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

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Sepsis

- Sepsis: Greek word meaning decay or putrefaction.
- Sepsis is defined as the presence of several clinical, hematologic, biochemical, and immunologic variables associated with an infection.
- Severe sepsis: Sepsis complicated by organ dysfunction.
- Septic shock - State of acute circulatory failure characterized by arterial hypotension despite adequate fluid resuscitation, so that vasopressor therapy is necessary to restore a minimally acceptable arterial pressure

Clin Chest Med 2008 ;29: 585–590

- Severe sepsis and septic shock are major healthcare problems, affecting millions of individuals around the world each year, killing one in four (and often more), and increasing in incidence.

- One of the greatest endeavors to date - Surviving Sepsis Campaign (SSC) - Originally launched in 2002 with the stated goal to reduce mortality by 25%.

- 2004 – SSC- First internationally accepted evidence based guidelines published. → SSC 2008.

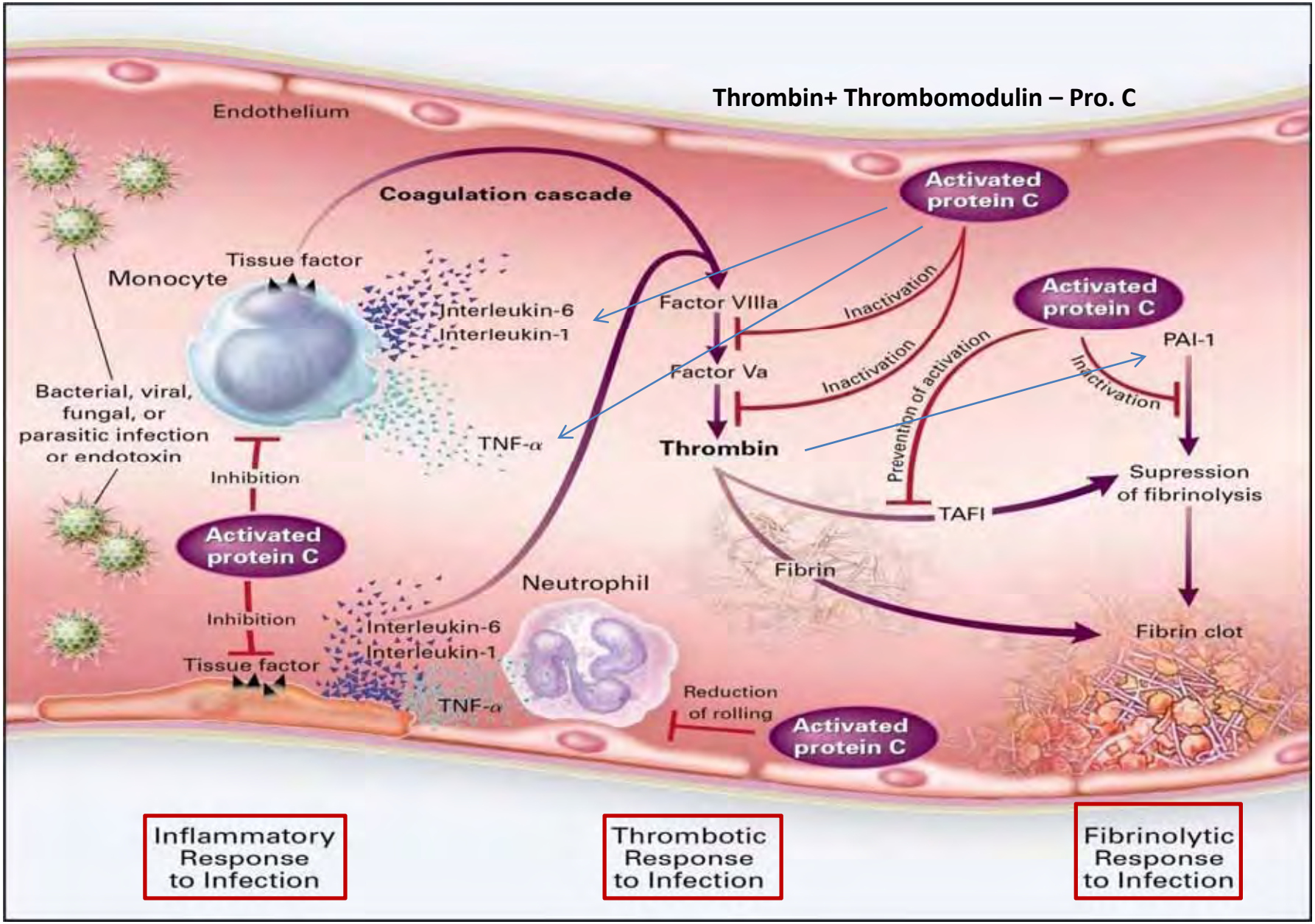
- Intended to provide guidance for the clinician caring for a patient with severe sepsis or septic shock.

Crit Care Med 2008 ;36 :1

Sepsis Trials – " Graveyard of pharmaceutical companies" ??

- ***Advances in management in the last decade***
- Anticoagulants in Sepsis.
- Vasopressors
- Role of Corticosteroids
- Initial resuscitation of patients with sepsis
- Fluid therapy – Colloids/Crystalloids
- Novel therapies

Link between coagulation & inflammation - YES



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

- *Hartman DL, Bernard GR, Helterbrand JD, Yan SB, Fisher CJ. Recombinant human activated protein C (rhAPC) improves coagulation abnormalities associated with severe sepsis. Intensive Care Med 1998;24: Suppl.*
- Placebo-controlled phase 2 trial in patients with severe sepsis
- rhAPC resulted in dose-dependent reductions in the plasma levels of D - dimer and serum levels of interleukin-6, markers of coagulopathy and inflammation, respectively.

- Recombinant Human Protein C Worldwide Evaluation in Severe Sepsis *(PROWESS)* study.

- Administration of Drotrecogin Alfa (Activated) in Early Stage Severe Sepsis *(ADDRESS)* study.

- Researching Severe Sepsis and Organ Dysfunction in Children: A Global Perspective *(RESOLVE)* trial.

- Xigris and Prophylactic Heparin Evaluation in Severe Sepsis *(X-PRESS)*

The New England Journal of Medicine

VOLUME 344 MARCH 8, 2001 NUMBER 10

EFFICACY AND SAFETY OF RECOMBINANT HUMAN ACTIVATED PROTEIN C FOR SEVERE SEPSIS

GORDON R. BERNARD, M.D., JEAN-LOUIS VINCENT, M.D., PH.D., PIERRE-FRANCOIS LATERRE, M.D., STEVEN P. LAROSA, M.D., JEAN-FRANCOIS DHAINAUT, M.D., PH.D., ANGEL LOPEZ-RODRIGUEZ, M.D., JAY S. STEINGRUB, M.D., GARY E. GARBER, M.D., JEFFREY D. HELTERBRAND, PH.D., E. WESLEY ELY, M.D., M.P.H., AND CHARLES J. FISHER, JR., M.D., FOR THE RECOMBINANT HUMAN ACTIVATED PROTEIN C WORLDWIDE EVALUATION IN SEVERE SEPSIS (PROWESS) STUDY GROUP*

Randomized, double blind, placebo controlled trial
N=1690 , 164 centres, 11 countries
1:1 Drot-AA/placebo
Primary end point – 28 day all cause mortality

