Hydrocortisone plus Fludrocortisone for Adults with Septic Shock

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ICU Journal Club

N Engl J Med 2018;378:809-18.
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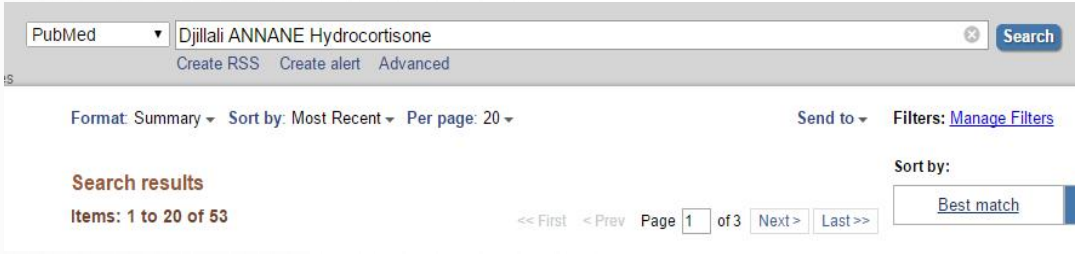
Contents

First Author



Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock, 2012.

Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, Sevransky JE, Sprung CL, Douglas IS, Jaeschke R, Osborn TM, Nunnally ME, Townsend SR, Reinhart K, Kleinpell RM, Angus DC, Deutschman CS, Machado FR, Rubenfeld GD, Webb S, Beale RJ, Vincent JL, Moreno R; Surviving Sepsis Campaign Guidelines Committee including The Pediatric Subgroup.

Intensive Care Med. 2013 Feb;39(2):165-228. doi: 10.1007/s00134-012-2769-8. Epub 2013 Jan 30.

PMID: 23361625

Similar articles

Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016.

Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, Kumar A, Sevransky JE, Sprung CL, Nunnally ME, Rochwerg B, Rubenfeld GD, Angus DC, Annane D, Beale RJ, Bellinghan GJ, Bernard GR, Chiche JD, Coopersmith C, De Backer DP, French CJ, Fujishima S, Gerlach H, Hidalgo JL, Hollenberg SM, Jones AE, Karnad DR, Kleinpell RM, Koh Y, Lisboa TC, Machado FR, Marini JJ, Marshall JC, Mazuski JE, McIntyre LA, McLean AS, Mehta S, Moreno RP, Myburgh J, Navalesi P, Nishida O, Osborn TM, Perner A, Plunkett CM, Ranieri M, Schorr CA, Seckel MA, Seymour CW, Shieh L, Shukri KA, Simpson SQ, Singer M, Thompson BT, Townsend SR, Van der Poll T, Vincent JL, Wiersinga WJ, Zimmerman JL, Dellinger RP.

Crit Care Med. 2017 Mar;45(3):486-552. doi: 10.1097/CCM.0000000000002255.

PMID: 28098591

Research resources

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

⚠ The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Read our disclaimer for details.

ClinicalTrials.gov Identifier: NCT00625209

Recruitment Status: Completed
First Posted: February 28, 2008
Last Update Posted: June 14, 2017

Am J Respir Crit Care Med. 2013 May 15;187(10):1091-7. doi: 10.1164/rccm.201211-2020OC.

Recombinant human activated protein C for adults with septic shock: a randomized controlled trial.

Annane D[1], Timsit JF, Megarbane B, Martin C, Misset B, Mourvillier B, Siami S, Chagnon JL, Constantin JM, Petitpas F, Souweine B, Amathieu R, Forceville X, Charpentier C, Tesnière A, Chastre J, Bohe J, Colin G, Cariou A, Renault A, Brun-Buisson C, Bellissant E; APROCCHSS Trial Investigators.

Author information

Masking:	Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)
Primary Purpose:	Treatment
Official Title:	Phase III of Recombinant Human Activated Protein C and Low Dose of Hydrocortisone and Fludrocortisone in Adult Septic Shock
Study Start Date:	March 2008
Actual Primary Completion Date:	June 2015
Actual Study Completion Date:	July 2016

Resource links provided by the National Library of Medicine NIH NLM

MedlinePlus related topics: Shock

Drug Information available for: Hydrocortisone acetate Hydrocortisone Hydrocortisone sodium succinate Hydrocortisone cypionate Fludrocortisone acetate Hydrocortisone valerate Blood-coagulation factor XIV Hydrocortisone probutate

U.S. FDA Resources

Septic shock – High mortality & Cognitive decline

Table 2. Random Effects Meta-Analysis by Septic Shock Criteria Groups

Key messages

- More than half of sepsis survivors have long-term cognitive impairment
- Cerebrovascular damage, metabolic disorders, and brain inflammation are hallmarks of sepsis and precede cognitive impairment
- Brain changes during sepsis mainly include disruption of the blood–brain barrier, microglial activation, and altered neurotransmission; these lesions can be diffuse and often target the limbic system, specifically the hippocampus
- Appropriate management of the acute phase of sepsis—eg, following the Surviving Sepsis Campaign guidelines, can prevent cognitive impairment
- No specific treatment is available; future treatment might target the blood–brain barrier, microglial cell activation, or neurotransmission

Overall	52	70 058/166 479 (46.5) [42.7-50.3]	11026.7	51	<.001	99.5	182.5

Abbreviations: MAP, mean arterial pressure; qSOFA, quick SOFA; SOFA: Sequential [Sepsis-related] Organ Failure Assessment.

Lancet Respir Med 2015; 3: 61-9

Surviving Sepsis Campaign: international guidelines for management of sepsis and septic shock: 2016

A. INITIAL RESUSCITATION

1. Sepsis and septic shock are medical emergencies, and we recommend that treatment and resuscitation begin immec
2. We rec be give
3. We rec hemoc Remar variabl others
4. We rec if the c
5. We su recom
6. We rec vasopr
7. We su hypop

M. MECHANICAL VENTILATION

1. We recommend using a target tidal volume of 6 mL/kg predicted body weight compared with 12 mL/kg in adult patients with sepsis-induced acute respiratory distress syndrome (ARDS) (strong recommendation, high quality of evidence)
2. We recor patients
3. We sugg moderat
4. We sugg moderat
5. We recor 150 (stro
6. We recor recomme
7. We make
8. We sugg PaO_2/FIO_2
9. We recommend a conservative fluid strategy for patients with established sepsis-induced ARDS who do not have evidence of tissue hypoperfusion (strong recommendation, moderate quality of evidence).
10. We recommend against the use of ß-2 agonists for the treatment of patients with sepsis-induced ARDS without bronchospasm (strong recommendation, moderate quality of evidence).
11. We recommend against the routine use of the pulmonary artery catheter for patients with sepsis-induced ARDS (strong recommendation, high quality of evidence).

D. ANTIMICROBIAL THERAPY

1. We recommend that administration of IV antimicrobials should be initiated as soon as possible after recognition and within one hour for both sepsis and septic shock (strong recommendation, moderate quality of evidence).
2. We recommend empiric broad-spectrum therapy with one or more antimicrobials for patients presenting with sepsis or septic shock to cover all likely pathogens (including bacterial and potentially fungal or viral coverage) (strong recommendation, moderate quality of evidence).
3. We recommend that empiric antimicrobial therapy be narrowed once pathogen identification and sensitivities are established and/or adequate clinical improvement is noted (BPS).
4. We recommend against sustained systemic antimicrobial prophylaxis in patients with severe inflammatory states of noninfectious origin (e.g., severe pancreatitis, burn injury) (BPS).
5. We recommend that dosing strategies of antimicrobials be optimized based on accepted pharmacokinetic/pharmacodynamic principles and specific drug properties in patients with sepsis or septic shock

Intensive Care Med 2017; 43: 304-77

APC – Withdrawal its commercial use from market

Lilly

Lilly Announces Withdrawal of Xigris® Following Recent Clinical Trial Results

INDIANAPOLIS, October 25, 2011 /PRNewswire/ --

Eli Lilly and Company announces withdrawal of its Xigris(R) [drotrecogin alfa (activated)] product in all markets following results of the PROWESS-SHOCK study, which showed the study did not meet the primary endpoint of a statistically significant reduction in 28-day all-cause mortality in patients with septic shock. The company is working with regulatory agencies on this withdrawal, and is in the process of notifying health care professionals and clinical trial investigators.

"While there were no new safety findings, the study failed to demonstrate that Xigris improved patient survival and thus calls into question the benefit-risk profile of Xigris and its continued use," said Timothy Garnett, M.D., Lilly's Senior Vice President and Chief Medical Officer. "Patients currently receiving treatment with Xigris should have treatment discontinued, and Xigris treatment should not be initiated for new patients."

HPA axis in sepsis and septic shock

TABLE 1 | Mechanism explaining hypothalamic–pituitary–adrenal axis disruption in sepsis.

