MANAGEMENT OF SEPSIS

HAVE WE COME A FULL CIRCLE??

AIMS OF THIS SEMINAR

- Not to discuss in detail the management of Sepsis

- Only to discuss those issues/practices which have undergone a change over the last decade
  - Activated Protein C
  - Use of corticosteroids
  - Use of vasopressors
  - Early Goal Directed Therapy
  - Fluid management in sepsis
  - Glycemic control in the ICU

- Only discuss RCTs and metaanalysis published in core clinical journals

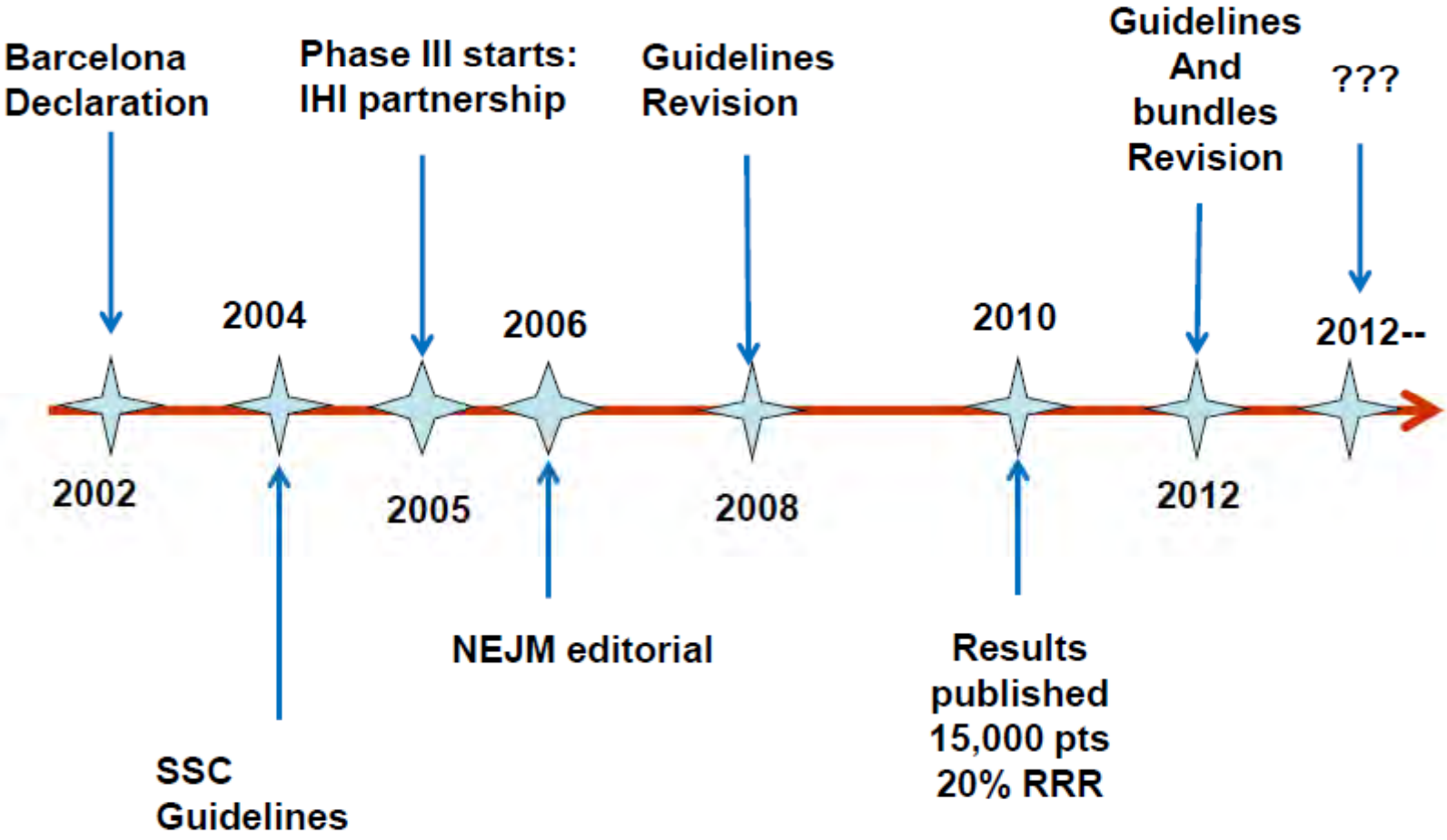
- SURVIVING SEPSIS CAMPAIG N

Launched in 2002.

Collaboration of
1. Society of Critical Care medicine
2. European Society of Intensive care medicine
3. International Sepsis Forum

Goal : Decrease in mortality due to sepsis by
25% in the next 5 years.

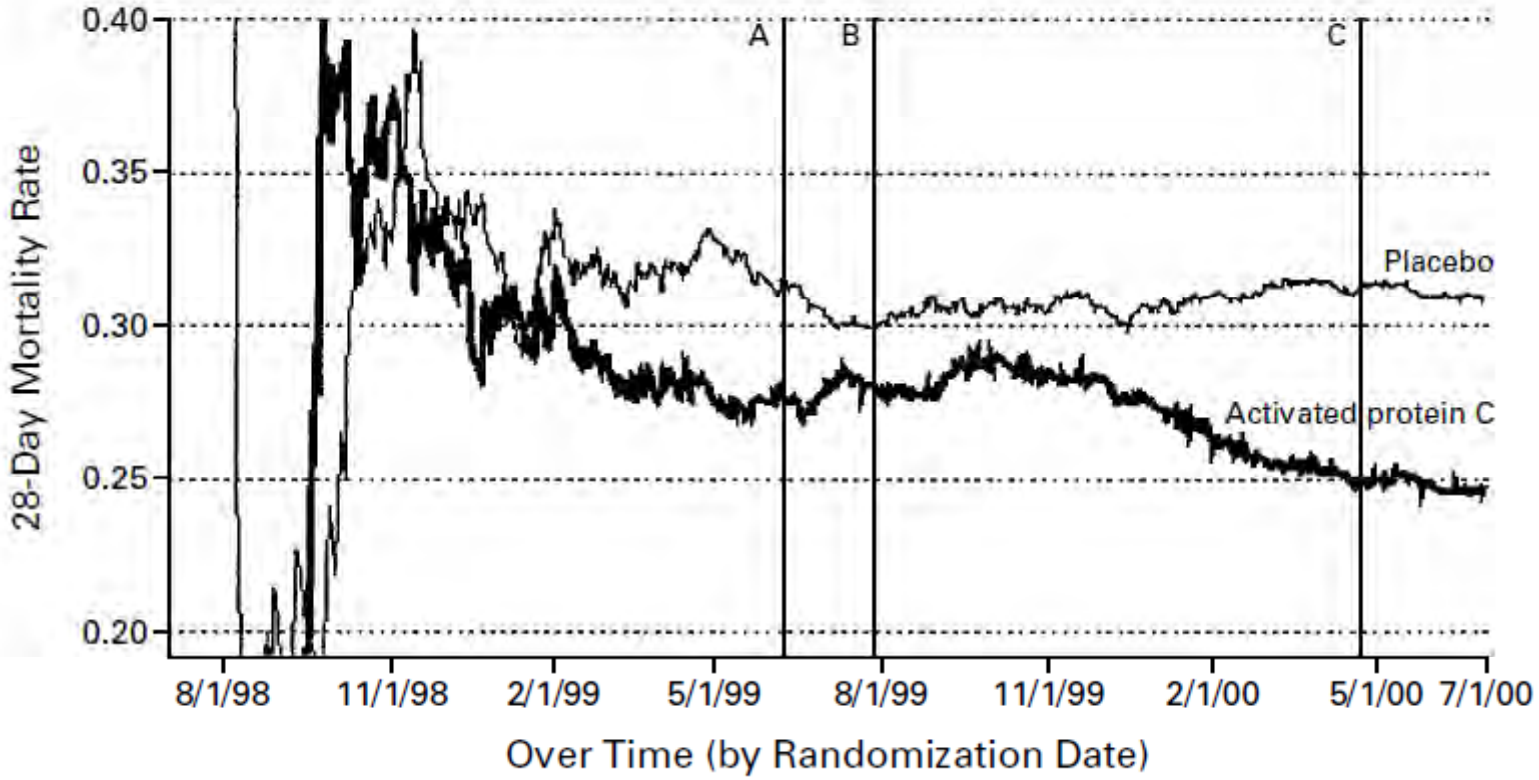
Surviving Sepsis Campaign: Timeline



PROWESS Trial – Protein C Worldwide Evaluation in Severe Sepsis

- RCT of 1690 patients (NEJM 2001)
- First trial ever to show mortality benefit in sepsis (Relative risk reduction of 19.4%, Absolute risk reduction of 6.1%)

- Approved for use by FDA
- Recommended by SSC 2004 for use in severe sepsis (APACHE $\geq$ 25) when no contraindications exist.(Grade B)

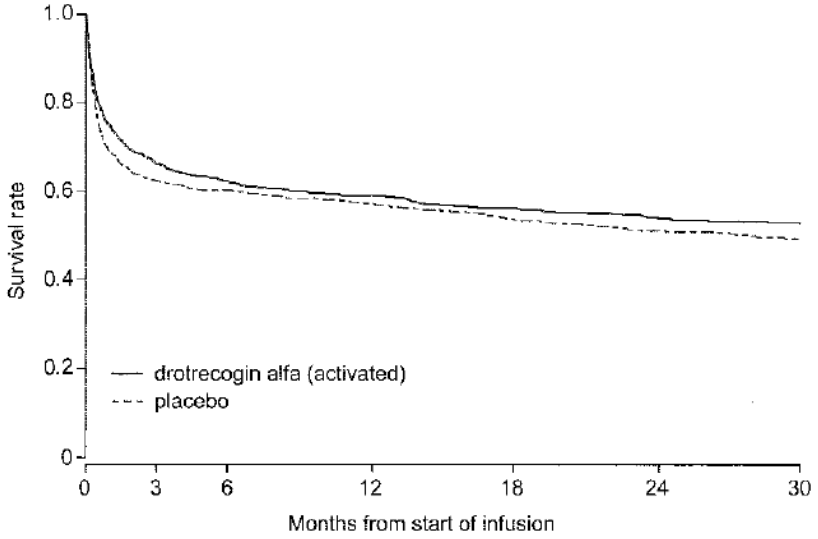


- The trial was conducted in two phases (Phase 1 – 720 pts).
- Changes before the second phase
  - Change in inclusion criteria (exclusion of patients post transplant, metastatic cancer and pancreatitis, exclusion of patients with illness > 24 hrs)
  - Change in the placebo used
  - Change in the technique of drug manufacturing

N Engl J Med, Vol. 347, No. 13 September 26, 2002

The effect of drotrecogin alfa (activated) on long-term survival after severe sepsis*

Crit Care Med 2004 Vol. 32, No. 11



Number at Risk							
Placebo	840	487	467	441	391	260	147
Treatment	850	509	475	447	401	256	154

Conclusions: **The acute survival benefit observed in subjects with severe sepsis who received DrotAA persists to hospital discharge. The survival benefit loses statistical significance thereafter. *Post hoc* analysis suggests the effect of DrotAA varies by APACHE II score with improved long-term survival in subjects with APACHE II scores ≥25 but no benefit in those with lower scores. (Crit Care Med 2004; 32:2199–2206)**

