Should “Roids” Be the Rage in Septic Shock?

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Learning Objectives

- 1. Review the mechanism of action for the use of corticosteroids in septic shock
- 2. Appraise recent evidence for the utilization of corticosteroids in septic shock

Outline

- Overview of Septic Shock
- Corticosteroids
- Research
- Recommendations
- The Future
- Applying Our Knowledge

Overview of Septic Shock

Guidelines for Septic Shock

- Society of Critical Care Medicine (SCCM) + European Society of Intensive Care Medicine (ESICM)
  - Increase awareness of both patient and clinician
  - develop evidence-based guidelines for the management of sepsis/septic shock
  - Implementation of those guidelines
- Surviving Sepsis Campaign Guidelines: 2004, 2008, 2012, 2016
- Studies show…. IT WORKS!

(Levy et al., 2014)

Surviving Sepsis Campaign 2016 Definition

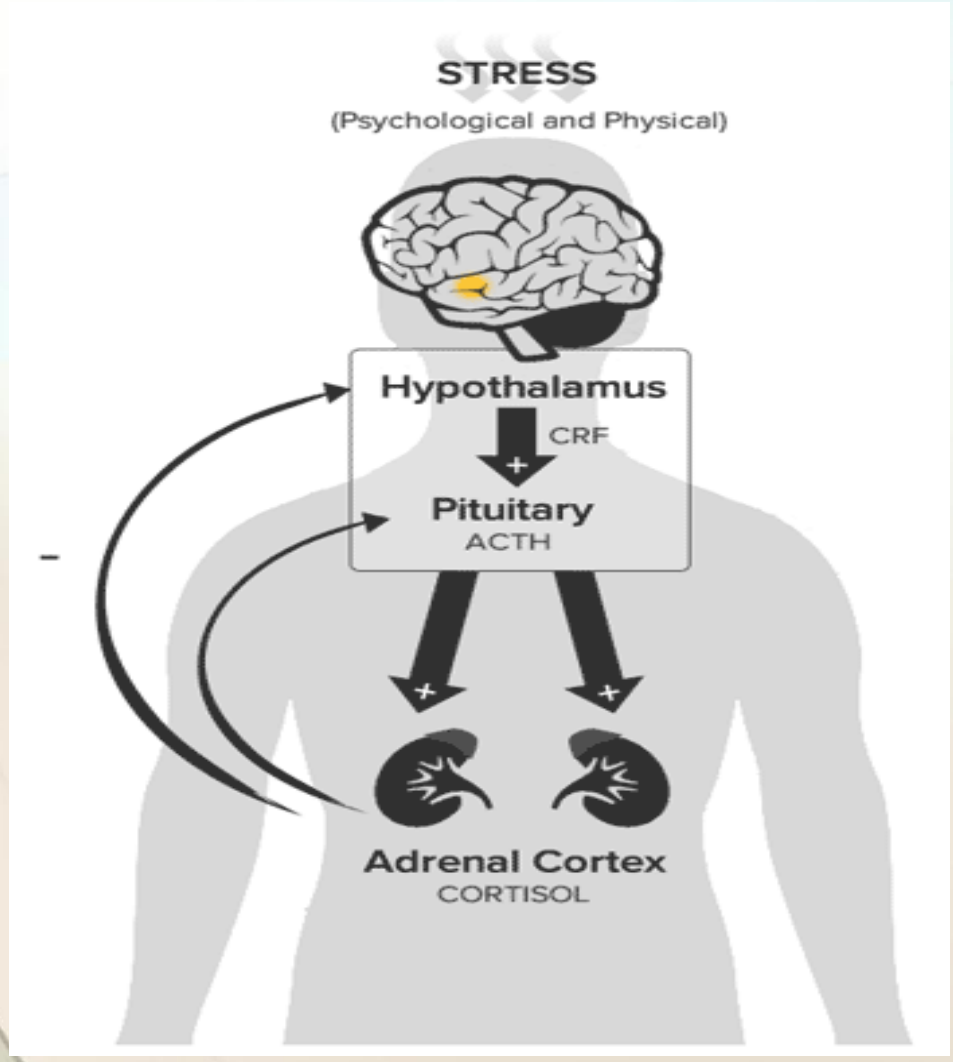
SEPSIS	SEPTIC SHOCK
"life-threatening organ dysfunction caused by a dysregulated host response to infection"	"subset of sepsis with circulatory and cellular/metabolic dysfunction associated with a higher risk of mortality"

(Levy et al., 2014)