HPA axis level	Main mechanisms	Precipitating factors
Hypothalamus	Necrosis or hemorrhage	Anticoagulants, brisk variations in blood pressure, high dose of vasopressors Coagulopathy, severe hypoxia, hyperglycemia
	Decreased CRH/AVP synthesis/release	Treatment with corticosteroids, psychoactive drugs Increased brain levels of proinflammatory cytokines (mainly TNF and IL-1) Hypercortisolemia
Pituitary gland	Necrosis or hemorrhage	Anticoagulants, brisk variations in blood pressure, high dose of vasopressors Coagulopathy, severe hypoxia, hyperglycemia
	Decreased ACTH synthesis/release	Treatment with corticosteroids, psychoactive drugs, anti-infective drugs, megestrol acetate medroxyprogesterone Increased blood levels of proinflammatory cytokines (mainly TNF and IL-1) Coagulopathy, severe hypoxia, hypercortisolemia
Adrenals	Necrosis or hemorrhage	Anticoagulants, brisk variations in blood pressure, high dose of vasopressors Coagulopathy, severe hypoxia
	Decreased steroidogenesis	
	Depletion of lipid droplets	Cholesterol-lowering drugs
	Decreased expression of scavenger receptor B1	Proinflammatory mediators
	Enzymes inhibition	Aminoglutethimide, ketoconazole, fluconazole, etomidate, dexmedetomidine Proinflammatory mediators
	Decreased sensitivity of ACTH receptors	Circulating and adrenals proinflammatory mediators (e.g., corticostatins)
Tissue resistances	Decreased cortisol delivery to tissues	Proinflammatory mediators, liver failure, severe denutrition
	Accelerated glucose clearance	Phenobarbital, phenytoin, rifampin
	Decreased binding capacity and affinity of glucocorticoid receptor	Proinflammatory mediators

HPA, hypothalamic–pituitary–adrenal.

Front Endocrinol (Lausanne) 2016; 7: 70

Controversial analysis for corticosteroids in sepsis

Study or Subgroup	steroids Events	Total	control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
2.1.1 lower risk of bias						
Annane 2002	102	150	112	149	8.4%	0.90 [0.78, 1.04]
Arabi 2010	34	39	32	36	8.0%	0.98 [0.83, 1.16]
Bernard 1987	30	50	31	49	5.8%	0.95 [0.69, 1.29]
Bollaert 1998	7	22	12	19	2.3%	0.50 [0.25, 1.02]
Bone 1987	65	191	48	190	5.8%	1.35 [0.98, 1.84]
Briegel 1999	5	20	6	20	1.2%	0.83 [0.30, 2.29]
Cicarelli 2007	7	14	12	15	3.0%	0.63 [0.35, 1.12]
Confalonieri 2005	1	23	9	23	0.4%	0.11 [0.02, 0.81]
De Gans 2002	11	157	21	144	2.3%	0.48 [0.24, 0.96]
Snijders 2010	6	104	6	109	1.1%	1.05 [0.35, 3.15]
Sprung 1984	33	43	11	16	5.0%	1.12 [0.77, 1.61]
Sprung 2008	137	242	127	235	8.1%	1.05 [0.89, 1.23]
Thwaites 2004	87	274	112	271	7.1%	0.77 [0.61, 0.96]
VASSCSG 1987	23	112	24	111	3.6%	0.95 [0.57, 1.58]
Yildiz 2002	8	20	12	20	2.6%	0.67 [0.35, 1.27]
Yildiz 2011	16	27	15	28	4.0%	1.11 [0.69, 1.76]
Subtotal (95% CI)		**1488**		**1435**	**68.6%**	**0.92 [0.82, 1.03]**
Total events	572		590			
Heterogeneity: Tau² = 0.02; Chi² = 26.31, df = 15 (P = 0.03); I² = 43%						
Test for overall effect: Z = 1.38 (P = 0.17)						
2.1.2 high risk of bias						
Cicarelli 2006	5	15	3	14	0.9%	1.56 [0.45, 5.33]
Gordon 2014	8	31	9	30	1.8%	0.86 [0.38, 1.93]
Hoffman 1984	2	20	10	18	0.7%	0.18 [0.05, 0.71]
Hu 2009	4	34	5	33	0.9%	0.78 [0.23, 2.64]
Klastersky 1971	23	46	18	39	4.2%	1.08 [0.69, 1.69]
Luce 1988	22	38	20	37	4.6%	1.07 [0.72, 1.60]
Marik 1993	1	14	3	16	0.3%	0.38 [0.04, 3.26]
Meduri 2009	23	48	6	32	1.9%	2.56 [1.17, 5.57]
Nafae 2013	4	60	6	20	1.0%	0.22 [0.07, 0.71]
Oppert 2005	7	18	11	23	2.2%	0.81 [0.40, 1.67]
Rinaldi 2006	2	20	2	20	0.4%	1.00 [0.16, 6.42]
Ruolan 2014	4	20	7	20	1.1%	0.57 [0.20, 1.65]
Scarborough 2007	140	231	127	228	8.2%	1.09 [0.93, 1.27]
Schumer 1976	9	86	33	86	2.4%	0.27 [0.14, 0.53]
Wan 2011	3	35	5	35	0.7%	0.60 [0.16, 2.32]
Subtotal (95% CI)		**716**		**651**	**31.4%**	**0.79 [0.58, 1.08]**
Total events	257		265			
Heterogeneity: Tau² = 0.18; Chi² = 38.78, df = 14 (P = 0.0004); I² = 64%						
Test for overall effect: Z = 1.49 (P = 0.14)						
Total (95% CI)		**2204**		**2086**	**100.0%**	**0.89 [0.79, 1.01]**
Total events	829		855			
Heterogeneity: Tau² = 0.04; Chi² = 65.01, df = 30 (P = 0.0002); I² = 54%						
Test for overall effect: Z = 1.87 (P = 0.06)						
Test for subgroup differences: Chi² = 0.84, df = 1 (P = 0.36), I² = 0%						

Risk Ratio M-H, Random, 95% CI

0.5 0.7 1 1.5 2

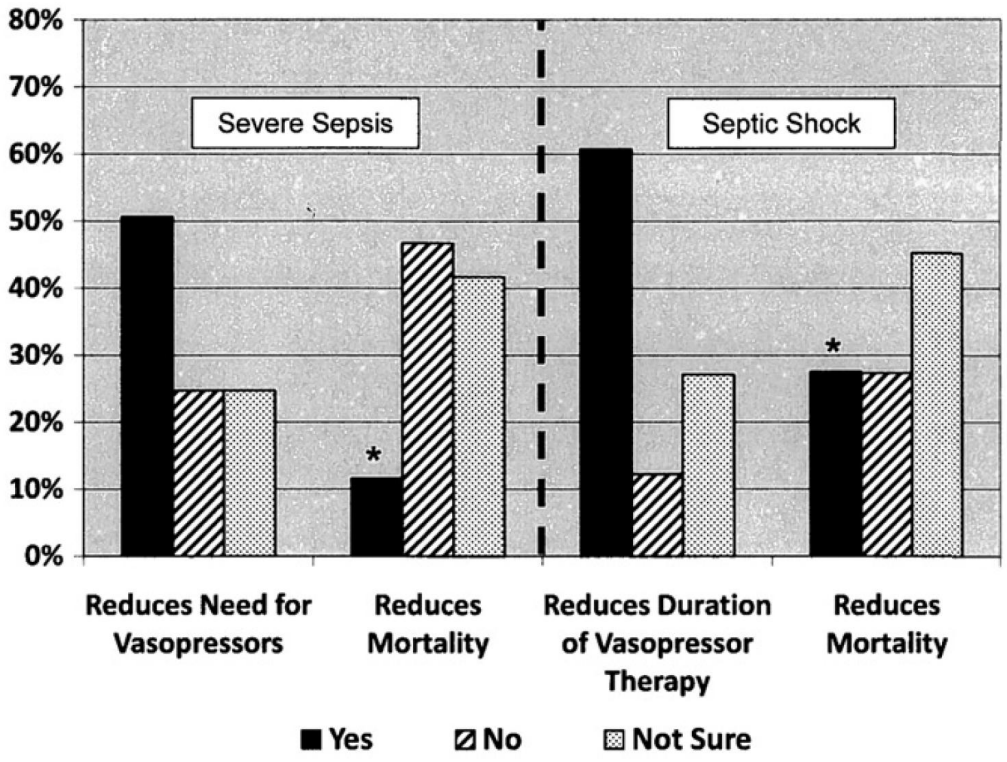
Favours steroids Favours control

Fig. 2 Forest plot of mortality at longest follow-up of all trials evaluating steroids for sepsis with subgroups according to risk of bias (random-effects model)

Syst Rev 2015; 12: CD002243

e Care Med 2015; 41: 1220-34

Physicians' opinions regarding corticosteroid



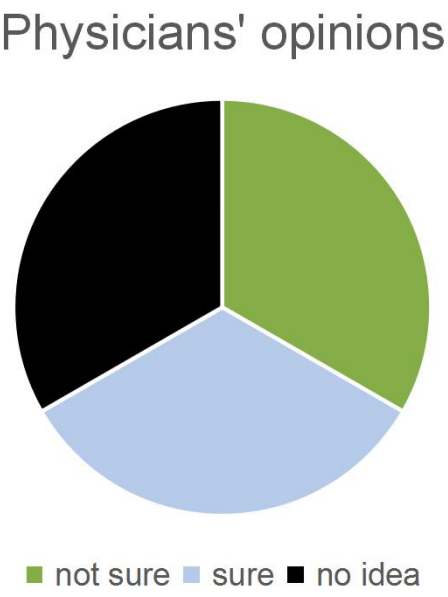


Fig. 1 Opinions regarding corticosteroid impact in severe sepsis and septic shock. *$P < .001$ for the comparison of "yes" response for reduces mortality in patients with severe sepsis vs those with septic shock.

