MINERALOCORTICOID : ADD ON ROLE IN SEPTIC SHOCK

(REVIEW ARTICLE)

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ORIGINAL ARTICLE

Hydrocortisone plus Fludrocortisone for Adults with Septic Shock

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MINERALOCORTICOID
in septic shock AS….

INTRODUCTION..

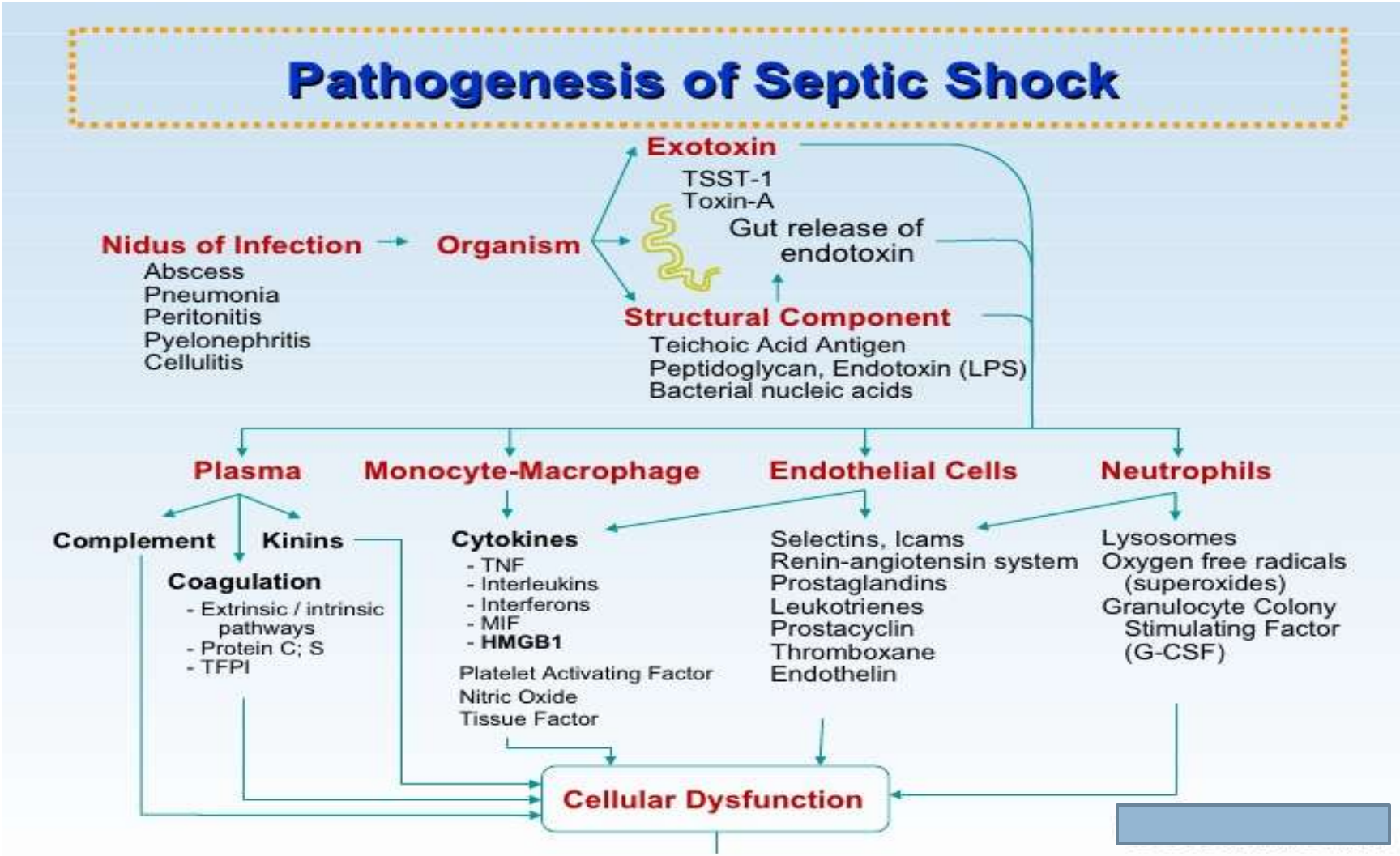
- Septic shock is characterized **by dysregulation of the host response to infection, with circulatory, cellular, and metabolic abnormalities.**

- We hypothesized that therapy with **hydrocortisone plus fludrocortisone** which can **modulate the host response, would improve the clinical outcomes of patients with septic shock.**

SEPSIS & STEROID

- Experimental and clinical evidence suggests that sepsis is associated with a **dysregulated response of the hypothalamic–pituitary–adrenal axis that may involve any of the steps from cortisol production to cortisol use by cells.**
- Corticosteroids have been used in the treatment of patients with severe infections since the **mid-twentieth** century.
- However, their **benefit-to-risk ratio, evaluated in numerous trials, remains controversial**.