Corticosteroids

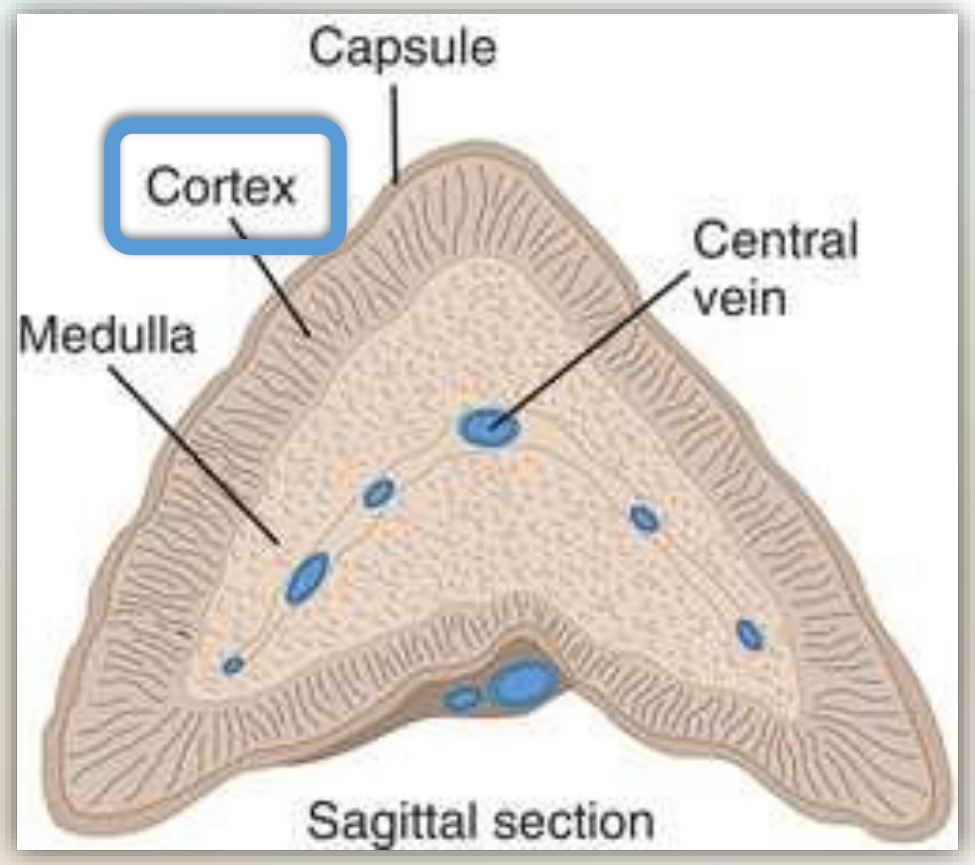
Pathophysiology Overview

Hypothalamic Pituitary Adrenal Axis



https://www.integrativepro.com/Resources/Integrative-Blog/2016/The-HPA-Axis

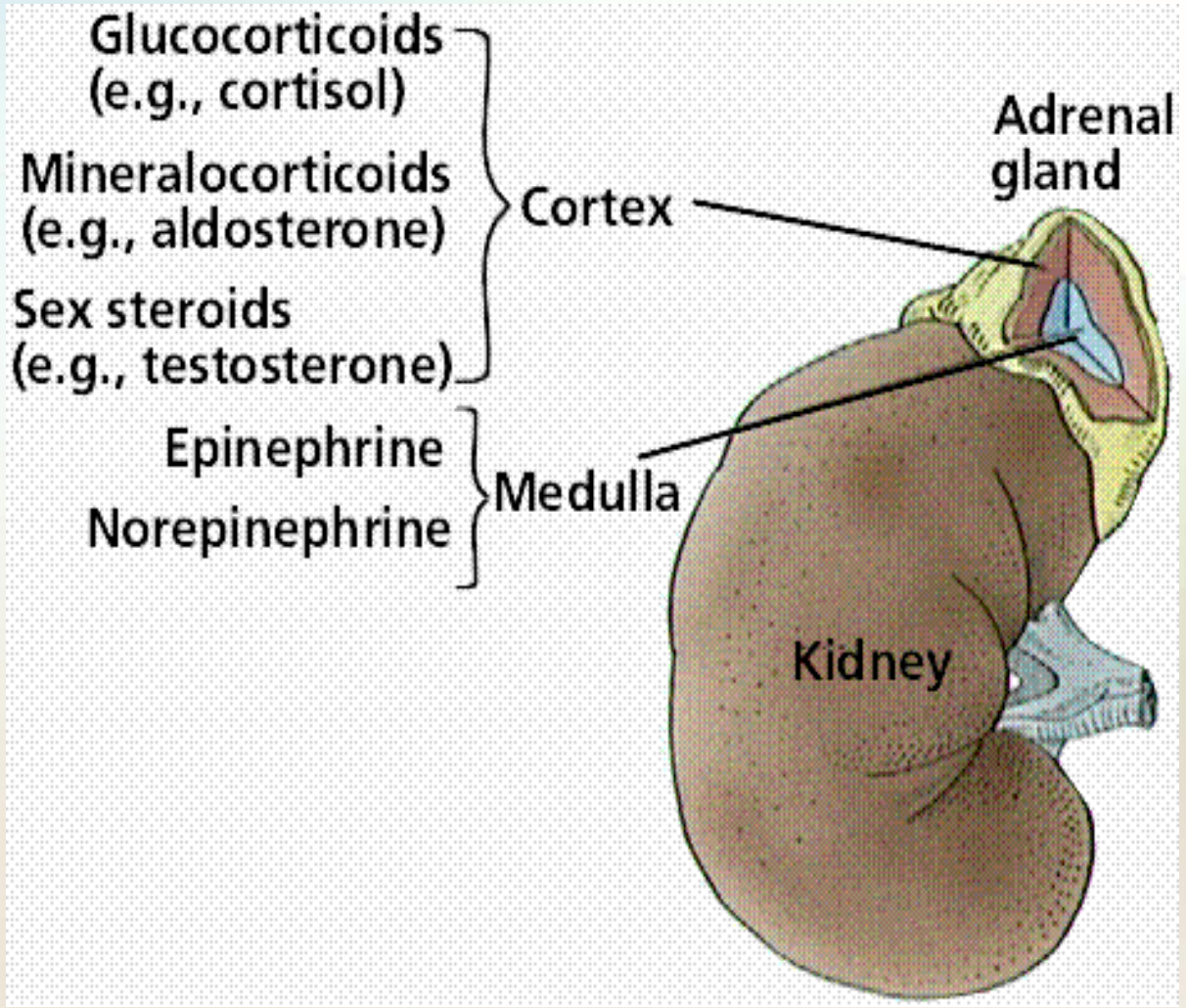
Adrenal Gland



https://medical-dictionary.thefreedictionary.com/adrenal+gland

Types of Adrenal Cortex Hormones

Glucocorticoids	Mineralocorticoids
Hydrocortisone	Fludrocortisone



https://www2.estrellamountain.edu/faculty/farabee/biobk/BioBookENDOCR.html

Critical Illness-Related Corticosteroid Insufficiency (CIRCI)

- Type of adrenal insufficiency
  - Describes impairment of HPA Axis during stress response
  - Corticosteroid levels are inadequate for stress response
    - ACTH stimulation test (Cosyntropin Test)

- Signs and Symptoms:
  - Hypotension refractory to fluid resuscitation and vasopressors
  - Confusion/Delirium
  - Hypoglycemia
  - Hyponatremia
  - Hyperkalemia

(Annane et al., 2017)

Research

https://sciencing.com/

Timeline of Trials

FRENCH TRIAL (2002)- Breakdown

- Objective: To assess whether low doses of corticosteroids improve 28 day survival in patients with septic shock and relative adrenal insufficiency.
- Design: Randomized, double blind trial
- Setting: 19 ICUs across France
- Number of participants: 300 Patients
- Intervention:
  - Group #1 (n=149): Placebo
  - Group #2 (n=151): Hydrocortisone (50mg IV q 6 hours) AND fludrocortisone (50 mcg PO daily)