J Crit Care 2012; 27: 351-61

Steroids - survival benefits for pts with septic shock

Table 4. Frequency of Fatal Events in 299 Patients with Septic Shock*

Variable	No. (%) Placebo	Steroids	Adjusted OR (95% CI)	*P* Value
Nonresponders				
No. of patients	115	114		
28-day mortality	73 (63)	60 (53)	0.54 (0.31-0.97)	.04
ICU mortality	81 (70)	66 (58)	0.50 (0.28-0.89)	.02
Hospital mortality	83 (72)	70 (61)	0.53 (0.29-0.96)	.04
1-Year mortality	88 (77)	77 (68)	0.57 (0.31-1.04)	.07
Responders				
No. of patients	34	36		
28-Day mortality	18 (53)	22 (61)	0.97 (0.32-2.99)	.96
ICU mortality	20 (59)	24 (67)	0.99 (0.31-3.16)	.99
Hospital mortality	20 (59)	25 (69)	1.20 (0.38-3.76)	.75
1-Year mortality	24 (71)	25 (69)	0.70 (0.20-2.40)	.57
All Patients				
No. of patients	149	150		
28-Day mortality	91 (61)	82 (55)	0.65 (0.39-1.07)	.09
ICU mortality	101 (68)	90 (60)	0.61 (0.37-1.02)	.06
Hospital mortality	103 (69)	95 (63)	0.67 (0.40-1.12)	.12
1-Year mortality	112 (75)	102 (68)	0.62 (0.36-1.05)	.08

*Results are based on patient responses to a short corticotropin test. Using baseline cortisol, cortisol response, McCabe classification, Logistic Organ Dysfunction score, arterial lactate levels and PaO_2/FiO_2 results for adjustment, analyses were performed with use of logistic models. OR indicates, odds ratios; CI, confidence intervals; and ICU, intensive care unit.

JAMA 2002; 288: 862-71
N Engl J Med 2008; 358: 111-24

Table 3. Outcomes According to Subgroup.*

Variable	No Response to Corticotropin		P Value	Response to Corticotropin		P Value	All Patients		P Value
	Hydrocortisone (N=125)	Placebo (N=108)		Hydrocortisone (N=118)	Placebo (N=136)		Hydrocortisone (N=251)	Placebo (N=248)	
Death within 28 days — no. (%)	49 (39.2)	39 (36.1)	0.69	34 (28.8)	39 (28.7)	1.00	86 (34.3)	78 (31.5)	0.51
Relative risk (95% CI)	1.09 (0.77 to 1.52)			1.00 (0.68 to 1.49)			1.09 (0.84 to 1.41)		
Absolute difference — % (95% CI)	3.1 (–9.5 to 15.7)			0.1 (–11.2 to 11.4)			2.8 (–5.5 to 11.2)		
Death in ICU — no./total no. (%)	58/125 (46.4)	44/108 (40.7)	0.43	41/118 (34.7)	45/135 (33.3)	0.89	102/251 (40.6)	89/247 (36.0)	0.31
Relative risk (95% CI)	1.14 (0.85 to 1.53)			1.04 (0.74 to 1.47)			1.13 (0.90 to 1.41)		
Absolute difference — % (95% CI)	5.7 (–7.1 to 18.4)			1.4 (–10.3 to 13.1)			4.6 (–3.9 to 13.1)		
Death during hospitalization — no./total no. (%)	60/125 (48.0)	50/108 (46.3)	0.90	48/118 (40.7)	50/133 (37.6)	0.70	111/251 (44.2)	100/245 (40.8)	0.47
Relative risk (95% CI)	1.04 (0.79 to 1.36)			1.08 (0.79 to 1.47)			1.08 (0.88 to 1.33)		
Absolute difference — % (95% CI)	1.7 (–11.1 to 14.6)			3.1 (–9.0 to 15.2)			3.4 (–5.3 to 12.1)		
Death at 1 yr — no./total no. (%)	73/124 (58.9)	60/105 (57.1)	0. 89	61/111 (55.0)	67/126 (53.2)	0.80	137/242 (56.6)	127/235 (54.0)	0.58
Relative risk (95% CI)	1.03 (0.83 to 1.29)			1.03 (0.82 to 1.31)			1.05 (0.89 to 1.23)		
Length of stay — days									
In ICU	17±19	17±17	0.47	18±22	19±16†	0.26	19±31	18±17†	0.51
In hospital	29±26	31±27	0.82	36±40	35±43‡	0.68	34±41	34±37‡	0.47

* Relative risks and percent differences are for the comparison between the hydrocortisone group and the placebo group. P values for categorical variables were calculated with the use of Fisher's exact test. P values for continuous variables were calculated with the use of the Wilcoxon rank-sum test. ICU denotes intensive care unit.
† Data were missing for one patient.
‡ Data were missing for three patients.

Divergent findings result from different designs

Table 1 Comparison of (a) targeted population, (b) experimental treatments of four trials on corticosteroids for septic shock

	Ger-Inf-05	CORTICUS	APROCCHSS	ADRENALS
(a)				
Expected sample size	300	800	1240	3800
Actual sample size	300	500	1241	?
Time window for inclusion since onset of shock	3 h then protocol amended for 8 h	72 h	24 h	24 h
Age	≥18 years	≥18 years	≥18 years	≥18 years
Shock criteria	SBP < 90 mm Hg for at least 1 h despite adequate fluid replacement and >5 μg/kg/h of dopamine or epinephrine or norepinephrine; Arterial lactate >2 mmol/l	SBP < 90 mmHg or decrease >50 mmHg in SBP in previous hypertensive patients despite adequate fluid replacement or need for vasopressors to maintain SBP ≥ 90 mmHg Administration of vasopressor for ≥1 h	Norepinephrine or epinephrine at a rate ≥0.25 μg/kg/min or ≥1 mg/h) or any other vasopressor to maintain SBP ≥ 90 mmHg or MBP ≥ 65 mmHg Administration of vasopressors for ≥6 h	Vasopressors or inotropes to maintain a SBP > 90 mmHg, or MBP > 60 mmHg, or a MBP target set by the treating clinician for maintaining perfusion Administration of vasopressors or inotropes for =4 h
Mechanical ventilation as a mandatory entry criteria	Yes	No	No	Yes
Organ failure	Urinary output of <0.5 ml/kg for ≥1 h Or PaO_2/FIO_2 < 280 mmHg	Urine output <0.5 ml/kg/h for ≥1 h Or pH < 7.3, or arterial base deficit ≥5.0 mmol/l, or arterial lactate >2 mmol/l Or PaO_2/FIO_2 < 280 in the absence of pneumonia, and <200 in the presence of pneumonia Or platelet count ≤100,000 cells/mm^3 Or Glasgow Coma Scale <14 or acute change from baseline)	Sequential Organ Failure Assessment (SOFA) score ≥3 for ≥2 organs for ≥6 consecutive hours	Not mentioned
Non-responders to the Synacthen test as the primary subgroup of interest	Yes	Yes	Yes	No
(b)				
Type of corticosteroids	Hydrocortisone hemisuccinate and 9-α-fludrocortisone	Hydrocortisone hemisuccinate	Hydrocortisone hemisuccinate and 9-α-fludrocortisone	Hydrocortisone
Dose per day	Hydrocortisone 200 mg Fludrocortisone 50 μg	200 mg	Hydrocortisone 200 mg Fludrocortisone 50 μg	200 mg
Route of administration	Hydrocortisone: four intravenous bolus of 50 mg Fludrocortisone: 50 μg via the nasogastric tube	Four intravenous bolus of 50 mg	Hydrocortisone: four intravenous bolus of 50 mg Fludrocortisone: 50 μg via the nasogastric tube	Intravenous continuous infusion rate without loading dose
Duration	Seven days at full dose	Five days at full dose then tapered to 50 mg intravenously every 12 h for days 6 to 8, 50 mg every 24 h for days 9 to 11, and then stopped	Seven days at full dose	Seven days at full dose, while in the ICU

Ann Intensive Care 2016; 6: 43

Question

- The divergent findings may have resulted from differences in the design of the trials.

- which kind of outcomes may relate to the use of corticosteroids in sepsis patients?

Trial Design and Oversight

- Activated Protein C and Corticosteroids for Human Septic Shock (APROCCHSS) trial