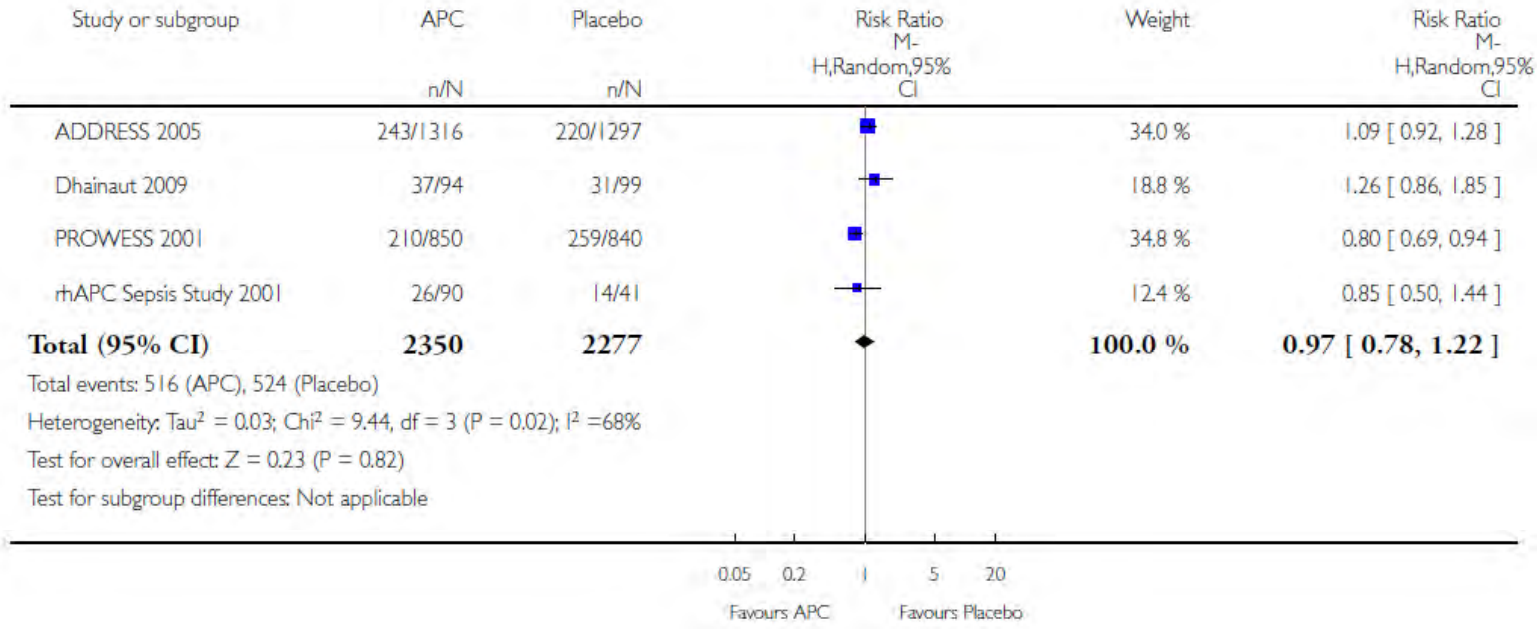
Trial	Journal/ Year	Type of study	Results
ADDRESS	NEJM 2005	RCT of 2640 patients with low risk of death	No mortality benefit and Increased serious bleeding
ENHANCE	Crit Care Med 2005	RCT of 2378 patients	Mortality benefit better when used < 24 hrs of sepsis
RESOLVE	Lancet 2007	RCT of 477 children	No Mortality benefit and Increased CNS bleed

Surviving Sepsis Guidelines 2008

- Changed from ‘We recommend’ to ‘We Suggest’
- Strength of recommendation decreased to Grade 2B (Inconsistency of results, Downgraded RCTs or Upgraded Observational studies)

Human recombinant activated protein C for severe sepsis (Review)

- Included 5 RCT (5000 patients)
- Conclusions :
  - No mortality benefit in adults/ Children
  - Increased risk of bleeding



Drotrecogin Alfa (Activated) in Adults with Septic Shock

V. Marco Ranieri, M.D., B. Taylor Thompson, M.D., Philip S. Barie, M.D., M.B.A., Jean-François Dhainaut, M.D., Ivor S. Douglas, M.D., Simon Finfer, F.R.C.P., Bengt Gårdlund, M.D., John C. Marshall, M.D., Andrew Rhodes, M.D., Antonio Artigas, M.D., Ph.D., Didier Payen, M.D., Ph.D., Jyrki Tenhunen, M.D., Ph.D., Hussein R. Al-Khalidi, Ph.D., Vivian Thompson, M.P.H., Jonathan Janes, M.B., B.Ch., William L. Macias, M.D., Ph.D., Burkhard Vangerow, M.D., and Mark D. Williams, M.D., for the PROWESS-SHOCK Study Group*

N Engl J Med 2012;366:2055-64.

RCT of 1697 patients of septic shock

CONCLUSIONS

DrotAA did not significantly reduce mortality at 28 or 90 days, as compared with placebo, in patients with septic shock. (Funded by Eli Lilly; PROWESS-SHOCK ClinicalTrials.gov number, NCT00604214.)

On October 25 2011, Eli Lilly withdrew the drug from the market and also announced discontinuation of all ongoing clinical trials

IS THE STORY OVER??

Evaluating the use of recombinant human activated protein C in adult severe sepsis: Results of the Surviving Sepsis Campaign*

Brian Casserly, MD; Herwig Gerlach, MD, PhD; Gary S. Phillips, MAS; John C. Marshall, MD; Stanley Lemeshow, PhD; Mitchell M. Levy, MD

Crit Care Med 2012 Vol. 40, No. 5

- Of the database of 15022 patients, 1009 patients received APC. (Jan 2005 – Mar 2008)
- Survival benefit seen (OR= 0.76)
- Better when used < 24 hrs and when MODS present.

Two other observational studies also shown mortality benefit

AJRCCM 2009;180:861-866

Crit Care Med 2010;38:1101-1107

RATIONALE FOR USE OF STEROIDS

A. Anti inflammatory property :

Sepsis is a pro inflammatory state.

Steroids by their anti inflammatory action can reduce this inflammatory storm in severe sepsis.

B. Critical illness Related Corticosteroid Insufficiency (CIRCI) :

   A. Decrease in adrenal steroid production
   B. Tissue resistance to glucocorticoids

Causes inadequate suppression of proinflammatory cytokines and perpetuation of the inflammatory cascade

C. Directly affect the Vasomotor tone. Reverse the depressed vasomotor sensitivity to catecholomines.

Potential Risks

Crit Care Clin 25 (2009) 825–834

- Increased risk of secondary infections
- Neuro muscular weakness
- Hyperglycemia
- Hypernatremia
- Gastro intestinal bleed
- Arrhythmias
- Psychosis
- Poor Wound healing

ACTH Stimulation test

- 250 ug ACTH given i.v. Rise in total serum cortisol by <9 ug/dl or a serum cortisol of < 10 ug/dl identifies CIRCI.

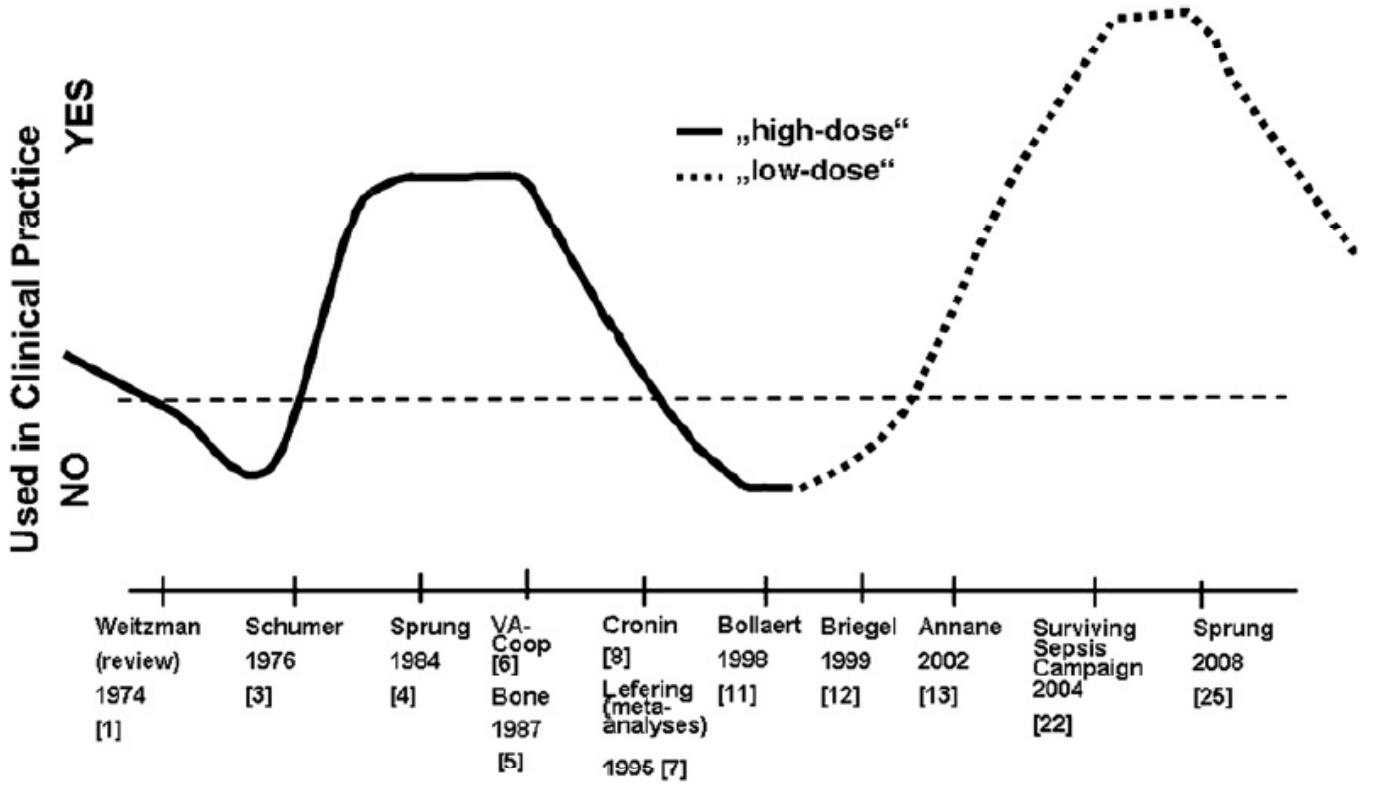
- Drawbacks :
  - Does not identify tissue resistance
  - Does not test the adrenal gland responsiveness to physiologic stressors like hypotension, hypoglycemia
  - Poorly reproducible
  - Exact cutoffs in critically ill patients is a subject of debate.

- Free cortisol a better predictor of CIRCI as compared to total cortisol (but not widely available)

Living With Uncertainty in the Intensive Care Unit

Should Patients With Sepsis Be Treated With Steroids?

Crit Care Clin 25 (2009) 825–834



IN THE 70S, WE LIKED THE STEROIDS

Schumer, 1976:

- Double blind randomized trial. 328 patients, 172 prospective
- 1/3rd got dex, 1/3rd got methylprednisone, 1/3rd got saline
  - Dex group: 9.3% mortality (3-4 mg/kg)
  - Methylprednisone group: 11.5\6% mortality (30mg/kg)
  - Saline group: 38.4% mortality

Schumer W: **Steroids in the treatment of clinical septic shock.** *Ann Surg* 1976

In the early 80s, we loved the steroids

High dose steroids came into popularity

Beller et al, Brigham et al,

- Massive doses or constant infusions of steroids
- Interest arising from animal studies

Doses as large as 30mg/kg of methylprednisone were used

Beller BT, et al **Effectiveness of Modified Steroid-Antibiotic Therapies for Lethal Sepsis in the Dog** *Arch Surg.* 1983;118(11):1293-1299.

Brigham et al. **Methylprednisolone Prevention of Increased Lung Vascular Permeability following Endotoxemia in Sheep** J Clin Invest. 1981 April; 67(4): 1103–1110.

