio¶
	no./total no. (%)			%		
Patients who underwent randomization and infusion						
28-day mortality	150/382 (39.3)	140/396 (35.4)	0.26	3.9 (−2.9 to 10.7)	0.90 (0.75 to 1.08)	0.88 (0.62 to 1.26)
90-day mortality	188/379 (49.6)	172/392 (43.9)	0.11	5.7 (−1.3 to 12.8)	0.88 (0.76 to 1.03)	0.81 (0.57 to 1.16)
Patients who underwent randomization						
28-day mortality	154/395 (39.0)	144/404 (35.6)	0.33	3.3 (−3.4 to 10.1)	0.91 (0.76 to 1.09)	
90-day mortality	194/392 (49.5)	177/400 (44.2)	0.14	5.2 (−1.7 to 12.2)	0.89 (0.77 to 1.04)	
	median (interquartile range)					
Days alive‖						
Free of organ dysfunction						
Cardiovascular	17 (0–24)	19 (0–24)	0.58			
Vasopressor use**	17 (0–24)	19 (0–24)	0.61			
Respiratory	2 (0–14)	3.5 (0–16)	0.15			
Ventilation††	6 (0–20)	8.5 (0–20)	0.24			
Renal	18.5 (3–28)	21.5 (4–28)	0.54			
Renal-replacement therapy	23 (5–28)	25 (6–28)	0.64			
Hepatic	24.5 (3–28)	25 (5–28)	0.80			
Hematologic	23 (3–28)	24 (5–28)	0.48			
Neurologic	15 (0–24)	15 (0–24)	0.57			
Free of any organ failure	0 (0–6)	0 (0–9)	0.14			
Free of the systemic inflammatory response syndrome‡‡	6 (0–15)	6 (0–18)	0.21			
Free of corticosteroid use	13.5 (1–24)	16 (1–25)	0.33			
Length of stay (days)						
In ICU	16 (8–32)	15 (7–29)	0.14			
In hospital	26 (15–53)	27 (13–52)	0.23			

VASST Study, NEJM 2008

Table 3. Serious Adverse Events in Patients Who Had Septic Shock.

Variable	Norepinephrine Group (N=382)	Vasopressin Group (N=396)	P Value*
	no. (%)		
At least one serious adverse event	40 (10.5)	41 (10.3)	1.00
Acute myocardial infarction or ischemia	7 (1.8)	8 (2.0)	1.00
Cardiac arrest	8 (2.1)	3 (0.8)	0.14
Life-threatening arrhythmia	6 (1.6)	8 (2.0)	0.79
Acute mesenteric ischemia	13 (3.4)	9 (2.3)	0.39
Hyponatremia†	1 (0.3)	1 (0.3)	1.00
Digital ischemia	2 (0.5)	8 (2.0)	0.11
Cerebrovascular accident	1 (0.3)	1 (0.3)	1.00
Other‡	2 (0.5)	5 (1.3)	0.45

Infusions of low-dose vasopressin increased plasma vasopressin levels from extremely low baseline.

Vasopressin infusion allowed a rapid decrease in the total norepinephrine dose while maintaining MAP.

Limitations – Mean time of entry 12 hrs, Levels not measured to guide infusion, MAP at baseline 72-73.

VASST Study, NEJM 2008

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)

Low dose dopamine for renoprotection - NO

Low-dose dopamine in patients with early renal dysfunction: a placebo-controlled randomised trial

Lancet 2000; **356:** 2139–43

*Australian and New Zealand Intensive Care Society (ANZICS) Clinical Trials Group**

	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 µmol/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 (−1 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)

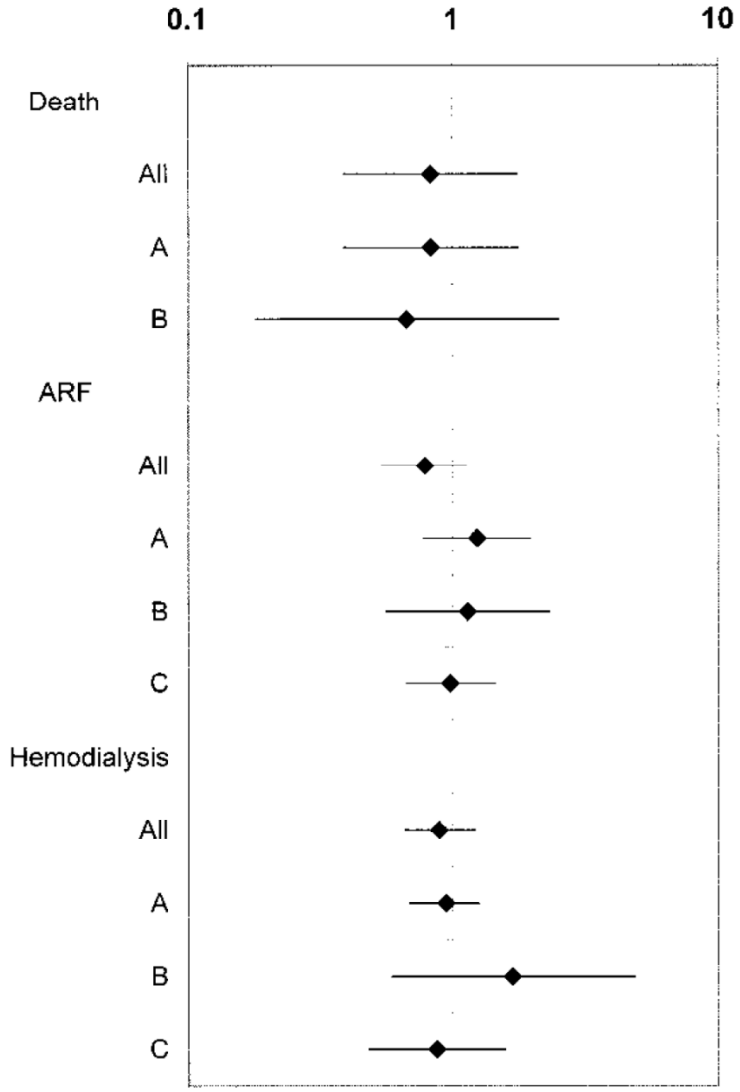
Continuous infusion of 2 µg/kg/min vs placebo

Primary endpoint - Peak serum creatinine concentration during the infusion.