- Multicenter, Double-blind, Randomized trial with A 2-by-2 factorial design

Inclusion criteria

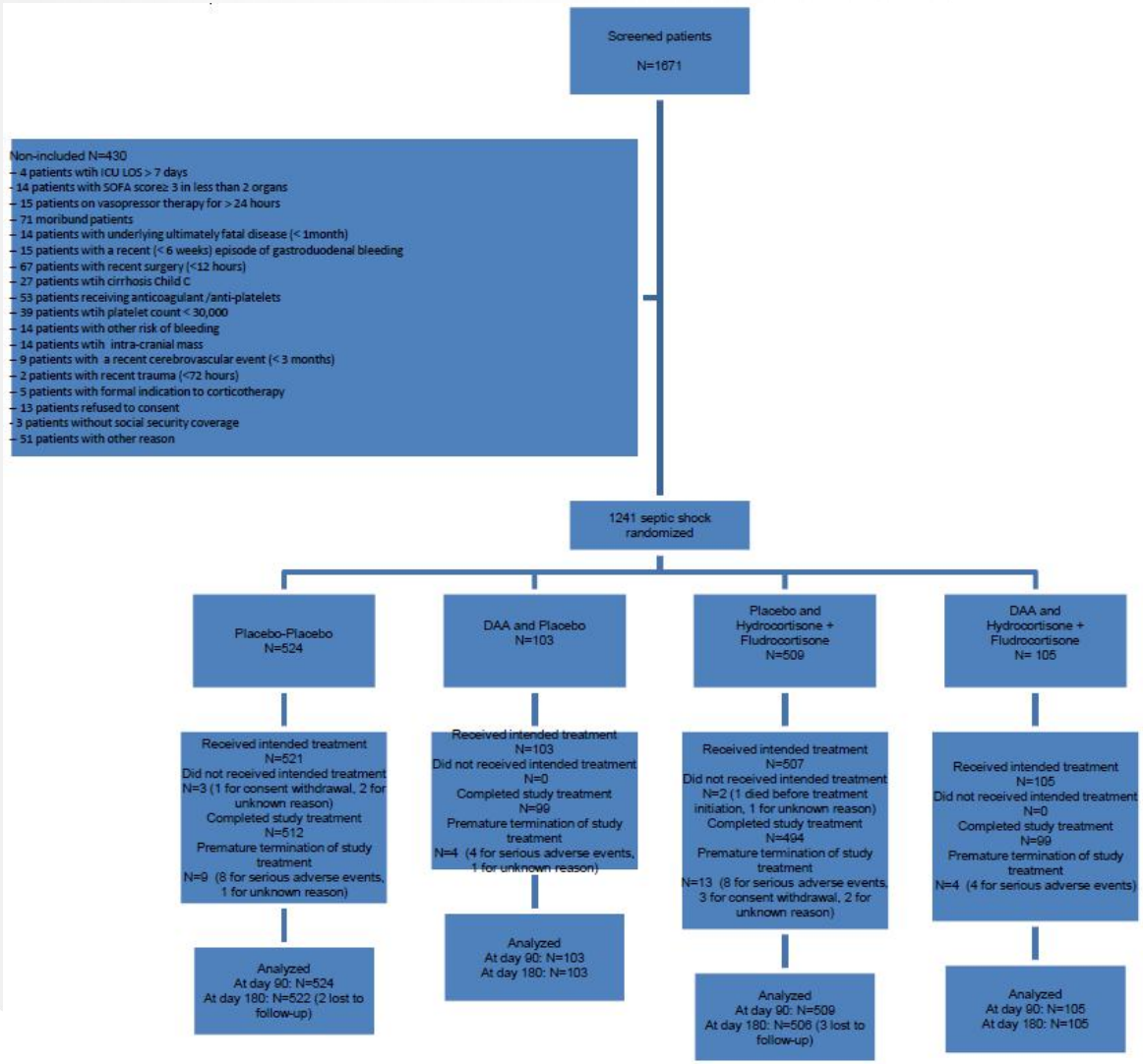
- Patients in intensive care units (ICUs) were eligible for inclusion in the trial if they had indisputable or probable septic shock for less than 24 hours.

- Septic shock:
  - the presence of a clinically or microbiologically documented Infection.
  - SOFA 3 or 4, at least two organs and at least 6 hours
  - Vasopressor therapy (Norepinephrine,Epinephrine, or any other vasopressor at a dose of ≥0.25 μg /kg/min or ≥1 mg per hour) for at least 6 hours

Exclusion criteria

- Major exclusion criteria were the presence of septic shock for at least 24 hours, a high risk of bleeding,pregnancy or lactation
- Underlying conditionsthat could affect short-term survival, known hypersensitivity to drotrecogin alfa (activated),
- Previous treatment with corticosteroids.

Flow chart of patient selection for the trial



Baseline characteristic

Table 1. Baseline Characteristics of the Patients.*

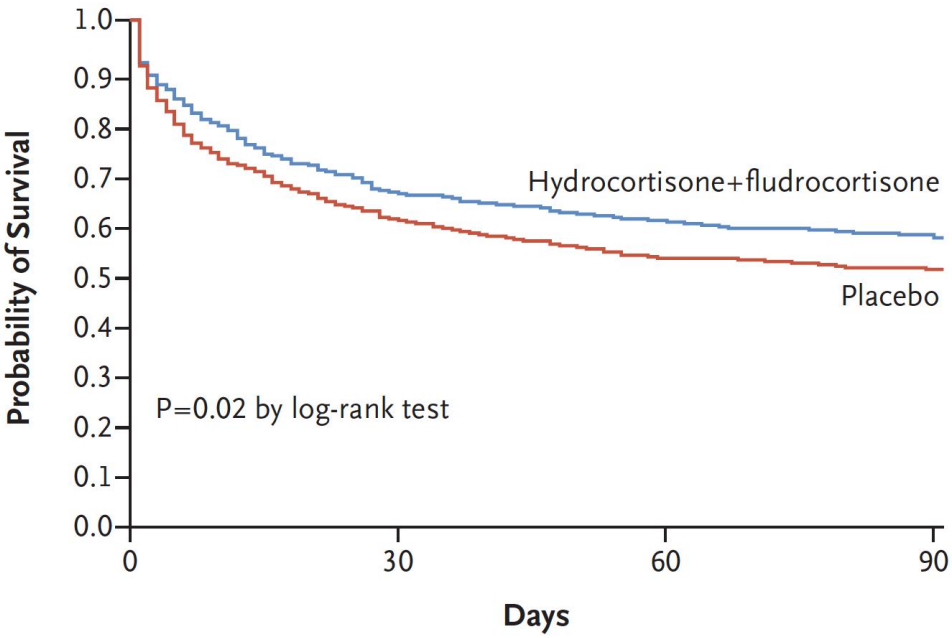
Characteristic	Placebo (N=627)	Hydrocortisone plus Fludrocortisone (N=614)	All Patients (N=1241)
Male sex — no./total no. (%)	424/626 (67.7)	402/614 (65.5)	826/1240 (66.6)
Age — yr†	66±15	66±14	66±14
Admission from a medical ward — no./total no. (%)	499/616 (81.0)	495/601 (82.4)	994/1217 (81.7)
SAPS II‡	56±19	56±19	56±19
SOFA score§	11±3	12±3	12±3
Community-acquired infection — no./total no. (%)	459/608 (75.5)	468/602 (77.7)	927/1210 (76.6)
Site of infection — no./total no. (%)¶			
Unknown	18/626 (2.9)	11/614 (1.8)	29/1240 (2.3)
Lung	363/626 (58.0)	373/614 (60.7)	736/1240 (59.4)
Abdomen	68/626 (10.9)	74/614 (12.1)	142/1240 (11.5)
Urinary tract	118/626 (18.8)	102/614 (16.6)	220/1240 (17.7)
Positive blood culture — no./total no. (%)	229/626 (36.6)	225/614 (36.6)	454/1240 (36.6)
Documented pathogen — no./total no. (%)	441/626 (70.4)	450/614 (73.3)	891/1240 (71.9)
Gram-positive bacteria — no./total no. (%)	228/626 (36.4)	235/614 (38.3)	463/1240 (37.3)
Gram-negative bacteria — no./total no. (%)	264/626 (42.2)	261/614 (42.5)	525/1240 (42.3)
Adequate antimicrobial therapy — no./total no. (%)	602/626 (96.2)	595/614 (96.9)	1197/1240 (96.5)
Vasopressor administration			
Epinephrine			
No. of patients	58	53	111
Dose — μg/kg/min	1.74±2.41	2.31±6.62	2.01±4.88
Norepinephrine			
No. of patients	552	534	1086
Dose — μg/kg/min	1.14±1.66	1.02±1.61	1.08±1.63
Mechanical ventilation — no./total no. (%)	569/623 (91.3)	567/614 (92.3)	1136/1237 (91.8)
Renal-replacement therapy — no./total no. (%)	168/598 (28.1)	161/596 (27.0)	329/1194 (27.6)

Main outcomes

Table 2. Trial Outcomes.*

Outcome	Placebo (N=627)	Hydrocortisone plus Fludrocortisone (N=614)	All Patients (N=1241)	Relative Risk (95% CI)†	P Value
Primary outcome: death from any cause at day 90 — no. (%)	308 (49.1)	264 (43.0)	572 (46.1)	0.88 (0.78–0.99)	0.03
Secondary outcomes					
Death from any cause					
At day 28 — no. (%)	244 (38.9)	207 (33.7)	451 (36.3)	0.87 (0.75–1.01)	0.06
At ICU discharge — no./total no. (%)	257/627 (41.0)	217/613 (35.4)	474/1240 (38.2)	0.86 (0.75–0.99)	0.04
At hospital discharge — no./total no. (%)	284/627 (45.3)	239/613 (39.0)	523/1240 (42.2)	0.86 (0.76–0.98)	0.02
At day 180 — no./total no. (%)	328/625 (52.5)	285/611 (46.6)	613/1236 (49.6)	0.89 (0.79–0.99)	0.04
Decision to withhold or withdraw active treatment by day 90 — no./total no. (%)	61/626 (9.7)	64/614 (10.4)	125/1240 (10.1)	1.07 (0.77–1.49)	0.69
Vasopressor-free days to day 28‡					
Mean	15±11	17±11	16±11	—	<0.001
Median (IQR)	19 (1–26)	23 (5–26)	21 (2–26)		
Ventilator-free days to day 28‡					
Mean	10±11	11±11	11±11	—	0.07
Median (IQR)	4 (0–21)	10 (0–22)	8 (0–21)		
Organ-failure–free days to day 28‡					
Mean	12±11	14±11	13±11	—	0.003
Median (IQR)	12 (0–24)	19 (0–25)	15 (0–24)		