In the late 80s, we abandoned the use of steroids

1987: Multicenter randomized, double-blind, placebo-controlled trial

- Testing high dose methylprednisone on conscious septic patients
- 223 patients
- No reduction in mortality

1987: prospective, randomized, double-blind, placebo-controlled trial

- Strict entry criteria; high dose 30mg/kg methylprednisone
- 136 patients
- INCREASE in 14-day mortality (secondary infection)

Veterans Administration Systemic Sepsis Cooperative Study Group: **Effect of high-dose glucocorticoid therapy on mortality in patients with clinical signs of systemic sepsis.** *N Engl J Med* 1987 , **317:**659-665

Bone RC, et al **A controlled clinical trial of high-dose methylprednisolone in the treatment of severe sepsis and septic shock.** N Engl J Med. 1987;317:653–658.

RESURGENT INTEREST: LATE 1990S

Small, "stress" doses of steroids

- aim is to reduce vasopressor requirements
- Theory is that the stress doses of steroids supplement endogenous steroid release in "relative adrenal insufficiency"

9 patients had their cortisol levels cortisol response and norad dose-response curves measured by Annane et.al; patients with sepsis had impaired response to cortisol and to noradrenaline

Annane et al. **Impaired pressor sensitivity to noradrenaline in septic shock patients with and without impaired adrenal function reserve**. Br J Clin Pharmacol. 1998;46:589–597.

EFFECT OF TREATMENT WITH LOW DOSES OF HYDROCORTISONE AND FLUDROCORTISONE ON MORTALITY IN PATIENTS WITH SEPTIC SHOCK

- An RCT of 300 patients by Annane et al published in JAMA 2002.
- All patients underwent ACTH stimulation test using 250 ug ACTH. Response defined as increase in cortisol by >9 ug/dl.
- Patients received (a) Inj. Hydrocortisone 50 mg Q6H and (b) Tab. Fludrocortisone 50 ug OD for 7 days followed by abrupt stopping of steroids.
- Significant decrease in ICU and In hospital mortality in non responders an faster time to resolution of shock. No increase in ADR.

JAMA 2002 ;288:862-871

COCHRANE REVIEW: 2004

ANNANE, BELLISANT, BOLLAERT, BRIEGEL, KEH AND KUPFER

Corticosteroids for treating severe sepsis and septic shock

15 trials identified (N = 2023)

- **Corticosteroids did not improve 28 day mortality from all causes**
- **Corticosteroids DID improve ICU mortality**
- **Corticosteroids DID increase the proportion of shock reversal by day 7**
- **Low dose steroids over > 5 days DID reduce 28 day mortality**

Surviving Sepsis Guidelines 2004

- Use Inj.hydrocortisone (200-300 mg/day in divided doses or continuous infusion) for 7 days in all patients with septic shock requiring vasopressors. (Grade C)
- Use of ACTH stimulation test to identify nonresponders (Grade E)
- Use of fludrocortisone (Grade E)
- Tapering steroids instead of abrupt stop (Grade E)
- Do not use steroid in patients without shock (Grade A)
- Do not use high dose steroids (Grade A)

N Engl J Med 2008;358:111-24.

Hydrocortisone Therapy for Patients with Septic Shock

Charles L. Sprung, M.D., Djillali Annane, M.D., Ph.D., Didier Keh, M.D., Rui Moreno, M.D., Ph.D., Mervyn Singer, M.D., F.R.C.P., Klaus Freivogel, Ph.D., Yoram G. Weiss, M.D., Julie Benbenishty, R.N., Armin Kalenka, M.D., Helmuth Forst, M.D., Ph.D., Pierre-Francois Laterre, M.D., Konrad Reinhart, M.D., Brian H. Cuthbertson, M.D., Didier Payen, M.D., Ph.D., and Josef Briegel, M.D., Ph.D., for the CORTICUS Study Group*

- RCT of 499 patients of fluid refractory septic shock.
- Received Inj Hydrocortisone 50 mg Q6h for 5 days and tapered over the next 6 days.

- No mortality benefit shown (including ACTH non responders).
- Increased risk of superinfection (sepsis and septic shock)
- However, in the subgroup of patients with Refractory septic shock (despite inotropes) , there was absolute mortality reduction of 11.2 %

Table 1
Differences in Annane[12] and Corticus[24] studies

	Annane	Corticus
Entry window	8 hours	72 hours
SBP < 90 mmHg	>1 hour	<1 hour
Treatment	Fludrocortisone	None
Treatment duration	7 days	11 days
Weaning	No	Yes
SAPS II score	59 ± 21	49 ± 17
Nonresponders	229 (77%)	233 (47%)
Steroid effect by		
Corticotropin response	Yes	No
Superinfection	No	Yes
Practice or guidelines	None	Steroids used

Surviving Sepsis Guidelines 2008

- IV Hydrocortisone to be only given to those patients who are vasopressor refractory.
- ACTH test should not be used.
- No role of dexamethasone in septic shock.

Unanswered questions:

- Should we use a fixed duration of steroids or till the cessation of shock?
- Should we abruptly withdraw steroids or should we taper them?

Recommendations for the diagnosis and management of corticosteroid insufficiency in critically ill adult patients: Consensus statements from an international task force by the American College of Critical Care Medicine

Crit Care Med 2008 Vol. 36, No. 6

1. Should be considered in those patients of septic shock who are poorly responsive to fluids and vasopressors.

2. Dose should be 200 mg/ day in 4 divided doses or as a 100 mg bolus followed by an infusion of 10 mg/hr.

3. Should be treated for at least 7 days before tapering.

4. Should be tapered slowly and not stopped abruptly.

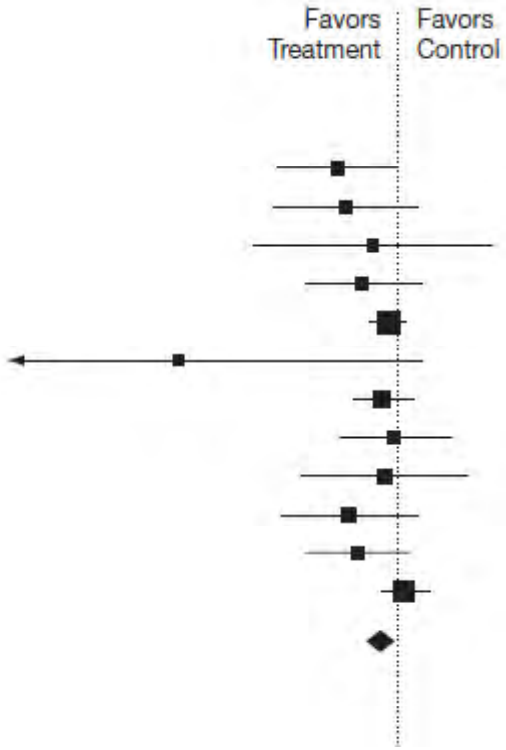
Corticosteroids in the Treatment of Severe Sepsis and Septic Shock in Adults

A Systematic Review

JAMA. 2009;301(22):2362-2375

Source	Treatment, No. Events	Treatment, No. Total Patients	Control, No. Events	Control, No. Total Patients	Risk Ratio (95% CI)
Long course of low-dose corticosteroids					
Bollaert et al,[15] 1998	7	22	12	19	0.50 (0.25-1.02)
Chawla et al,[17] 1999	6	23	10	21	0.55 (0.24-1.25)
Briegel et al,[16] 1999	3	20	4	20	0.75 (0.19-2.93)
Yildiz et al,[19] 2002	8	20	12	20	0.67 (0.35-1.27)
Annane et al,[18] 2002	82	151	91	149	0.89 (0.73-1.08)
Confalonieri et al,[50] 2005	0	23	6	23	0.08 (0.00-1.29)
Tandan et al,[52] 2005	11	14	13	14	0.85 (0.62-1.15)
Oppert et al,[51] 2005	10	23	11	25	0.99 (0.52-1.88)
Rinaldi et al,[53] 2006	6	26	7	26	0.86 (0.33-2.21)
Meduri et al,[56] 2007	10	42	8	19	0.57 (0.27-1.20)
Cicarelli et al,[55] 2007	7	14	12	15	0.63 (0.35-1.12)
Sprung et al,[22] 2008	86	251	78	248	1.09 (0.85-1.40)
Subtotal	236	629	264	599	0.84 (0.72-0.97)

Test for heterogeneity: $\tau = 0.01$; $\chi^2 = 12.89$, df = 11 ($P = .30$); $I^2 = 15\%$
Test for overall effect: $z = 2.31$ ($P = .02$)



Low dose corticosteroids :

Mortality reduction, Shorter ICU stay, Faster shock reversal

DO LOW-DOSE CORTICOSTEROIDS IMPROVE MORTALITY OR SHOCK REVERSAL IN PATIENTS WITH SEPTIC SHOCK? A SYSTEMATIC REVIEW AND POSITION STATEMENT PREPARED FOR THE AMERICAN ACADEMY OF EMERGENCY MEDICINE

Table 3. Summary of Included Studies

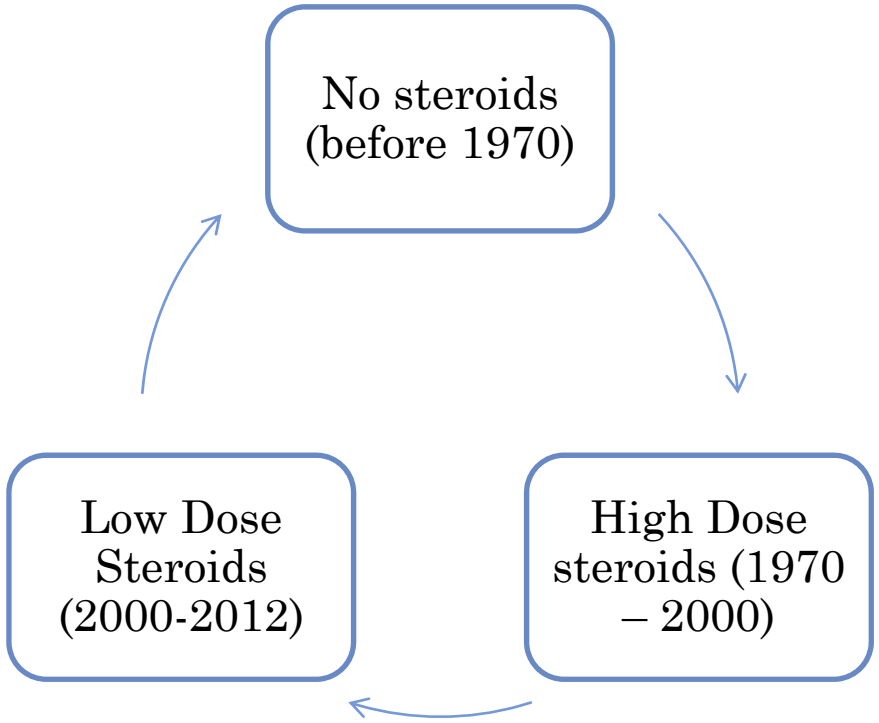
Author, Year	n	28-day Mortality Relative Risk (95% CI)	Shock Reversal Relative Benefit (95% CI)
Annane et al., 2002 (10)	300	0.89 (0.73–1.08)	1.28 (1.01–1.62)
Sprung et al., 2008 (29)	499	1.09 (0.85–1.40)	1.07 (0.98–1.18)
Bollaert et al., 1998 (12)	41	0.50 (0.25–1.02)	3.24 (1.30–8.10)
Keh et al., 2003 (19)	40	Not reported	2.33 (1.12–4.83)
Briegel et al., 1999 (13)	40	0.75 (0.19–2.93)	1.13 (0.87–1.46)
Chawla et al., 1999 (14)	44	0.55 (0.24–1.25)	2.09 (1.08–4.05)
Oppert et al., 2005 (25)	41	0.81 (0.40–1.67)	0.61 (0.37–0.99)
Overall	1005	0.92 (0.79–1.07)	1.17 (1.07–1.28)

The Journal of Emergency Medicine, Vol. 43, No. 1, pp. 7–12, 2012

Low dose corticosteroids :
No mortality reduction, Faster shock reversal

Living With Uncertainty in the Intensive Care Unit

Should Patients With Sepsis Be Treated With Steroids?