TABLE 4. ANALYSIS OF THE RATES AND RISKS OF DEATH FROM ANY CAUSE AT 28 DAYS.*

VARIABLE	PLACEBO GROUP	DROTRECOGIN ALFA ACTIVATED GROUP	P VALUE†	RELATIVE RISK OF DEATH (95% CI)‡	ABSOLUTE REDUCTION IN RISK (95% CI)§
	no./total no. (%)				%
Treated patients					
Nonstratified analysis	259/840 (30.8)	210/850 (24.7)	0.005	0.80 (0.69 to 0.94)	6.1 (1.9 to 10.4)
Stratified analysis¶			0.005	0.81 (0.70 to 0.93)	6.2 (1.6 to 10.8)
Protein C deficiency					
Yes	215/670 (32.1)	182/709 (25.7)	0.009	0.80 (0.68 to 0.95)	6.4 (1.6 to 11.2)
No	28/105 (26.7)	14/90 (15.6)	0.06	0.58 (0.33 to 1.04)	11.1 (−0.4 to 22.6)
Unknown	16/65 (24.6)	14/51 (27.5)	0.73	1.12 (0.60 to 2.07)	−2.8 (−19.0 to 13.4)
Randomized patients‖					
Nonstratified analysis	268/857 (31.3)	216/871 (24.8)	0.003	0.79 (0.68 to 0.92)	6.5 (2.2 to 10.7)

- Study was stopped prematurely after the second interim analysis for treatment efficacy.(n=1520) , NNT-16.
- Sig. decrease in plasma d-dimer & IL-6 levels.
- Increased risk of serious bleeding during infusion (3.5% versus 2%, P=0.06)
- Regulatory agencies in the US and in Europe approved the marketing of Drot-AA in Prowess subgroups (At high risk of death)..

Post hoc analyses of the Prowess study showed a trend toward higher mortality rates in Drot-AA–treated patients whose APACHE II score was below 20.

- No evidence for patients whose APACHE II score was between 20 and 24, or for those who had a single organ dysfunction.

- Limitations –
- Amendment of the protocol after enrolment of 720 patients to modify exclusion criteria and to change the placebo.

- 5 months later, a modification in the manufacturing of the study drug. (BDS2 -----BDS2+).

- Regulatory agencies requested additional RCT'S to evaluate the benefit/ risk profile of Drot-AA in
- (1) patients with mild to moderate sepsis (ie, APACHE II score of less than 25 or one organ dysfunction)
- (2) children with sepsis
- (3) patients with concomitant heparin treatment.

Drotrecogin alfa (activated) treatment in severe sepsis from the global open-label trial ENHANCE: Further evidence for survival and safety and implications for early treatment*

Jean-Louis Vincent, MD, PhD, FCCM; Gordon R. Bernard, MD; Richard Beale, MD; Christopher Doig, MD; Christian Putensen, MD, PhD; Jean-Francois Dhainaut, MD, PhD; Antonio Artigas, MD, PhD; Roberto Fumagalli, MD; William Macias, MD, PhD; Theressa Wright, MD; Kar Wong, PhD; David P. Sundin, PhD; Mary Ann Turlo, RN, MSc; Jonathan Janes, MRCP; for the ENHANCE Study Group

- Single arm, open label trial. N=2375. 25 countries.
- 28-day all-cause mortality approximated that observed in PROWESS (25.3% vs. 24.7%).
- ENHANCE patients treated within 0–24 hrs from their first sepsis-induced organ dysfunction had lower observed mortality rate than those treated after 24 hrs (22.9% vs. 27.4%, p = .01).
- Provided supportive evidence for the favorable benefit/risk ratio observed in PROWESS and suggested that more effective use of drotrecogin alfa (activated) might be obtained by initiating therapy earlier.

Crit Care Med 2005; 33:2266–2277

Why open label trial??

- The very success of PROWESS raised difficult issues concerning follow-up studies.
- Conducting a randomized, placebo controlled trial, in the light of evidence from a successful trial, presents serious ethical issues for investigators.
- Regulatory approval of DrotAA introduced a potential bias in conducting a placebo-controlled trial in severe sepsis.
- Option of unblinding study patients who decline rapidly.
- Patients randomized to placebo must always be included in the placebo “intent-to-treat” group – Confound interpretation.
- FDA required the sponsor to conduct a study to evaluate the efficacy of DrotAA for adults who had severe sepsis and a low risk of death.

THE NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Drotrecogin Alfa (Activated) for Adults with Severe Sepsis and a Low Risk of Death

Edward Abraham, M.D., Pierre-François Laterre, M.D., Rekha Garg, M.D., Howard Levy, M.D., Ph.D., Deepak Talwar, M.D., Benjamin L. Trzaskoma, M.S., Bruno François, M.D., Jeffrey S. Guy, M.D., Martina Bröckmann, M.D., Álvaro Rea-Neto, M.D., Rolf Rossaint, M.D., Dominique Perrotin, M.D., Armin Sablotzki, M.D., Ph.D., Nancy Arkins, R.N., Barbara G. Utterback, M.S., M.B.A., and William L. Macias, M.D., for the Administration of Drotrecogin Alfa (Activated) in Early Stage Severe Sepsis (ADDRESS) Study Group*

N=2640. 516 centres, 34 countries.
Individuals with sepsis and low risk of death (APACHE II<25, Single organ dysfunction)

Table 2. Mortality in Prespecified Subgroups.*

Variable	28-Day Mortality				In-Hospital Mortality			
	No. of Patients	Placebo	DrotAA	P Value	No. of Patients	Placebo	DrotAA	P Value
		%				%		
Overall	2613	17.0	18.5		2624	20.5	20.6	
APACHE II score†				0.81				0.64
<20	1554	13.3	14.3		1563	15.5	16.6	
20–24	737	21.6	22.4		737	26.0	23.7	
>24	321	24.7	29.5		323	32.7	32.3	
Organ dysfunction				0.38				0.59
Single	1739	14.8	17.4		1746	18.3	19.3	
Multiple	862	21.9	20.7		866	25.3	23.1	
Recent surgery‡				0.41				0.88
Yes	993	16.4	20.4		997	22.0	23.1	
No	1614	17.4	17.2		1621	19.6	19.0	
First patient enrolled§				0.04				0.22
Yes	509	14.5	22.3		511	19.7	23.7	
No	2104	17.7	17.5		2113	20.7	19.8	
Use of heparin at baseline				0.91				0.84
Yes	1536	16.9	18.2		1540	21.3	21.1	
No	1077	17.3	18.9		1084	19.4	19.9	

N Engl J Med 2005;353:1332-41.

- Significant increase in the rate of serious bleeding with Drot-AA (3.9% versus 2.2%, P=0.02).

- In the two populations with severe sepsis among the Address population, the basal risk of death was much lower than in the corresponding subgroups from the Prowess trial.

- In both the Prowess and Address trials, exploratory analysis suggested an increased 28-day mortality in patients who had one organ dysfunction and a recent surgery before Drot-AA treatment.

- The risk–benefit ratio for the administration of DrotAA in patients with severe sepsis who are at low risk for death is not favorable.

- DrotAA should not be used in patients with severe sepsis who are at low risk for death, such as those with single-organ failure or an APACHE II score of less than 25.

Drotrecogin alfa (activated) in children with severe sepsis: a multicentre phase III randomised controlled trial

*Simon Nadel, Brahm Goldstein, Mark D Williams, Heidi Dalton, Mark Peters, William L Macias, Shamel A Abd-Allah, Howard Levy, Robinette Angle, Dazhe Wang, David P Sundin, Brett Giroir for the REsearching severe Sepsis and Organ dysfunction in children: a gLobal perspective (RESOLVE) study group**

N=477.