No difference between the dopamine and placebo groups

Use of dopamine in acute renal failure: A meta-analysis

John A. Kellum, MD; Janine M. Decker, RN



- **58 studies, n=2149.**
- **Dopamine did not prevent mortality, (relative risk, 0.90 [0.44 –1.83]; p=0.92), onset of acute renal failure (relative risk, 0.81 [0.55–1.19]; p=0.34), or need for dialysis, (relative risk, 0.83 [0.55–1.24]; p=0.42).**
- **Sufficient statistical power to exclude any large (>50%) effect of dopamine on the risk of acute renal failure or need for dialysis.**
- **No differences between dopamine and control with respect to any outcome for any of the subgroups analyzed.**

Crit Care Med 2001; 29:1526–1531

Use of dopamine in acute renal failure: A meta-analysis

John A. Kellum, MD; Janine M. Decker, RN

The use of low-dose dopamine for the treatment or prevention of acute renal failure cannot be justified on the basis of available evidence and should be eliminated from routine clinical use.

Crit Care Med 2001; 29:1526–1531

Emerging concerns with Dopamine ??

- May increase heart rate and can produce tachyarrhythmias.
- Dopamine decreases serum prolactin concentrations and, thereby, induces a transient decrease in T-cell function, which may impair resistance to infection.
- Dopamine also decreases growth-hormone secretion and thyrotropin release.
- Growth-hormone deficiency can contribute to a negative nitrogen balance in critical illness.
- Dopamine clearance and metabolism are altered in acutely ill patients, leading to extreme variability in plasma dopamine concentrations even at steady-state infusion rates.

Lancet 2000;356:2139-43

Does dopamine administration in shock influence outcome? Results of the Sepsis Occurrence in Acutely Ill Patients (SOAP) Study*

Yasser Sakr, MB, BCh, MSc; Konrad Reinhart, MD, PhD; Jean-Louis Vincent, MD, PhD, FCCP; Charles L. Sprung, MD; Rui Moreno, MD, PhD; V. Marco Ranieri, MD; Daniel De Backer, MD, PhD; Didier Payen, MD

- **Cohort, multiple-center, observational study. N= 3147**
- **35.4% received dopamine (dopamine group) and 64.6% never received dopamine. (Comparable Age, Gender, SAPS & SOFA scores).**

	All Patients (n = 1058)	No Dopamine (n = 683)	Dopamine (n = 375)	p Value
SOFA score, median (IQR)				
Maximum SOFA score	10 (8–13)	10 (8–13)	10 (8–14)	.579
Mean SOFA score	7 (5–9)	7 (5–9)	7 (5–10)	.408
ICU-acquired infection	158 (14.9)	93 (13.6)	65 (17.3)	.105
Hemofiltration (%)	182 (17.2)	121 (17.7)	61 (16.3)	.550
Hemodialysis (%)	78 (7.4)	48 (7.0)	30 (8.0)	.563
ICU stay, days, median (IQR)	6 (3–14)	6 (3–13)	7 (3–15)	.165
Hospital stay,[a] days, median (IQR)	20 (8–43)	20 (8–46)	20 (8–38)	.102
ICU mortality (%)	405 (38.3)	244 (35.7)	161 (42.9)	.021
Mortality at 30 days (%)	419 (39.6)	252 (36.9)	167 (44.5)	.013
Hospital mortality[b] (%)	468 (44.6)	283 (41.7)	185 (49.9)	.011

Crit Care Med 2006; 34:589–597

Tendency toward lower 30-day survival in patients with septic shock treated with dopamine than others (log rank = 2.8, *p* = *.09).*

- No high-quality primary evidence to recommend one catecholamine over another.

- No clinical evidence that epinephrine results in worse outcomes, and it should be the first chosen alternative to dopamine or norepinephrine.

- Norepinephrine is more potent than dopamine and may be more effective at reversing hypotension in patients with septic shock.

Norepinephrine or dopamine for the treatment of hyperdynamic septic shock?

C Martin, L Papazian, G Perrin, P Saux and F Gouin

Chest 1993;103;1826-1831
DOI 10.1378/chest.103.6.1826

Norepinephrine more effective and reliable than dopamine to reverse the abnormalities of hyperdynamic septic shock.

Able to increase mean perfusing prossure without apparent adverse effect on peripheral blood flow or on renal blood flow (since urine flow was re established).

Vasopressors in Sepsis

- What SSC says-
- Norepinephrine and dopamine centrally administered are the initial vasopressors of choice *(1C)*

- Epinephrine, phenylephrine, or vasopressin should not be administered as the initial vasopressor in septic shock (2C).

- Vasopressin 0.03 units/min may be subsequently added to norepinephrine with anticipation of an effect equivalent to norepinephrine alone.

- Use epinephrine as the first alternative agent in septic shock when blood pressure is poorly responsive to norepinephrine or dopamine (2B).

- Do not use low-dose dopamine for renal protection *(1A)*

- In patients requiring vasopressors, insert an arterial catheter as soon as practical *(1D)*

Vasopressors in Septic Shock – What's in the pipeline ????

- Terlipressin - Synthetic, long-acting vasopressin analogue.

- Commonly considered as last resort therapy in the late phase of septic shock, when high dosages of catecholamines fail to counteract sepsis-related arterial hypotension.

- Long effective half-life of 4-6 hrs – Commonly administered as high-dose bolus infusion (about 1 mg every four to six hours).

- Potential problem - May contribute to excessive vasoconstriction and a reflectory decrease in cardiac output with a proportional depression in oxygen delivery.

- Preliminary experimental and clinical reports have shown that TP may also be administered as low-dose continuous infusion, thereby mitigating, or even preventing such adverse events.

Research

Open Access

Continuous terlipressin versus vasopressin infusion in septic shock (TERLIVAP): a randomized, controlled pilot study

Andrea Morelli[1], Christian Ertmer[2], Sebastian Rehberg[2], Matthias Lange[2], Alessandra Orecchioni[1], Valeria Cecchini[1], Alessandra Bachetoni[3], Mariadomenica D'Alessandro[3], Hugo Van Aken[2], Paolo Pietropaoli[1] and Martin Westphal[2]

- Septic shock patients (n = 45) with a MAP <65 mmHg despite adequate volume resuscitation.
- Randomized to receive continuous infusions of either terlipressin (1.3 μg·kg-1·h-1), vasopressin (.03 U·min-1) or norepinephrine (15 μg·min-1; n = 15 per group).
- In all groups, open-label norepinephrine was added to achieve a mean arterial pressure between 65 and 75 mmHg, if necessary.
- No differences among groups in terms of systemic and regional hemodynamics.

Critical Care 2009

Compared with infusion of Vasopressin & NE, 1.3 μg·kg-1·h-1 of terlipressin allowed a marked reduction in catecholamine requirements ($P < 0.05$) and was associated with less rebound hypotension ($P < 0.05$).