WHAT IS THE FINAL TAKE?

- Answered Questions :
  - ACTH test : No role
  - Fludrocortisone : Not to be used (COIITSS trial)
  - High dose Steroids : No role

- Unanswered Questions :
  - Low dose corticosteroids role : May be used in refractory septic shock (vasopressor resistant)
  - Duration of steroids ?
  - How to end the therapy ?

The New England Journal of Medicine

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

N Engl J Med, Vol. 345, No. 19

November 8, 2001

- RCT of 263 patients
- Management during the initial 6 hours

  EGDT vs Standard therapy
- EGDT group had higher Scv02, lower base deficit, higher pH ,lower lactate values and lower mean APACHE scores at the end of 6 hours (7 -72 hrs).
- In hospital mortality was significantly reduced by EGDT (30.5% vs 46.5%)

SURVIVING SEPSIS GUIDELINES (2004 & 2008)

We recommend the protocolized resuscitation of a patient with sepsis-induced shock, defined as tissue hypoperfusion (hypotension persisting after initial fluid challenge or blood lactate concentration ≥4 mmol/L).

- During the first 6 hours , all the goals should be achieved.
  - CVP : 8-12 mm Hg
  - MAP > 65 mm Hg
  - Urine output >0.5 ml/kg/hr
  - ScvO2 > 70% or SvO2 >65%

Initial resuscitation Bundle in Sepsis – First six hours

SEPSIS SIX – FIRST HOUR

Role of Lactate - Sepsis

- A marker of tissue perfusion.
- Highly sensitive but low specificity
- Venous lactate can be used as a surrogate to arterial lactate if long tourniquet times are avoided.

A) <u>Prognostic marker:</u>

- Raised lactate levels predict mortality. (mortality 40% if lactate > 4 mmol/L vs 15% if lactate <2 mmol/L).
- CRYPTIC SHOCK: Patients with normal BP but raised lactate levels.
- Outcomes similar to those with overt shock.
- Early institution of aggressive measures.

ROLE OF LACTATE - SEPSIS

- Serial monitoring : Early clearance of the lactate improves mortality.

Crit Care Med 2004; 32:1637–1642

- No added advantage of monitoring lactate if goals of MAP, CVP and Scv02 are met.(RCT)

JAMA. 2010 Feb 24;303(8):739-46.

Ongoing RCTs of EGDT

- ProCESS
- ProMISe
- ARISE

Fluid Management in Sepsis – Unanswered Questions?

Questions to be Answered..

1. How much fluid to be given and when ?

2. Which fluid to be given?

3. How do we monitor the need for fluid infusion.
   How do we assess fluid responsiveness?

FLUID STRATEGY- CURRENT CONCEPTS

Adequate Initial fluid Resuscitation:

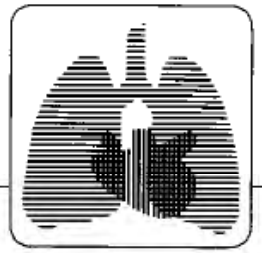
- In the initial phase of sepsis, there is hypovolemia due to
  - Venodilation
  - Increased Capillary Permeability
  - Decreased Oral intake
  - Increased insensible losses.

- Hence the need of liberal fluids during the initial resuscitation.
- Survival benefit shown in the EGDT trial.

- Give ≥ 20 ml/kg of crystalloids to and maintain CVP >8 mm Hg in the first 6 hours.

FLUID STRATEGY- CURRENT CONCEPTS

- **Conservative late fluid management:**
  - Achieving net negative fluid balance in the first week of sepsis.
  - Several studies in septic shock support this.
- Rationale:
  - Unnecessary fluid (ie, fluid that does not enhance perfusion) will cause or exacerbate edema in lungs, heart, gut, skin, brain, and other tissues.
  - This creates clinically obvious organ failure, such as respiratory failure, abdominal compartment syndrome, cerebral edema and herniation



critical care review

Negative Fluid Balance Predicts Survival in Patients With Septic Shock*

A Retrospective Pilot Study

(CHEST 2000; 117:1749–1754)

300 patients of septic shock

Conclusion: These results suggest that at least 1 day of negative fluid balance (≤ −500 mL) achieved by the third day of treatment may be a good independent predictor of survival in patients with septic shock. These findings suggest the hypothesis "that negative fluid balance achieved in any of the first 3 days of septic shock portends a good prognosis," for a larger prospective cohort study.

Sepsis in European intensive care units: Results of the SOAP study*

Crit Care Med 2006 Vol. 34, No. 2

- Observational study of 1177 patients of sepsis
- SOAP – Sepsis Occurrence in Acutely ill Patients

Table 7. Multivariate, forward stepwise logistic regression analysis in sepsis patients (n = 1177), with intensive care unit mortality as the dependent factor

	OR (95% CI)	*p* Value
SAPS II score[a] (per point increase)	1.0 (1.0–1.1)	<.001
Cumulative fluid balance[b] (per liter increase)	1.1 (1.0–1.1)	.001
Age (per year increase)	1.0 (1.0–1.0)	.001
Initial SOFA score (per point increase)	1.1 (1.0–1.1)	.002
Blood stream infection	1.7 (1.2–2.4)	.004
Cirrhosis	2.4 (1.3–4.5)	.008
Pseudomonas infection	1.6 (1.1–2.4)	.017
Medical admission	1.4 (1.0–1.8)	.049
Female gender	1.4 (1.0–1.8)	.044

The Importance of Fluid Management in Acute Lung Injury Secondary to Septic Shock

(CHEST 2009; 136:102–109)

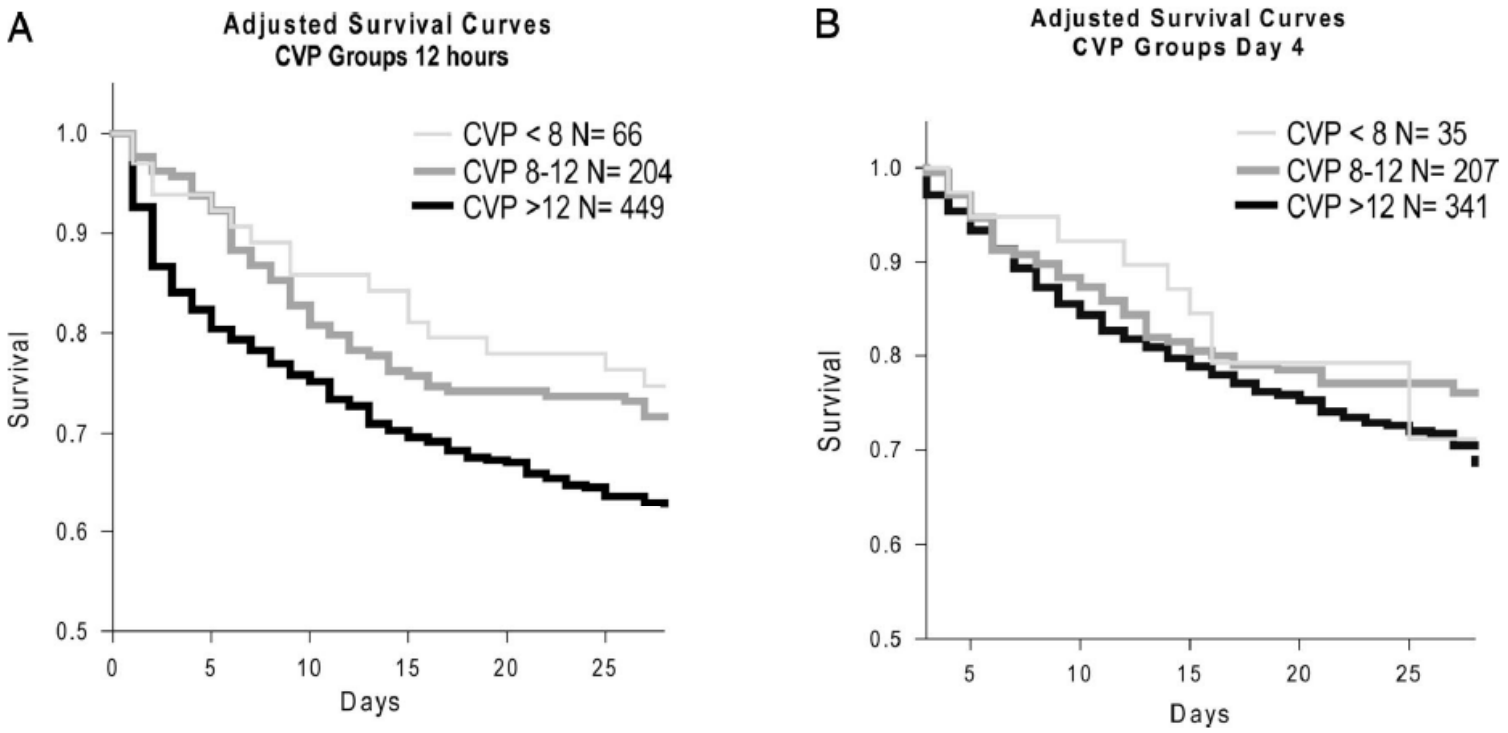
- 212 patients assessed for achievement of Adequate initial fluid resuscitation (AIFR) and conservative late fluid management (CLFM)

- Mortality rate :
  - AIFR and CLFM : 18.3%
  - AIFR alone : 56.6%
  - CLFM alone : 41.9%
  - None : 77.7%

Fluid resuscitation in septic shock: A positive fluid balance and elevated central venous pressure are associated with increased mortality*

Crit Care Med 2011 Vol. 39, No. 2

- Retrospective analysis of 778 patients from VaSST trial .



CONCLUSIONS-

- A more positive fluid balance both early in the resuscitation and cumulatively over four days predicts mortality in patients with septic shock.
- However in the group with CVP < 8 mm Hg, positive fluid balance improved survival.
- The optimal survival occurred with a positive fluid balance at 12 hr of 3 litres.
- CVP is an unreliable marker of fluid balance after 12 hrs.

Monitoring Fluid Responsiveness

Static Indices

- Central Venous Pressure(CVP) or Rt Atrial pressure (Pra)
- Pulmonary artery occlusion pressure(PAOP)
- Left ventricular End Diastolic Area
- Right Ventricular End Diastolic Volume Index

Dynamic indices

- Pulse Pressure variability
- Inspiratory Decrease in Pra
- Respiratory variation in IVC diameter
- Peak aortic blood flow velocity variability
- Passive Leg raising

CVP – SHOULD IT BE THE GOAL?

- EGDT and SSC recommend the use of CVP target in the resuscitation of sepsis.

- The PPV of CVP as a marker of fluid responsiveness was only 47 %.

Crit Care Med 2007; 35, 64-68

- The use of CVP to guide fluid infusions should be discouraged after the initial resuscitation.

DYNAMIC CHANGES IN PULSE PRESSURE

- Passive Inspiration (Rise in pleural pressure):
  - Increase in LV contractility
  - Decrease in LV afterload
  - Decrease in RV filling leading to decrease in RV output which will cause decrease in LV preload in the succeeding expiration.
- Succeeding Expiration :
  - Decrease in LV preload decreases LV stroke volume and decreases the pulse pressure.
- These changes occur significantly if the heart is operating on the steeper portion of the frank starling curve, thus indicating fluid responsiveness

TECHNIQUE OF ASSESSING PPV

Check that cardiac rhythm is regular

Raise the tidal volume to 10 mL/kg of predicted body weight

Ensure that the patient is receiving ventilation passively or adjust further the rate, tidal volume, or degree of sedation to achieve this

Display or print the arterial pressure waveform for 30 s

Measure the minimum and maximum pulse pressure

Calculate PPV $(PPmax - PPmin)/([PPmax + PPmin]/2) \times 100\%$

A value $\geq 13\%$ predicts fluid responsiveness

CHEST.January 2008;133(1):252-263.

