Spreading knowledge – improving outcomes

Evidence-based Management of Steroid Use in Septic Shock

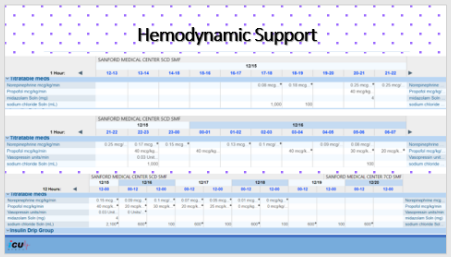
MAZEN KHERALLAH, MD, FCCP

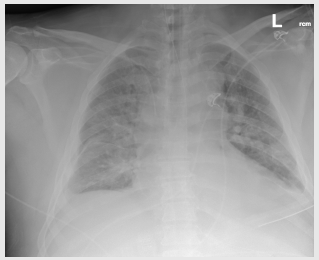
Case Presentation

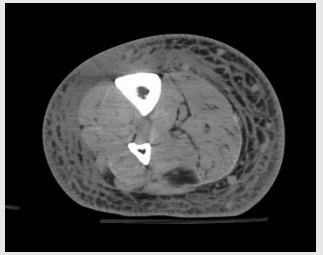
58 year old male with medical history significant for CML on tyrosine kinase inhibitor, diabetes mellitus, hypertension, peripheral neuropathy, venous thromboembolism admitted 12/15/2023 with right lower extremity swelling, pain and redness, associated with fever and chills. He has a history of right lower extremity cellulitis.

Assessment

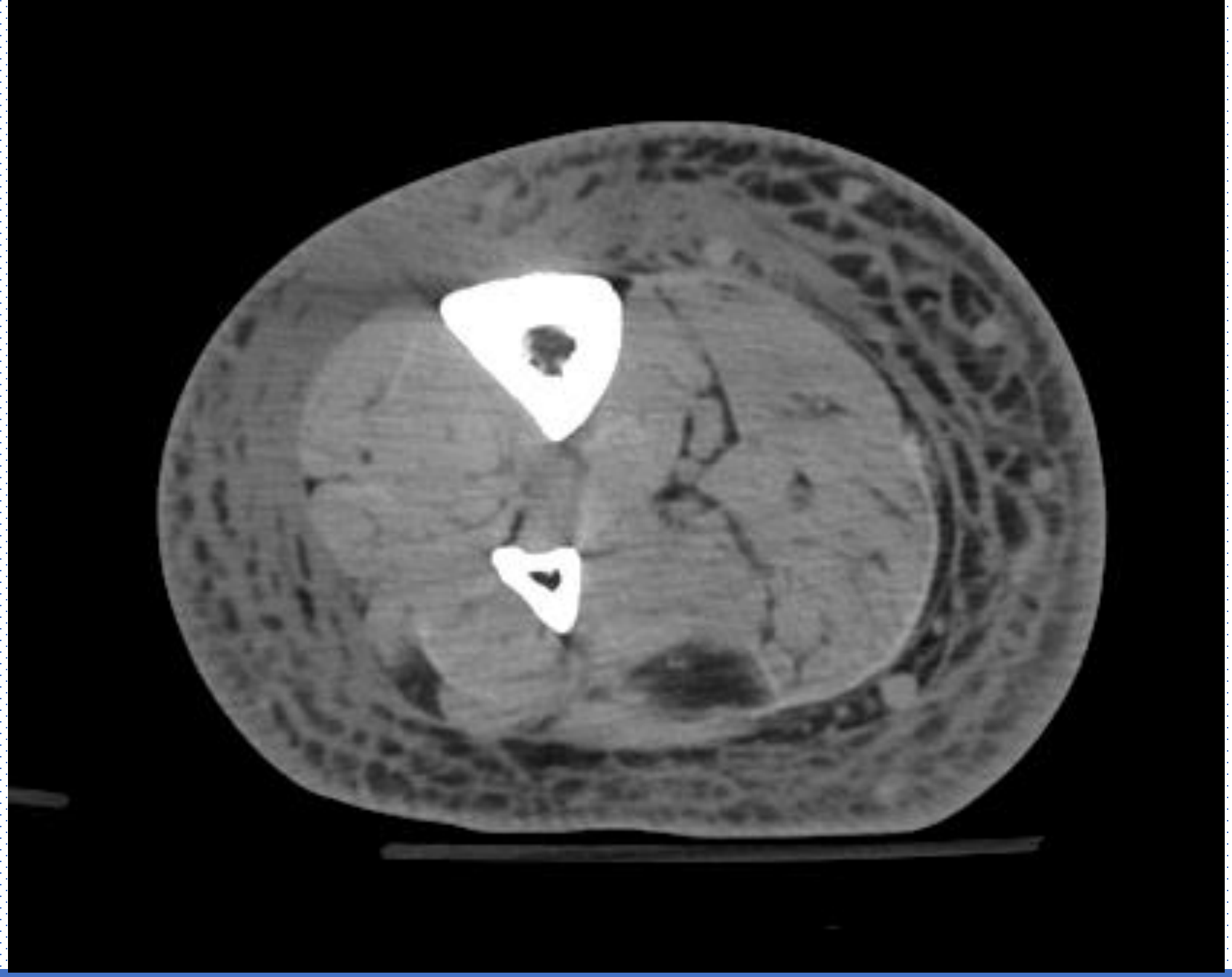
Hemodynamics	**Respiratory**	**ID**	**Renal**
BP 89/52 HR 140/min **LA 3.7**	RR 24 breaths/min **7.20/58/84/94%** **4-5 L/min**	WBC 19.3 Procalcitonin 80.7	Low urine output **Creatinine 4.46 BUN 45**
Fluid bolus 3.5 L then 150 mL/hour Norepinephrine	BiPAP	Pip/taz	IV boluses
Vasopressin	Intubated on APVcmv	Meropenem/vancomycin/clindamycin	Fluid maintenance








L
rcm



Hemodynamic Support

SANFORD MEDICAL CENTER 5CD SMF

1 Hour:	12/15 12-13	13-14	14-15	15-16	16-17	17-18	18-19	19-20	20-21	21-22	
Titratable meds											
Norepinephrine mcg/kg/min						0.08 mcg...	0.18 mcg...		0.25 mcg...	0.25 mcg/...	Norepinephrine ...
Propofol mcg/kg/min									40 mcg/kg...		Propofol mcg/kg/...
midazolam Soln (mg)									4		midazolam Soln ...
sodium chloride Soln (mL)						1,000	100				sodium chloride ...

SANFORD MEDICAL CENTER 5CD SMF

1 Hour:	12/15 21-22	22-23	23-00	12/16 00-01	01-02	02-03	03-04	04-05	05-06	06-07	
Titratable meds											
Norepinephrine mcg/kg/min	0.25 mcg/...	0.17 mcg...	0.15 mcg...		0.13 mcg...	0.1 mcg/...		0.09 mcg/...	0.08 mcg/...		Norepinephrine ...
Propofol mcg/kg/min		40 mcg/kg...		40 mcg/kg...			40 mcg/k...		30 mcg/k...	20 mcg/k...	Propofol mcg/kg/...
Vasopressin units/min		0.03 Unit...									Vasopressin unit...
sodium chloride Soln (mL)		1,000							100		sodium chloride ...

	SANFORD MEDICAL CENTER 5CD SMF							SANFORD MEDICAL CENTER 7CD SMF			
12 Hours:	12/15 12-00	12/16 00-12	12-00	12/17 00-12	12-00	12/18 00-12	12-00	12/19 00-12	12-00	12/20 00-12	12-00	
Titratable meds												
Norepinephrine mcg/kg/min	0.15 mcg...	0.09 mcg...	0.1 mcg/...	0.07 mcg...	0.05 mcg...	0.01 mcg...	0 mcg/kg...					Norepinephrine mcg...
Propofol mcg/kg/min	40 mcg/k...	20 mcg/k...	30 mcg/k...	20 mcg/k...	25 mcg/k...	0 mcg/kg...	0 mcg/kg/...					Propofol mcg/kg/min
Vasopressin units/min	0.03 Unit...	0 Units/...										Vasopressin units/min
midazolam Soln (mg)	4											midazolam Soln (mg)
sodium chloride Soln (mL)	2,100	600	100	600	100	600	100	600	100	600		sodium chloride Sol...
Insulin Drip Group												

Questions?

What is the rational of using steroid in sepsis?

What are the benefits of steroid in sepsis?

Should adrenal reserve be assessed?

Does the use of steroid prevent progression to shock in sepsis?

When to start steroids and how much?

Do we need to add fludrocortisone?

What are the expected adverse events with steroid?

How long do we keep on steroids?

Do we stop or taper?