At the end of the 48-hour intervention period, bilirubin concentrations were higher in the vasopressin and norepinephrine groups as compared with the terlipressin group. (each $P < 0.05$).

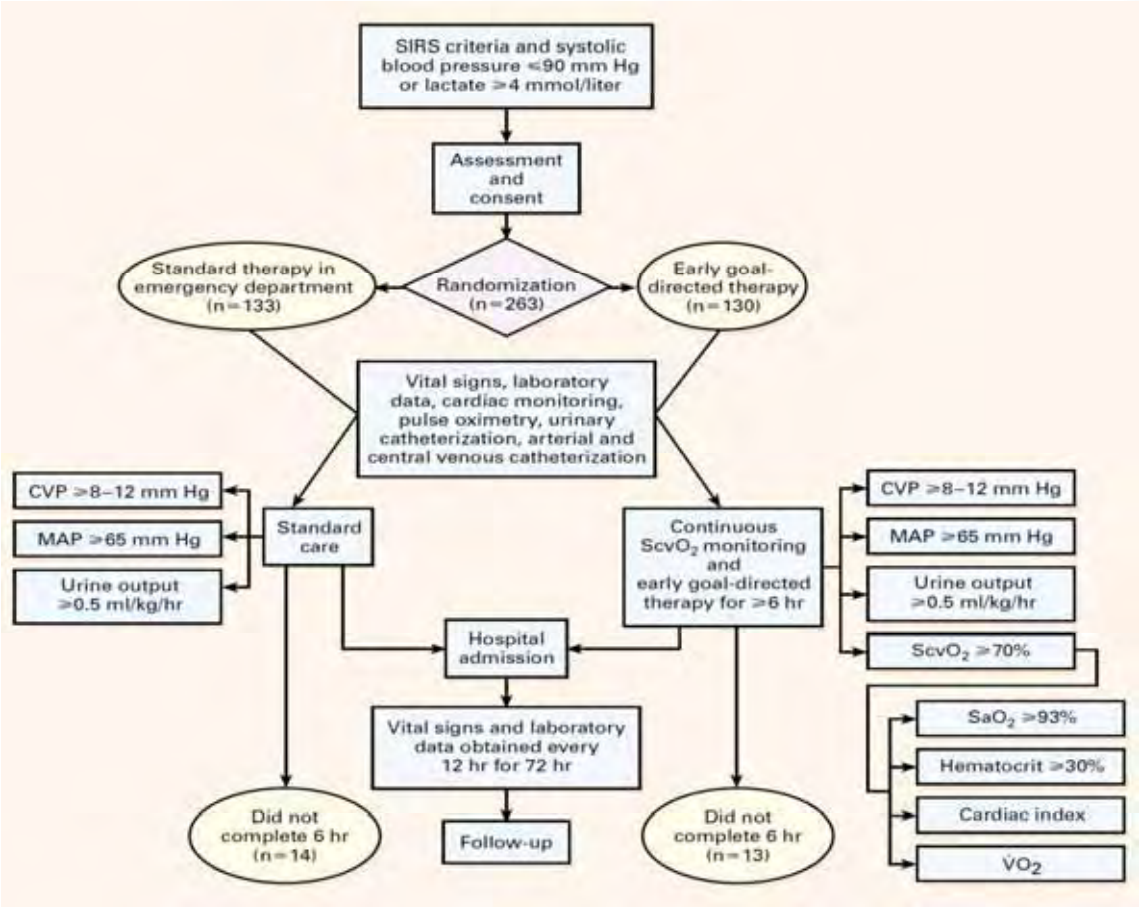
A time-dependent decrease in platelet count was only observed in the terlipressin group ($P < 0.001$ 48 hours vs. BL).

Initial resuscitation (EGDT)