Relation between Respiratory Changes in Arterial Pulse Pressure and Fluid Responsiveness in Septic Patients with Acute Circulatory Failure

Am J Respir Crit Care Med Vol 162. pp 134–138, 2000

Threshold change of Pulse pressure of 13 % best predictor of fluid responsiveness.

CHEST.January 2008;133(1):252-263.

OTHER DYNAMIC VARIABLES

- **IVC diameter Variability** : Increases in passive inspiration and decreases in expiration. A variability of 12 – 18% indicates fluid responsiveness.

- **Passive leg raising test :** Increase of aortic blood flow by 10% on PLR detects fluid responsiveness

- **Peak Aortic Blood Flow Variation :** Using TEE, > 12% change in aortic blood flow signifies fluid responsiveness

CHEST.January 2008;133(1):252-263

MONITORING FLUID RESPONSIVENESS

For the first 6 h of severe sepsis, infuse fluids liberally, targeting Svo_2 or $Scvo_2$ > 70%
Subsequently, do not use “maintenance” fluids
For new hypotension, tachycardia, or unexplained oliguria, ascertain the cause and consider a fluid challenge:
When fluid challenge is of low risk, administer 500 to 1,000 mL of crystalloid;
When the risk of fluid challenge is not trivial (ALI/ARDS; oliguria; right ventricular dysfunction), use a dynamic predictor to guide fluid boluses
PLR for those with some measure of cardiac output;
PPV for those with regular rhythm and lack of spontaneous breathing;
Change in Pra for those with substantial inspiratory effort
Reassess the patient frequently because the hemodynamic state changes often

Which Fluid to be given?

CRYSTALLOIDS

- Normal Saline
- Ringers Lactate

COLLOIDS

- Albumen
- Hydroxy Ethyl Starch
- Gelatin
- Dextran

Use of Colloids -

	Hydroxyethyl starches	Albumin
Coagulopathy	yes	yes
Transmission viral infection	no	yes
Anaphylaxis	yes (<0.006%)	yes (<0.1%)
Pruritis	yes	no
Renal Failure	yes	?

Grocott, M, Anesthesia and Analgesia, 2005

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*

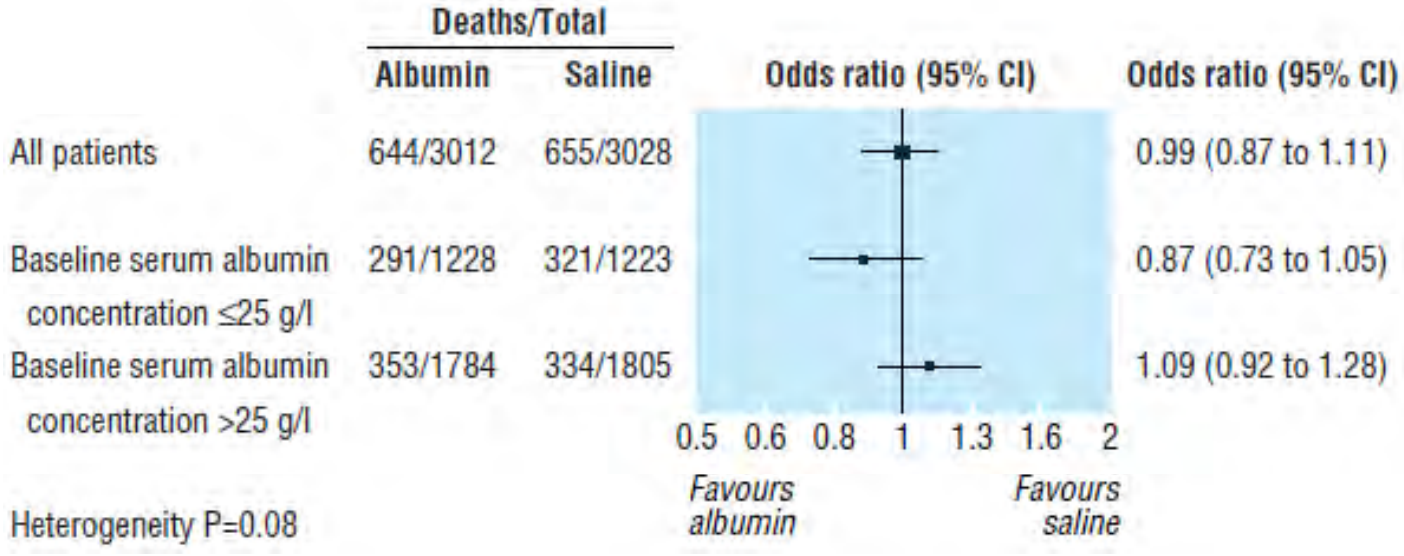
N Engl J Med 2004;350:2247-56.

- RCT of 6997 patients.
- Saline vs 4% albumin
- Similar outcomes at 28 days (Mortality rate, Days of ICU, Days of ventilation)

Effect of baseline serum albumin concentration on outcome of resuscitation with albumin or saline in patients in intensive care units: analysis of data from the saline versus albumin fluid evaluation (SAFE) study

Saline versus Albumin Fluid Evaluation Study Investigators

BMJ



Intensive Care Med (2011) 37:86–96
DOI 10.1007/s00134-010-2039-6

ORIGINAL

The SAFE Study Investigators

Impact of albumin compared to saline on organ function and mortality of patients with severe sepsis

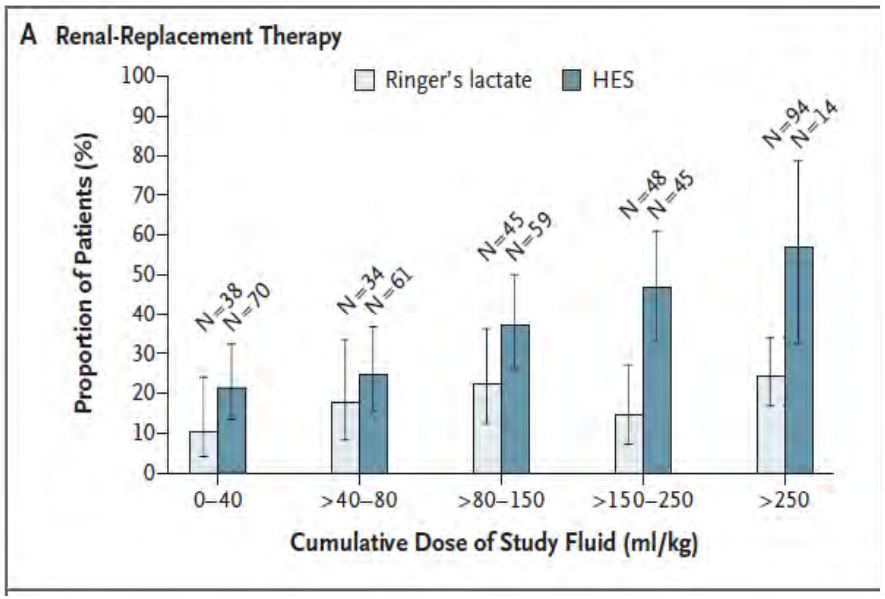
- RCT of 1218 patients
- Odds ratio for death in the albumin group vs saline is o.71 (p=0.03).
- No increase in the adverse events

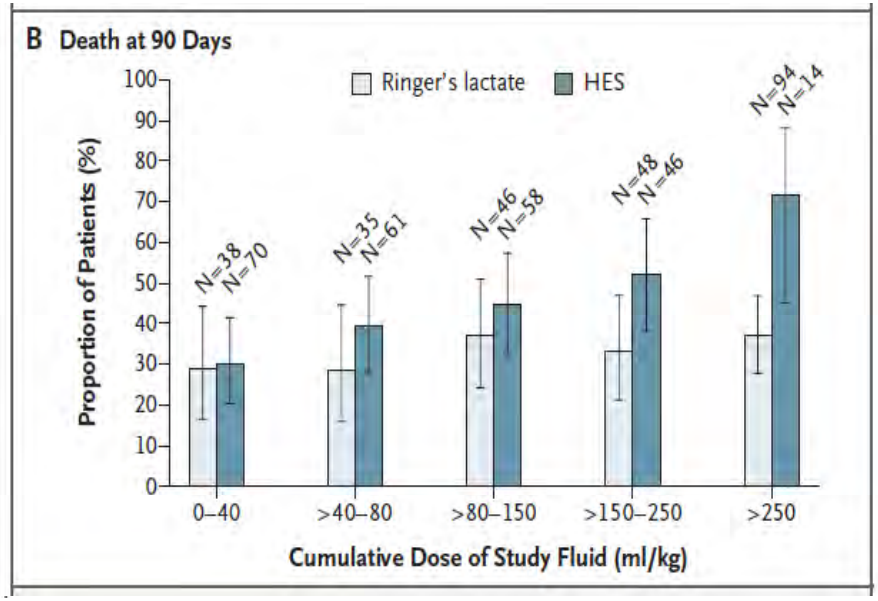
ORIGINAL ARTICLE

Intensive Insulin Therapy and Pentastarch Resuscitation in Severe Sepsis

- VISEP trial : Volume Substitution and Insulin therapy in Severe Sepsis.
- HES (200/0.5) versus Ringers Lactate

N Engl J Med 2008;358:125-39.





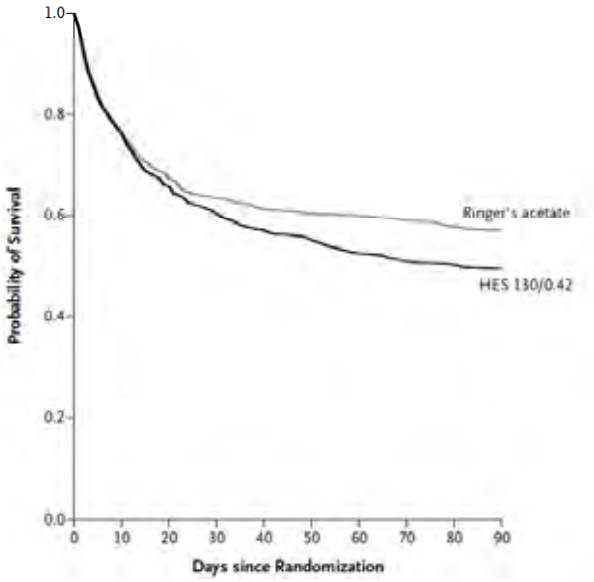
ORIGINAL ARTICLE

N Engl J Med 2012;367:124-34.

Hydroxyethyl Starch 130/0.42 versus Ringer's Acetate in Severe Sepsis

- 6S trial : Scandinavian Starch for Severe Sepsis/Septic Shock.
- HES (130/0.42) vs Ringers acetate
- RCT of 800 patients

- Results:
  - HES increases mortality and Renal failure



RESEARCH Open Access

Assessment of hemodynamic efficacy and safety of 6% hydroxyethylstarch 130/0.4 vs. 0.9% NaCl fluid replacement in patients with severe sepsis: The CRYSTMAS study

Critical Care 2012, **16**:R94

- RCT of 174 patients
- No difference in the rates of kidney injury/ coagulopathy in both the groups.

SPECIAL ARTICLE

Intensive Care Med (2012) 38:368–383

Consensus statement of the ESICM task force on colloid volume therapy in critically ill patients

1. We recommend not to use HES with molecular weight ≥ 200 K.Da and/or substitution factor of ≥ 0.4 in patients with severe sepsis or risk of AKI.

2. We suggest not to use 6% HES with 130/0.4 or gelatin in such patients.

3. Albumin may be used in the resuscitation of severe sepsis.

SO, WHICH FLUID TO BE USED??

- No benefit of colloids over crystalloids
  - Surviving Sepsis Guidelines 2008
  - Cochrane meta analysis 2012 and 2011

- SSC 2012: Initial fluid resuscitation should be with crystalloids (Grade 1A).1lt or more with a minimum of 30 ml/kg in the first 4-6 hours. Albumin may be added to the crystalloids (2B)

- HES : Not to be used as increases the risk of AKI and also coagulopathy.