Rationales for Glucocorticoid in Septic Shock

HPA* activation (resulting in increased levels of circulating cortisol)

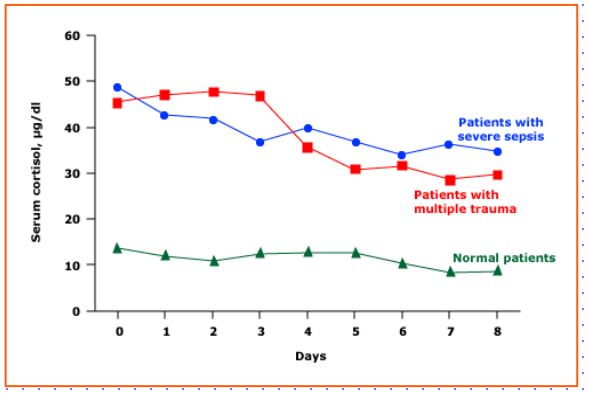
- Diurnal variation is lost and serum cortisol increases, reaching levels as high as 40 to 50 mcg/dL^
- Modulation of an excess inflammatory response

HPA impairment (resulting in adrenocortical hyporesponsiveness)

- By head injury, central nervous system depressants, pituitary infarction, adrenal hemorrhage, infections, malignancy, previous glucocorticoid therapy, and several drugs (phenytoin, and etomidate)

Glucocorticoid resistance

- Higher expression levels of the beta-isoform of the glucocorticoid receptors



Critical illness-related corticosteroid insufficiency
Relative adrenal insufficiency
(suboptimal cortisol production for total body demands)

No consensus about the diagnostic criteria

* HPA: hypothalamic-pituitary-adrenal axis

^Vadas P, Pruzanski W. Plasma cortisol levels in patients with septic shock. Crit Care Med. 1991 Feb;19(2):300-1.

STEROIDS IN SEPSIS & SEPTIC SHOCK

EVOLUTION OF EVIDENCE

It seems that despite seemingly contradictory outcomes of these trials, there is a consistent trend towards faster shock reversal and potential benefit of combining hydrocortisone and fludrocortisone.

Mortality

PIRRACCHIO

Patient-level Meta-analysis

17 Trials with individual patient data (n=7882), and 7 trials with 90-day mortality (n=5929).
No significant reduction in 90-day mortality of hydrocortisone compared to placebo, and no difference in secondary outcomes except for vasopressor-free days.
When hydrocortisone was combined with fludrocortisone, there was a lower relative risk of mortality compared to hydrocortisone alone
Hydrocortisone was not associated with increased risk of superinfection, hyperglycemia, or gastrointestinal bleeding, but there was a potential risk of hypernatremia and muscle weakness.

NEJM Evidence — 2023

BOSCH

Retrospective cohort study among 88,275 patients with septic shock receiving norepinephrine who initiated hydrocortisone treatment, the addition of fludrocortisone to hydrocortisone was associated with a 3.7% lower adjusted absolute risk difference in the primary composite outcome of mortality or discharge to hospice compared with initiation of hydrocortisone alone.

JAMA — 2023

CORTICUS

No difference in 28-day mortality between 50 mg hydrortisone IV every 6 hours for 5 days then tapered compared to placebo but a faster resolution of shock and a non-significant increased risk of superinfection in a total of 499 septic shock patients.

NEJM — 2018

APROCCHSS

90-day mortality was lower in the hydrocortisone plus fludrocortisone group compared to placebo in 1,241 septic shock patients (43.0% vs 49.3%) with a faster shock reversal and no difference in ventilator free days.

ADRENAL

No significant difference in 90-day mortality with continuous infusion of hydrocortisone (200 mg per day for 7 days) but a shorter time to resolution of shock in a total of 3658 septic shock patients.

JAMA — 2016

HYPRESS

Continuous infusion of 200 mg of hydrocortisone for 5 days followed by dose tapering until day 11 (n = 190) or placebo (n = 190) did not prevent the deterioration of sepsis into septic shock (21.2% vs 22.9%).

NEJM — 2008

JAMA — 2002

BOLLAERT

"supra-physiologic" dose of methylprednisolone (100 mg IV three times daily for 5 days) in 22 patients compared to placebo in 19 patients resulted in a significant improvement in hemodynamics (68% vs 21%) and lower mortality (22% vs 63%).

ANANNE

28-day mortality and shock reversal were better in ACTH stimulation responders with hydrocortisone (50-mg IV bolus every 6 hours) and fludrocortisone (50-µg tablet once daily) compared to placebo in a total of 300 septic shock patients.

Society of Critical Care Medicine — 1998

Annals of Surgery Open — 1976

SCHUMER

Prospective study showed a morality rate of 38.4% in 86 saline-treated patients compared to 10.4% in 86 steroid treated. Retrospective data showed a mortality of 42.5% in 160 patients treated without steroids compared to 14% in 168 patients treated with steroids.

STEROIDS IN SEPSIS & SEPTIC SHOCK

EVOLUTION OF EVIDENCE

It seems that despite seemingly contradictory outcomes of these trials, there is a consistent trend towards faster shock reversal and potential benefit of combining hydrocortisone and fludrocortisone.

Shock Reversal

PIRRACCHIO

Patient-level Meta-analysis

17 Trials with individual patient data (n=7882), and 7 trials with 90-day mortality (n=5929).
No significant reduction in 90-day mortality of hydrocortisone compared to placebo, and no difference in secondary outcomes except for vasopressor-free days.
When hydrocortisone was combined with fludrocortisone, there was a lower relative risk of mortality compared to hydrocortisone alone
Hydrocortisone was not associated with increased risk of superinfection, hyperglycemia, or gastrointestinal bleeding, but there was a potential risk of hypernatremia and muscle weakness.

NEJM Evidence 2023

BOSCH

JAMA 2023

Retrospective cohort study among 88,275 patients with septic shock receiving norepinephrine who initiated hydrocortisone treatment, the addition of fludrocortisone to hydrocortisone was associated with a 3.7% lower adjusted absolute risk difference in the primary composite outcome of mortality or discharge to hospice compared with initiation of hydrocortisone alone.

CORTICUS

NEJM 2018

No difference in 28-day mortality between 50 mg hydrortisone IV every 6 hours for 5 days then tapered compared to placebo but a faster resolution of shock and a non-significant increased risk of superinfection in a total of 499 septic shock patients.

APROCCHSS

90-day mortality was lower in the hydrocortisone plus fludrocortisone group compared to placebo in 1,241 septic shock patients (43.0% vs 49.3%) with a faster shock reversal and no difference in ventilator free days.

ADRENAL

No significant difference in 90-day mortality with continuous infusion of hydrocortisone (200 mg per day for 7 days) but a shorter time to resolution of shock in a total of 3658 septic shock patients.

HYPRESS

JAMA 2016

Continuous infusion of 200 mg of hydrocortisone for 5 days followed by dose tapering until day 11 (n = 190) or placebo (n = 190) did not prevent the deterioration of sepsis into septic shock (21.2% vs 22.9%).

BOLLAERT

NEJM 2008

"supra-physiologic" dose of methylprednisolone (100 mg IV three times daily for 5 days) in 22 patients compared to placebo in 19 patients resulted in a significant improvement in hemodynamics (68% vs 21%) and lower mortality (22% vs 63%).

ANANNE

JAMA 2002

28-day mortality and shock reversal were better in ACTH stimulation responders with hydrocortisone (50-mg IV bolus every 6 hours) and fludrocortisone (50-µg tablet once daily) compared to placebo in a total of 300 septic shock patients.

SCHUMER

Society of Critical Care Medicine 1998

Prospective study showed a morality rate of 38.4% in 86 saline-treated patients compared to 10.4% in 86 steroid treated. Retrospective data showed a mortality of 42.5% in 160 patients treated without steroids compared to 14% in 168 patients treated with steroids.

Annals of Surgery Open 1976

JAMA The Journal of the American Medical Association

August 21, 2002, Vol 288, No. 7 >

< Previous Article Next Article >

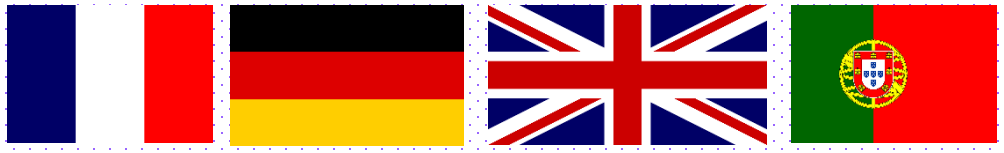
Caring for the Critically Ill Patient | August 21, 2002

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

Djillali Annane, MD, PhD; Véronique Sébille, PhD; Claire Charpentier, MD; Pierre-Edouard Bollaert, MD, PhD; Bruno François, MD; Jean-Michel Korach, MD; Gilles Capellier, MD, PhD; Yves Cohen, MD, PhD; Elie Azoulay, MD; Gilles Troché, MD; Philippe Chaumet-Riffaut, MD; Eric Bellissant, MD, PhD

63% vs 53% Mortality

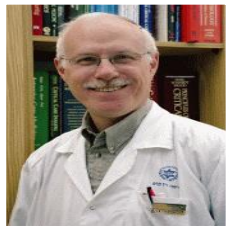
Hydrocortisone Therapy for Patients with Septic Shock