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*

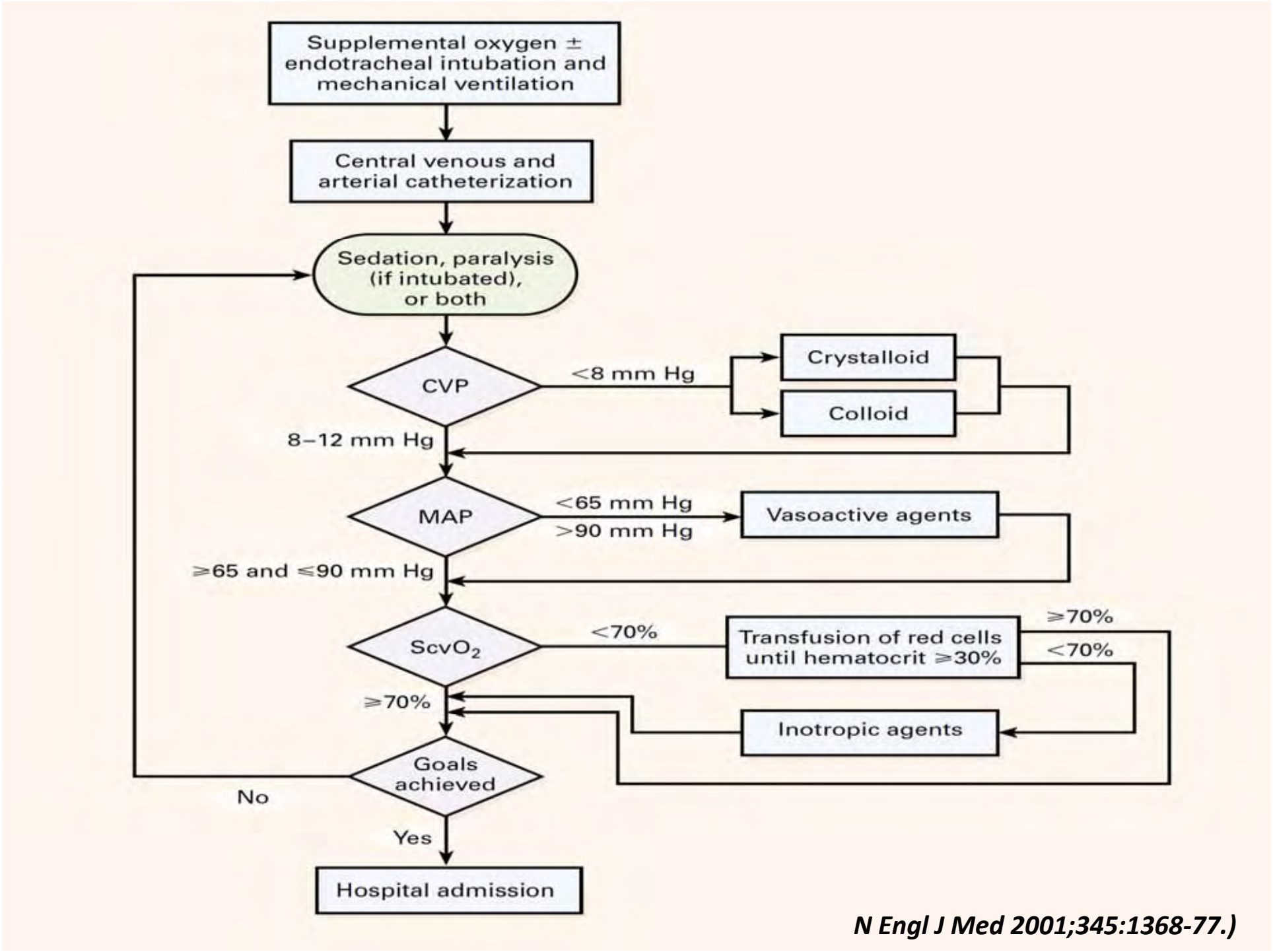


EGDT approach involves adjustments of cardiac preload, afterload, and contractility to balance oxygen delivery with oxygen demand.

To evaluate the efficacy of early goal-directed therapy before admission to the intensive care unit

Single centre trial

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



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

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

7 – 72 hrs – EGDT
Significantly higher mean central venous oxygen saturaion, lower lactate, lower base deficit, higher ph & lower APACHE II scores.

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

Recommendations from SSC

- Begin resuscitation immediately in patients with hypotension or elevated serum lactate 4 mmol/L; do not delay pending ICU admission *(1C)*

- Resuscitation goals *(1C)*

1. CVP 8–12 mm Hg
2. Mean arterial pressure > 65 mm Hg
3. Urine output 0.5 ml/kg/hr
4. Central venous (superior vena cava) oxygen saturation 70% or mixed venous 65%.

- If venous oxygen saturation target is not achieved (2C)

  Consider further fluid

  Transfuse packed red blood cells if required to hematocrit of 30% and/or

  Start dobutamine infusion, maximum 20 μg/kg/min.

Antibiotics in Sepsis

Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock*

Anand Kumar, MD; Daniel Roberts, MD; Kenneth E. Wood, DO; Bruce Light, MD; Joseph E. Parrillo, MD; Satendra Sharma, MD; Robert Suppes, BSc; Daniel Feinstein, MD; Sergio Zanotti, MD; Leo Taiberg, MD; David Gurka, MD; Aseem Kumar, PhD; Mary Cheang, MSc

Multicenter retrospective cohort study. N=2154

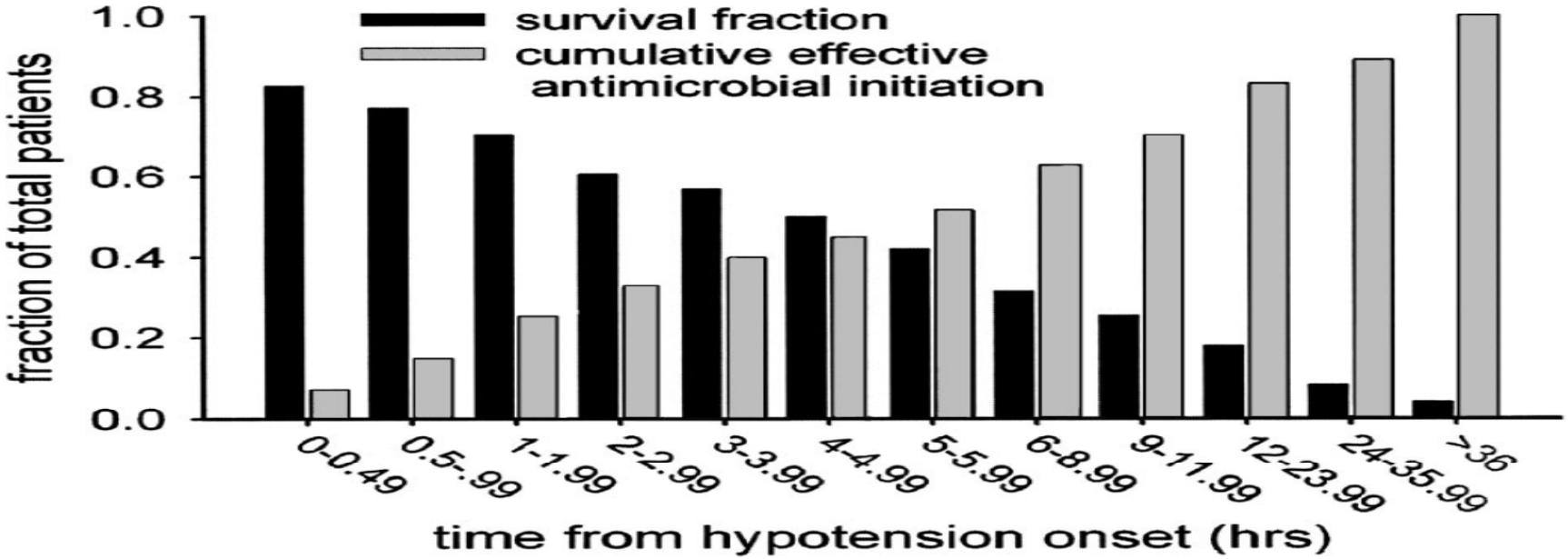
Each hour of delay in antimicrobial administration over the ensuing 6 hrs was associated with an average decrease in survival of 7.6%.