Inclusion Criteria

Age ≥18 years

Hospitalized in ICU

Documented site or strong suspicion of infection

Temperature ≥38.3°C or ≤35.6°C

Heart rate ≥90 BPM

SBP <90 mmHg for ≥1 hour despite IVF

dopamine >5mcg/kg/min, any epinephrine, or any norepinephrine

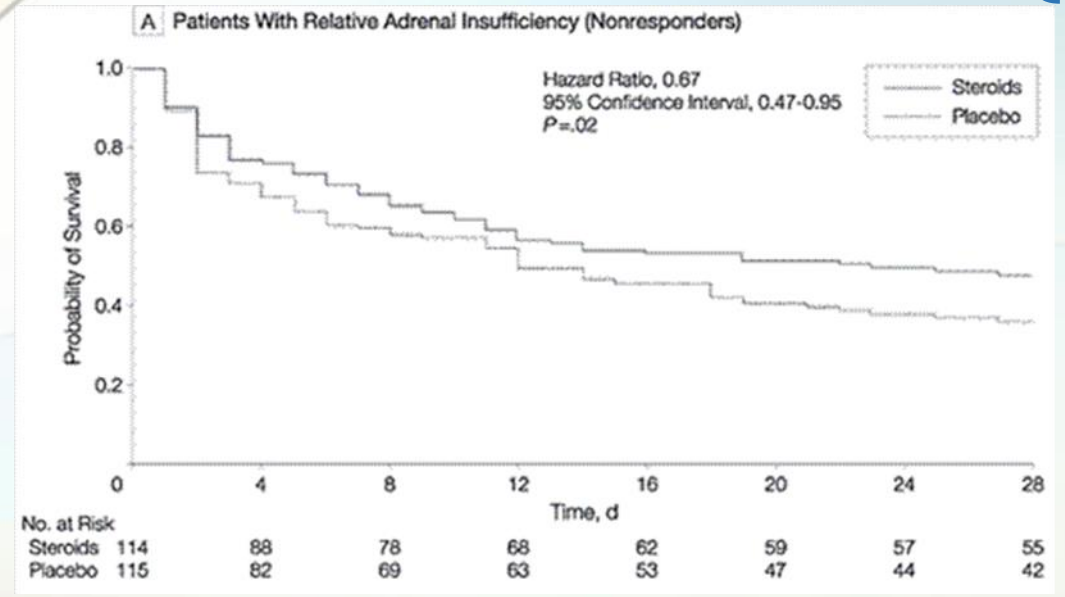
Urine output ≤0.5 mL/kg for ≥1 hour

or the PaO_2/FiO_2 ≤280 mmHg

Lactate levels ≥2 mmol/L

Mechanical ventilation

FRENCH TRIAL (2002) – The Results



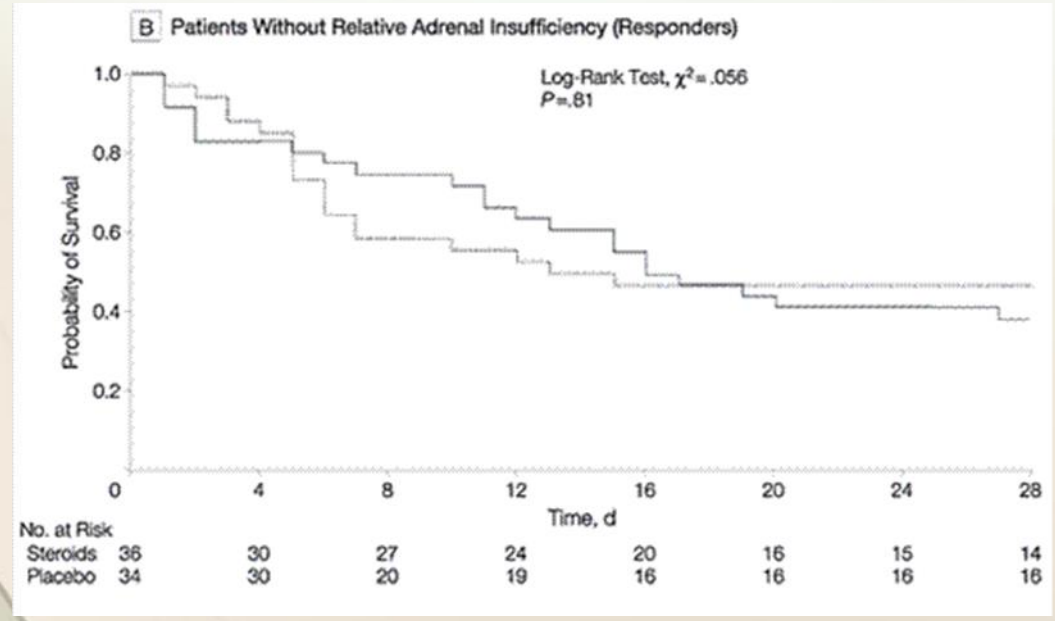


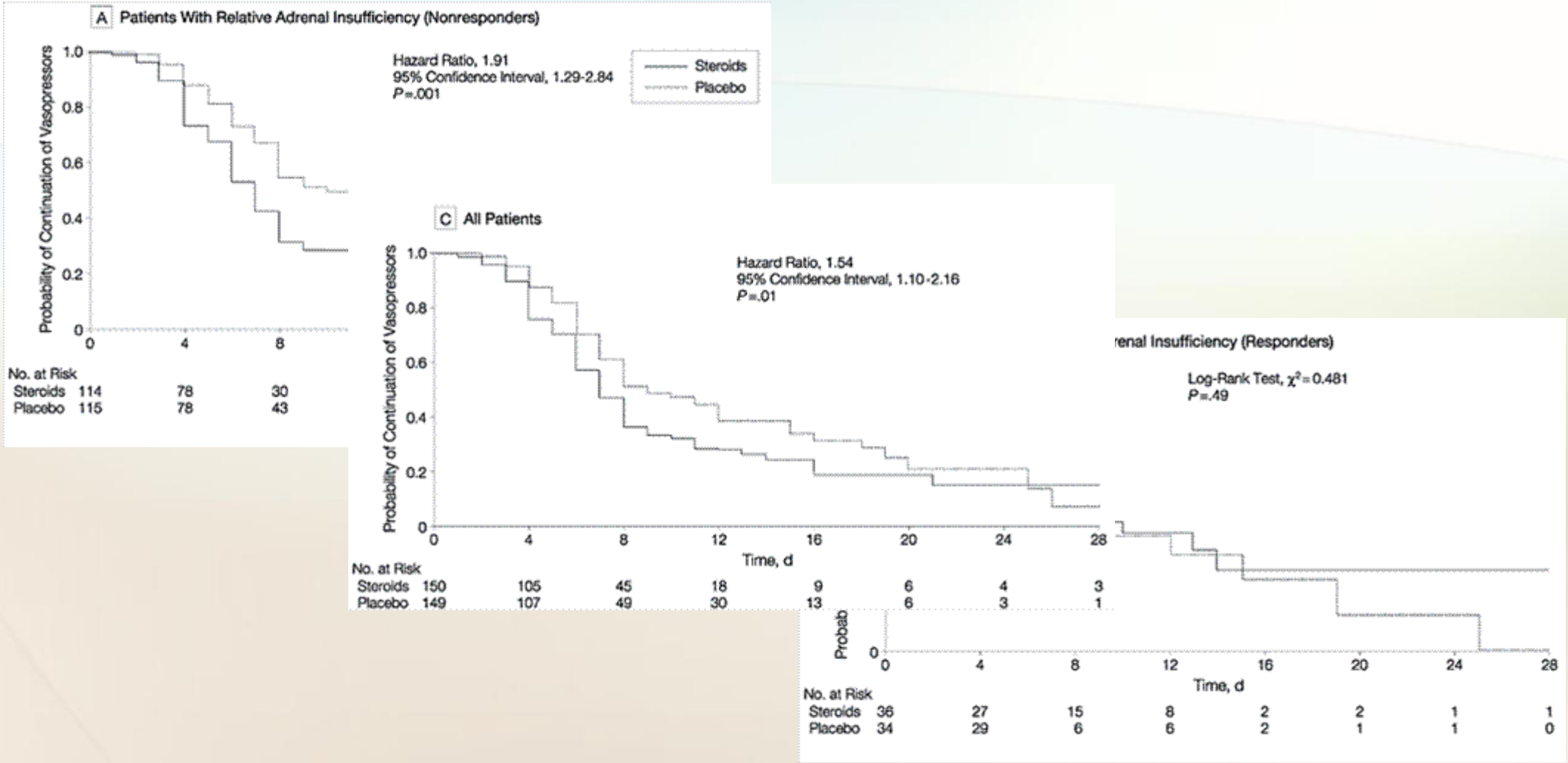
Table 4. Frequency of Fatal Events in 299 Patients with Septic Shock*

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.

(Annane et al., 2017)

FRENCH TRIAL (2002) – The Results



(Annane et al., 2017)

CORTICUS TRIAL (2008) - Breakdown

- Objective: To assess the safety and efficacy of low-dose hydrocortisone therapy for patients with septic shock and to compare outcomes based on response to corticotropin testing.
- Design: double-blind, randomized, controlled trial
- Setting: 52 ICUs
- Number of participants: 499 Patients
- Intervention:
  - Group #1 (n=251): Placebo
  - Group #2 (n=248): Hydrocortisone
    - 50-mg IV q 6 hours for 5 days
    - Then 50 mg IV q 12 hours for days 6 to 8
    - Then 50 mg q 24 hours for days 9 to 11
    - then stopped. (A total of 29 doses)

Inclusion Criteria:
Patients 18 years and older

All patients hospitalized in ICU