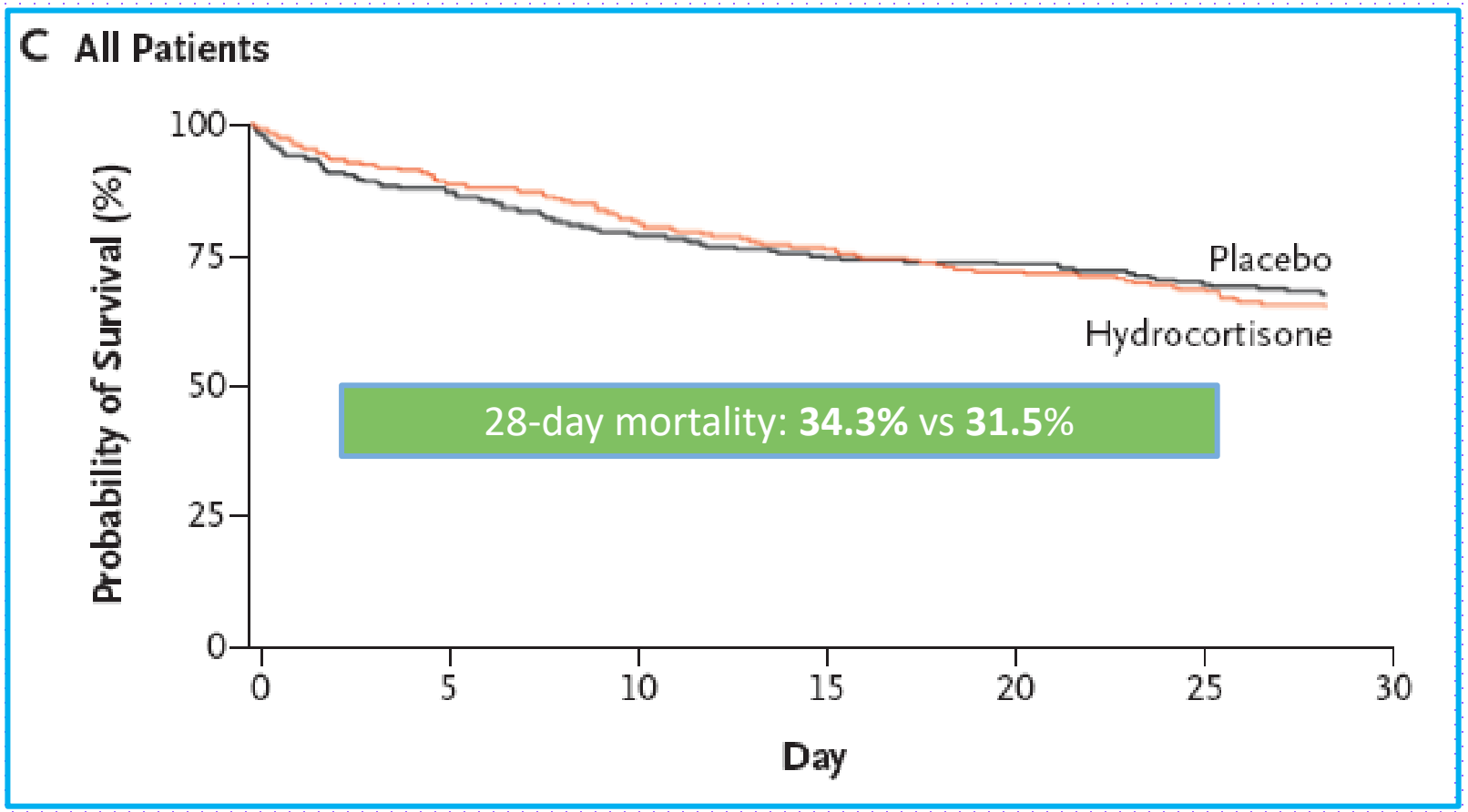
CORTICUS Trial

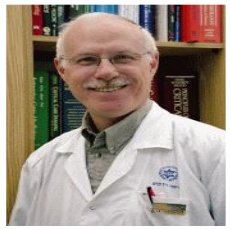
499 patients with septic shock, 52 ICUs Mar 2002 to Nov. 2005		
	Hydrocortisone	**Placebo**
# of Patients	251	248
28 Day Mortality	**34.3%**	**31.5%**

X

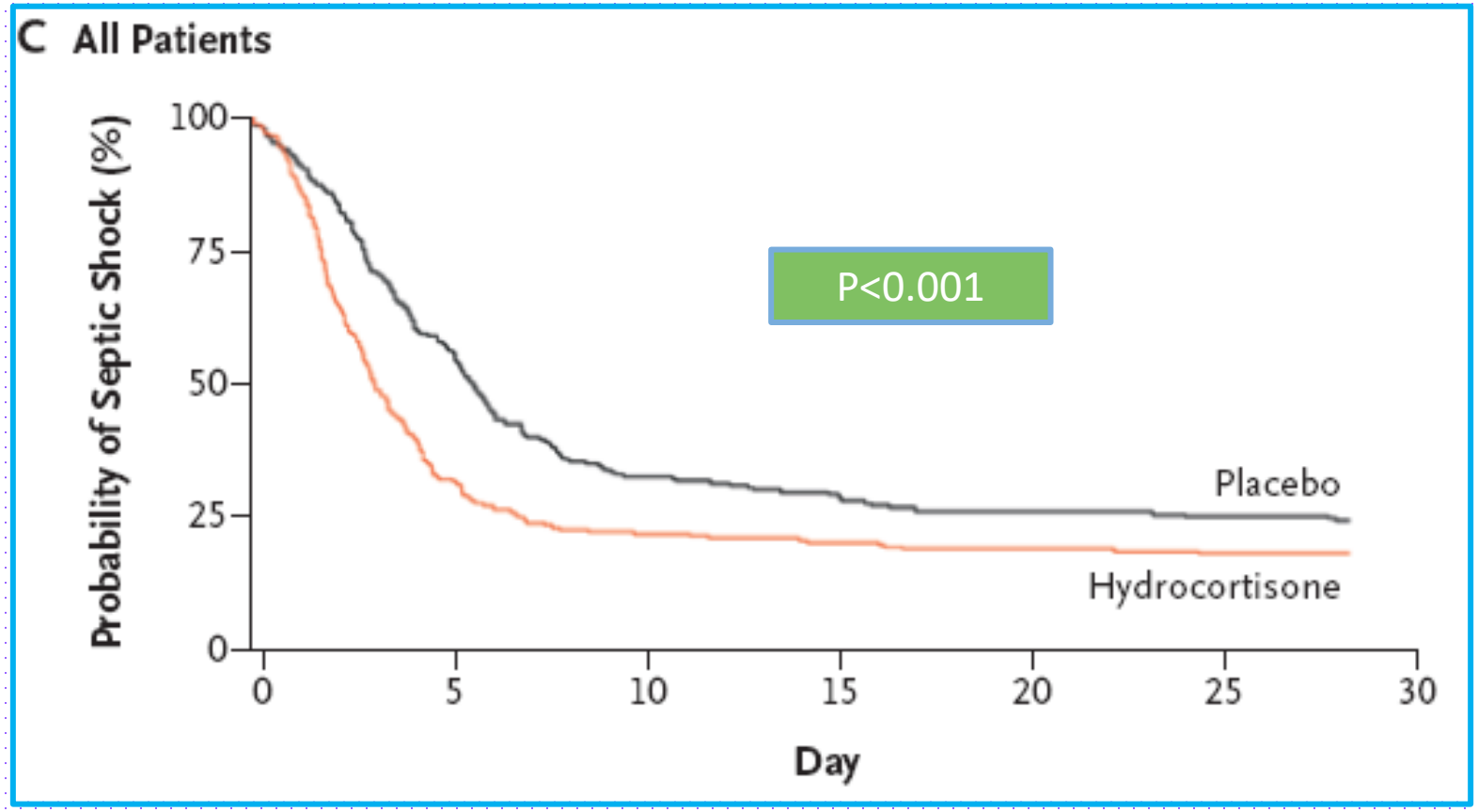


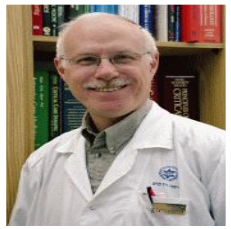
Hydrocortisone Therapy for Patients with Septic Shock





Kaplan–Meier Curves for the Time to Reversal of Shock





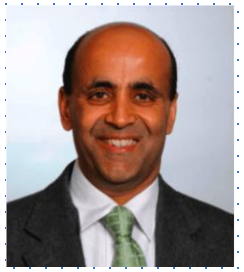
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Adjunctive Glucocorticoid Therapy in Patients with Septic Shock

Balasubramanian Venkatesh, M.D., Simon Finfer, M.D., Jeremy Cohen, M.D., Ph.D., Dorrilyn Rajbhandari, R.N., Yaseen Arabi, M.D., Rinaldo Bellomo, M.D., Laurent Billot, M.Sc., M.Res., Maryam Correa, Ph.D., Parisa Glass, Ph.D., Meg Harward, R.N., Christopher Joyce, M.D., Ph.D., Qiang Li, M.Sc., et al., for the ADRENAL Trial Investigators and the Australian–New Zealand Intensive Care Society Clinical Trials Group*

The ADRENAL Trial

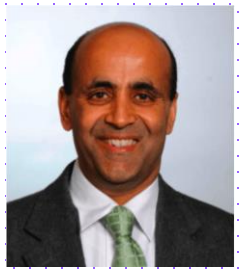


Adjunctive Glucocorticoid Therapy in Patients with Septic Shock

The ADRENAL Trial

3800 ICU patients on mechanical ventilation with septic shock
Multicenter, randomized, and controlled: March 2013 through April 2017