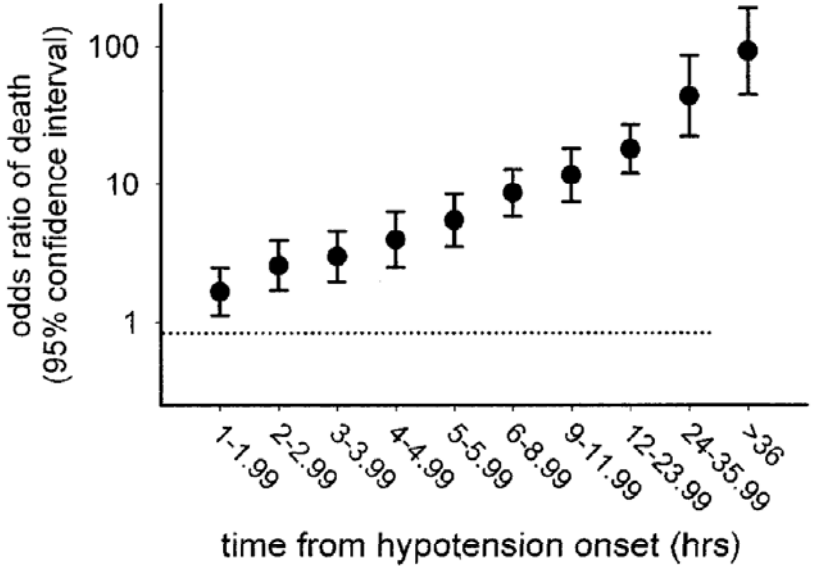
By the second hour after onset of persistent/recurrent hypotension, in-hospital mortality rate was significantly increased relative to receiving therapy within the first hour (odds ratio 1.67; 95% confidence interval, 1.12–2.48).

In multivariate analysis, time to initiation of effective antimicrobial therapy was the single strongest predictor of outcome.

Median time to effective antimicrobial therapy was 6 hrs (25–75th percentile, 2.0 –15.0 hrs).

Crit Care Med 2006; 34:1589–1596





SSC - Begin intravenous antibiotics as early as possible and always within the first hour of recognizing severe sepsis (1D) and septic shock (1B)

Crit Care Med 2006; 34:1589–1596

Supportive treatment

- DVT Prophylaxis & Stress ulcer prophylaxis.
- No trials specifically in sepsis but strong recommendations in favour of use.

- Selective digestive decontamination
- Controversial area.
- No trials specifically in patients with sepsis.

- Sedation – Sedation protocols with sedation goals.
- *Brook AD, Ahrens TS, Schaiff R, et al: Effect of a nursing-implemented sedation protocol on the duration of mechanical ventilation. Crit Care Med 1999; 27:2609–2615*

Outcome	Protocol-Directed Sedation (n = 162)	Non-Protocol-Directed Sedation (n = 159)	*p*
Duration of mechanical ventilation (hrs)	89.1 ± 133.6	124.0 ± 153.6	.003
Length of ICU stay (days)	5.7 ± 5.9	7.5 ± 6.5	.013
Length of hospital stay (days)	14.0 ± 17.3	19.9 ± 24.2	<.001
Mortality, No. (%)	49 (30.3)	57 (35.9)	.342
Acquired organ system derangements	2.8 ± 1.4	2.9 ± 1.5	.737
Reintubation, No. (%)	14 (8.6)	21 (13.2)	.213
Tracheostomy, No. (%)	10 (6.2)	21 (13.2)	.038

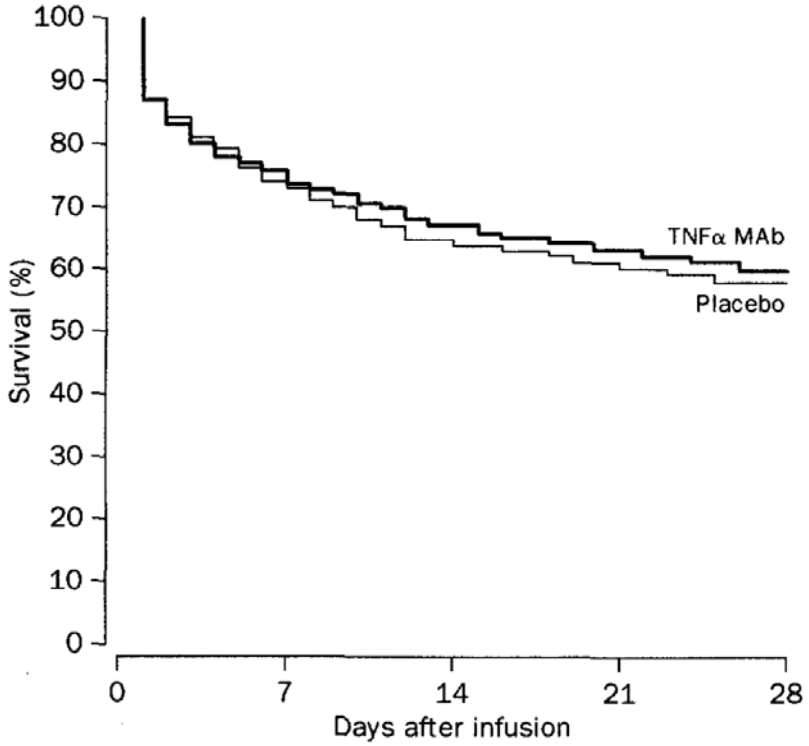
ICU, intensive care unit.

Other novel therapies

Anti TNF α therapy

Double-blind randomised controlled trial of monoclonal antibody to human tumour necrosis factor in treatment of septic shock

*Edward Abraham, Antonio Anzueto, Guillermo Gutierrez, Sidney Tessler, Gerry San Pedro, Richard Wunderink, Anthony Dal Nogare, Stanley Nasraway, Steve Berman, Robert Cooney, Howard Levy, Robert Baughman, Mark Rumbak, R Bruce Light, Lona Poole, Randy Allred, John Constant, James Pennington, Steven Porter, for the NORASEPT II Study Group**



NORASEPT 2 study

Prev. NORASEPT 1 & INTERCEPT (3 vs15)

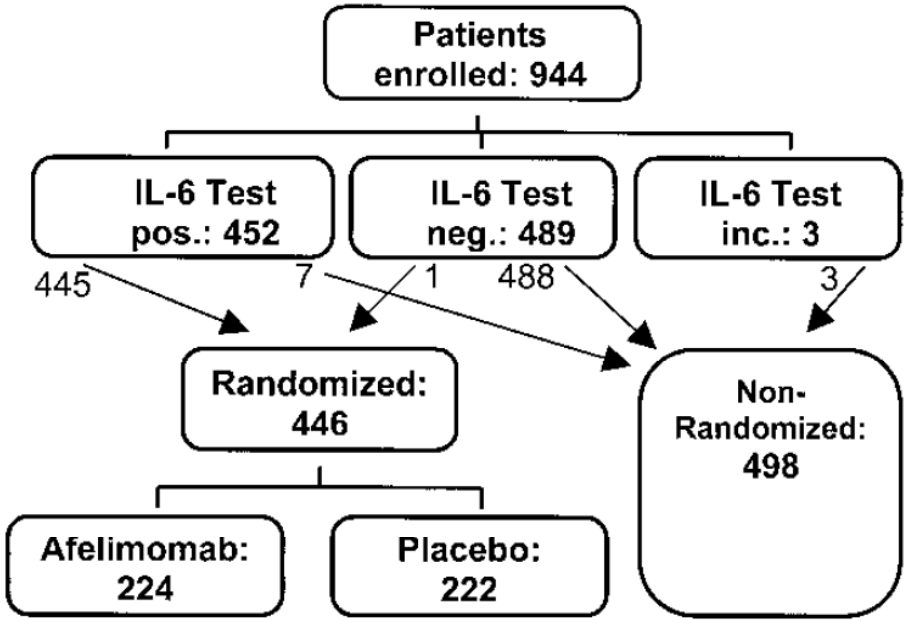
No improvement in survival after septic shock with TNF MAb.