Septic shock within prior 72h (defined by systolic BP <90 despite adequate fluid replacement or need for vasopressors >1h) and hypoperfusion or organ dysfunction attributable to sepsis

Exclusion Criteria:
long-term corticosteroids within past 6 months or short-term corticosteroids within past 4 weeks

(Sprung et al., 2008)

CORTICUS TRIAL (2008) – The Results

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.

(Sprung et al., 2008)

CORTICUS TRIAL (2008) – The Results *Bonus*

- <u>Etomidate and Steroid use in patients with adrenal insufficiency</u>
  - Etomidate 60% mortality rate vs. no etomidate 43% mortalitiy rate (P=0.004)

- <u>Shock reversal</u>
  - Steroid group (3.3 days) vs. Placebo group (5.8 days) (P<0.001)

(Sprung et al., 2008)

ADRENAL TRIAL (2018) - Breakdown

- Objective: To see if a week long continuous infusion of hydrocortisone improve 90 day mortality in patients with septic shock requiring ventilatory and vasopressor support
- Design: Multicenter, double-blind, randomized, controlled trial
- Setting: 69 ICUs (International)
- Number of participants: 3,658 Pts
- Intervention:
  - Group #1 (n=1,826): Placebo
  - Group #2 (n=1,832): Hydrocortisone
    - Continuous infusion of hydrocortisone 200 mg IV daily for 7 days or ICU discharge or death

Inclusion Criteria:

Age ≥18 years
Mechanical ventilation
Strong clinical suspicion of infection
≥2 SIRS criteria
Continuous vasopressors/inotropes for SBP >90mmHg or MAP >60mmHg for ≥4 hours

Exclusion Criteria:

Receiving systemic corticosteroids for indication other than septic shock
Received etomidate