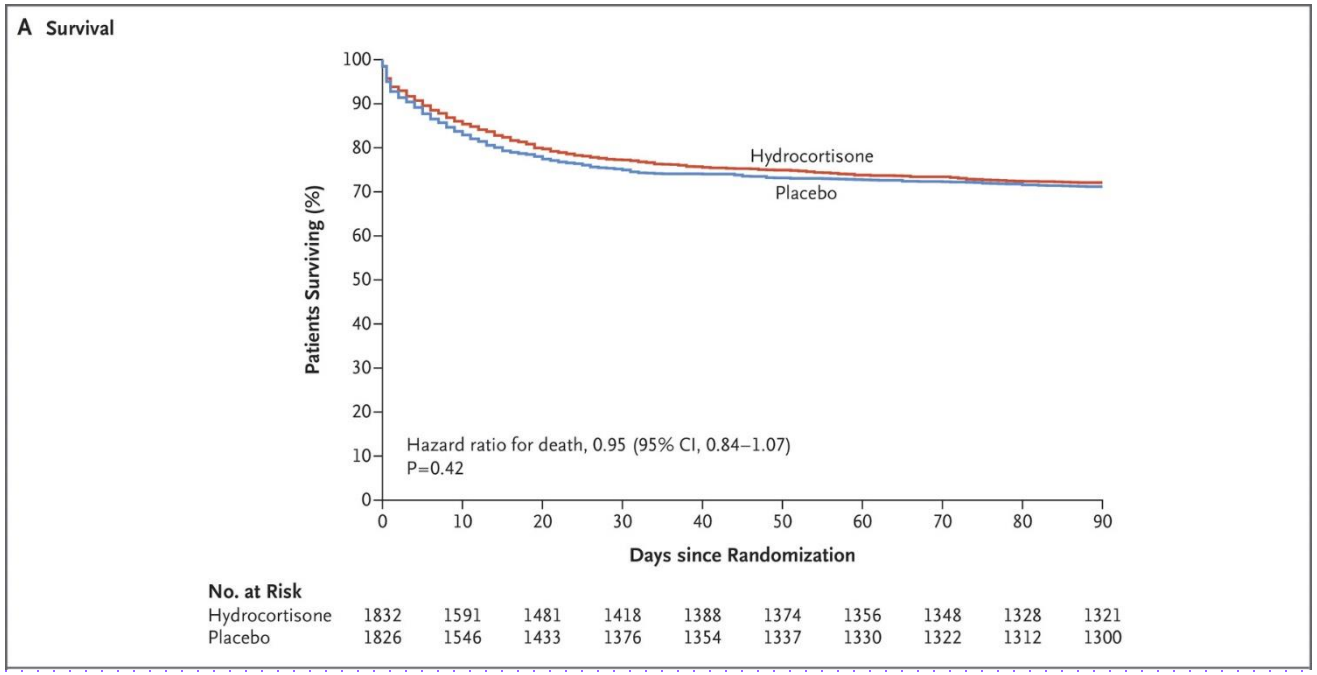
	Hydrocortisone	Placebo	
# of Patients	1832	1826	
90 Day Mortality (%)	**27.9%**	**28.8%**	X
Resolution of Shock (median)	**3 days**	**4 days**	✓

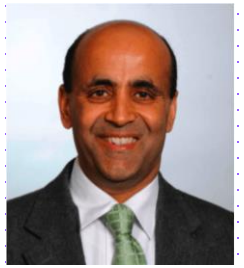


X odds ratio, 0.95; 95% confidence interval [CI], 0.82 to 1.10; P=0.50

✓ hazard ratio, 1.32; 95% CI, 1.23 to 1.41; P<0.001

Adjunctive Glucocorticoid Therapy in Patients with Septic Shock





The NEW ENGLAND JOURNAL of MEDICINE

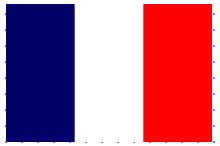
ORIGINAL ARTICLE

Hydrocortisone plus Fludrocortisone for Adults with Septic Shock

Djillali Annane, M.D., Ph.D., Alain Renault, M.Sc., Christian Brun-Buisson, M.D., Bruno Megarbane, M.D., Jean-Pierre Quenot, M.D., Shidasp Siami, M.D., Alain Cariou, M.D., Xavier Forceville, M.D., Ph.D., Carole Schwebel, M.D., Claude Martin, M.D., Jean-François Timsit, M.D., Benoît Misset, M.D., et al., for the CRICS-TRIGGERSEP Network*

The APROCCHSS Trial

Hydrocortisone plus Fludrocortisone for Adults with Septic Shock



The APROCCHSS Trial

1241 ICU patients with septic shock
Multicenter, randomized, and controlled

	Hydrocortisone	Placebo	
# of Patients	614	627	
90 Day Mortality (%)	**43%**	**49.1%**	√ *P=0.03*
Vasopressor-free days	**17 days**	**15 days**	√ *P<0.001*

Original Article

Patient-Level Meta-Analysis of Low-Dose Hydrocortisone in Adults with Septic Shock

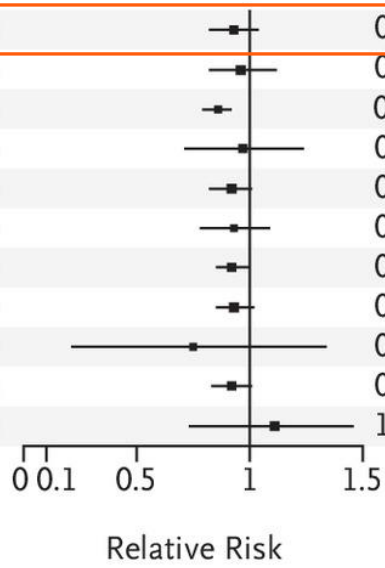
Romain Pirracchio, M.D., M.P.H., Ph.D., Djillali Annane, M.D., Ph.D., Andre K. Waschka, Ph.D., François Lamontagne, M.D., M.Sc., Yaseen M. Arabi, M.D., Pierre-Edouard Bollaert, M.D., Laurent Billot, M.D., Bin Du, M.D., Josef Briegel, M.D., Jeremy Cohen, M.D., Simon Finfer, M.D., Anthony Gordon, M.D., Naomi Hammond, R.N., M.P.H., Ph.D., Herve Hyvernat, M.D., Didier Keh, M.D., Yi Li, M.D., Ling Liu, M.D., Gianfranco Umberto Meduri, M.D., Liliana Mirea, M.D., John A. Myburgh, M.D., Charles L. Sprung, M.D., Ph.D., Neijla Tilouche, M.D., Surat Tongyoo, M.D., Balasubramanian Venkatesh, M.D., Ruiqiang Zheng, M.D., and Anthony Delaney, M.D., Ph.D.

NEJM Evid
Volume 2(6):EVIDoa2300034
May 23, 2023

Association between Steroid and 90-Day Mortality

A

Treatment	Subgroup	Total No. of Patients (treatment+ control) (%)	No. Treated (%)	No. of Deaths in Treated (%)	No. Placebo (%)	No. of Deaths in Placebo (%)	Relative Risk (CI)
Overall		5929 (100)*	2966 (100)	1026 (36)	2963 (100)	1069 (37)	0.93 (0.82–1.04)
Hydrocortisone	Without fludrocortisone	4389 (74)	2202 (74)	665 (31)	2187 (74)	656 (31)	0.96 (0.82–1.12)
	With fludrocortisone	1540 (26)	764 (26)	361 (47)	776 (26)	413 (53)	0.86 (0.79–0.92)
Taper	Taper	657 (11)	329 (11)	135 (51)	328 (11)	127 (49)	0.97 (0.71–1.24)
	No taper	5272 (89)	2637 (89)	891 (34)	2635 (89)	942 (36)	0.92 (0.82–1.01)
Continuous	Continous	3844 (65)	1922 (65)	538 (29)	1922 (65)	552 (30)	0.93 (0.78–1.09)
	Bolus	2085 (35)	1044 (35)	488 (48)	1041 (35)	517 (51)	0.92 (0.85–1.00)
Steroid duration	Fixed	5771 (97)	2888 (97)	999 (35)	2883 (97)	1043 (37)	0.93 (0.85–1.02)
	Shock reversal	158 (3)	78 (3)	27 (60)	80 (3)	26 (63)	0.75 (0.21–1.34)
Steroid initiation	<24 h	5723 (97)	2865 (97)	982 (35)	2858 (97)	10,255 (37)	0.92 (0.83–1.01)
	>24 h	176 (3)	85 (3)	40 (56)	91 (3)	39 (50)	1.11 (0.73–1.46)



Pirracchio R, Annane D, Waschka AK, et al. Patient-level meta-analysis of low-dose hydrocortisone in adults with septic shock. *NEJM Evid* 2023;2(6).