Novel primary endpoint CTCOFR - 3 organ systems: cardiovascular, respiratory, and renal.

	Placebo (n=235)	DrotAA (n=239)	p
CTCOFR score			
Days 1–14,* median (IQR)	6·0 (4·0–8·0)	6·0 (4·0–8·0)	0·72
Day 15, number not resolved (%)	47 (19·8%)	46 (19·2%)	
Day 16, number who died during study(%)	41 (17·3%)	41 (17·1%)	
Mortality			
28-day mortality†, n (%)	41 (17·5%)	41 (17·2%)	0·93
14-day mortality, n (%)	32 (13·6%)	35 (14·6%)	0·78
In-hospital mortality, n (%)	41 (17·3%)	41 (17·1%)	0·95

No difference in overall serious bleeding events during the 28-day study period (placebo 6·8%; DrotAA 6·7%; p=0·97)

Numerically more instances of CNS bleeding in the DrotAA group (11 [4·6%], *vs 5 [2·1%] in placebo, p=0·13), particularly in children younger than 60 days*

Lancet 2007; 369: 836–43

Prophylactic Heparin in Patients with Severe Sepsis Treated with Drotrecogin Alfa (Activated)

Marcel Levi[1], Mitchell Levy[2], Mark D. Williams[3], Ivor Douglas[4], Antonio Artigas[5], Massimo Antonelli[6], Duncan Wyncoll[7], Jonathan Janes[3], Frank V. Booth[3], Dazhe Wang[3], David P. Sundin[3], and William L. Macias[3], for the Xigris and Prophylactic HepaRin Evaluation in Severe Sepsis (XPRESS) Study Group*

Why X-Press??

- DrotAA might provide adequate VTE prophylaxis itself.
- Secondary analyses from the PROWESS suggested higher 28-day mortality in DrotAA patients receiving baseline heparin than if they were not.
- In vitro studies - High doses of heparin may increase the rate of inhibition of APC by protein C inhibitor.
- Equivalence design trial – Heparin equal to placebo.
- N=1994. International, double blind, placebo controlled trial
- Drot AA indicated - LMWH/UFH 12 hrly or placebo.

Am J Respir Crit Care Med Vol 176. pp 483–490, 2007

- **No evidence for an increased proportion of serious bleeding events with the use of prophylactic heparin (3.8% versus 5.2%, P = .06).**

- **Patients who were receiving heparin before randomization and were allocated to heparin had a lower 28-day mortality rate than the placebo treated patients (26.9% versus 35.6%, P =.03).**

- **Patients receiving placebo exposed to heparin at baseline had higher mortality than patients receiving heparin- ? Rebound thrombin gen.**

- Concomitant prophylactic heparin does not cause an increase in 28-day mortality.
- Acceptable safety profile in patients with severe sepsis receiving DrotAA treatment.
- Small increased risk of nonserious bleeding.
- Coadministration of prophylactic heparin and DrotAA was associated with a reduction in ischemic stroke incidence in patients with severe sepsis.
- Prophylactic heparin should not be abruptly discontinued unless the potential risks of heparin outweigh the potential benefits.

BMC Emergency Medicine

BioMed Central

Research article

Open Access

A meta-analysis of controlled trials of recombinant human activated protein C therapy in patients with sepsis

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Table 1: Meta-analysis of effects of rhAPC on 28-day mortality in patients with severe sepsis and APACHE II score of ≥25 at study entry

Clinical Trial	N	rhAPC	Control	RR	95% CI	p-Value
PROWESS	817	30.9	43.7	0.71	0.59 – 0.85	0.0002 [1]
ADDRESS	324	29.7	24.5	1.21	0.85 – 1.74	0.32 [1]
Total	1141	30.6	38.3	0.80	0.68 – 0.94	0.007 [1,2,3]

[1] two-sided Fishers exact test
[2] Cochran-Mantel-Haenszel test, p = 0.006
[3] Breslow-Day test homogeneity, p = 0.005.

Table 2: Meta-analysis of effects of rhAPC on 28-day mortality in patients with severe sepsis and APACHE II score of <25 at study entry

Clinical Trial	N	rhAPC	Control	RR	95% CI	p-Value
PROWESS	873	18.8	19.0	0.99	0.75–1.30	1.0 [1]
ADDRESS	2315	16.8	16.0	1.05	0.88–1.27	0.6 [1]
Total	3188	17.3	16.8	1.03	0.89–1.20	0.7 [1,2,3]

- Total of 4329 patients - Effect on 28-day mortality relative to control treatment - 0.92 (0.83–1.02).
- Suggests that recombinant human activated protein C is not beneficial in severe sepsis.
- In low-risk stratum, no effect of recombinant human activated protein C administration on 28-day mortality was observed.
- Consistent and homogenous.
- Heterogeneity between the two studies- APACHE II score ≥ 25 - Effective in PROWESS whereas a tendency toward harm was present in ADDRESS.
- Even though the overall treatment effect in this high-risk population was still in favour of treatment, the observed heterogeneity suggests that the efficacy of recombinant human activated protein C is not robust.

Human recombinant activated protein C for severe sepsis (Review)

Martí-Carvajal AJ, Salanti G, Cardona-Zorrilla AF

Marti-Carvajal A, Salanti G, Cardona A. Human recombinant activated protein C for severe sepsis. Cochrane Database Syst Rev 2008;(1):CD004388.

Use of Drot-AA be suspended pending the results of additional trials.

4 studies accounting for 4911 patients.

No evidence suggesting that APC should be used in treating patients with sepsis or septic shock.

Associated with higher risk of bleeding.

Clinicians should not promote the use of Drot-AA until further RCT's available.

What Surviving sepsis campaign says

- *Consider rhAPC in adult patients with sepsis-induced organ dysfunction with clinical assessment of high risk of death (typically APACHE II 25 or multiple organ failure) if there are no contraindications (2B, 2C for postoperative patients).*

- *Adult patients with severe sepsis and low risk of death (typically, APACHE II 20 or one organ failure) should not receive rhAPC (1A).*

- Likely maximal benefit if administered within the first 24 hours.
- In addition, its benefit/risk profile may be greater in the medical population than among surgical patients.
- Prophylactic heparin should not be stopped when initiating Drot-AA.

High-Dose Antithrombin III in Severe Sepsis
A Randomized Controlled Trial

Multicentre double blind placebo controlled trial, N=2314

1:1 Iv Antithrombin III (30000 IU in total over 4 days) or a placebo (1% human albumin).

High-dose antithrombin III was associated with a significantly increased risk of hemorrhage when administered with heparin.

Some evidence to suggest a treatment benefit of antithrombin III in the subgroup of patients not receiving concomitant heparin.

Table 2. 28-Day Mortality Overall and in Subpopulations*

Population	No. of Patients	28-Day Mortality, %		
		Placebo	Antithrombin III	RR (95% CI)
Primary efficacy	2314	38.7	38.9	1.01 (0.91-1.11)†
Concomitant heparin administration§				
No heparin	698	43.6	37.8	0.86 (0.73-1.02)
Heparin (within or above limits)	1616	36.6	39.4	1.08 (0.96-1.22)

KyberSept Trial

JAMA. 2001;286:1869-1878

- **Heparin interactions with AT-III**
- Decreased 28 day mortality in subgroup not exposed to heparin. (p=0.08).