(Venkatesh et al., 2018)

ADRENAL TRIAL (2018) – The Results

Table 2. Outcomes.*

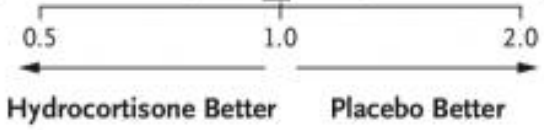
Outcome	Hydrocortisone (N=1853)	Placebo (N=1860)	Odds Ratio, Hazard Ratio, or Absolute Difference (95% CI)	P Value
Primary outcome				
90-day mortality — no./total no. (%)	511/1832 (27.9)	526/1826 (28.8)	0.95 (0.82 to 1.10)†	0.50
Secondary outcomes				
28-day mortality — no./total no. (%)	410/1841 (22.3)	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

(Venkatesh et al., 2018)

ADRENAL TRIAL (2018) – The Results

B Subgroup Analysis of Death at 90 Days

Subgroup	Hydrocortisone	Placebo	Odds Ratio (95% CI)	P Value for Interaction
	no. of patients with event/total no. of patients (%)			
Sex				0.53
Male	312/1106 (28.2)	336/1122 (29.9)	0.92 (0.76–1.10)	
Female	199/726 (27.4)	190/704 (27.0)	1.01 (0.80–1.28)	
Admission type				0.73
Surgical	125/568 (22.0)	138/580 (23.8)	0.91 (0.69–1.21)	
Medical	386/1264 (30.5)	388/1245 (31.2)	0.97 (0.81–1.15)	
Catecholamine dose				0.25
≤15 μg/min	224/968 (23.1)	228/995 (22.9)	1.02 (0.82–1.26)	
>15 μg/min	281/849 (33.1)	291/805 (36.1)	0.86 (0.70–1.05)	
Site of sepsis				0.63
Pulmonary	243/799 (30.4)	250/828 (30.2)	0.99 (0.80–1.23)	
Other	268/1033 (25.9)	276/998 (27.7)	0.92 (0.76–1.12)	
APACHE II score				0.17
≥25	326/840 (38.8)	297/785 (37.8)	1.01 (0.83–1.24)	
<25	184/990 (18.6)	229/1039 (22.0)	0.82 (0.66–1.02)	
Time from shock onset to randomization				0.08
<6 hr	110/352 (31.2)	96/344 (27.9)	1.16 (0.83–1.61)	
6 to <12 hr	127/511 (24.9)	153/486 (31.5)	0.71 (0.54–0.94)	
12 to <18 hr	119/437 (27.2)	106/423 (25.1)	1.13 (0.83–1.54)	
≥18 hr	154/525 (29.3)	167/566 (29.5)	0.99 (0.76–1.29)	



(Venkatesh et al., 2018)