Table 2. Primary and Secondary Outcomes and Adverse Events.*

Outcome	Trials	Participants	Estimate of Effect†	95% CI	P Value
Primary outcome: 90-day all-cause mortality					
Adjusted RR	7	5929	0.93	0.82 to 1.04	0.22
Unadjusted RR	7	5929	0.95	0.89 to 1.02	0.21
TMLE	7	5029	0.96	0.90 to 1.02	0.21
Cox model — marginal hazard ratio	17	7873	0.92	0.81 to 1.05	0.27
Trial level meta-analysis — RR	21	7670	0.93	0.86 to 1.01	0.11
Including patient with sepsis‡ — RR	8	6138	0.95	0.88 to 1.02	0.24
Secondary outcomes					
Mortality at day 28 — RR	17	7864	0.92	0.83 to 1.00	—
Mortality at day 180 — RR	6	1997	0.92	0.74 to 1.10	—
Mortality at ICU discharge — RR	12	7314	0.92	0.83 to 1.01	—
Mortality at hospital discharge — RR	10	6676	0.95	0.88 to 1.03	—
Vasopressor-free days§ — MD	13	6422	1.24	0.74 to 1.73	—
Ventilation-free days§ — MD	15	7061	0.46	−0.08 to 0.99	—
Organ failure–free days§ — MD	12	1082	0.27	−0.65 to 0.92	—
Duration of ICU admission — MD, d	15	7636	0.13	−0.65 to 0.92	—
Duration of hospital admission — MD, d	14	7591	0.22	−1.17 to 1.62	—
Adverse events					
Superinfection	10	6970	1.04	0.95 to 1.15	
Hyperglycemia	10	7017	1.05	0.98 to 1.12	
Hypernatremia	6	5033	2.01	1.56 to 2.60	
Gastroduodenal bleeding	8	2748	1.11	0.83 to 1.48	
Muscle weakness	5	2647	1.73	1.49 to 1.99	

* The widths of the CIs have not been adjusted for multiplicity. Thus, the CIs should not be used to reject or not reject treatment effects. CI denotes confidence interval; ICU, intensive care unit; MD, mean difference; RR, relative risk; and TMLE, targeted maximum likelihood estimation.

† Estimates of effects are marginal risk ratio unless indicated.

‡ Patients with sepsis but no shock.

§ Vasopressor-, ventilation-, and organ failure–free days are calculated up to day 28.

Should Adrenal Reserve be Assessed?

ACTH Stimulation Test

- Change in baseline cortisol at 60 min of <9 mcg/dL after corticotropin (250 mcg; ie, high-dose ACTH stimulation) administration*

Random Plasma Cortisol

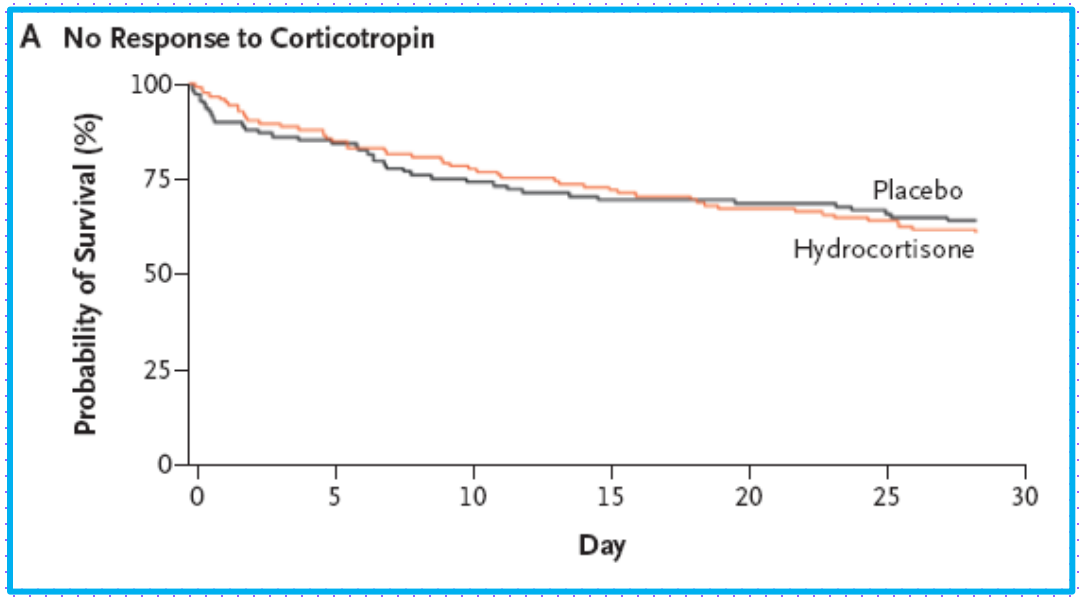
- ≤10 mcg/dL (total).
- Free cortisol level is more accurate but not available in most centers

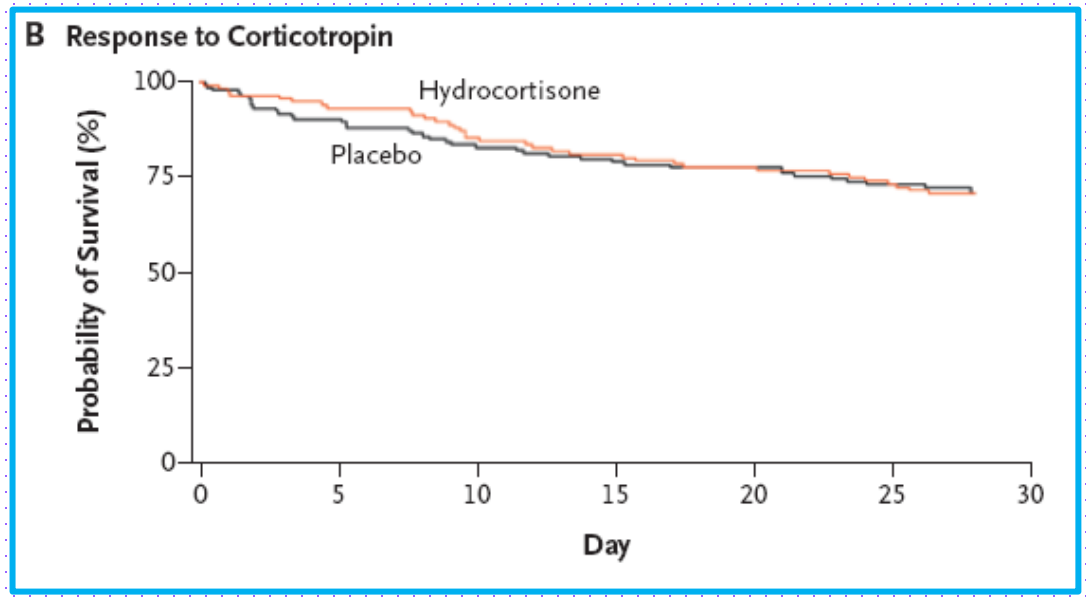
Unreliable in critically ill patients

Failed to consistently identify patients with septic shock who benefit from glucocorticoid use in major RCTs

*Studies using high-dose ACTH stimulation (250 mcg cosyntropin) have yielded variable results in septic shock

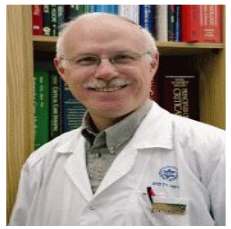
CORTICUS Trial





28-day mortality: **39.2**% vs **36.1**% , P = 0.69

28-day mortality: **28.8%** **vs 28.7%** , P = 1.00



Research

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Effect of Hydrocortisone on Development of Shock Among Patients With Severe Sepsis

The HYPRESS Randomized Clinical Trial

Didier Keh, MD; Evelyn Trips; Gernot Marx, MD; Stefan P. Wirtz, MD; Emad Abduljawwad, MD; Sven Bercker, MD; Holger Bogatsch, MD; Josef Briegel, MD; Christoph Engel, MD; Herwig Gerlach, MD, PhD, MBA; Anton Goldmann, MD; Sven-Olaf Kuhn, MD; Lars Hüter, MD; Andreas Meier-Hellmann, MD; Axel Nierhaus, MD; Stefan Kluge, MD; Josefa Lehmke, MD; Markus Loeffler, MD; Michael Oppert, MD; Kerstin Resener, MD; Dirk Schädler, MD; Tobias Schuerholz, MD; Philipp Simon, MD; Norbert Weiler, MD; Andreas Weyland, MD; Konrad Reinhart, MD; Frank M. Brunkhorst, MD; for the SepNet-Critical Care Trials Group

JAMA®
The Journal of the American Medical Association

Effect of Hydrocortisone on Development of Shock Among Patients With Severe Sepsis

The HYPRESS Randomized Clinical Trial

353 septic patients without septic shock January 13, 2009, to August 27, 2013,		
	Hydrocortisone	**Placebo**
# of Patients	170	170
Occurrence of septic shock	**21.2%**	**22.9%**

JAMA®
The Journal of the American Medical Association

difference, −1.8%; 95% CI, −10.7% to 7.2%; *P* = .70

Keh D, et al. JAMA. 2016;316(17):1775–1785

Recommendations

58. For adults with septic shock and an ongoing requirement for vasopressor therapy we suggest using IV corticosteroids.	***Weak** , moderate-quality evidence*	**UPGRADE from *Weak* recommendation** , *low quality of evidence* "We suggest against using IV hydrocortisone to treat septic shock patients if adequate fluid resuscitation and vasopressor therapy are able to restore hemodynamic stability (see goals for Initial Resuscitation). If this is not achievable, we suggest IV hydrocortisone at a dose of 200 mg/day."