- Antithrombin III resulted in a 15% absolute improvement in 90-day mortality in this subgroup of patients. (n=680; 44.9% for AT-III vs 52.5% for placebo; *P = .03).*

- *Heparin decreases AT-III binding to glycosaminoglycans.*

Efficacy and Safety of Tifacogin (Recombinant Tissue Factor Pathway Inhibitor) in Severe Sepsis

A Randomized Controlled Trial

Patients with severe sepsis and a high INR (1.2) Primary efficacy pop.
Randomly assigned to iv tifacogin (0.025 mg/kg per hour for 96 hours) or placebo (arginine citrate buffer).
N= 1754

Table 2. 28-Day Mortality Overall and in Prespecified Subpopulations

Population	No. of Patients		28-Day Mortality Rate, No. (%)		Relative Risk (95% Confidence Interval)
	Placebo	Tifacogin	Placebo	Tifacogin	
Primary efficacy (baseline INR ≥1.2)	874	880	296 (33.9)	301 (34.2)	1.01 (0.89-1.15)
Baseline INR ≥1.5 and coagulation organ dysfunction score <4	149	125	68 (45.6)	52 (41.6)	0.91 (0.69-1.20)
Baseline INR <1.5 or coagulation organ dysfunction score ≥4	724	753	228 (31.5)	248 (32.9)	1.05 (0.90-1.21)
Shock at baseline					
No	208	245	62 (29.8)	70 (28.6)	0.96 (0.72-1.28)
Yes	666	635	234 (35.1)	231 (36.4)	1.04 (0.90-1.20)
Baseline APACHE II score					
<20	207	188	45 (21.7)	33 (17.6)	0.81 (0.54-1.21)
≥20	665	689	249 (37.4)	267 (38.8)	1.03 (0.90-1.19)
Baseline Pao_2/Fio_2 ratio <300	767	752	264 (34.4)	263 (35.0)	1.02 (0.89-1.17)
Baseline Pao_2/Fio_2 ratio ≥300	107	127	32 (29.9)	38 (29.9)	1.00 (0.67-1.48)

Optimized phase 3 tifacogin in multicenter international sepsis trial **(OPTIMIST) study**
JAMA. 2003;290:238-247

No effect on all-cause mortality in patients with severe sepsis and high INR.

- Associated with an increase in risk of bleeding, irrespective of baseline INR.

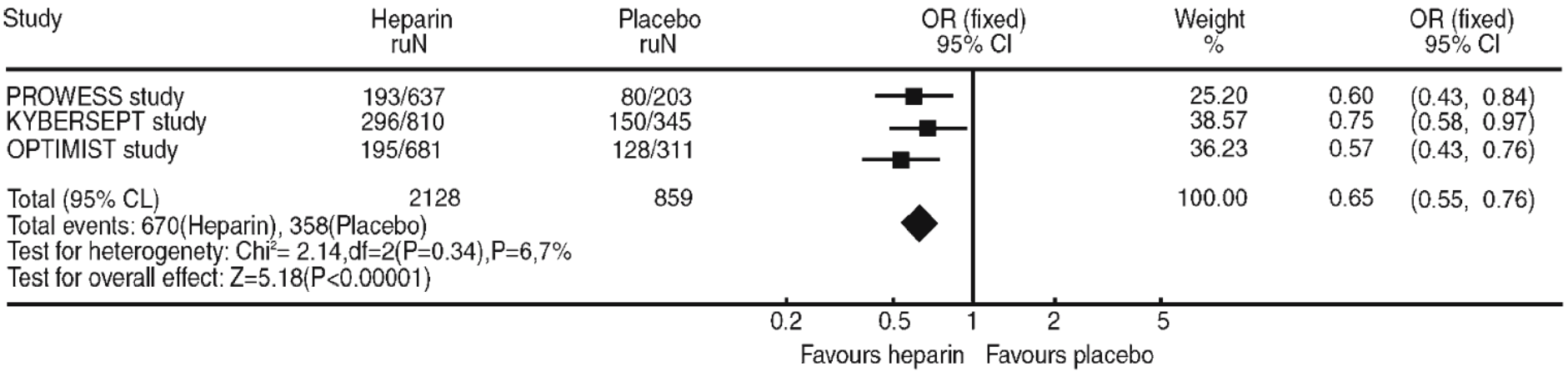
- Heparin use in all the trials ----- implications ????

Intensive Care Med (2005) 31:1297–1298
DOI 10.1007/s00134-005-2723-0

Ritesh Agarwal
Dheeraj Gupta

Anticoagulation in sepsis: Is low-dose heparin as effective as activated protein C?

Trial and treatment	28-day survival		OR of death (95% CI)	*p* value
	Yes	No		
PROWESS study (n=1690)[a]				
Placebo				
Heparin	458	179	0.6 (0.43–0.84)	0.002
No heparin	123	80		
Activated Protein C				
Heparin	476	158	1.05 (0.73–1.5)	0.8
No heparin	164	52		
KyberSept study (n=2314)[b]				
Placebo				
Heparin	514	296	0.75 (0.58–0.97)	0.03
No heparin	195	150		
Antithrombin III				
Heparin	489	318	1.07 (0.83–1.38)	0.62
No heparin	220	134		
OPTIMIST study (n=1754)[c]				
Placebo				
Heparin	486	195	0.57 (0.43–0.76)	0.00009
No heparin	183	128		
Tissue factor pathway inhibitor				
Heparin	453	212	0.94 (0.7–1.26)	0.68
No heparin	199	99		



- Most patients received heparin at the same time as the study drug.
- In each trial, heparin use was associated with improved survival among placebo recipients only.
- NNT to prevent one death with heparin - 10 (95% CI: 7–16).
- Limitations of post hoc analysis , Sicker patients might not have received heparin, Died early.
- Conclusions - A large randomized, prospective trial is warranted to compare low-dose heparin with placebo with or without aPC, in order to assess the relative contributions of these agents to the survival of patients with sepsis.

Early intravenous unfractionated heparin and mortality in septic shock*

Ryan Zarychanski, MD; Steven Doucette, MSc; Dean Fergusson, PhD; Daniel Roberts, MD; Donald S. Houston, MD; Satendra Sharma, MD; Harlena Gulati, MD; Anand Kumar, MD

Table 3. Mortality over 28 days

Septic Shock Cohort	Sample Size, n	Mortality Rate by Heparin Status, No. Deaths/Total No. Patients (%)		Hazard Ratio (95% Confidence Interval)	*p*
		Heparin	Control		
28-day mortality					
Adjusted for propensity score	1390	279/695 (40.1)	307/695 (44.2)	0.85 (0.73–1.00)	0.05
Stratified 28-day mortality analysis in matched cohort (APACHE II quartile)					
5–18	333	41/166 (24.7)	36/167 (21.6)	1.11 (0.70–1.73)	0.65
19–23	381	63/186 (33.9)	68/195 (34.9)	0.93 (0.66–1.342	0.70
24–28	324	81/175 (46.3)	76/149 (51.0)	0.86 (0.63–1.18)	0.34
29–53	352	94/168 (56.0)	127/184 (69.0)	0.70 (0.54–0.92)	0.01

Retrospective multicenter cohort study

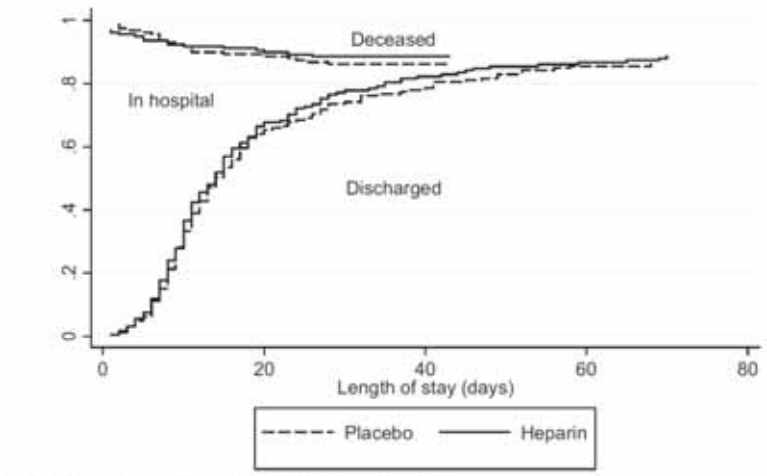
Benefits especially in patients with higher severity of illness, No sig. increase in bleeding complications

Need for prospective RCT's.