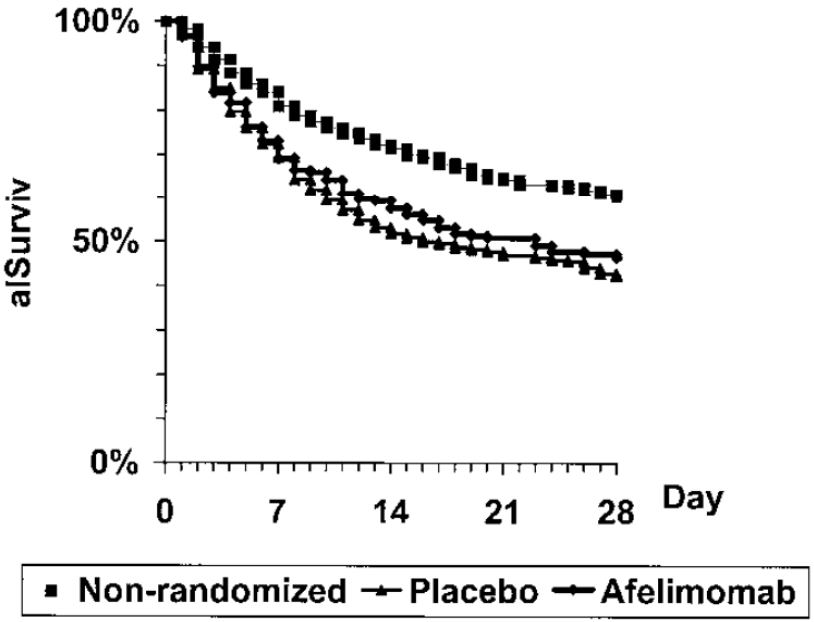
Baseline plasma IL- 6 concentrations or detectable circulating TNF concentrations were not associated with improvement in survival

Coagulopathy significantly decreased as compared to placebo

Lancet 1998; 351: 929-33

Randomized, placebo-controlled trial of the anti-tumor necrosis factor antibody fragment afelimomab in hyperinflammatory response during severe sepsis: The RAMSES Study

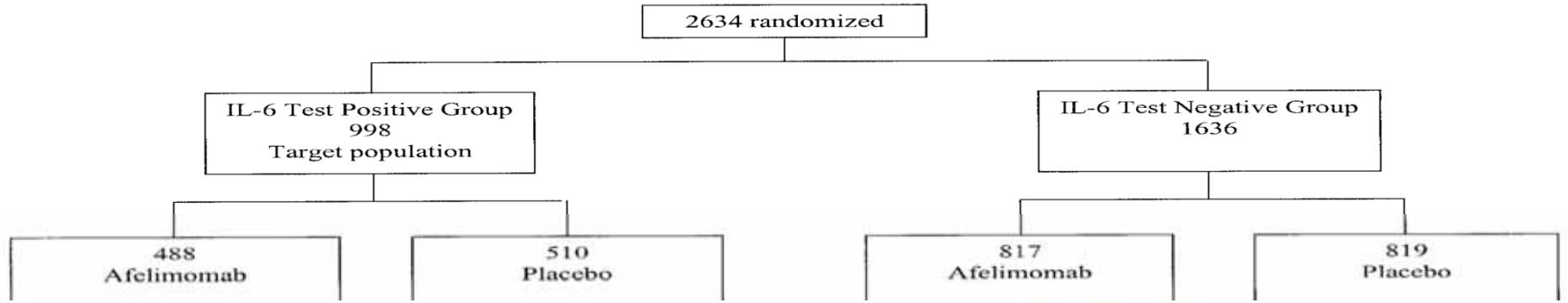




- Trail prematurely terminated.
- Mortality in non randomized significantly lower than randomized.
- Mortality in Afelimomab vs placebo similar.
- IL-6 strip test can identify patients at increased risk of death.

(Crit Care Med 2001; 29:765–769)

Efficacy and safety of the monoclonal anti-tumor necrosis factor antibody $F(ab')_2$ fragment afelimomab in patients with severe sepsis and elevated interleukin-6 levels*



Population	Crude Mortality, %		Chi-Square	Adjusted Mortality, %[a]		Absolute Risk Reduction,[a]	Odds Ratio[a]	Logistic Regression
	Afelimomab	Placebo	*p* Value	Afelimomab	Placebo	%	(95% CI)	*p* Value[a]
IL-6 test positive	213/488 (43.6)	243/510 (47.6)	.205	42.8	48.6	5.8	0.744 (0.559–0.988)	.041
IL-6 test negative	208/817 (25.5)	234/819 (28.6)	.157	26.4	27.7	1.3	0.921 (0.720–1.177)	.511
All patients	421/1305 (32.3)	477/1329 (35.9)	.049	32.7	35.4	2.7	0.856 (0.713–1.028)	.097

- **Associated with sig. dec. in TNF and IL-6 conc. And improvement in organ failure scores as comp. to placebo.**

MONARCS TRIAL (Crit Care Med 2004; 32:2173–2182)

Randomized, double-blind, placebo-controlled trial of granulocyte colony-stimulating factor in patients with septic shock

	G-CSF (n = 81)	Placebo (n = 83)	*p* Value
Hospital mortality, all, n (%)	22 (27%)	21 (25%)	.79
Hospital mortality, comorbidities associated with neutrophil dysfunction subgroup, n (%)	18 (33%)	15 (29%)	.62
Hospital mortality, pneumonia subgroup, n (%)	12 (26%)	11 (24%)	.86
Duration of ICU stay[a] in days, median (IQR)	8.0 (3–14)	7.5 (4–14)	.68
Duration of hospital admission in days, median (IQR)	17 (9.5–30.5)	20 (11–43)	.52
Highest white cell count, $\times 10^6$/L, mean (SD)	33.5 (1.72)	22.8 (1.17)	<.0001
Time to resolution of shock in days, mean (SD)	4.97 (0.37)	4.48 (0.32)	.33
Days on mechanical ventilation, mean (SD)	5.00 (0.43)	4.28 (0.39)	.23