- Crystalloids are to be preferred as they are widely available and much cheaper than colloids.

N Engl J Med, Vol. 345, No. 19 · November 8, 2001

INTENSIVE INSULIN THERAPY IN CRITICALLY ILL PATIENTS

- RCT conducted at Leuven, Belgium on 1648 patients in a primarily Surgical ICU.

- Intensive Insulin therapy to maintain a blood glucose <110 mg/dl by an insulin infusion reduced the ICU mortality rate from 8 % to 4.6%

- Also showed that Intensive insulin therapy
  - Decreases bloodstream infections by 46%
  - Decreases AKI needing RRT by 41%
  - Decreases RBC transfusions by 50%
  - Decreases critical illness polyneuropathy by 44%
  - Less likely to require prolonged ventilation

N Engl J Med 2006;354:449-61.

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.

RCT of 1200 patients in the medical ICUs

Results :

- No reduction in the In-hospital mortality
- Morbidity decreased :
  - Decrease in new AKI
  - Accelerated weaning from the ventilator
  - Accelerated discharge from the ICU and hospital

- In the subgroup of patients who stayed in the ICU for more than 3 days, mortality decreased by 12 %.

EVIDENCE – 2008/2009

Author	Journal /Year	No of pts	Intensive control	Standard control	Results
De La Rosa	Crit care 2008	RCT 504 pts	80-110	180-200	No decrease in mortality or morbidity but increase in severe hypoglycemia
Arabi	Crit Care Med 2008	RCT 523 pts	80-110	180-200	No decrease in mortality
Brunkhorst et al (VISEP TRIAL)	NEJM 2008	RCT 537 pts	80-110	180-200	Increased incidence of severe hypoglycemia
Prieser et al (GLUCONTROL STUDY)	Intensiv Care Med 2009	RCT 1101 pts	80-110	180-200	Increased incidence of hypoglycemia

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

Intensive versus Conventional Glucose Control in Critically Ill Patients

The NICE-SUGAR Study Investigators*

- RCT of 6104 patients
- Intensive Insulin therapy increased mortality (27.5% vs 24.9%)
- Increased mortality mainly due to cardiovascular causes

	NICE SUGAR 2009	Van den Berg 2001
Centre	Multicentric trial	Single center
Feeds	Enteral	TPN
Control group target	140-180	180-200
Hypoglycemia risk	6.8%	5.1 %
Type of ICU	Medical/Surgical	Surgical

CHEST

From: Glycemic Control in the ICUGlycemic Control in the ICU

CHEST. 2011;140(1):212-220. doi:10.1378/chest.10-1478

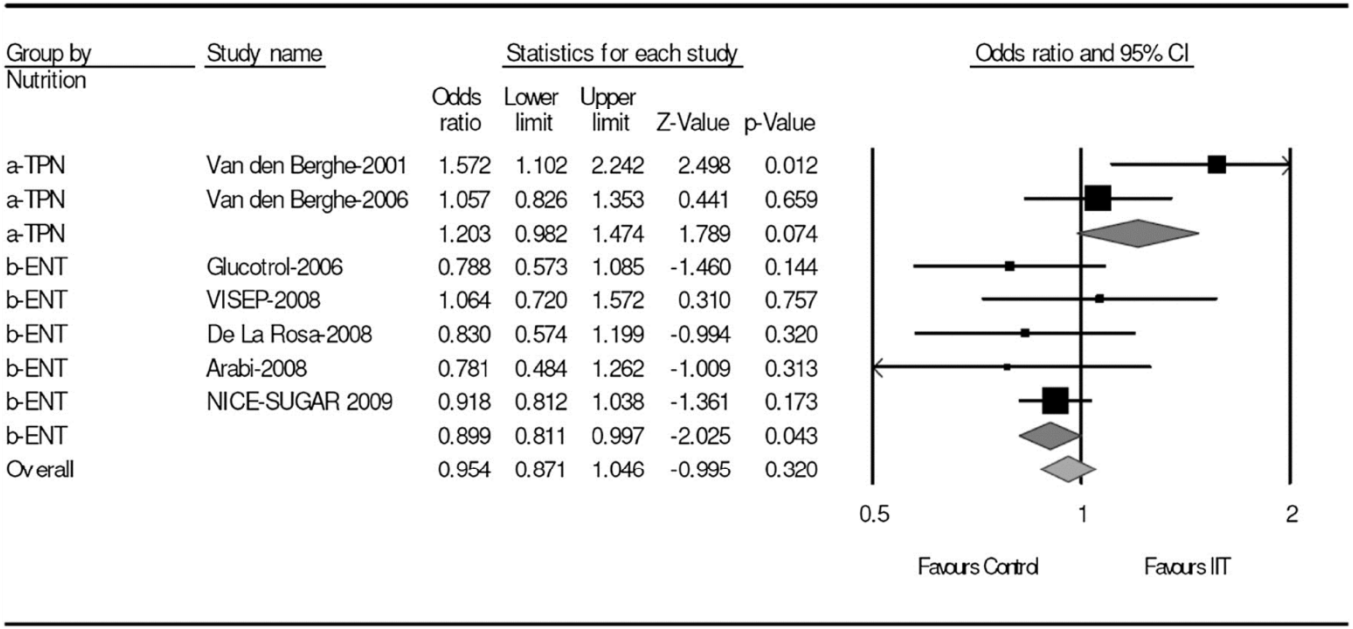
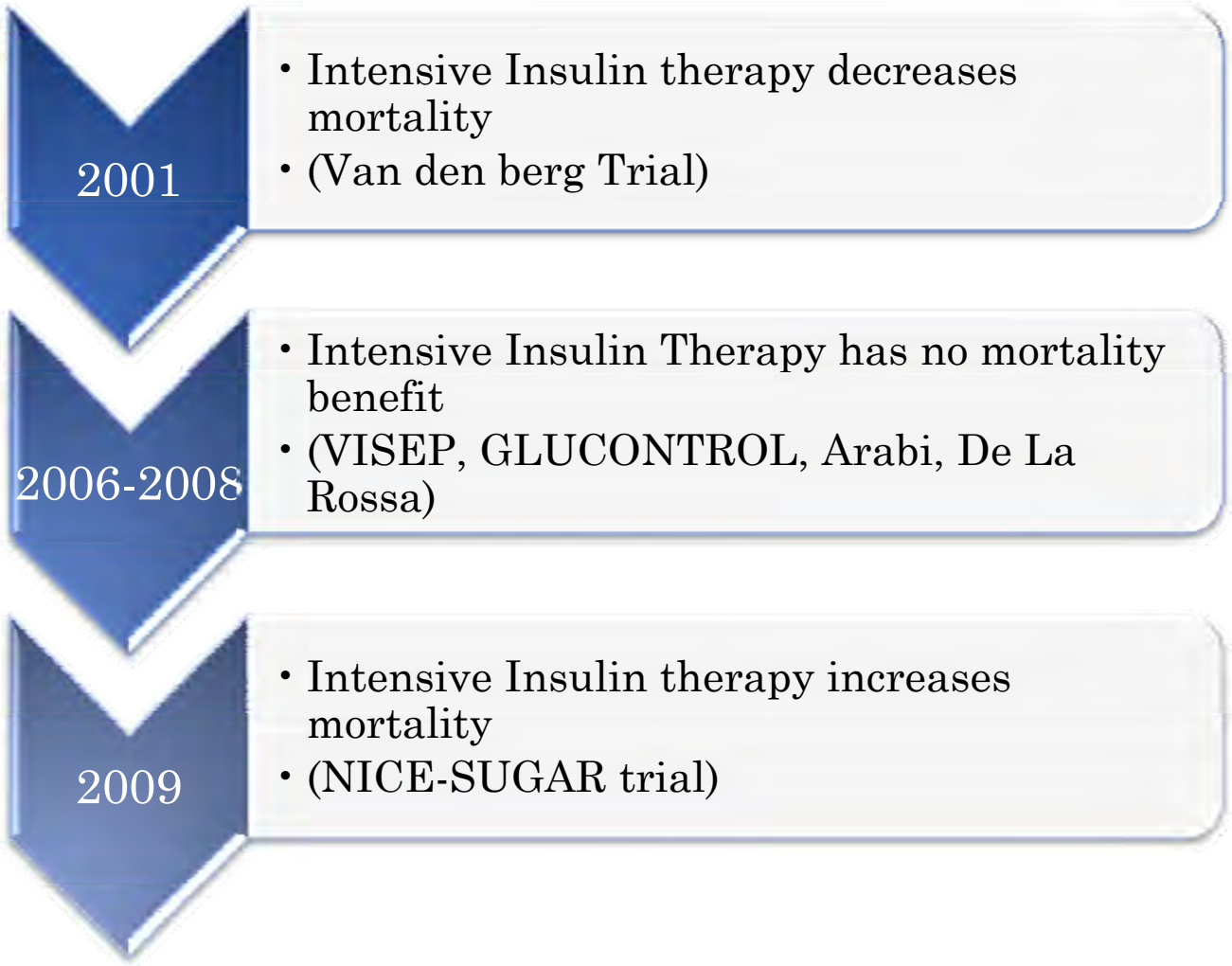


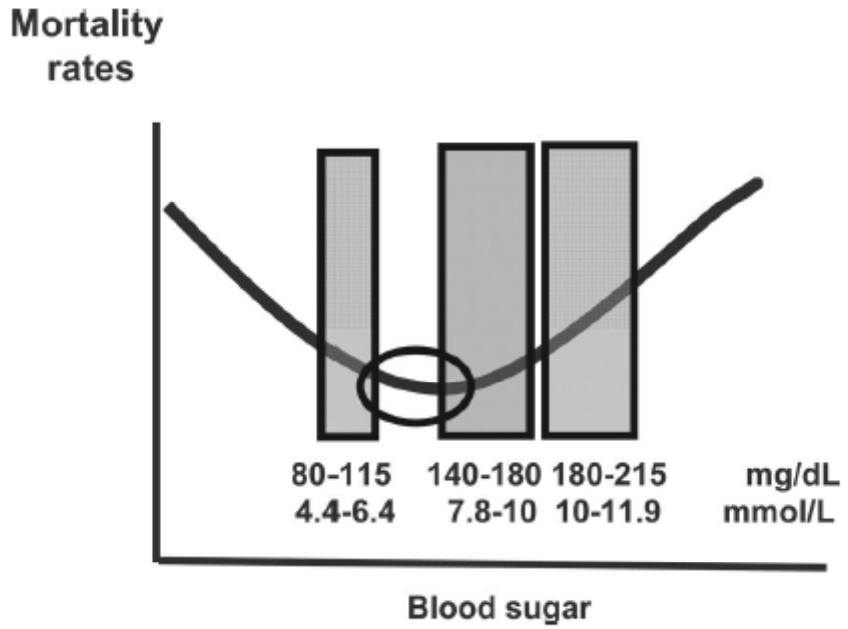
Figure Legend:

Forest plot from a meta-analysis showing risk ratios of mortality in clinical trials comparing IIT to conventional glycemic control stratified by predominant route of feeding. a-TPN = parenteral nutrition; b-ENT = enteral nutrition; ITT = intensive insulin therapy. (Reprinted with permission from Marik and Preiser.[37])

Intensive Insulin Therapy – Over the years



WHAT SHOULD BE THE TARGET?