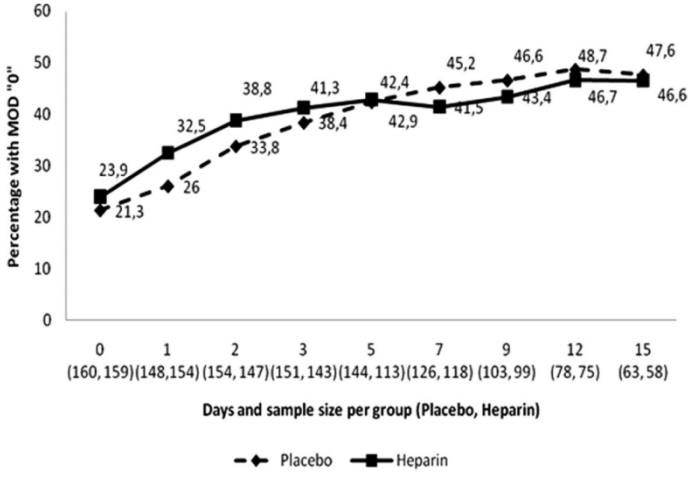
Crit Care Med 2008; 36: 2973–2979

Unfractioned heparin for treatment of sepsis: A randomized clinical trial (The HETRASE Study)*

Fabián Jaimes, MD, MSc, PhD; Gisela De La Rosa, MD; Carlos Morales, MD, MSc; Fernando Fortich, MD; Clara Arango, MD; Daniel Aguirre, MSc; Álvaro Muñoz, PhD



gure 2. Discharged alive with competing risk of death.



Randomized, placebo-controlled, **single-center clinical trial, testing low dose UFH as complementary treatment for sepsis. (Columbia).**

N=319, 550 U/hr infusion *7 days.

Primary aims – LOS (Length of stay) & MOD (Multiple organ dysfunction) score.

Secondary aims – 28 day all cause mortality.

Study was not able to demonstrate a beneficial effect on the chosen primary outcomes or in the 28-day mortality rate.

Heparin may be a feasible and safe intervention in Sepsis.

Crit Care Med 2009; 37: 1185–1196

Anticoagulation in Sepsis – Where do we stand ??

- rhAPC – To use or not to use??
- Need for more multicentre large RCT's to elucidate the role of rhAPC and Heparin in Sepsis.
- Heparin – An exceedingly feasible option in the major population in the developing world.
- Pharmaceutical driven expensive treatment may not be a feasible option till role of rhAPC is conclusively proven.

Ongoing trials

- Phase III trial of Recombinant Human Activated Protein C and Low Dose of Hydrocortisone and Fludrocortisone in Adult Septic Shock

  Activated Protein C and Corticosteroids for Human Septic Shock ***(APROCCHS)***

  NCT00625209

- A Randomized, Double-blind, Placebo-controlled, Multicenter, Phase 3 Study of Drotrecogin Alfa (Activated) Administered as a Continuous 96-hr Infusion to Adult Patients With Septic Shock.

  NCT00604214

Corticosteroids in Sepsis

	Corticosteroids
Inflammation	Reduce inflammation by decreasing cytokines, adhesion molecules, and receptor synthesis; modulating expression of Toll-like receptors 2 and 4; promoting shift toward Th-2 immune response; and stimulating activation of mechanisms for resolving inflammation
Coagulation and fibrinolysis	Promote coagulation by increasing levels of factor VIII and von Willebrand factor; inhibit fibrinolysis by increasing plasminogen activator inhibitor–1 activity; inhibit coagulation by inhibiting platelet aggregation and decreasing tissue factor–mediated procoagulant activity
Apoptosis	Provide proapoptotic effects upon T-lymphocytes, eosinophils, osteoblasts, osteocysts, fibroblasts; provide antiapoptotic effects on neutrophils, erythroblasts, and cells of the mammary gland, ovaries, and liver
Haemodynamics	Help maintain vascular tone, endothelium integrity, capillary permeability, myocardial inotropic activity

Effects of corticosteroids in patients with sepsis have been investigated for half a century.

Recent introduction of the term Critical illness–related corticosteroid insufficiency (CIRCI).

Several small studies have reported a decrease in the duration of vasopressor therapy withdrawal with low doses of corticosteroids.

Clin Chest Med 29 (2008) 705–712

JAMA®

Online article and related content current as of August 24, 2009.

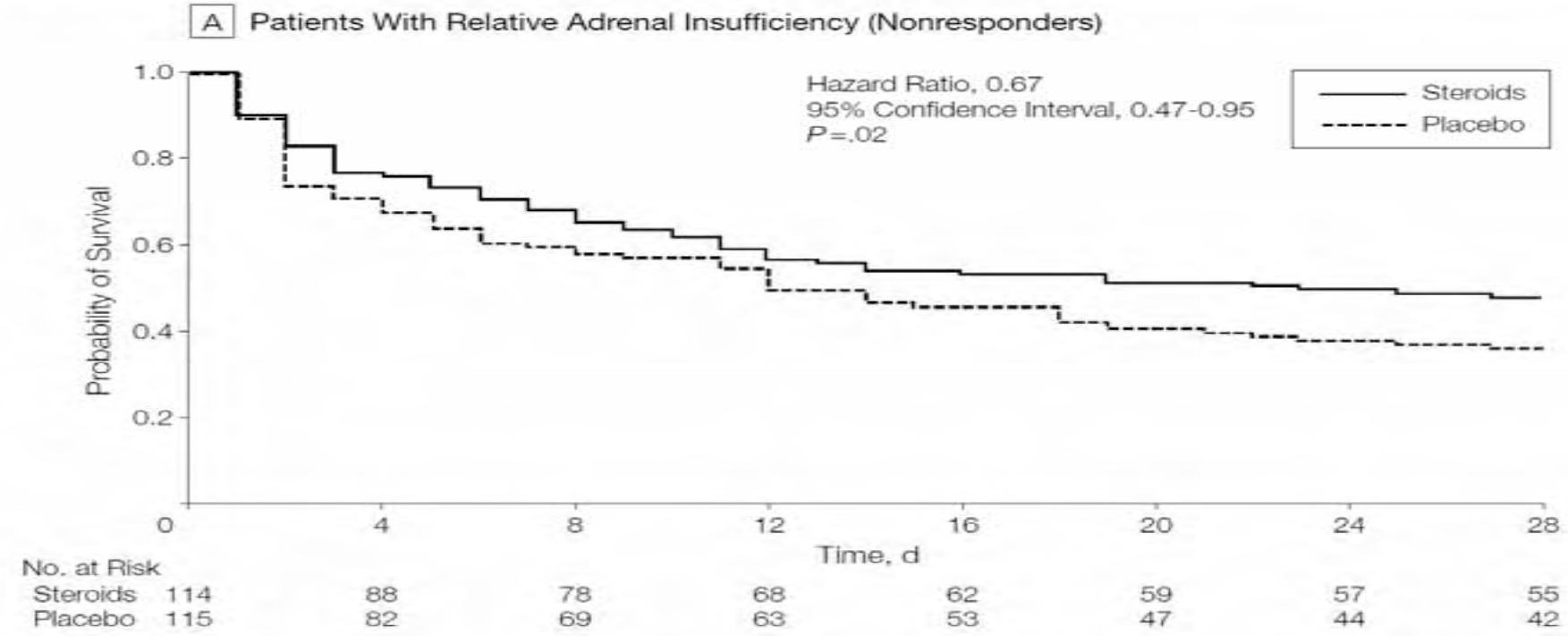
Effect of Treatment With Low Doses of Hydrocortisone and Fludrocortisone on Mortality in Patients With Septic Shock