Evans, L. et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock 2021, Critical Care Medicine: November 2021 - Volume 49 - Issue 11

Steroid Use in Septic Shock

Septic shock

Volume & norepinephrine

Ongoing vasopressor need in first 1-3 hours

Hydrocortisone 50 mg IV q 6hrs

May consider fludrocortisone 100 mcg orally

STEROIDS IN SEPSIS & SEPTIC SHOCK

EVOLUTION OF EVIDENCE

It seems that despite seemingly contradictory outcomes of these trials, there is a consistent trend towards faster shock reversal and potential benefit of combining hydrocortisone and fludrocortisone.

Mortality Benefit

PIRRACCHIO

Patient-level Meta-analysis

17 Trials with individual patient data (n=7882), and 7 trials with 90-day mortality (n=5929).
No significant reduction in 90-day mortality of hydrocortisone compared to placebo, and no difference in secondary outcomes except for vasopressor-free days.
When hydrocortisone was combined with fludrocortisone, there was a lower relative risk of mortality compared to hydrocortisone alone
Hydrocortisone was not associated with increased risk of superinfection, hyperglycemia, or gastrointestinal bleeding, but there was a potential risk of hypernatremia and muscle weakness.

NEJM Evidence — 2023

BOSCH

Retrospective cohort study among 88,275 patients with septic shock receiving norepinephrine who initiated hydrocortisone treatment, the addition of fludrocortisone to hydrocortisone was associated with a 3.7% lower adjusted absolute risk difference in the primary composite outcome of mortality or discharge to hospice compared with initiation of hydrocortisone alone.

JAMA — 2023

CORTICUS

No difference in 28-day mortality between 50 mg hydrortisone IV every 6 hours for 5 days then tapered compared to placebo but a faster resolution of shock and a non-significant increased risk of superinfection in a total of 499 septic shock patients.

New England Journal of Medicine — 2018

APROCCHSS

90-day mortality was lower in the hydrocortisone plus fludrocortisone group compared to placebo in 1,241 septic shock patients (43.0% vs 49.3%) with a faster shock reversal and no difference in ventilator free days.

JAMA — 2016

HYPRESS

Continuous infusion of 200 mg of hydrocortisone for 5 days followed by dose tapering until day 11 (n = 190) or placebo (n = 190) did not prevent the deterioration of sepsis into septic shock (21.2% vs 22.9%).

New England Journal of Medicine — 2008

ADRENAL

No significant difference in 90-day mortality with continuous infusion of hydrocortisone (200 mg per day for 7 days) but a shorter time to resolution of shock in a total of 3658 septic shock patients.

JAMA — 2002

ANANNE

28-day mortality and shock reversal were better in ACTH stimulation responders with hydrocortisone (50-mg IV bolus every 6 hours) and fludrocortisone (50-µg tablet once daily) compared to placebo in a total of 300 septic shock patients.

Society of Critical Care Medicine — 1998

BOLLAERT

"supra-physiologic" dose of methylprednisolone (100 mg IV three times daily for 5 days) in 22 patients compared to placebo in 19 patients resulted in a significant improvement in hemodynamics (68% vs 21%) and lower mortality (22% vs 63%).

Annals of Surgery Open — 1976

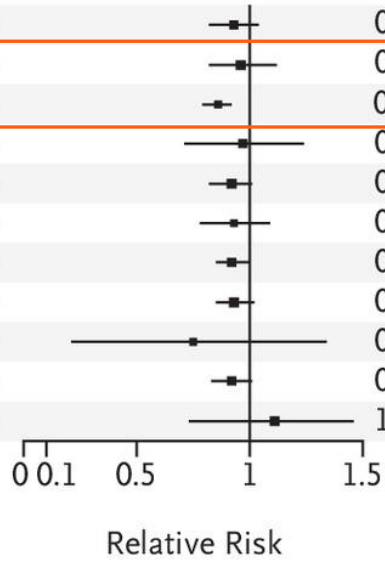
SCHUMER

Prospective study showed a morality rate of 38.4% in 86 saline-treated patients compared to 10.4% in 86 steroid treated. Retrospective data showed a mortality of 42.5% in 160 patients treated without steroids compared to 14% in 168 patients treated with steroids.

Association between Steroid and 90-Day Mortality

A

Treatment	Subgroup	Total No. of Patients (treatment+ control) (%)	No. Treated (%)	No. of Deaths in Treated (%)	No. Placebo (%)	No. of Deaths in Placebo (%)	Relative Risk (CI)
Overall		5929 (100)*	2966 (100)	1026 (36)	2963 (100)	1069 (37)	0.93 (0.82–1.04)
Hydrocortisone	Without fludrocortisone	4389 (74)	2202 (74)	665 (31)	2187 (74)	656 (31)	0.96 (0.82–1.12)
	With fludrocortisone	1540 (26)	764 (26)	361 (47)	776 (26)	413 (53)	0.86 (0.79–0.92)
Taper	Taper	657 (11)	329 (11)	135 (51)	328 (11)	127 (49)	0.97 (0.71–1.24)
	No taper	5272 (89)	2637 (89)	891 (34)	2635 (89)	942 (36)	0.92 (0.82–1.01)
Continuous	Continous	3844 (65)	1922 (65)	538 (29)	1922 (65)	552 (30)	0.93 (0.78–1.09)
	Bolus	2085 (35)	1044 (35)	488 (48)	1041 (35)	517 (51)	0.92 (0.85–1.00)
Steroid duration	Fixed	5771 (97)	2888 (97)	999 (35)	2883 (97)	1043 (37)	0.93 (0.85–1.02)
	Shock reversal	158 (3)	78 (3)	27 (60)	80 (3)	26 (63)	0.75 (0.21–1.34)
Steroid initiation	<24 h	5723 (97)	2865 (97)	982 (35)	2858 (97)	10,255 (37)	0.92 (0.83–1.01)
	>24 h	176 (3)	85 (3)	40 (56)	91 (3)	39 (50)	1.11 (0.73–1.46)



Pirracchio R, Annane D, Waschka AK, et al. Patient-level meta-analysis of low-dose hydrocortisone in adults with septic shock. *NEJM Evid* 2023;2(6).

Results should be interpreted with caution!

Only two trials included fludrocortisone

More severe shock than did the patients that comprised the overall meta-analysis cohort

- mean norepinephrine dose of the cohort was 1.08 micgs/kg/min of norepinephrine, whereas only 26% of patients in the overall cohort of the meta-analysis had a norepinephrine equivalent dose that was greater than 0.6 micg/kg/min

Higher percentage of patients with a pulmonary source of infection compared with the overall meta-analysis cohort

- 59.4% vs. 32%

Fludrocortisone subgroup represents a minority of patients in the cohort, making the statistical validity of this finding difficult to assess

Annals of Pharmacotherapy

Impact Factor: **2.9** / 5-Year Impact Factor: **2.9**

JOURNAL HOMEPAGE

SUBMIT PAPER

Restricted access | Research article | First published online April 6, 2023

Fludrocortisone Plus Hydrocortisone Versus Hydrocortisone Alone as Adjunctive Therapy in Septic Shock: A Retrospective Cohort Study

Ashley E. Lock, PharmD, BCPS, G. Christina Gutierrez, PharmD, BCPS, [...], and Rebecca L. Attridge, PharmD, MSc, BCPS, BCCCP +2 View all authors and affiliations

Volume 57, Issue 12 | https://doi.org/10.1177/10600280231164210

FC + HC was not associated with shock reversal at greater than 72 hours or decreased in-hospital mortality in a retrospective study that included 251 patients.

Effectiveness of Fludrocortisone Plus Hydrocortisone *Versus* Hydrocortisone Alone in Septic Shock: A Systematic Review and Network Meta-Analysis of Randomized Controlled Trials

Bijan Teja , **Megan Berube** , **Tiago V. Pereira** , **Anica C. Law** , **Carly Schanock** , **Brandon Pang** , **Hannah Wunsch** , **Allan J. Walkey** , and **Nicholas A. Bosch**

+ Author Information

https://doi.org/10.1164/rccm.202310-1785OC **PubMed:** 38271488

Received: October 12, 2023 Accepted: January 24, 2024

In a systematic review and Bayesian network meta-analysis of 17 trials (7,688 patients), fludrocortisone plus hydrocortisone showed a lower risk of all-cause mortality in adult septic shock compared to hydrocortisone alone and placebo/usual care. The combination treatment had a 0.85 relative risk of mortality (moderate-certainty evidence) and was 12% more effective than hydrocortisone alone (low-certainty evidence). The analysis relied mainly on indirect evidence due to limited direct comparisons.