APROCCHSS TRIAL (2018) – Breakdown

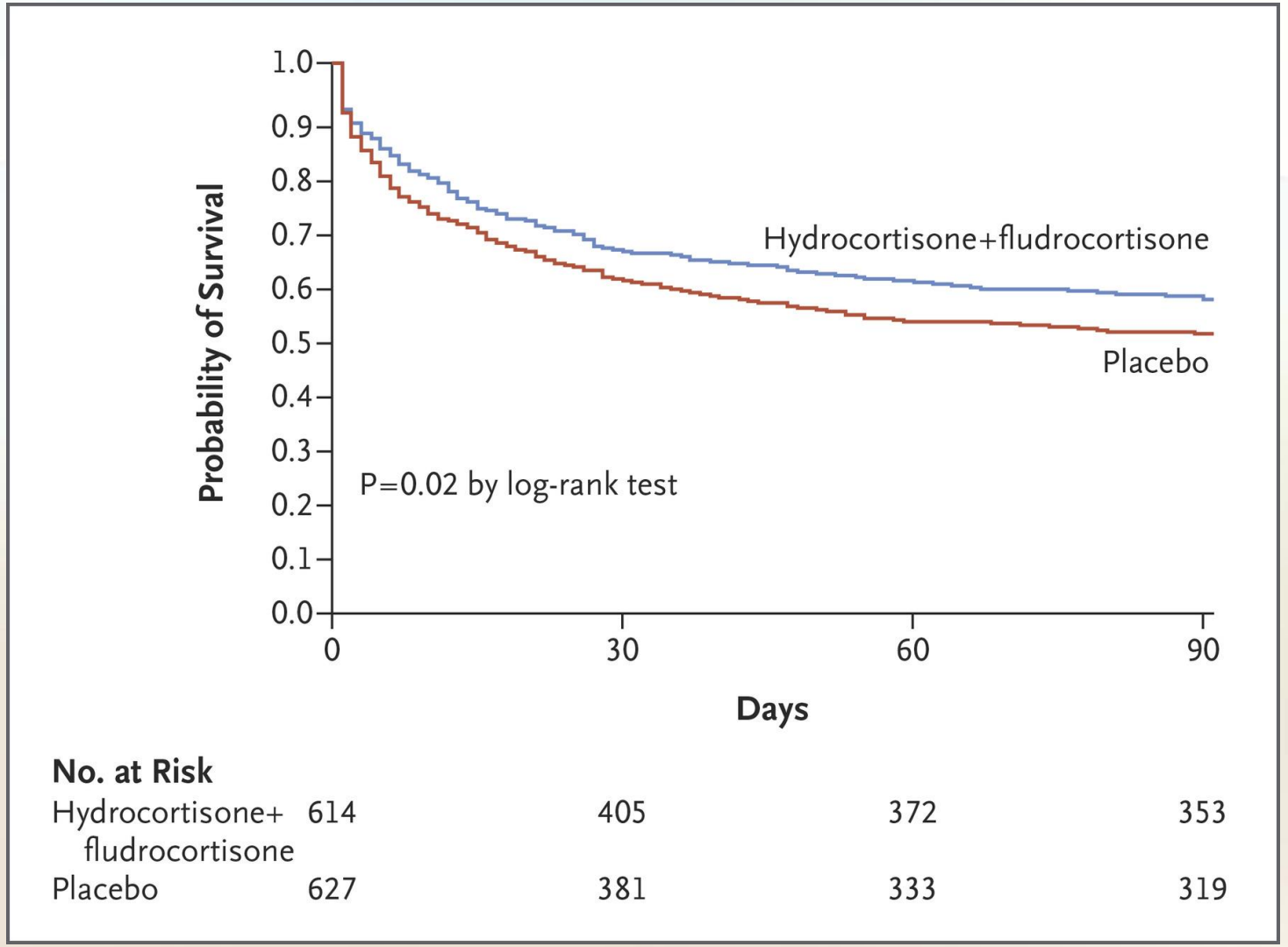
- Objective: To asses if low dose hydrocortisone plus fludrocortisone for 7 days affect mortality at 90 days in septic shock patients.
- Design: Multicenter, double-blind, randomized trial
- Setting: 34 ICUs
- Number of participants: 1241
- Intervention:
  - Group #1 (n=627): Placebo
  - Group #2 (n=614): Hydrocortisone 50mg IV q 6 hours ***and*** fludrocortisone 50 mcg NG daily for 7 days without taper

Inclusion Criteria:
admitted to the ICU < 7 days
septic shock < 24 hours
admitted to the ICU < 7 days
receipt of vasopressor therapy (norepinephrine, epinephrine, or any other vasopressor at a dose of ≥ 0.25 mcg/kg/min or ≥ 1 mg per hour) for ≥ 6 hours to maintain SBP ≥ 90 mm Hg or MAP ≥ 65 mm Hg

Exclusion Criteria:
septic shock > 24 hours
high risk of bleeding pregnancy or lactation

(Annane et al., 2018).

APROCCHSS TRIAL (2018) – The Results



No. at Risk

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

(Annane et al., 2018)

APROCCHSS TRIAL (2018) – The Results

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)		

* Plus–minus values are means ±SD. IQR denotes interquartile range.
† Shown is the relative risk for hydrocortisone plus fludrocortisone versus placebo.
‡ Patients who died before day 28 were assigned zero free days.

(Annane et al., 2018)

Trial Result Summary

- **French Trial**: Hydrocortisone in Septic patients showed ***benefit*** in both mortality and shock reversal (vasopressors).
- **CORTICUS**: Hydrocortisone in septic shock patients found to reverse shock faster, but ***no benefit*** on mortality.
- **ADRENAL**: Hydrocortisone in septic shock patient found to have small benefit with reversal of shock, but no difference/***no benefit*** on mortality
- **APROCCHSS**: Fludrocortisone + hydrocortisone in septic shock patients showed ***benefit*** in patient mortality rates and shock reversal (Vasopressors)

Recommendations

Surviving Sepsis Guideline Recommendations

"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 200mg per day (weak recommendation, low quality of evidence)."**

Do Cortisol levels need to be drawn on patients before starting steroids?

"for septic shock patients who have relative adrenal insufficiency random cortisol levels have not been demonstrated to be useful."

Should a bolus of steroids be given before starting schedule stress dose steroids?

No specific recommendation

Mention of Hyperglycemia with bolus

Should Steroids be tapered?

"We suggest tapering steroids when vasopressors are no longer needed"

(Annane et al., 2017)

What about the little ones?