- SSC 2004 guidelines : Target <150 mg/dl
- SSC 2008 guidelines : Target <150 mg/dl
- SSC 2009 statement : Target glucose around 150mg/dl

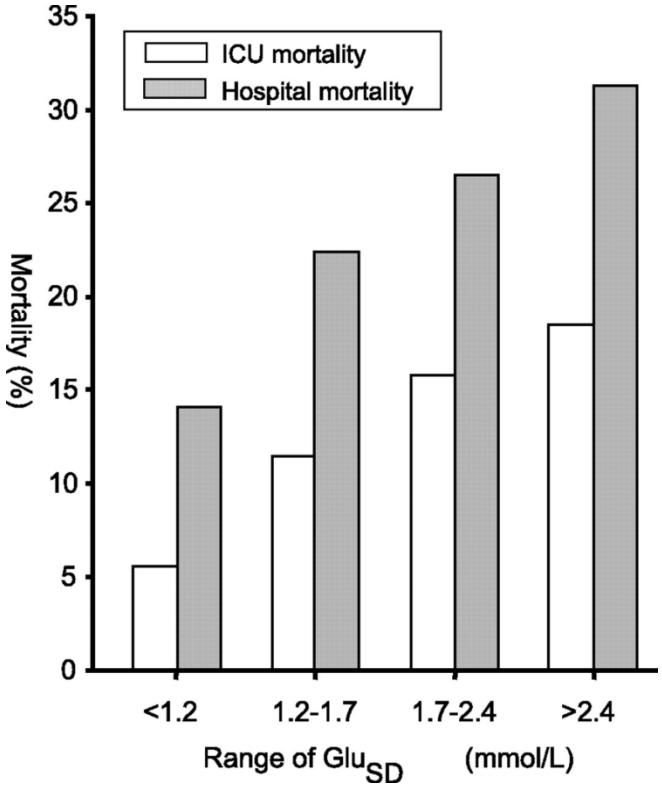
Newer Concepts – Glucose variability in the ICU

CLINICAL INVESTIGATIONS

Anesthesiology 2006; 105:244–52

Variability of Blood Glucose Concentration and Short-term Mortality in Critically Ill Patients

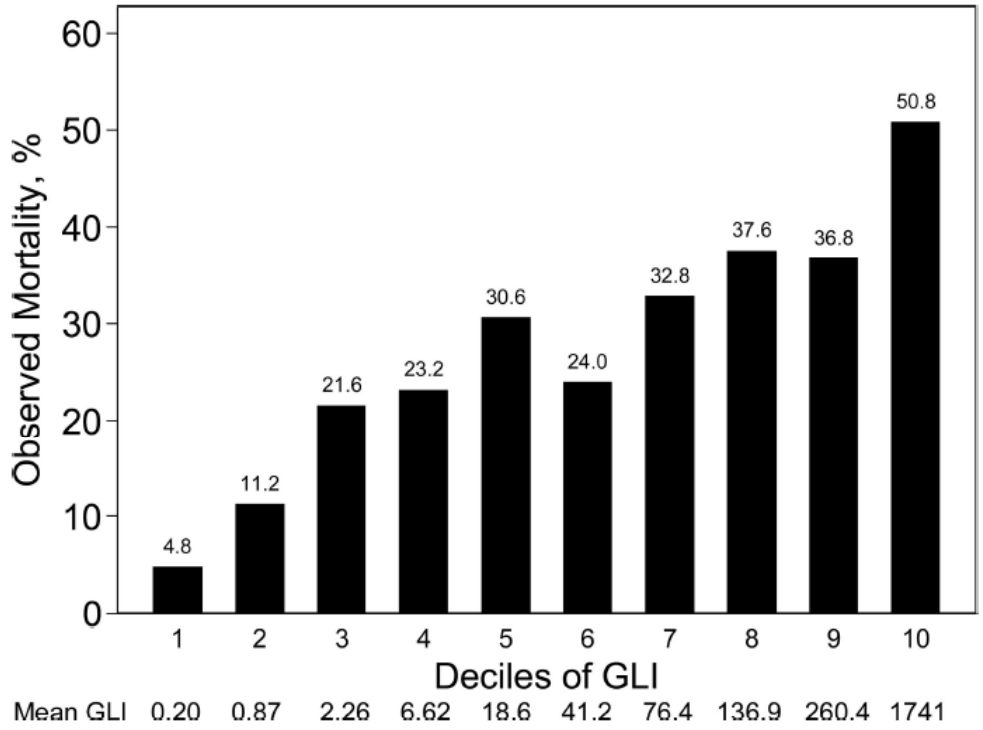
- Retrospective observational study of 7049 critically ill patients.
- Greater glycemic variability is an independent predictor of ICU and Hospital mortality



Crit Care Med 2008 Vol. 36, No. 8

Glucose variability and mortality in patients with sepsis*

Naeem A. Ali, MD; James M. O'Brien Jr, MD, MSc; Kathleen Dungan, MD; Gary Phillips, MAS; Clay B. Marsh, MD; Stanley Lemeshow, PhD; Alfred F. Connors Jr, MD; Jean-Charles Preiser, MD, PhD



Glucose variability is associated with intensive care unit mortality*

Jeroen Hermanides, MD; Titia M. Vriesendorp, MD, PhD; Robert J. Bosman, MD, PhD;
Durk F. Zandstra, MD, PhD; Joost B. Hoekstra, MD, PhD; J. Hans DeVries, MD, PhD

Crit Care Med 2010 Vol. 38, No. 3

Observational study of 5728 patients

Highest mortality in patients with high blood glucose and high glycemic variability.

The glycemia threat in sepsis: Too high, too low, or too . . . variable!*

Anesthesiology 2006; 105:233–4

Blood Glucose Variability

A New Paradigm in Critical Care?

Blood glucose control in 2010: 110 to 150 mg/dL and minimal variability*

How “sweet” complexity is and how “bitter” variability can be; the new aspect of intensive care unit hyperglycemia*

GLUCOSE MONITORING- SCOPE OF ERROR

- The routine glucometers used in the ICU

1. Measure blood glucose and use an algorithm to extrapolate plasma glucose assuming a normal hematocrit. In anemic patients , this leads to falsely high glucose concentrations.

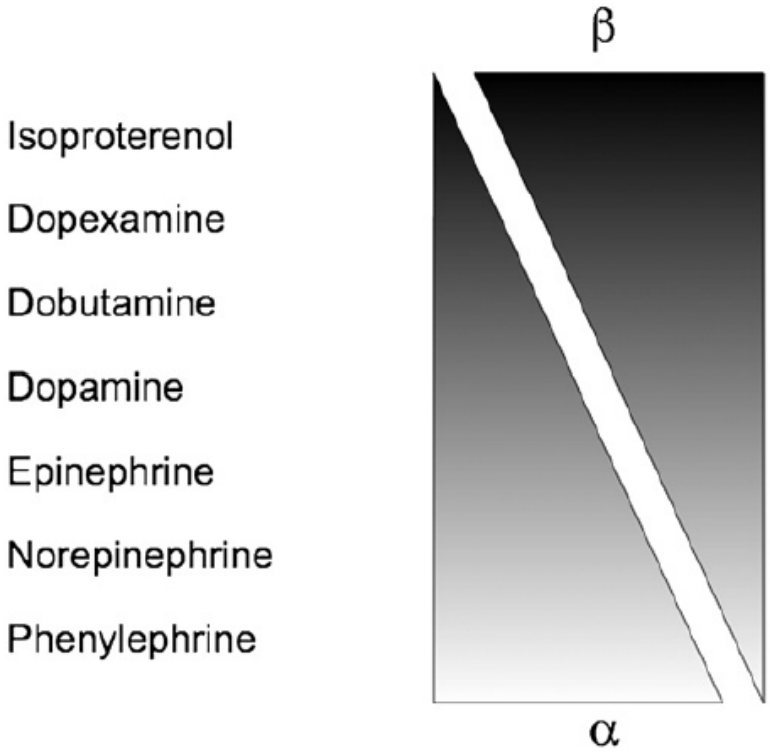
2. Use Glucose oxidase technique to estimate blood glucose. Errors occur with hyperoxia (Pao2 >100) and Hypoxia (Pao2<44). May falsely report high glucose in critically ill patients with hypoxia.

In severe sepsis, patients are usually hypoxic and anemic. False high glucose measurements can lead to inappropriate increases in insulin and increased hypoglycemia.

CHEST. 2011;140(1):212-220.

Crit Care Clin 25 (2009) 781–802

VASOPRESSORS - PHYSIOLOGY



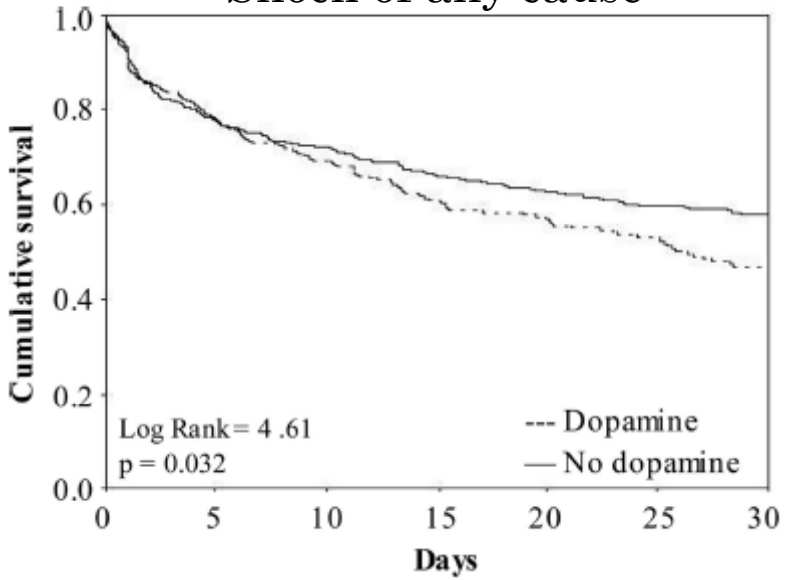
α receptor : vasoconstriction
ß1 receptor : Increase heart rate and cardiac contractility
ß2 receptor : vasodilatation

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

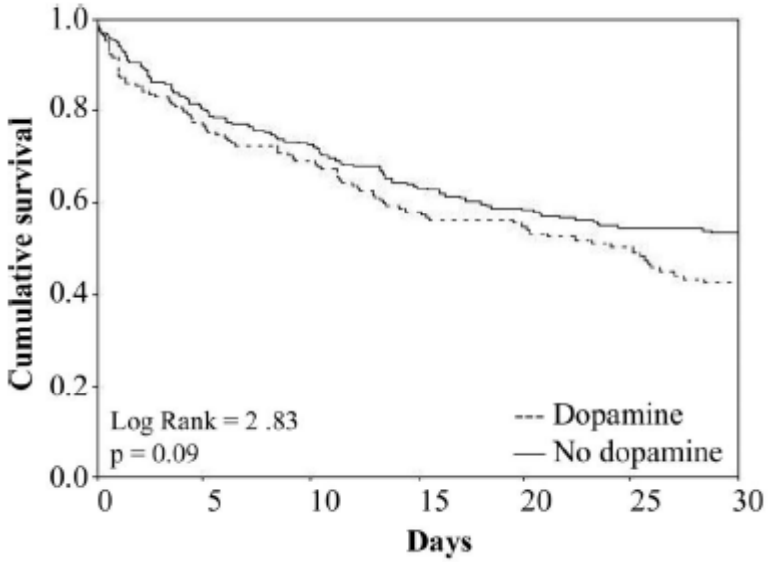
Crit Care Med 2006 Vol. 34, No. 3

- Observational study of 3147 pts in European ICUs
- Patients receiving Dopamine had higher ICU and 30 day mortality rates (Multivariate regression model)
- Median dose of Dopamine used 8.5 ug/kg/min

Shock of any cause



Septic shock



N Engl J Med 2010;362:779-89.