- **Single centre trial, non neutropenic patients & excluding meliodosis.**
- **G-CSF/placebo iv daily for 10 days.**
- **No improvement in outcomes.**
- **Greater incidence of new organ dysfunction in treatment arm.**

(Crit Care Med 2008; 36:448–454)

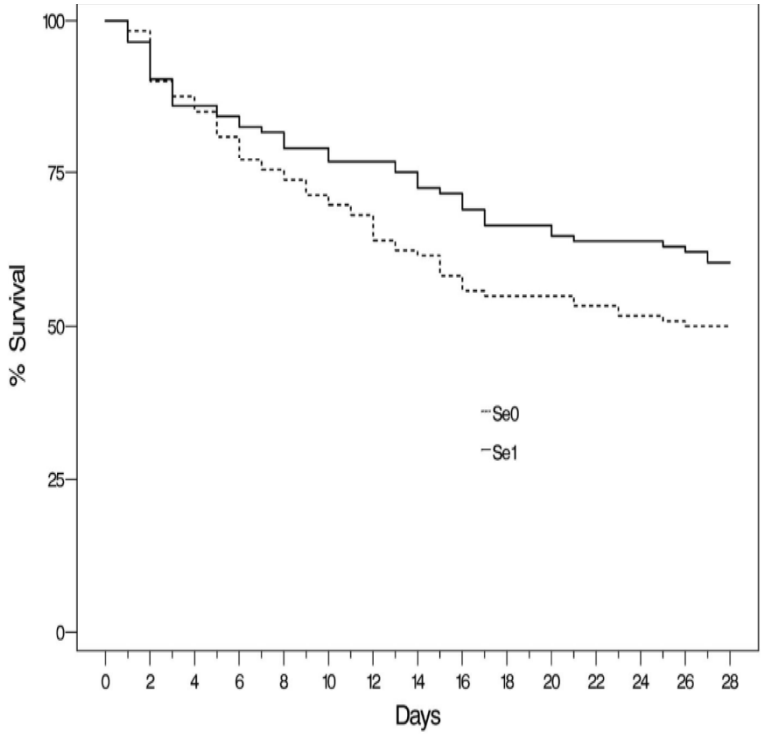
Table 4. Markers of organ dysfunction and adverse events in this study

	G-CSF	Placebo	*p* Value
New organ failure (SOFA 0–2 at baseline and 3–4 at any time during study)	41/81 (50%)	27/83 (33%)	.029
Cardiovascular: commenced noradrenaline or adrenaline	3/3 (100%)	4/4 (100%)	1.0
Coagulation: platelet count fell to $<51 \times 10^3/mm^3$	18/74 (24%)	9/78 (11%)	.039
Liver: bilirubin rose to >101 μmol/L	9/76 (11%)	1/81 (1%)	.007
Respiratory: Pao_2/Fio_2 fell to <201	19/43 (44%)	13/40 (32%)	.27
Renal: creatinine rose to >299 μmol/L or urine output fell to <500 mL/day	21/72 (29%)	12/68 (17%)	.11
Mechanical ventilation at any time during study	65 (80%)	67 (81%)	.78
CVVHF at any time during study	28 (35%)	35 (42%)	.40
Acute myocardial infarction	3 (4%)	5 (6%)	
Troponin >0.08, mg/dL	55/71 (78%)	49/74 (66%)	.09
CK-MB >2%	38/53 (71%)	26/45 (57%)	.15
Highest troponin I, mg/dL, median (IQR)	0.5 (0.11, 1.03)	0.14 (0.07, 0.74)	<.0001
Any ST segment and/or T wave changes on ECG[a]	37/60 (61%)	35/64 (54%)	.43
Any segmental wall abnormality on echocardiography[a]	8/48 (16%)	8/48 (16%)	1.0
Global systolic dysfunction on echocardiography[a]	9/48 (18%)	11/48 (22%)	.62

(Crit Care Med 2008; 36:448–454)

Selenium in Intensive Care (SIC): Results of a prospective randomized, placebo-controlled, multiple-center study in patients with severe systemic inflammatory response syndrome, sepsis, and septic shock*

- Selenium – Gpx and Thioredox. Reductases.
- 1000 g of sodium-selenite as a 30-min bolus injection, followed by 14 daily continuous infusions of 1000 g intravenously, or placebo.
- Whole blood selenium concentrations and glutathione peroxidase-3 activity were within the upper normal range during selenium treatment.
- No side effects



(Crit Care Med 2007; 35:118–126)