Critical Care Medicine
Society of Critical Care Medicine
The Intensive Care Professionals

ONLINE REVIEW ARTICLE

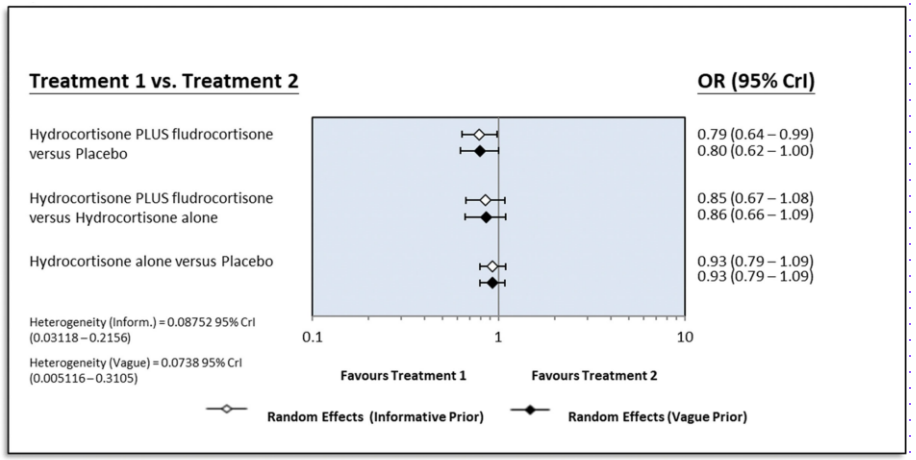
Do We Need to Administer Fludrocortisone in Addition to Hydrocortisone in Adult Patients With Septic Shock? An Updated Systematic Review With Bayesian Network Meta-Analysis of Randomized Controlled Trials and an Observational Study With Target Trial Emulation*

Lai, Pei-Chun MD, PhD[1,2]; Lai, Chao-Han MD, PhD[3–5]; Lai, Edward Chia-Cheng PhD[6]; Huang, Yen-Ta MD, MSc, PhD[3]

Author Information

Critical Care Medicine 52(4):p e193-e202, April 2024. | *DOI:* 10.1097/CCM.0000000000006161

A



B

A total of 19 studies involving 95,841 patients were included. Hydrocortisone plus fludrocortisone showed the lowest short-term mortality versus placebo (odds ratio [OR]: 0.79; 95% credible interval [CrI], 0.64–0.99; number needed to treat [NNT]: 21, range: 12–500; low certainty of evidence)

C

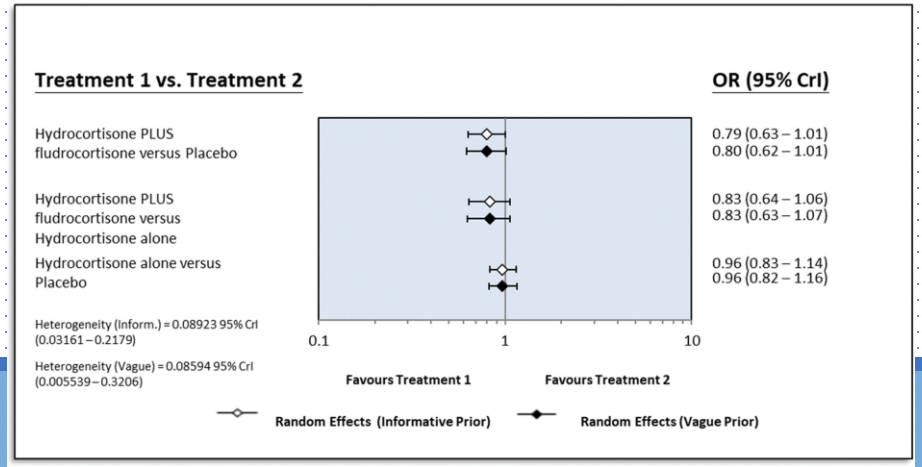


Table 2. Primary and Secondary Outcomes and Adverse Events.*

Outcome	Trials	Participants	Estimate of Effect†	95% CI	P Value
Primary outcome: 90-day all-cause mortality					
Adjusted RR	7	5929	0.93	0.82 to 1.04	0.22
Unadjusted RR	7	5929	0.95	0.89 to 1.02	0.21
TMLE	7	5029	0.96	0.90 to 1.02	0.21
Cox model — marginal hazard ratio	17	7873	0.92	0.81 to 1.05	0.27
Trial level meta-analysis — RR	21	7670	0.93	0.86 to 1.01	0.11
Including patient with sepsis‡ — RR	8	6138	0.95	0.88 to 1.02	0.24
Secondary outcomes					
Mortality at day 28 — RR	17	7864	0.92	0.83 to 1.00	—
Mortality at day 180 — RR	6	1997	0.92	0.74 to 1.10	—
Mortality at ICU discharge — RR	12	7314	0.92	0.83 to 1.01	—
Mortality at hospital discharge — RR	10	6676	0.95	0.88 to 1.03	—
Vasopressor-free days§ — MD	13	6422	1.24	0.74 to 1.73	—
Ventilation-free days§ — MD	15	7061	0.46	−0.08 to 0.99	—
Organ failure–free days§ — MD	12	1082	0.27	−0.65 to 0.92	—
Duration of ICU admission — MD, d	15	7636	0.13	−0.65 to 0.92	—
Duration of hospital admission — MD, d	14	7591	0.22	−1.17 to 1.62	—
Adverse events					
Superinfection	10	6970	1.04	0.95 to 1.15	
Hyperglycemia	10	7017	1.05	0.98 to 1.12	
Hypernatremia	6	5033	2.01	1.56 to 2.60	
Gastroduodenal bleeding	8	2748	1.11	0.83 to 1.48	
Muscle weakness	5	2647	1.73	1.49 to 1.99	

* The widths of the CIs have not been adjusted for multiplicity. Thus, the CIs should not be used to reject or not reject treatment effects. CI denotes confidence interval; ICU, intensive care unit; MD, mean difference; RR, relative risk; and TMLE, targeted maximum likelihood estimation.

† Estimates of effects are marginal risk ratio unless indicated.

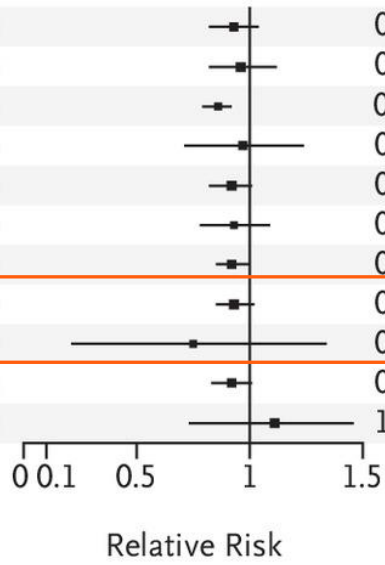
‡ Patients with sepsis but no shock.

§ Vasopressor-, ventilation-, and organ failure–free days are calculated up to day 28.