Survival curve



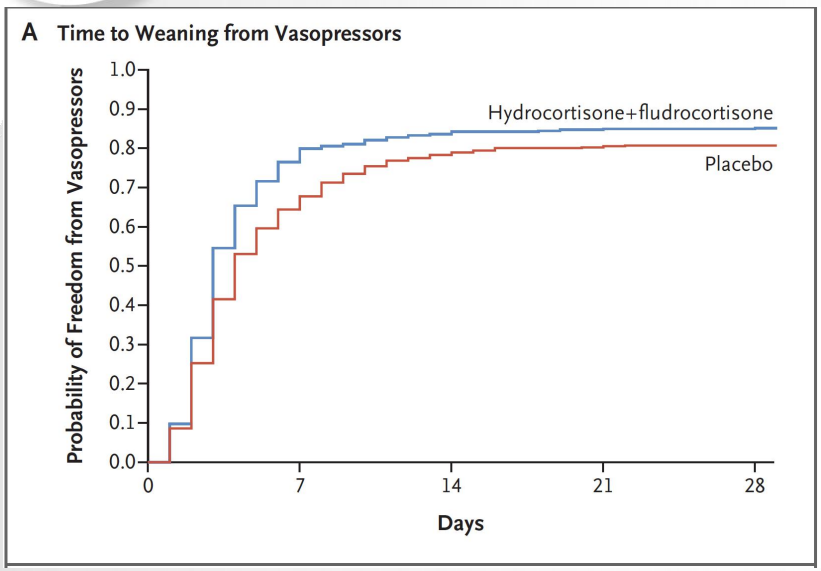
No. at Risk

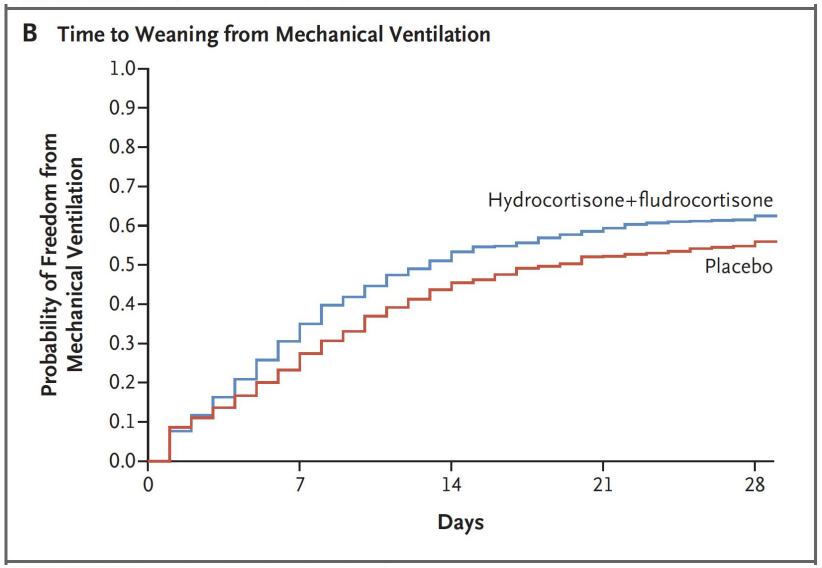
Hydrocortisone+ fludrocortisone	614	405	372	353
Placebo	627	381	333	319

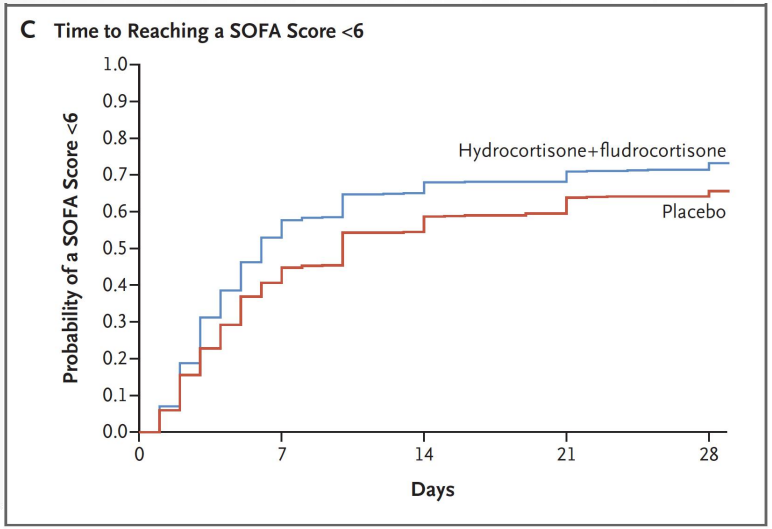
Figure 1. 90-Day Survival Distributions.

Shown are survival curves from randomization up to 90 days. The survival rate was significantly higher in the hydrocortisone-plus-fludrocortisone group than in the placebo group.

Time to weaning from Vaso, MV & to reaching SOFA<6







Adverse Events

Table 3. Adverse Events.*

Event	Placebo (N=627)	Hydrocortisone plus Fludrocortisone (N=614)	Relative Risk (95% CI)†	P Value
≥1 Serious event by day 180 — no./total no. (%)	363/626 (58.0)	326/614 (53.1)	0.92 (0.83–1.01)	0.08
≥1 Serious bleeding event by day 28 — no./total no. (%)	119/626 (19.0)	127/614 (20.7)	1.09 (0.87–1.36)	0.46
Gastroduodenal bleeding — no./total no. (%)	45/626 (7.2)	39/614 (6.4)	0.88 (0.58–1.34)	0.56
≥1 Episode of superinfection by day 180 — no./total no. (%)	178/626 (28.4)	191/614 (31.1)	1.09 (0.92–1.30)	0.30
Site of superinfection — no./total no. (%)				
Lung	116/626 (18.5)	127/614 (20.7)	1.12 (0.89–1.40)	0.34
Blood	48/626 (7.7)	49/614 (8.0)	1.04 (0.71–1.53)	0.84
Catheter-related	37/626 (5.9)	40/614 (6.5)	1.10 (0.71–1.70)	0.66
Urinary tract	33/626 (5.3)	40/614 (6.5)	1.24 (0.79–1.93)	0.35
Other	57/626 (9.1)	70/614 (11.4)	1.25 (0.90–1.74)	0.18
New sepsis — no./total no. (%)	122/626 (19.5)	134/614 (21.8)	1.12 (0.90–1.39)	0.31
New septic shock — no./total no. (%)	103/626 (16.5)	109/614 (17.8)	1.08 (0.84–1.38)	0.54
Hyperglycemia				
≥1 Episode of blood glucose levels ≥150 mg/dl by day 7 — no./total no. (%)	520/626 (83.1)	547/614 (89.1)	1.07 (1.03–1.12)	0.002
No. of days with ≥1 episode of blood glucose levels ≥150 mg/dl by day 7				
Mean	3.4±2.5	4.3±2.5	—	<0.001
Median (IQR)	3 (1–6)	5 (2–6)		
Neurologic sequelae by day 28 — no./total no. (%)‡				
Last MDRS score >1	130/626 (20.8)	153/614 (24.9)	1.20 (0.98–1.47)	0.08
Last MDRS score >3	92/626 (14.7)	108/614 (17.6)	1.20 (0.93–1.54)	0.17
Last MDRS score =5	65/626 (10.4)	73/614 (11.9)	1.15 (0.84–1.57)	0.40

Summary

- All-cause mortality was lower with hydrocortisone plus fludrocortisone than with placebo at day 90, at discharge from the ICU and hospital, and at day 180.
- The time to weaning from vasopressors, to weaning from mechanical ventilation, and to reaching a SOFA score below 6 was shorter with hydrocortisone plus fludrocortisone than with placebo.
- The number of days alive and free of vasopressors and organ failure was higher with hydrocortisone plus fludrocortisone than with placebo.
- The risk of secondary infections, gastroduodenal bleeding, or neurologic sequelae was not significantly higher with hydrocortisone plus fludrocortisone than with placebo, but the risk of hyperglycemia was significantly higher with hydrocortisone plus fludrocortisone.
- There was some imbalance between the two groups in the distribution of pathogens, with slightly more viral infections in the hydrocortisone-plus fludrocortisone group than in the placebo group.