Djillali Annane; Véronique Sébille; Claire Charpentier; et al.

JAMA. 2002;288(7):862-871 (doi:10.1001/jama.288.7.862)

Primary end point – 28 day mortality in corticotrophin nonresponders

Figure 2. Kaplan-Meier Analysis of the Probability of Survival of Patients With Septic Shock



- 300 vasopressor- and ventilator-dependent septic shock patients.
- Randomized within the first 8 hours to receive 50 mg hydrocortisone every 6 hours and 50 mg of fludrocortisone for 7 days.
- Corticosteroid effects were seen in all the patients but mainly in the group of patients who did not respond to a short corticotrophin test.
- In nonresponders, 73 deaths (63%) in the placebo group and 60 deaths (53%) in the corticosteroid group (hazard ratio, 0.67; 95% confidence interval, 0.47-0.95; P=.02).
- Vasopressor therapy was withdrawn within 28 days in 46 patients (40%) in the placebo group and in 65 patients (57%) in the corticosteroid group (hazard ratio, 1.91; 95% confidence interval, 1.29-2.84; P=.001).
- There was no significant difference between groups in responders.
- No evidence was found for an increased risk of gastroduodenal bleeding, superinfection, or neuromuscular weakness.

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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*

- Five hundred patients randomized to receive 50 mg of intravenous hydrocortisone every 6 hours for 5 days, then every 12 hours for 3 days and once daily for 3 days.

- At 28 days, the primary outcome was death among patients who did not have a response to a corticotropin test.

European Corticosteroid Therapy of Septic Shock (Corticus) trial

At 28 days, there was no significant difference in mortality between patients in the two study groups who did not have a response to corticotropin (39.2%/36.1%, p = 0.69) or between those who had a response to corticotropin (28.8% /28.7%, p = 1.00).

- **Faster resolution of shock but at 28 days the proportion of patients with shock reversed was not significantly greater in the treated patients.**
- **Use of ACTH test did not predict resolution of shock.**
- **Some patients in the hydrocortisone group experienced new episodes of shock and superinfection.**
- **Finally, the corticosteroid therapy increased the risk of hyperglycemia and hypernatremia**

Differences between two studies

	FRENCH STUDY (Annane et al)	CORTICUS
Time window for inclusion	8 hours Early septic shock	72 hours Early+Late septic shock
Fludrocortisone	Yes	No
Treatment duration	7 days	11 days
Weaning	None	Tapering of steroids
Severity of shock	> 1 hour	< 1 hour
SAPS II	59	49
% of non responders	77 %	47 %
Prop. Of medical patients	66 %	36 %
Primary source of infection	Lung	Abdomen

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

A Systematic Review

Djillali Annane, MD

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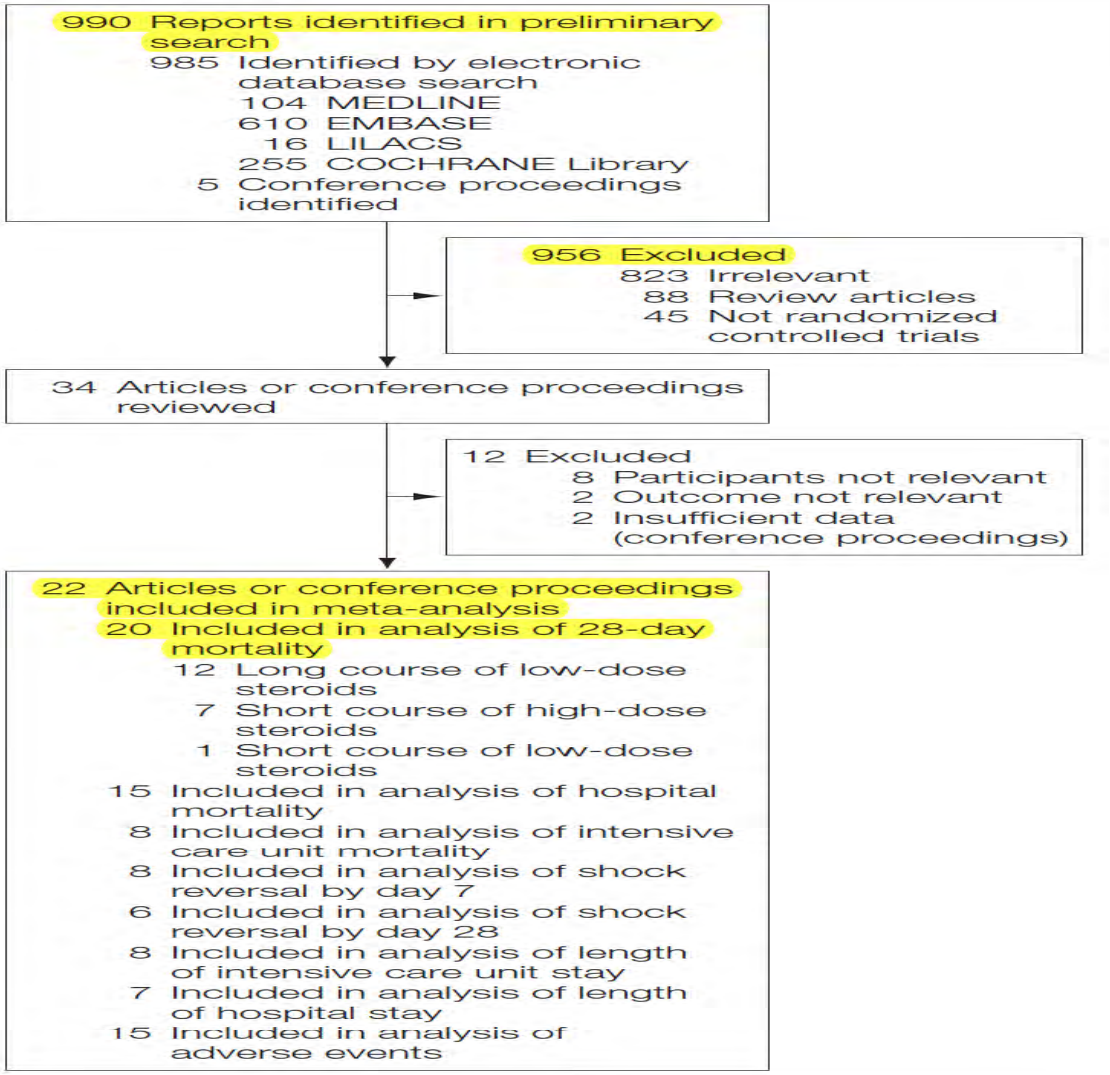