Association between Steroid and 90-Day Mortality

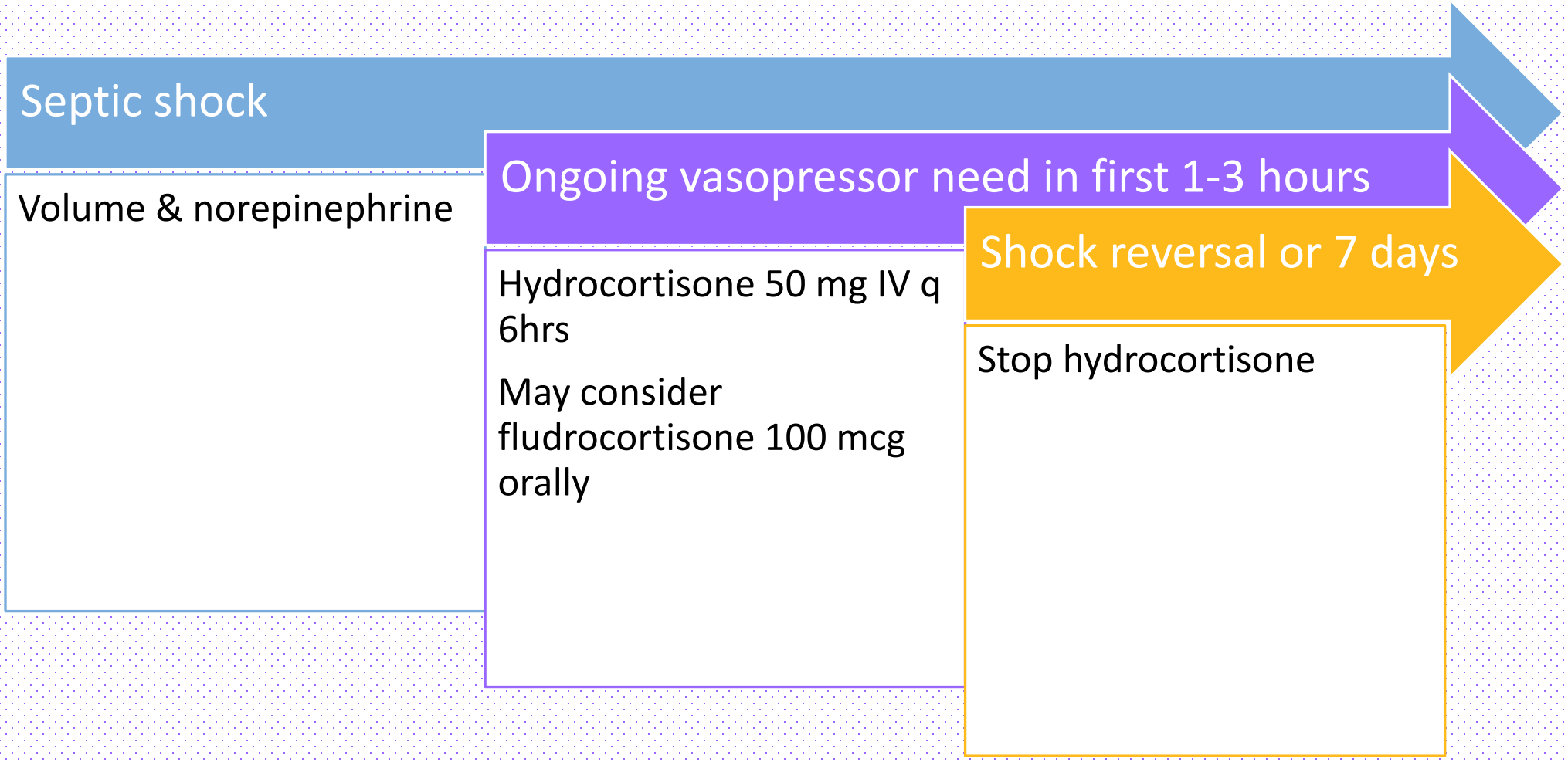
A

Treatment	Subgroup	Total No. of Patients (treatment+ control) (%)	No. Treated (%)	No. of Deaths in Treated (%)	No. Placebo (%)	No. of Deaths in Placebo (%)	Relative Risk (CI)
Overall		5929 (100)*	2966 (100)	1026 (36)	2963 (100)	1069 (37)	0.93 (0.82–1.04)
Hydrocortisone	Without fludrocortisone	4389 (74)	2202 (74)	665 (31)	2187 (74)	656 (31)	0.96 (0.82–1.12)
	With fludrocortisone	1540 (26)	764 (26)	361 (47)	776 (26)	413 (53)	0.86 (0.79–0.92)
Taper	Taper	657 (11)	329 (11)	135 (51)	328 (11)	127 (49)	0.97 (0.71–1.24)
	No taper	5272 (89)	2637 (89)	891 (34)	2635 (89)	942 (36)	0.92 (0.82–1.01)
Continuous	Continous	3844 (65)	1922 (65)	538 (29)	1922 (65)	552 (30)	0.93 (0.78–1.09)
	Bolus	2085 (35)	1044 (35)	488 (48)	1041 (35)	517 (51)	0.92 (0.85–1.00)
Steroid duration	Fixed	5771 (97)	2888 (97)	999 (35)	2883 (97)	1043 (37)	0.93 (0.85–1.02)
	Shock reversal	158 (3)	78 (3)	27 (60)	80 (3)	26 (63)	0.75 (0.21–1.34)
Steroid initiation	<24 h	5723 (97)	2865 (97)	982 (35)	2858 (97)	10,255 (37)	0.92 (0.83–1.01)
	>24 h	176 (3)	85 (3)	40 (56)	91 (3)	39 (50)	1.11 (0.73–1.46)



Pirracchio R, Annane D, Waschka AK, et al. Patient-level meta-analysis of low-dose hydrocortisone in adults with septic shock. *NEJM Evid* 2023;2(6).

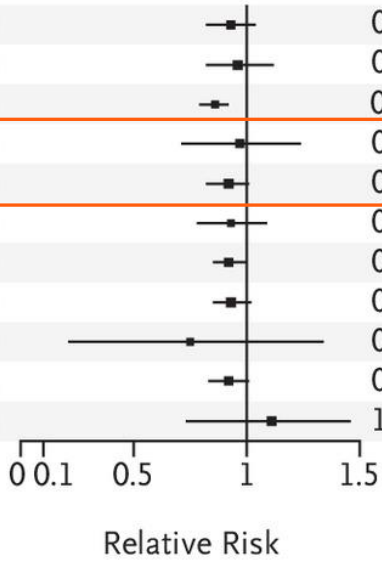
Steroid Use in Septic Shock



Association between Steroid and 90-Day Mortality

A

Treatment	Subgroup	Total No. of Patients (treatment+ control) (%)	No. Treated (%)	No. of Deaths in Treated (%)	No. Placebo (%)	No. of Deaths in Placebo (%)	Relative Risk (CI)
Overall		5929 (100)*	2966 (100)	1026 (36)	2963 (100)	1069 (37)	0.93 (0.82–1.04)
Hydrocortisone	Without fludrocortisone	4389 (74)	2202 (74)	665 (31)	2187 (74)	656 (31)	0.96 (0.82–1.12)
	With fludrocortisone	1540 (26)	764 (26)	361 (47)	776 (26)	413 (53)	0.86 (0.79–0.92)
Taper	Taper	657 (11)	329 (11)	135 (51)	328 (11)	127 (49)	0.97 (0.71–1.24)
	No taper	5272 (89)	2637 (89)	891 (34)	2635 (89)	942 (36)	0.92 (0.82–1.01)
Continuous	Continous	3844 (65)	1922 (65)	538 (29)	1922 (65)	552 (30)	0.93 (0.78–1.09)
	Bolus	2085 (35)	1044 (35)	488 (48)	1041 (35)	517 (51)	0.92 (0.85–1.00)
Steroid duration	Fixed	5771 (97)	2888 (97)	999 (35)	2883 (97)	1043 (37)	0.93 (0.85–1.02)
	Shock reversal	158 (3)	78 (3)	27 (60)	80 (3)	26 (63)	0.75 (0.21–1.34)
Steroid initiation	<24 h	5723 (97)	2865 (97)	982 (35)	2858 (97)	10,255 (37)	0.92 (0.83–1.01)
	>24 h	176 (3)	85 (3)	40 (56)	91 (3)	39 (50)	1.11 (0.73–1.46)



Pirracchio R, Annane D, Waschka AK, et al. Patient-level meta-analysis of low-dose hydrocortisone in adults with septic shock. *NEJM Evid* 2023;2(6).

Hemodynamic Support

SANFORD MEDICAL CENTER 5CD SMF

1 Hour:	12/15 12-13	13-14	14-15	15-16	16-17	17-18	18-19	19-20	20-21	21-22	
Titratable meds											
Norepinephrine mcg/kg/min						0.08 mcg...	0.18 mcg...		0.25 mcg...	0.25 mcg/...	Norepinephrine ...
Propofol mcg/kg/min									40 mcg/kg...		Propofol mcg/kg/...
midazolam Soln (mg)									4		midazolam Soln ...
sodium chloride Soln (mL)						1,000	100				sodium chloride ...

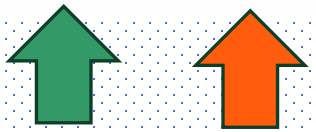
SANFORD MEDICAL CENTER 5CD SMF

1 Hour:	12/15 21-22	22-23	23-00	12/16 00-01	01-02	02-03	03-04	04-05	05-06	06-07	
Titratable meds											
Norepinephrine mcg/kg/min	0.25 mcg/...	0.17 mcg...	0.15 mcg...		0.13 mcg...	0.1 mcg/...		0.09 mcg/...	0.08 mcg/...		Norepinephrine ...
Propofol mcg/kg/min		40 mcg/kg...		40 mcg/kg...			40 mcg/k...		30 mcg/k...	20 mcg/k...	Propofol mcg/kg/...
Vasopressin units/min		0.03 Unit...									Vasopressin unit...
sodium chloride Soln (mL)		1,000							100		sodium chloride ...

SANFORD MEDICAL CENTER 5CD SMF | SANFORD MEDICAL CENTER 7CD SMF

12 Hours:	12/15 12-00	12/16 00-12	12-00	12/17 00-12	12-00	12/18 00-12	12-00	12/19 00-12	12-00	12/20 00-12	12-00	
Titratable meds												
Norepinephrine mcg/kg/min	0.15 mcg...	0.09 mcg...	0.1 mcg/...	0.07 mcg...	0.05 mcg...	0.01 mcg...	0 mcg/kg...					Norepinephrine mcg...
Propofol mcg/kg/min	40 mcg/k...	20 mcg/k...	30 mcg/k...	20 mcg/k...	25 mcg/k...	0 mcg/kg...	0 mcg/kg/...					Propofol mcg/kg/min
Vasopressin units/min	0.03 Unit...	0 Units/...										Vasopressin units/min
midazolam Soln (mg)	4											midazolam Soln (mg)
sodium chloride Soln (mL)	2,100	600	100	600	100	600	100	600	100	600		sodium chloride Sol...
Insulin Drip Group												

hydrocortisone sodium succinate (solu-CORTEF) preservative free injection 50 mg Dose: 50 mg Freq: Every six hours Route: IV Start: 12/15/23 1800 End: 12/19/23 0909	0050 BA (50 mg)- Given 1215 ME (50 mg)- Given	0535 BA (50 mg)- Given 1658 ME (50 mg)- Given	0046 BA (50 mg)- Given 1156 EL (50 mg)- Given	0526 BA (50 mg)- Given 1753 EL (50 mg)- Given	0005 BA (50 mg)- Given	0617 BA (50 mg)- Given	



Questions?

What is the rational of using steroid in sepsis?

- **Relative adrenal insufficiency**

What is the benefit of steroid in sepsis?

- **Shock reversal**

Should adrenal reserve be assessed?

- **No**

Does the use of steroid prevent progression to shock in sepsis?

- **No**

When to start steroids and how much?

- **Ongoing vasopressor support**

Do we need to add fludrocortisone?

- **Maybe**

What are the expected adverse events with steroid?

- **Muscle weakness and hypernatremia**

How long do we keep on steroids?

- **Till shock reversal**

Do we stop or taper?

- **Stop**


NEED CASH
FOR ALCOHOL
RESEARCH