HPA axis in Sepsis

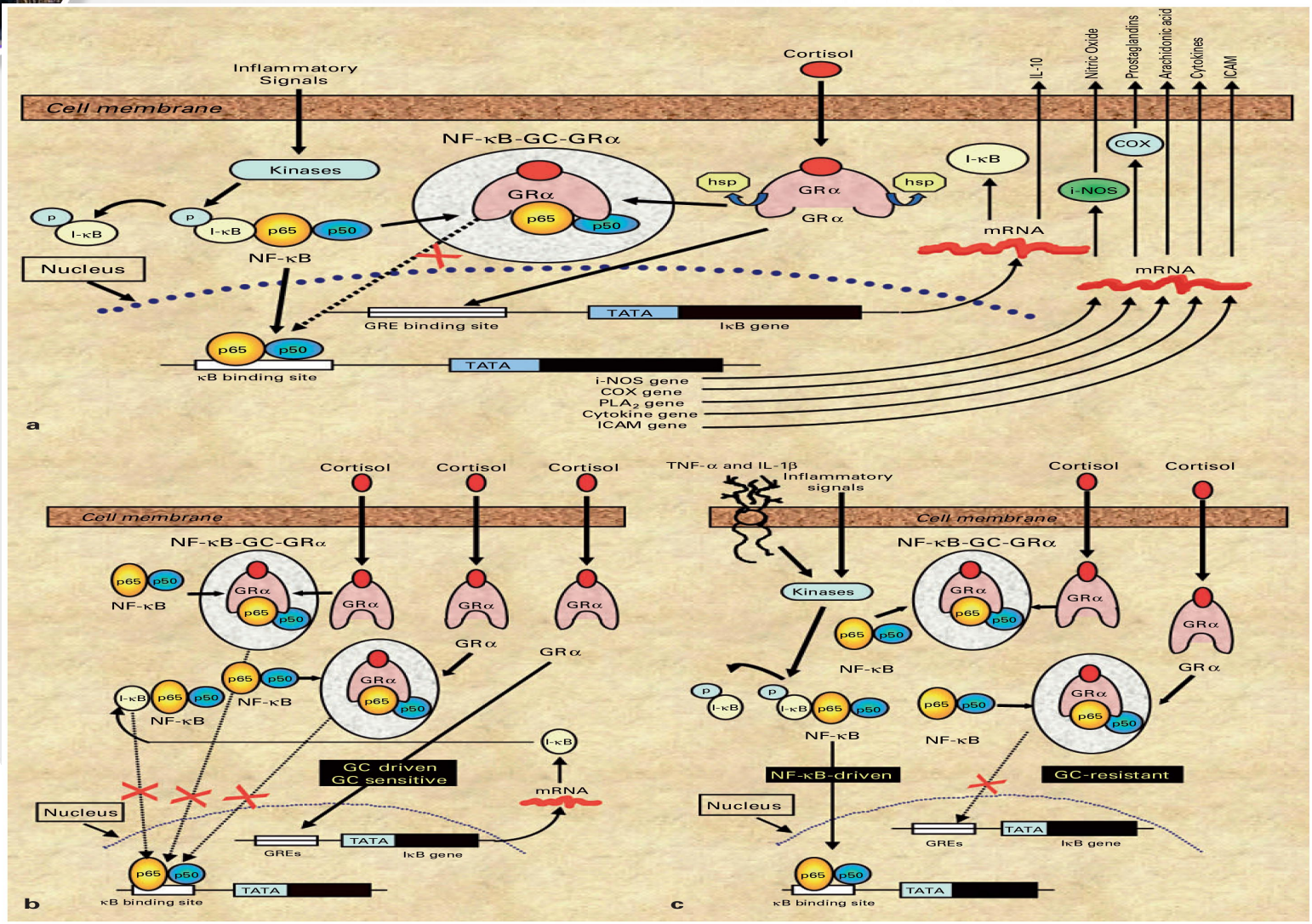
TABLE 1 | Mechanism explaining hypothalamic–pituitary–adrenal axis disruption in sepsis.

HPA axis level	Main mechanisms	Precipitating factors
Hypothalamus	Necrosis or hemorrhage	Anticoagulants, brisk variations in blood pressure, high dose of vasopressors Coagulopathy, severe hypoxia, hyperglycemia
	Decreased CRH/AVP synthesis/release	Treatment with corticosteroids, psychoactive drugs Increased brain levels of proinflammatory cytokines (mainly TNF and IL-1) Hypercortisolemia
Pituitary gland	Necrosis or hemorrhage	Anticoagulants, brisk variations in blood pressure, high dose of vasopressors Coagulopathy, severe hypoxia, hyperglycemia
	Decreased ACTH synthesis/release	Treatment with corticosteroids, psychoactive drugs, anti-infective drugs, megestrol acetate medroxyprogesterone Increased blood levels of proinflammatory cytokines (mainly TNF and IL-1) Coagulopathy, severe hypoxia, hypercortisolemia
Adrenals	Necrosis or hemorrhage	Anticoagulants, brisk variations in blood pressure, high dose of vasopressors Coagulopathy, severe hypoxia
	Decreased steroidogenesis	
	Depletion of lipid droplets	Cholesterol-lowering drugs
	Decreased expression of scavenger receptor B1	Proinflammatory mediators
	Enzymes inhibition	Aminoglutethimide, ketoconazole, fluconazole, etomidate, dexmedetomidine Proinflammatory mediators
	Decreased sensitivity of ACTH receptors	Circulating and adrenals proinflammatory mediators (e.g., corticostatins)
Tissue resistances	Decreased cortisol delivery to tissues	Proinflammatory mediators, liver failure, severe denutrition
	Accelerated glucose clearance	Phenobarbital, phenytoin, rifampin
	Decreased binding capacity and affinity of glucocorticoid receptor	Proinflammatory mediators

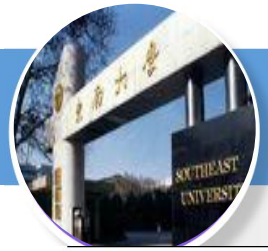
HPA, hypothalamic–pituitary–adrenal.

Front Endocrinol (Lausanne) 2016; 7: 70

NF-κB and GR mechanisms during sepsis and ARDS



Neuroimmunomodulation 2005; 12: 321-38
Proc Natl Acad Sci U S A 2013; 110: 306-11



Similar mortality with Ger-Inf-05

Table 4. Frequency of Fatal Events in 299 Patients with Septic Shock*

Variable	No. (%) Placebo	No. (%) Steroids	Adjusted OR (95% CI)	*P* Value
Nonresponders				
No. of patients	115	114		
28-day mortality	73 (63)	60 (53)	0.54 (0.31-0.97)	.04
ICU mortality	81 (70)	66 (58)	0.50 (0.28-0.89)	.02
Hospital mortality	83 (72)	70 (61)	0.53 (0.29-0.96)	.04
1-Year mortality	88 (77)	77 (68)	0.57 (0.31-1.04)	.07
Responders				
No. of patients	34	36		
28-Day mortality	18 (53)	22 (61)	0.97 (0.32-2.99)	.96
ICU mortality	20 (59)	24 (67)	0.99 (0.31-3.16)	.99
Hospital mortality	20 (59)	25 (69)	1.20 (0.38-3.76)	.75
1-Year mortality	24 (71)	25 (69)	0.70 (0.20-2.40)	.57
All Patients				
No. of patients	149	150		
28-Day mortality	91 (61)	82 (55)	0.65 (0.39-1.07)	.09
ICU mortality	101 (68)	90 (60)	0.61 (0.37-1.02)	.06
Hospital mortality	103 (69)	95 (63)	0.67 (0.40-1.12)	.12
1-Year mortality	112 (75)	102 (68)	0.62 (0.36-1.05)	.08

*Results are based on patient responses to a short corticotropin test. Using baseline cortisol, cortisol response, McCabe classification, Logistic Organ Dysfunction score, arterial lactate levels and PaO_2/FIO_2 results for adjustment, analyses were performed with use of logistic models. OR indicates, odds ratios; CI, confidence intervals; and ICU, intensive care unit.

- Pacebo-controlled, randomized, double-blind, parallel-group trial
- 19 ICUs in France
- October 9, 1995 to February 23, 1999
- 300 septic shock patients were enrolled
- Hydrocortisone (50-mg IV q6h) and fludrocortisone (50-ug tablet qd) vs. placebo for 7days
- 28d survival distribution in paients with relative adrenal insufficiency (nonresponders)

JAMA 2002; 288: 862-71

Different results with CORTICUS

- Multicenter, randomized, double-blind, placebo-controlled trial
- 52 ICUs
- March 2002 to November 2005
- 500 septic shock patients were enrolled
- Hydrocortisone (50mg IV q6h) vs. placebo for 5 days
- The dose was then tapered during a 6-day period
- 28d mortality among patients who did not have a response to a corticotropin test

Table 3. Outcomes According to Subgroup.*

Variable	No Response to Corticotropin		P Value	Response to Corticotropin		P Value	All Patients		P Value
	Hydrocortisone (N=125)	Placebo (N=108)		Hydrocortisone (N=118)	Placebo (N=136)		Hydrocortisone (N=251)	Placebo (N=248)	
Death within 28 days — no. (%)	49 (39.2)	39 (36.1)	0.69	34 (28.8)	39 (28.7)	1.00	86 (34.3)	78 (31.5)	0.51
Relative risk (95% CI)	1.09 (0.77 to 1.52)			1.00 (0.68 to 1.49)			1.09 (0.84 to 1.41)		
Absolute difference — % (95% CI)	3.1 (–9.5 to 15.7)			0.1 (–11.2 to 11.4)			2.8 (–5.5 to 11.2)		
Death in ICU — no./total no. (%)	58/125 (46.4)	44/108 (40.7)	0.43	41/118 (34.7)	45/135 (33.3)	0.89	102/251 (40.6)	89/247 (36.0)	0.31
Relative risk (95% CI)	1.14 (0.85 to 1.53)			1.04 (0.74 to 1.47)			1.13 (0.90 to 1.41)		
Absolute difference — % (95% CI)	5.7 (–7.1 to 18.4)			1.4 (–10.3 to 13.1)			4.6 (–3.9 to 13.1)		
Death during hospitalization — no./total no. (%)	60/125 (48.0)	50/108 (46.3)	0.90	48/118 (40.7)	50/133 (37.6)	0.70	111/251 (44.2)	100/245 (40.8)	0.47
Relative risk (95% CI)	1.04 (0.79 to 1.36)			1.08 (0.79 to 1.47)			1.08 (0.88 to 1.33)		
Absolute difference — % (95% CI)	1.7 (–11.1 to 14.6)			3.1 (–9.0 to 15.2)			3.4 (–5.3 to 12.1)		
Death at 1 yr — no./total no. (%)	73/124 (58.9)	60/105 (57.1)	0. 89	61/111 (55.0)	67/126 (53.2)	0.80	137/242 (56.6)	127/235 (54.0)	0.58
Relative risk (95% CI)	1.03 (0.83 to 1.29)			1.03 (0.82 to 1.31)			1.05 (0.89 to 1.23)		
Length of stay — days									
In ICU	17±19	17±17	0.47	18±22	19±16†	0.26	19±31	18±17†	0.51
In hospital	29±26	31±27	0.82	36±40	35±43‡	0.68	34±41	34±37‡	0.47

* Relative risks and percent differences are for the comparison between the hydrocortisone group and the placebo group. P values for categorical variables were calculated with the use of Fisher's exact test. P values for continuous variables were calculated with the use of the Wilcoxon rank-sum test. ICU denotes intensive care unit.
† Data were missing for one patient.
‡ Data were missing for three patients.