JAMA. 2009;301(22):2362-2375

Figure 2. Twenty-Eight-Day Mortality in Randomized and Quasi-randomized Controlled Trials

Source	Treatment, No. Events	Treatment, No. Total Patients	Control, No. Events	Control, No. Total Patients	Risk Ratio (95% CI)	Weight, %
Randomized controlled trials						
Schumer,[39] 1976	9	86	33	86	0.27 (0.14-0.53)	3.9
Sprung et al,[42] 1984	33	43	11	16	1.12 (0.77-1.61)	7.9
Bone et al,[45] 1987	65	191	48	190	1.35 (0.98-1.84)	9.0
VASSCSG,[46] 1987	23	112	24	111	0.95 (0.57-1.58)	5.6
Luce et al,[47] 1988	22	38	20	37	1.07 (0.72-1.60)	7.3
Bollaert et al,[15] 1998	7	22	12	19	0.50 (0.25-1.02)	3.6
Chawla et al,[17] 1999	6	23	10	21	0.55 (0.24-1.25)	2.9
Briegel et al,[16] 1999	3	20	4	20	0.75 (0.19-2.93)	1.2
Annane et al,[18] 2002	82	151	91	149	0.89 (0.73-1.08)	11.7
Yildiz et al,[19] 2002	8	20	12	20	0.67 (0.35-1.27)	4.1
Oppert et al,[51] 2005	10	23	11	25	0.99 (0.52-1.88)	4.1
Confalonieri et al,[50] 2005	0	23	6	23	0.08 (0.00-1.29)	0.3
Tandan et al,[52] 2005	11	14	13	14	0.85 (0.62-1.15)	9.1
Rinaldi et al,[53] 2006	6	26	7	26	0.86 (0.33-2.21)	2.3
Meduri et al,[56] 2007	10	42	8	19	0.57 (0.27-1.20)	3.3
Cicarelli et al,[55] 2007	7	14	12	15	0.63 (0.35-1.12)	4.8
Sprung et al,[22] 2008	86	251	78	248	1.09 (0.85-1.40)	10.4
Subtotal	388	1099	400	1039	0.84 (0.71-1.00)	91.5
Test for heterogeneity: $\tau = 0.06$; $\chi^2 = 33.82$, df = 16 ($P = .006$); $I^2 = 53\%$						
Test for overall effect: $z = 1.96$ ($P = .05$)						
Quasi-randomized controlled trials						
Wagner et al,[34] 1955	1	52	1	61	1.17 (0.08-18.30)	0.3
Klastersky et al,[37] 1971	22	46	18	39	1.04 (0.66-1.63)	6.4
Lucas and Ledgerwood,[41] 1984	5	23	5	25	1.09 (0.36-3.27)	1.7
Subtotal	28	121	24	125	1.05 (0.69-1.58)	8.5
Test for heterogeneity: $\tau = 0.00$; $\chi^2 = 0.01$, df = 2 ($P = .99$); $I^2 = 0\%$						
Test for overall effect: $z = 0.21$ ($P = .83$)						
Total	416	1220	424	1164	0.87 (0.74-1.01)	100
Test for heterogeneity: $\tau = 0.04$; $\chi^2 = 34.18$, df = 19 ($P = .02$); $I^2 = 44\%$						
Test for overall effect: $z = 1.81$ ($P = .07$)						