Comparison of Dopamine and Norepinephrine in the Treatment of Shock

- RCT of 1679 patients
- Maximum doses:
  - Dopa : 20 ug/kg/min
  - NA : 0.19 Ug/kg/min

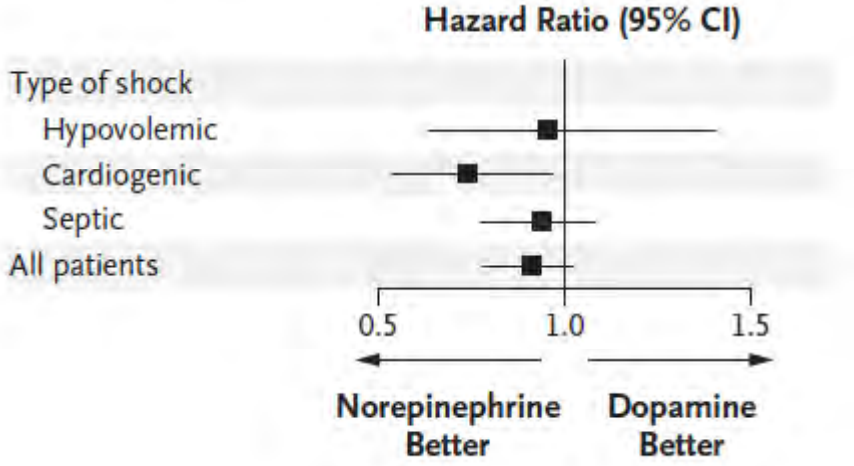
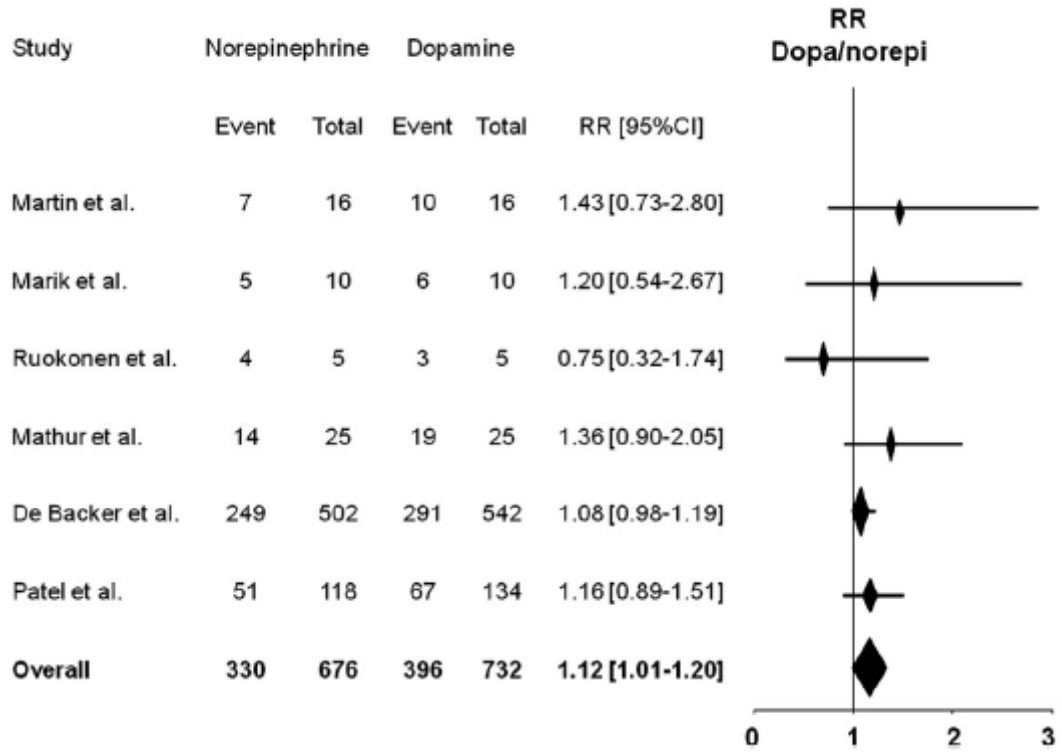


Table 2. Mortality Rates.*

Time Period	Dopamine	Norepinephrine	Odds Ratio (95% CI)†	P Value
	percent mortality			
During stay in intensive care unit	50.2	45.9	1.19 (0.98–1.44)	0.07
During hospital stay	59.4	56.6	1.12 (0.92–1.37)	0.24
At 28 days	52.5	48.5	1.17 (0.97–1.42)	0.10
At 6 mo	63.8	62.9	1.06 (0.86–1.31)	0.71
At 12 mo	65.9	63.0	1.15 (0.91–1.46)	0.34

Dopamine versus norepinephrine in the treatment of septic shock: A meta-analysis*

Crit Care Med 2012 Vol. 40, No. 3



Use of dopamine associated with increased 30 day mortality and increased cardiac arrhythmias

SSC GUIDELINES

SSC 2008 :

- We recommend either Dopamine or Norepinephrine as the first choice vasopressor therapy in septic shock. (Grade 1c)

SSC 2012:

- Strongly recommend Norepinephrine as the first choice for vasopressor therapy (Grade 1B)
- Dopamine to be used only in a select population with low risk of arrhythmia and with a low heart rate/ cardiac output.

VASOPRESSIN – PHYSIOLOGIC RATIONALE

1. Vascular smooth muscle contraction by acting on Vascular V1 receptors

2. Relative vasopressin Deficiency : Vasopressin levels increased early in shock and by 1-2 days fall back to normal, which is actually a relative deficiency.

3. Increases the responsiveness of the vasculature to catecholamines

4. Inhibit the vascular smooth muscle NO production and K ATP channels which cause vasodilation

N Engl J Med 2008;358:877-87.

Vasopressin versus Norepinephrine Infusion in Patients with Septic Shock

- RCT o of 778 patients
- Patients already on Norepinephrine 5 ug/min were randomized to either low dose vasopressin (0.01-0.03 U/min) or Norepinephrine (5-15 Ug/min)
- No difference in mortality or rate of ADR
- Critics :
  - Mean duration to start of vasopressin is 12 hours
  - Mean BP before starting drug was 72 mmHg
  - Patients with acute ischemia/ heart failure excluded

SSC Guidelines

SSC 2004:

- Vasopressin may be considered in patients with refractory shock (0.01-0.04 U/min) (Grade E)

SSC 2008:

- Vasopressin 0.03 U/min may be added to norepinephrine with an anticipation of an effect similar to that of norepinephrine alone (Grade 2C)

SSC 2012:

- Vasopressin 0.03 units / minute is an alternative to norepinephrine(as a first choice), or may be added to it (Grade 2A).

EPINEPHRINE -

Crit Care Clin 25 (2009) 781–802

- Very few studies
- Two large RCTs (Published in Lancet 2007 and Intensive care med 2008) showed no difference in mortality between epinephrine and norepinephrine in septic shock.
- Increased ADR :
  - Increase in serum lactate
  - Splanchnic vasoconstriction and ischemia (stress ulcer, paralytic ileus)
  - Tachycardia and cardiac events
- Hence Epinephrine used as a second line agent (SSC 2008 and 2012)

What should we Follow

- Norepinephrine : First choice vasopressor in septic shock
- Vasopressin : Second line agent in Septic shock (To be avoided if acute cardiac ischemia / cardiac failure)
- Dopamine : Preferably avoided
- Epinephrine : Used with caution only if Norepinephrine and vasopressin fail to reverse shock

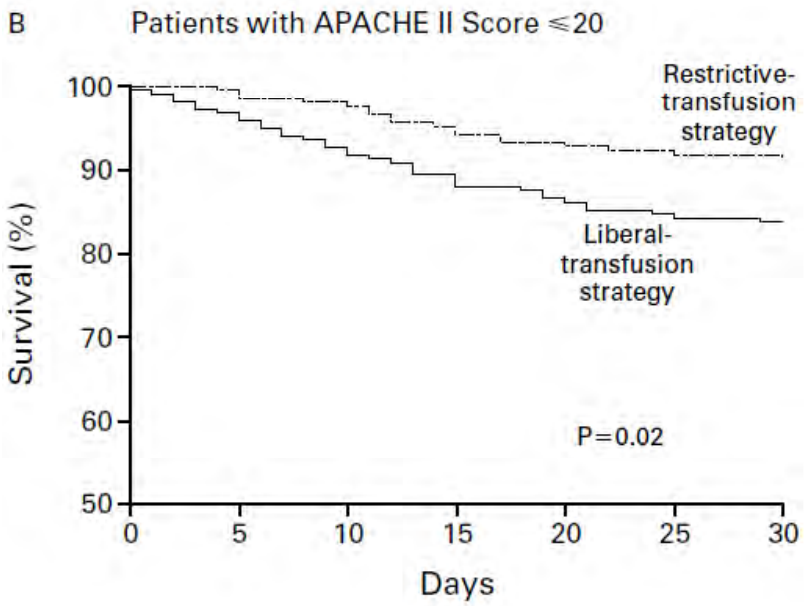
N Engl J Med 1999;340:409-17.

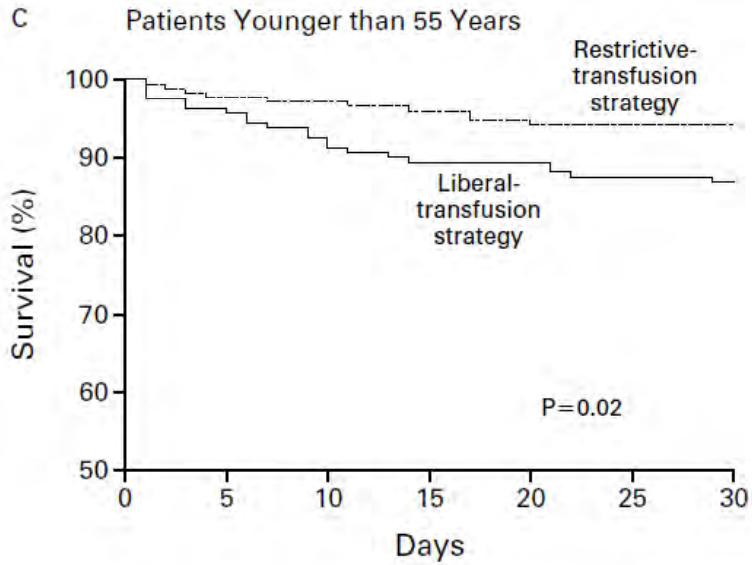
A MULTICENTER, RANDOMIZED, CONTROLLED CLINICAL TRIAL OF TRANSFUSION REQUIREMENTS IN CRITICAL CARE

- TRICC trial included 838 patients

1. Restrictive strategy : Transfusion trigger 7 g/dl, transfusion target 7-9 g/dl.
2. Liberal strategy : Transfusion trigger 9 g/dl, Transfusion target 10-12 g/dl

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





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

Blood Transfusion – How is it harmful?

- Transfusion related Immunosuppression – Increased incidence of infections.

- Stores red blood cells
  - Less deformable – causes perfusion defects.
  - Increase in 2-3 DPG – Less unloading of oxygen at the tissues.
  - Fall in pH, increase in potassium and free hemoglobin (not of clinical relevance except in neonates).

- Volume overload

CHEST 2007; 131:1583–1590

WHAT SHOULD BE THE TARGET?

- EGDT/SSC : Target Hct of 30% (If Scvo2 < 70%)
- TRICC : Target Hb 7-9 g/dl.

Consensus -

CHEST 2007; 131:1583–1590

Table 1—*Transfusion Recommendations*

Variables	Transfusion Trigger, g/L*	Goal, g/L
General critically ill (no acute bleeding)	70	70–90
Critically ill with septic shock (> 6 h)	70	70–90
Critically ill with septic shock (< 6 h)	80–100	100
Critically ill with chronic cardiac disease	70	70–90
Critically ill with acute cardiac disease	80–100	100

*Administer 1 U of RBCs at a time and remeasure hemoglobin concentrations.

Crit Care Med 2010 Vol. 38, No. 2

SSC- Despite Controversies

The Surviving Sepsis Campaign: Results of an international guideline-based performance improvement program targeting severe sepsis*

- 15022 patients from Jan 2005 – Mar 2008
- Absolute decrease in mortality of 8 % and RRR of 20%