N Engl J Med 2008; 358: 111-24

Different results with HYPRESS

- Double-blind, randomized clinical trial
- January 13, 2009, to August 27, 2013, with a follow-up of 180 days
- 34 intermediate or ICUs of university and community hospitals in Germany
- 380 adult patients with severe sepsis who were not in septic shock
- Continuous infusion of 200mg of hydrocortisone for 5 days followed by dose tapering until day 11 vs. placebo
- Development of septic shock within 14 days

End Point	Placebo (n = 176)	Hydrocortisone (n = 177)	Total (N = 353)	*P* Value
Primary				
Septic shock, No./total No. (%) [95% CI]				
ITT population	39/170 (22.9) [17.2-30.0]	36/170 (21.2) [15.6-28.1]	75/340 (22.1) [17.9-26.9]	.70
PP population	33/156 (21.2) [15.4-28.4]	29/155 (18.7) [13.3-25.7]	62/311 (19.9) [15.8-24.8]	.59
Secondary				
Mortality, No./total No. (%) [95% CI]				
28 d	14/170 (8.2) [5.0-13.4]	15/171 (8.8) [5.4-14.0]	29/341 (8.5) [6.0-12.0]	.86
90 d	28/168 (16.7) [11.8-23.0]	34/171 (19.9) [14.6-26.5]	62/339 (18.3) [14.5-22.8]	.44
180 d	37/167 (22.2) [16.5-29.0]	45/168 (26.8) [20.7-34.0]	82/335 (24.5) [20.2-29.4]	.32
ICU	14/172 (8.1) [4.9-13.2]	13/171 (7.6) [4.5-12.6]	27/343 (7.9) [5.5-11.2]	.85
Hospital	22/172 (12.8) [8.6-18.6]	23/171 (13.5) [9.1-19.4]	45/343 (13.1) [10.0-17.1]	.86
LOS, median (IQR), d				
ICU	9 (6-17)	8 (5-15)	8 (5-16)	.23
Hospital	25 (16-40)	26 (16-46)	26 (16-43)	.36
Mechanical ventilation, No./total No. (%) [95% CI]	103/172 (59.9) [52.4-66.9]	91/171 (53.2) [45.8-60.5]	194/343 (56.6) [51.3-61.7]	.21
MV-free time, median (IQR), d	5 (2-7)	4 (2-7)	4 (2-7)	.34
RRT, No./total No. (%) [95%CI]	21/172 (12.2) [8.1-17.9]	21/171 (12.3) [8.2-18.0]	42/343 (12.2) [9.2-16.1]	.98
RRT-free time, median (IQR), d	7 (4-14)	6 (4-12)	7 (4-13)	.35
SOFA score until day 14, median (IQR)[b]	5.0 (3.5-6.8)	4.7 (3.5-6.5)	4.8 (3.5-6.6)	.69
Delirium, No./total No. (%) [95% CI]	25/102 (24.5) [17.2-33.7]	11/98 (11.2) [6.4-19.0]	36/200 (18.0) [13.3-23.9]	.01

JAMA 2016; 316: 1775-85

Different results with ADRENAL

- Investigator-initiated, international, pragmatic, double-blind, parallel-group, randomized, controlled trial
- March 2013 to April 2017
- ICUs in Australia, the United Kingdom, New Zealand, Saudi Arabia, and Denmark
- 3800 septic shock patients who were undergoing mechanical ventilation
- Hydrocortisone (at a dose of 200 mg per day) vs. placebo for 7 days or until death or discharge from ICU, whichever came first
- 90d mortality

N Engl J Med. 2018 Mar 1;378(9):797-808

Table 2. Outcomes.*

Outcome	Hydrocortisone (N = 1853)	Placebo (N = 1860)	Odds Ratio, Hazard Ratio, or Absolute Difference (95% CI)	P Value
Primary outcome				
90-day mortality — no./total no. (%)	511/1832 (27.9)	526/1826 (28.8)	0.95 (0.82 to 1.10)†	0.50
Secondary outcomes				
28-day mortality — no./total no. (%)	410/1841 (22.3)	448/1840 (24.3)	0.89 (0.76 to 1.03)†	0.13
Median time to resolution of shock (IQR) — days	3 (2 to 5)	4 (2 to 9)	1.32 (1.23 to 1.41)‡	<0.001
Recurrence of shock — no. (%)	365 (19.7)	343 (18.4)	1.07 (0.94 to 1.22)†	0.32
Median time to discharge from the ICU (IQR) — days	10 (5 to 30)	12 (6 to 42)	1.14 (1.06 to 1.23)‡	<0.001
No. of days alive and out of the ICU	58.2±34.8	56.0±35.4	2.26 (0.04 to 4.49)§	0.047¶
Median time to discharge from the hospital (IQR) — days	39 (19 to NA)	43 (19 to NA)	1.06 (0.98 to 1.15)‡	0.13
No. of days alive and out of the hospital	40.0±32.0	38.6±32.4	1.45 (−0.59 to 3.49)§	0.16
Median time to cessation of initial mechanical ventilation (IQR) — days	6 (3 to 18)	7 (3 to 24)	1.13 (1.05 to 1.22)‡	<0.001
No. of days alive and free from mechanical ventilation	61.2±35.6	59.1±36.1	2.18 (−0.11 to 4.46)§	0.06
Recurrence of mechanical ventilation — no./total no. (%)	180/1842 (9.8)	154/1850 (8.3)	1.18 (0.96 to 1.45)†	0.11
No. of days alive and free from renal-replacement therapy	42.6±39.1	40.4±38.5	2.37 (−2.00 to 6.75)§	0.29
Use of renal-replacement therapy — no. (%)	567 (30.6)	609 (32.7)	0.94 (0.86 to 1.03)†	0.18
New-onset bacteremia or fungemia — no. (%)	262 (14.1)	262 (14.1)	1.00 (0.86 to 1.16)†	0.96
Blood transfusion — no./total no. (%)	683/1848 (37.0)	773/1855 (41.7)	0.82 (0.72 to 0.94)†	0.004