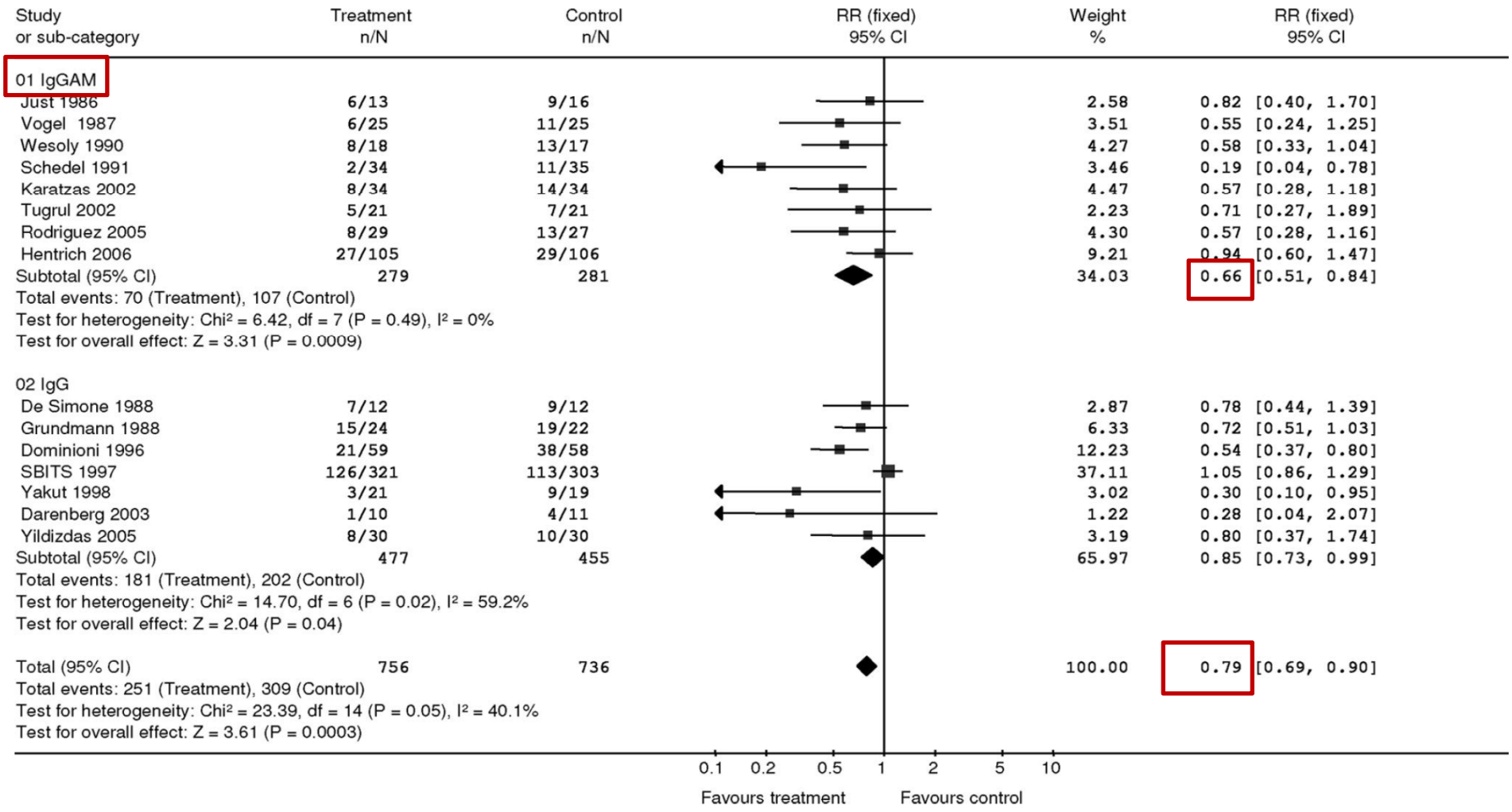
Recombinant human platelet-activating factor acetylhydrolase for treatment of severe sepsis: Results of a phase III, multicenter, randomized, double-blind, placebo-controlled, clinical trial*

- Role of PAF and related oxidised phospholipids.
- Randomized to receive either rPAF-AH 1.0 mg/kg or placebo administered iv once daily for five consecutive days.
- Terminated after the second of three planned interim analyses, and the enrollment of 1,425 patients.
- rPAF-AH did not decrease 28-day all-cause mortality compared with placebo (25% for rPAF-AH vs. 24% for placebo; relative risk, 1.03; 95% confidence interval, 0.85–1.25; *p .80).*

(COMPASS) Investigators *(Crit Care Med 2004; 32:332–341)*

Use of polyclonal immunoglobulins as adjunctive therapy for sepsis or septic shock*

K. Georg Kreymann, MD; Geraldine de Heer, MD; Axel Nierhaus, MD; Stefan Kluge, MD



Crit Care Med 2007; 35:2677–2685

Polyclonal intravenous immunoglobulin for the treatment of severe sepsis and septic shock in critically ill adults: A systematic review and meta-analysis*

Kevin B. Laupland, MD, MSc; Andrew W. Kirkpatrick, MD; Anthony Delaney, MBBS, MSc

- Significant reduction in mortality associated with use of iv Ig treatment with a pooled odds ratio of 0.66 (95% confidence interval 0.53– 0.83; *p* < *.0005).*

- When only high-quality studies were pooled, the odds ratio for mortality was 0.96 (95% confidence interval 0.71–1.3; *p .78).*

- *S*ignificant heterogeneity exists among the included trials and this result was not confirmed when only high-quality studies were analyzed.

- Results warrant a well-designed, adequately powered, and transparently reported clinical trial.

Crit Care Med 2007; 35:2686–2692

Score-based immunoglobulin G therapy of patients with sepsis: The SBITS study*

Karl Werdan, MD; Günter Pilz, MD; Oskar Bujdoso, MS; Peter Fraunberger, MD; Gertraud Neeser, MD; Roland Erich Schmieder, MD; Burkhard Viell, PhD; Walter Marget, MD; Margret Seewald, MD; Peter Walger, MD; Ralph Stuttmann, MD; Norbert Speichermann, MD; Claus Peckelsen, MD; Volkhard Kurowski, MD; Hans-Heinrich Osterhues, MD; Ljiljana Verner, MD; Roswita Neumann, PhD; Ursula Müller-Werdan, MD; for the Score-Based Immunoglobulin Therapy of Sepsis (SBITS) Study Group

- Randomized, double-blind, placebo-controlled, multicenter trial. N=653
- Score-defined sepsis (sepsis score 12–27) and score-defined sepsis-induced severity of disease (APACHE II score 20–35).
- The prospectively defined primary end point was death from any cause after 28 days
- Result – No significant difference in mortality in treatment group as compared to placebo.

Crit Care Med 2007; 35:2693–2701

Other RCT's on novel therapies

- **NOS inhibitor – Conflicting results**
- Administration of the nitric oxide synthase inhibitor NG-methyl-L-arginine hydrochloride (546C88) by intravenous infusion for up to 72 hours can promote the resolution of shock in patients with severe sepsis: Results of a randomized, double-blind, placebo-controlled multicenter study (study no. 144-002) Crit Care Med 2004; 32:1–12
- Multiple-center, randomized, placebo-controlled, double-blind study of the nitric oxide synthase inhibitor 546C88: Effect on survival in patients with septic shock Crit Care Med 2004; 32:21–30 – INC. MOR.

- **Fluconazole – possible other mechanisms in sepsis**
- Fluconazole improves survival in septic shock: A randomized double-blind prospective study. Crit Care Med 2003; 31:1938 –1946

- **E5 Murine Monoclonal Antiendotoxin Antibody**
- E5 Murine Monoclonal Antiendotoxin Antibody in Gram-Negative Sepsis A Randomized Controlled Trial JAMA. 2000;283:1723-1730

Conclusions

Role of APC needs to be defined as early as possible with well conducted and adequately powered studies in patients with varying severity of sepsis.

- Need for RCT's to further clarify the role of Heparin in sepsis.
- Low dose corticosteroids should be used in septic shock according to the available evidence but need for more studies.
- Target blood glucose to app. 150 – 180 mg/dl.
- A large number of modalities are being tried but use should only be considered after strong evidence emerges.
- Evidence based medicine coupled with good clinical judgement - Need of the hour.