SCCM Pediatric Recommendations

- Hydrocortisone is reserved for absolute adrenal insufficiency or persistent shock despite titration of epinephrine or norepinephrine. (Strong Recommendation)

The Future

Upcoming Studies - Adults

- **Vitamin C, Hydrocortisone and Thiamine for Septic Shock (CORVICTES)**
  - hypothesized that the combined use of vitamin C and stress-dose hydrocortisone may improve the outcomes (Mortality) of patients with septic shock
    - 400 Participants
    - **Started in September 2018**
    - **Estimated completion: 2020**

- **Evaluation of Hydrocortisone, Vitamin C and Thiamine for the Treatment of Septic Shock (HYVITS)**
  - explore the clinical benefits of using a combination of hydrocortisone, vitamin C, and thiamine (triple therapy) for the management of septic shock.
    - 212 Participants
    - **Started in March 2018**
    - **Estimated Completion: May 2019**

https://clinicaltrials.gov/ct2/home

Upcoming Studies - Pediatrics

- **Stress Hydrocortisone In Pediatric Septic Shock (SHIPSS)**
  - hypothesized that adjunctive hydrocortisone will significantly reduce the proportion of children with poor outcomes, defined as death or severely impaired health-related quality of life (HRQL), as assessed at 28 days following study enrollment (randomization).
    - 1032 participants
    - **Start: January 2019**
    - **Estimated Completion: 2023**

https://clinicaltrials.gov/ct2/home

Let’s Apply Our Knowledge!

Question #1

- According to the Surviving Sepsis Guidelines, what is the recommended daily dose of Hydrocortisone IV used for septic patients if fluid resuscitation and vasopressor therapy are unable to restore hemodynamic stability?
  - A) 100 mg per day
  - B) 200 mg per day
  - C) 300 mg per day
  - D) 400 mg per day
- Answer B is the correct answer because the Surviving Sepsis Guidelines reviewed current research and compared low dose steroid administration and mortality results. Their recommendation of 200 mg per day is labeled as a “weak recommendation, low quality of evidence”.

Question #2

- When should Hydrocortisone IV be stopped in the septic patient?

A) Stop after 1 day of therapy if hemodynamic stability is not reached

B) Stop steroids after 5 days of therapy

C) Taper steroids once vasopressors are no longer needed

D) Taper Steroids after 5-7 days of therapy

Answer C is the correct answer because the majority of studies taper the use of steroids in sepsis patients without adverse effects, and one crossover study highlighted rebound effects (both hemodynamic and immunologic effects) after abruptly stopping corticosteroids. Surviving Sepsis Guidelines recommend tapering steroids when vasopressors are no longer needed.

References

- Annane, D., Pastores, S. M., Rochwerg, B., Arlt, W., Balk, R. A., Beishuizen, A., . . . Van den Berghe, G. (2017). Guidelines for the Diagnosis and Management of Critical Illness-Related Corticosteroid Insufficiency (CIRCI) in Critically Ill Patients (Part 1): Society of Critical Care Medicine (SCCM) and European Society of Intensive Care Medicine (ESICM) 2017. *CCM Journal, 45*(12), 2078-2088.
- Annane, D., Renault, A., Brun-Buisson, C., Megarbane, B., Quenot, J. P., Siami, S., . . . Misset, B. (2018). Hydrocortisone plus Fludrocortisone for Adults with Septic Shock. *The New England Journal of Medicine, 378,* 809-818.
- Annane, D., Sebille, V., Charpentier, C., Bollaert, P. E., Francois, B., Korach, J. M., . . . Capellier, G. (2002). Effect of Treatment With Low Doses of Hydrocortisone and Fludrocortisone on Mortality in Patients With Septic Shock. *American Medical Association, 288*(7), 862-871.
- Levy, M. M., Evans, L. E., & Rhodes, A. (2018). The Surviving Sepsis Campaign Bundle: 2018 Update. *CCM Journal*, 997-1000. DOI: 10.1097/CCM.0000000000003119.
- Levy, M. M., Rhodes, A., Phillips, G. S., Townsend, S. R., Schorr, C. A., Beale, R., . . . Dellinger, R. P. (2014). Surviving Sepsis Campaign: association between performance metrics and outcomes in a 7.5 – year study. *Intensive Care Medicine, 40*(11), 1623-1633.
- Rhodes, A., Evans, L.E., Alhazzani, W., Levy, M. M., Antonelli, M., Ferrer R., . . . Dellinger, R. P. (2017). Surviving Sepsis Campaign: International Guides for Management of Sepsis and Septic Shock: 2016. *CCM Journal,* 45(5), 486-552.
- Sprung, C. L., Annane, D., Keh, D., Moreno, R., Singer, M., Freivogel, K., . . . Briegel, J. (2008). Hydrocortisone Therapy for Patients with Septic Shock. *The New England Journal of Medicine, 358*(2), 111-124.
- Venkatesh, B., Finfer, S., Cohen, J., Rajbhandari, D., Arabi, Y., Bellomo, R., . . . Qiang Li, M. (2018). Adjunctive Glucocorticoid Therapy in Patients with Septic Shock. *The New England Journal of Medicine, 378*, 797-808. (Venkatesh et al., 2018)

Thank You!