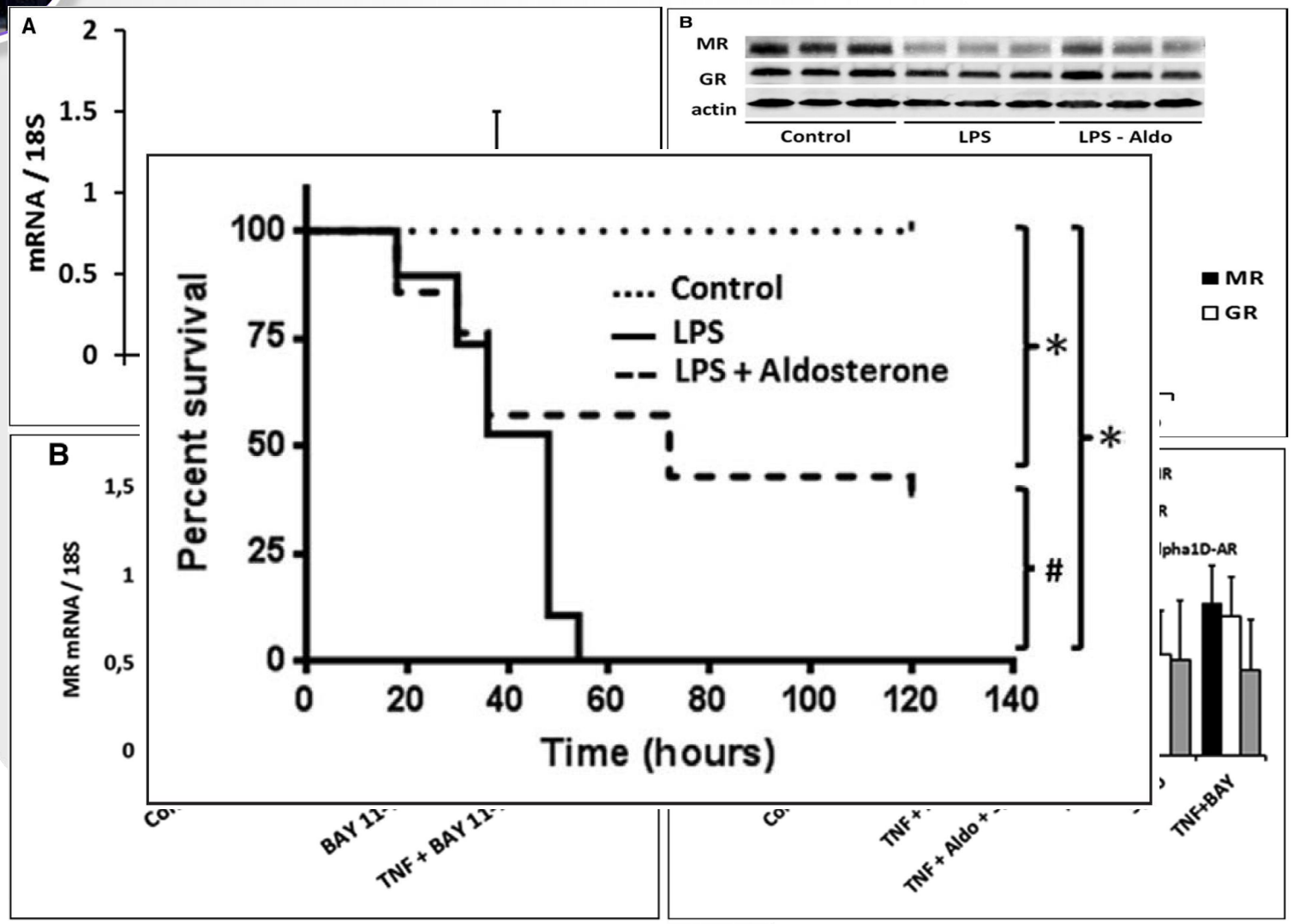
Comparison in 4 different studies

Studies	Survival benefits
APROCCHSS	✔
Ger-Inf-05	✔
CORTICUS	
HYPRESS	

Rational 1

- Fludrocortisone was added to hydrocortisone to provide additional mineralocorticoid potency

NF-κB–mediated down-regulation of vascular MR in sepsis



Crit Care Med 2017; 45(9): e954-e962

Comparison in 4 different studies

Rational 2

2012 RECOMMENDATIONS	2016 RECOMMENDATIONS
H. CORTICOSTEROIDS	**H. CORTICOSTEROIDS**
1. Not using IV hydrocortisone to treat adult septic shock patients if adequate fluid resuscitation and vasopressor therapy are able to restore hemodynamic stability (see goals for Initial Resuscitation). In case this is not achievable, we suggest IV hydrocortisone alone at a dose of 200 mg/day (grade 2C).	1. We suggest against using IV hydrocortisone to treat septic shock patients if adequate fluid resuscitation and vasopressor therapy are able to restore hemodynamic stability. If this is not achievable, we suggest IV hydrocortisone at a dose of 200 mg per day (weak recommendation, low quality of evidence).
2. Not using the adrenocorticotropic hormone stimulation test to identify adults with septic shock who should receive hydrocortisone (grade 2B).	
3. In treated patients, hydrocortisone tapered when vasopressors are no longer required (grade 2D).	
4. Corticosteroids not be administered for the treatment of sepsis in the absence of shock (grade 1D).	
5. When hydrocortisone is given, use continuous flow (grade 2D).	

2008

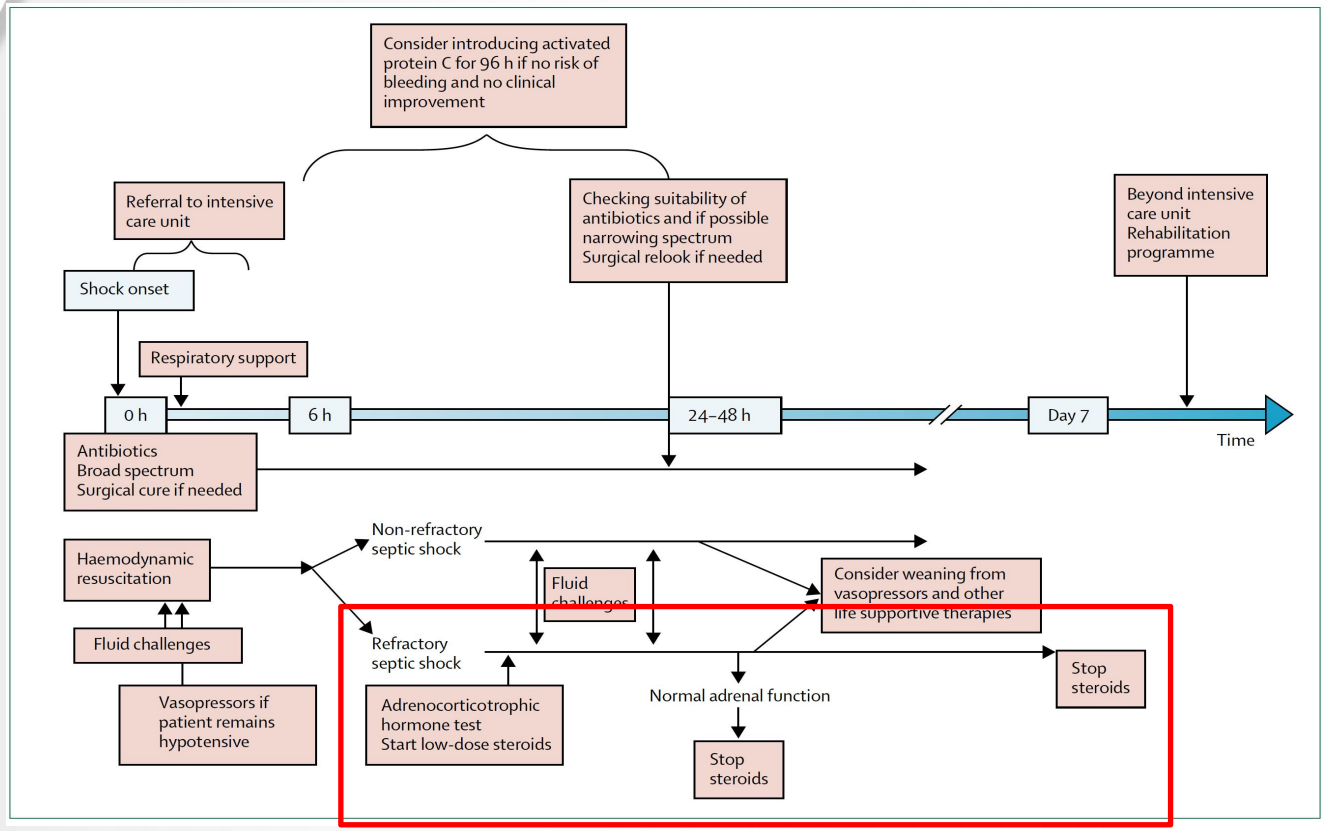
Steroids

- Consider intravenous hydrocortisone for adult septic shock when hypotension responds poorly to adequate fluid resuscitation and vasopressors (2C)
- ACTH stimulation test is not recommended to identify the subset of adults with septic shock who should receive hydrocortisone (2B)
- Hydrocortisone is preferred to dexamethasone (2B)
- Fludrocortisone (50 μg orally once a day) may be included if an alternative to hydrocortisone is being used that lacks significant mineralocorticoid activity. Fludrocortisone if optional if hydrocortisone is used (2C)
- Steroid therapy may be weaned once vasopressors are no longer required (2D)
- 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)

Intensive Care Med 2017; 43: 304-77

Crit Care Med 2008; 36: 296-327

Refractory septic shock – best target group for corticosteroids



	Target population	Main effects	Evidence
Replacing or enhancing host responses			
Endocrine response			
Low-dose corticosteroids	Refractory septic shock and basal cortisol concentrations <150 μg/L or cortisol response to adrenocorticotrophin <90 μg/L	Improve haemodynamics; reduce shock duration, organ dysfunction, systemic inflammation, and mortality	5 RCTs (n=465) 1 continuing RCT (n=800)

Lancet 2005; 365: 63-78

Differences in clinical characteristics

APROCCHSS

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Placebo (N=627)	Hydrocortisone plus Fludrocortisone (N=614)	All Patients (N=1241)
Male sex — no./total no. (%)	424/626 (67.7)	402/614 (65.5)	826/1240 (66.6)
Age — yr†	66±15	66±14	66±14
Admission from a medical ward — no./total no. (%)	499/616 (81.0)	495/601 (82.4)	994/1217 (81.7)
SAPS II‡	56±19	56±19	56±19
SOFA score§	11±3	12±3	12±3

CORTICUS

Table 2. Clinical Characteristics of the Patients at Baseline, According to Subgroup.*

Variable	No Response to Corticotropin				Response to Corticotropin				All Patients			
	No. of Patients	Hydrocortisone (N=125)	No. of Patients	Placebo (N=108)	No. of Patients	Hydrocortisone (N=118)	No. of Patients	Placebo (N=136)	No. of Patients	Hydrocortisone (N=251)	No. of Patients	Placebo (N=248)
Temperature — °C	124	37.7±1.6	108	37.9±1.6	116	38.0±1.4	135	38.1±1.3	248	37.9±1.5	247	38.0±1.4
Heart rate — bpm	124	121±24	108	119±23	115	116±29	136	117±26	247	119±26	248	118±25
Systolic blood pressure — mm Hg	124	92±22	108	97±25	116	94±24	136	95±29	248	94±23	248	95±27
SAPS II score†	125	50.7±17.8	108	49.0±16.3	117	47.9±18.0	136	48.4±16.9	250	49.5±17.8	248	48.6±16.7
SOFA score‡	125	11.0±3.4	108	10.7±3.4	118	10.3±3.4	136	10.5±2.9	251	10.6±3.4	248	10.6±3.2

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Thanks for your attention！