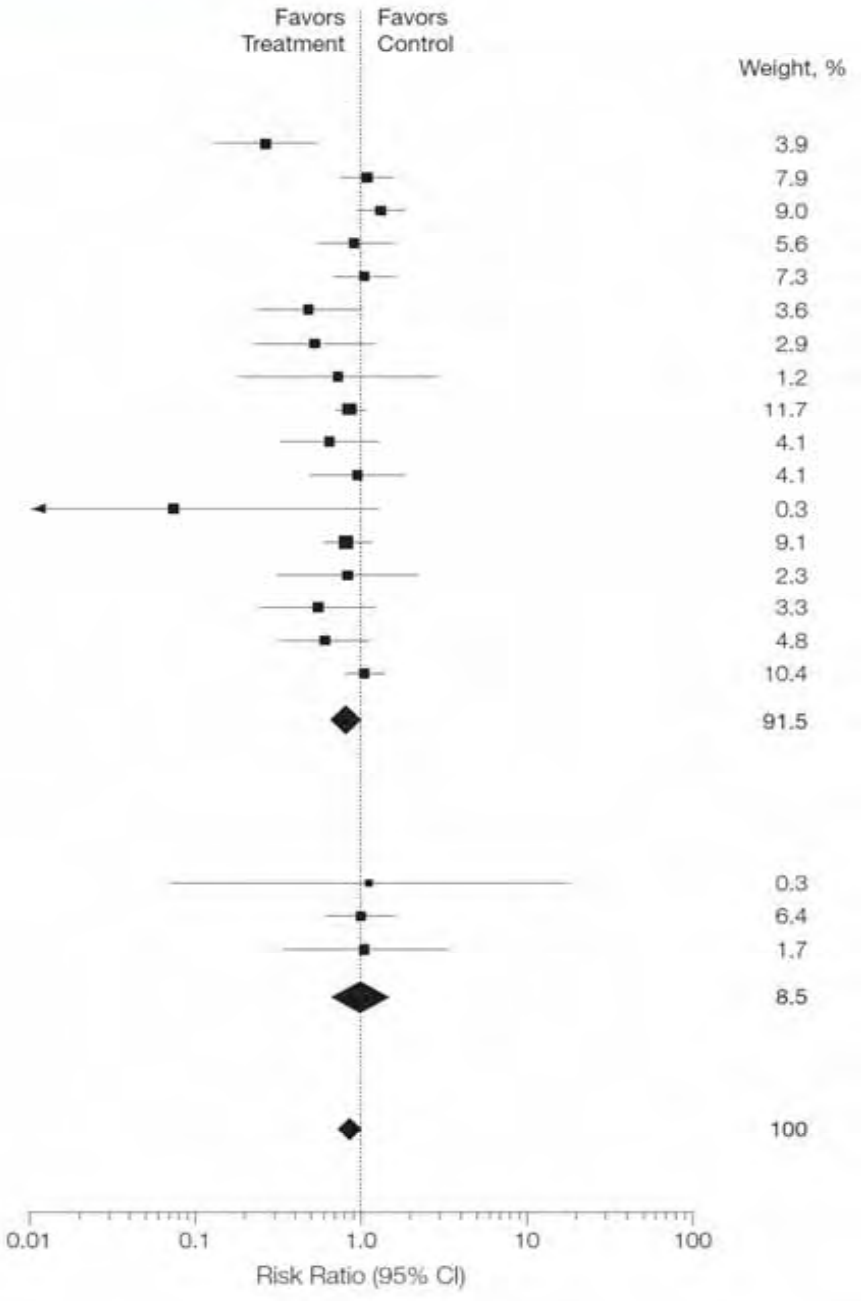

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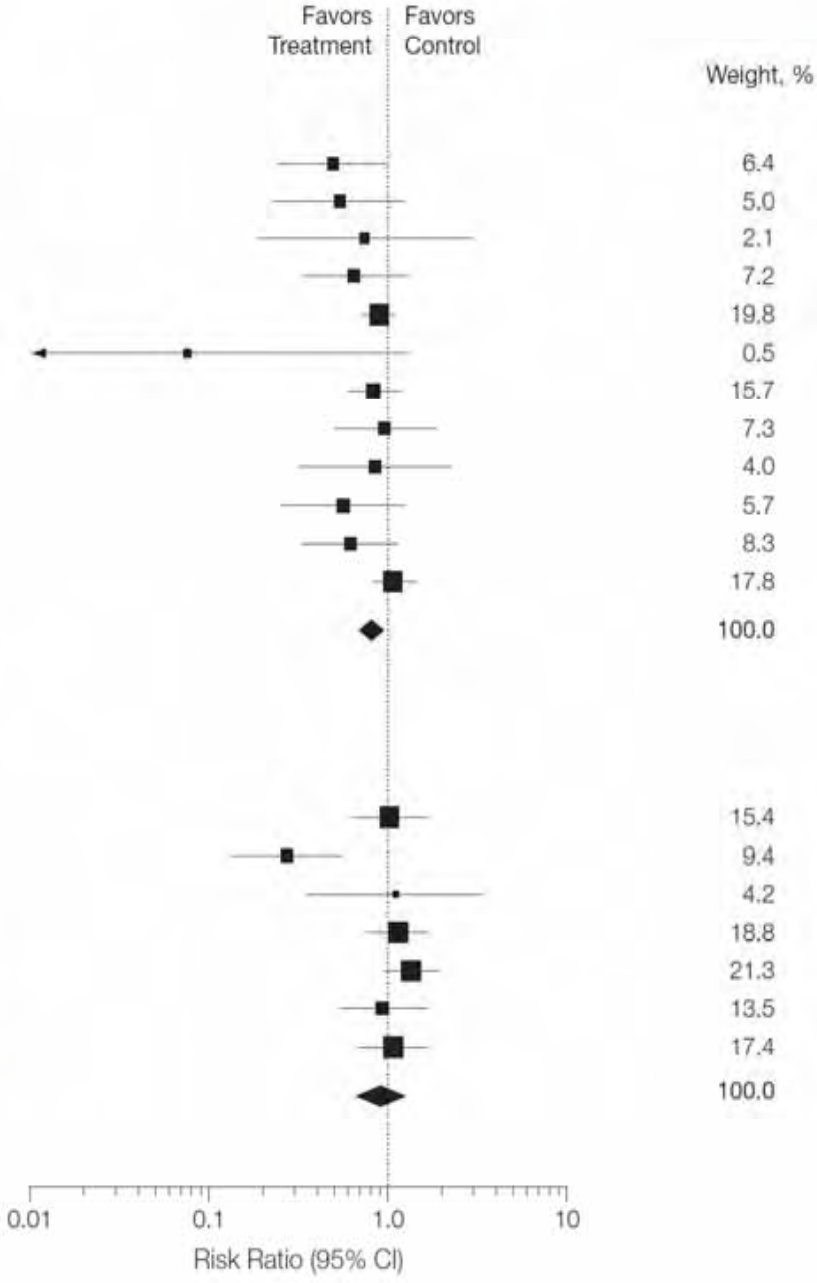
Figure 3. Twenty-Eight-Day Mortality by Subgroup Based on Dose/Duration of Corticosteroid Therapy

Source	Treatment, No. Events	Treatment, No. Total Patients	Control, No. Events	Control, No. Total Patients	Risk Ratio (95% CI)	Weight, %
Long course of low-dose corticosteroids						
Bollaert et al,[15] 1998	7	22	12	19	0.50 (0.25-1.02)	6.4
Chawla et al,[17] 1999	6	23	10	21	0.55 (0.24-1.25)	5.0
Briegel et al,[16] 1999	3	20	4	20	0.75 (0.19-2.93)	2.1
Yildiz et al,[19] 2002	8	20	12	20	0.67 (0.35-1.27)	7.2
Annane et al,[18] 2002	82	151	91	149	0.89 (0.73-1.08)	19.8
Confalonieri et al,[50] 2005	0	23	6	23	0.08 (0.00-1.29)	0.5
Tandan et al,[52] 2005	11	14	13	14	0.85 (0.62-1.15)	15.7
Oppert et al,[51] 2005	10	23	11	25	0.99 (0.52-1.88)	7.3
Rinaldi et al,[53] 2006	6	26	7	26	0.86 (0.33-2.21)	4.0
Meduri et al,[56] 2007	10	42	8	19	0.57 (0.27-1.20)	5.7
Cicarelli et al,[55] 2007	7	14	12	15	0.63 (0.35-1.12)	8.3
Sprung et al,[22] 2008	86	251	78	248	1.09 (0.85-1.40)	17.8
Subtotal	236	629	264	599	0.84 (0.72-0.97)	100.0
Test for heterogeneity: $\tau = 0.01$; $\chi^2 = 12.89$, df = 11 ($P = .30$); $I^2 = 15\%$						
Test for overall effect: $z = 2.31$ ($P = .02$)						
Short course of high-dose corticosteroids						
Klastersky et al,[37] 1971	22	46	18	39	1.04 (0.66-1.63)	15.4
Schumer,[39] 1976	9	86	33	86	0.27 (0.14-0.53)	9.4
Lucas and Ledgerwood,[41] 1984	5	23	5	25	1.09 (0.36-3.27)	4.2
Sprung et al,[42] 1984	33	43	11	16	1.12 (0.77-1.61)	18.8
Bone et al,[45] 1987	65	191	48	190	1.35 (0.98-1.84)	21.3
VASSCSG,[46] 1987	23	112	24	111	0.95 (0.57-1.58)	13.5
Luce et al,[47] 1988	22	38	20	37	1.07 (0.72-1.60)	17.4
Subtotal	179	539	159	504	0.94 (0.69-1.30)	100.0
Test for heterogeneity: $\tau = 0.11$; $\chi^2 = 18.63$, df = 6 ($P = .005$); $I^2 = 68\%$						
Test for overall effect: $z = 0.35$ ($P = .73$)						



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

- ***Conclusion from meta-analysis***
- Overall, corticosteroids did not affect 28-day all-cause mortality in severe sepsis and septic shock.

- Meta-analysis of a subgroup of 12 trials investigating prolonged low-dose corticosteroid treatment suggests a favourable effect on all cause mortality.

- Uniformly does not support the use of a short course of high dose corticosteroids in severe sepsis or septic shock.

- Corticosteroids should be considered at a daily dose of 200 to 300 mg of hydrocortisone (or equivalent) as intravenous bolus or continuous infusion.

- ***Surviving sepsis*** - We suggest intravenous hydrocortisone should be given only to adult septic shock patients after blood pressure is identified to be poorly responsive to fluid resuscitation and vasopressor therapy (2C).

- Hydrocortisone dose should be 300 mg/day (1A)

- Do not use corticosteroids to treat sepsis in the absence of shock unless the patient's endocrine or corticosteroid history warrants it (1D)

- ***NEED FOR FURTHER TRIALS***
- Combination of Corticotherapy and Intensive Insulin Therapy for Septic Shock ***(COIITSS)***

  Phase 3 Study of Corticotherapy (Hydrocortisone Alone Versus Hydrocortisone Plus Fludrocortisone) Versus Corticotherapy Plus Intensive Insulin Therapy for Septic Shock (Completed).

- APROCCHS

- Hydrocortisone Versus Hydrocortisone Plus Fludrocortisone for the Treatment of Adrenal Insufficiency in Severe Sepsis.

  (Terminated)