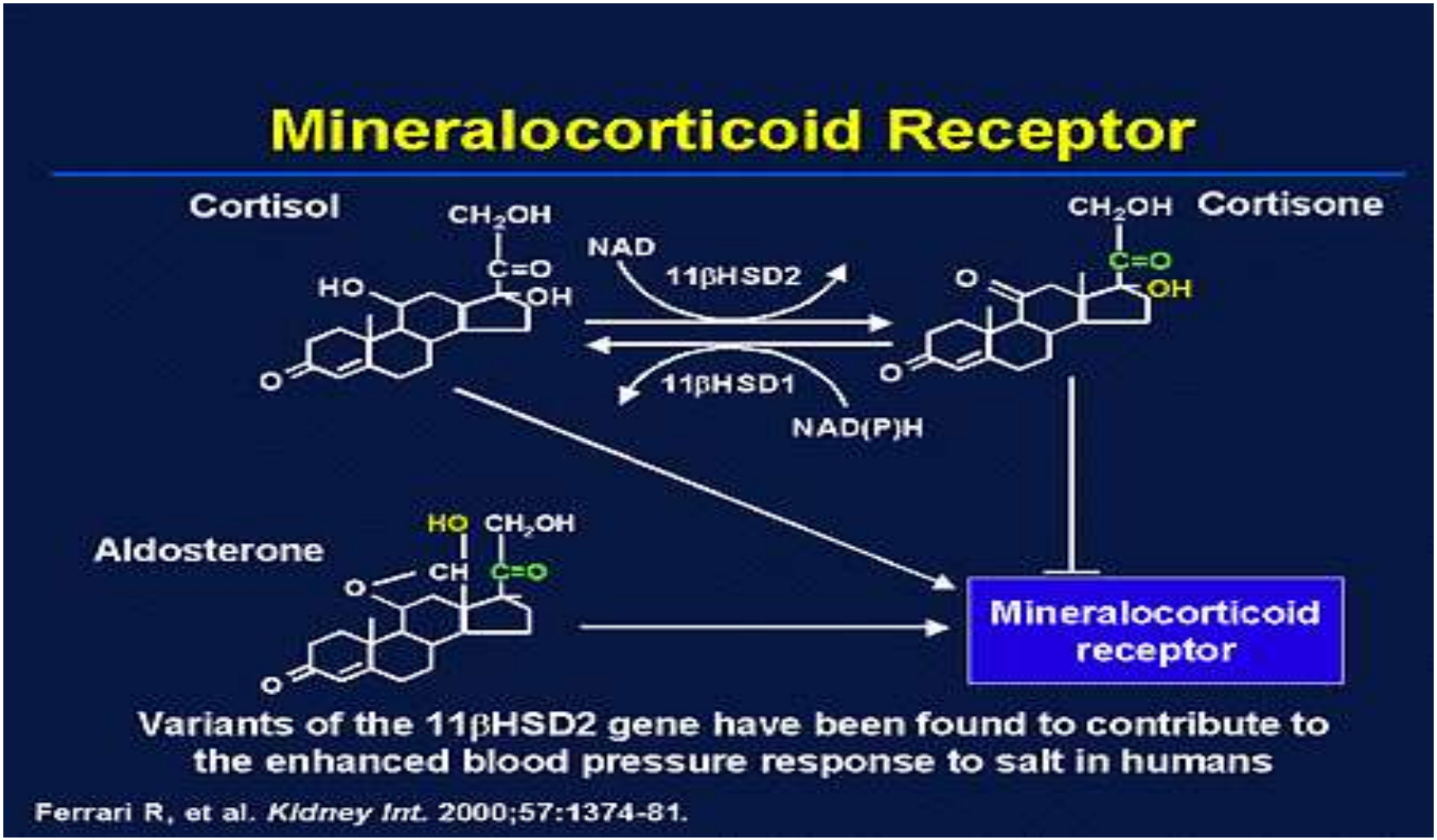
Pathogenesis of Septic Shock



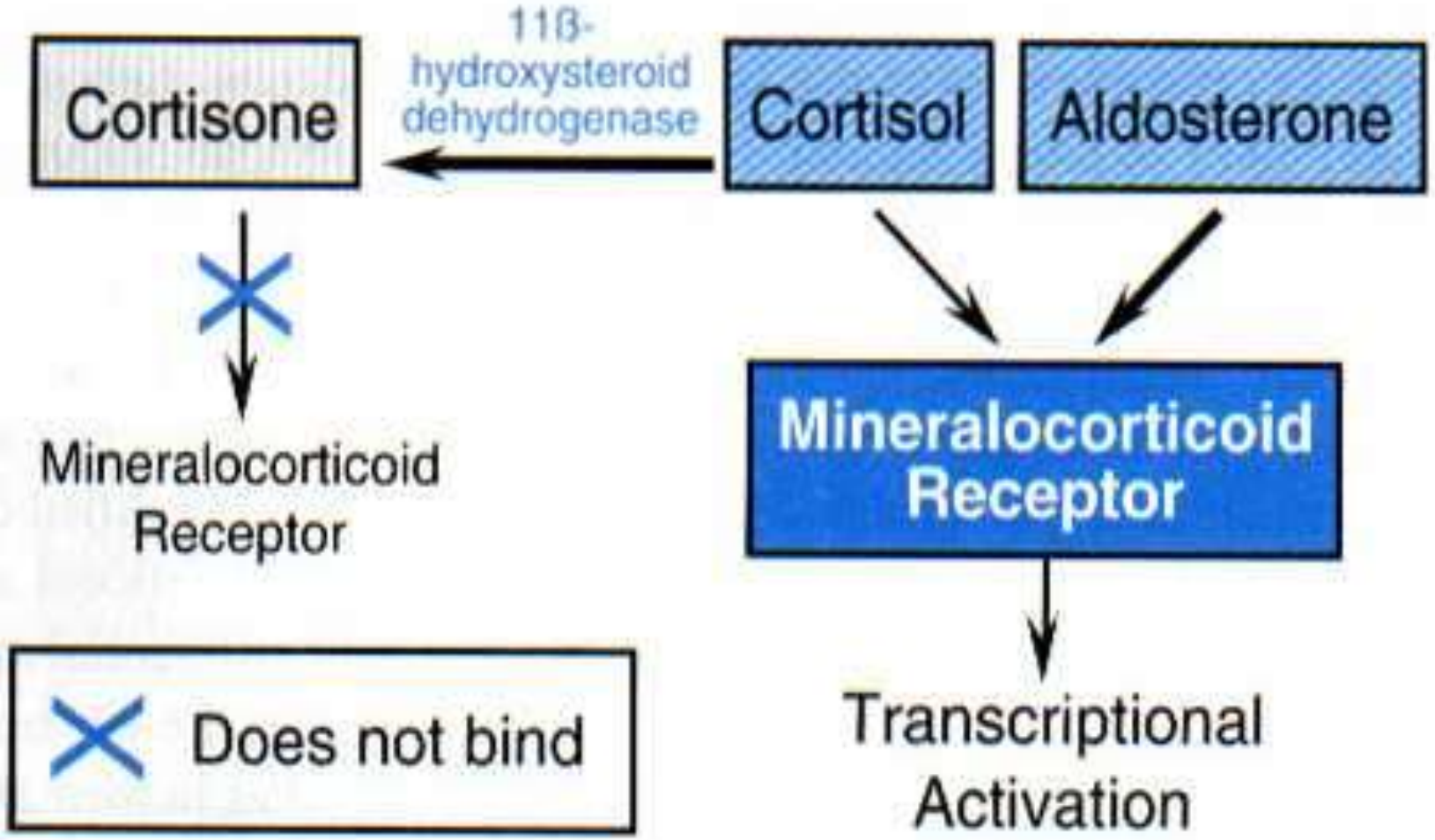
SEPSIS & STEROID

- Uncertainty about the use of corticosteroids may relate to the differences in the results of the two largest trials. Although both trials showed **treatment benefits in terms of hemodynamic status and organ function, only one trial showed survival benefits.**
- The divergent findings may have resulted from differences in the design of the trials. To resolve this discrepancy,a **TRIAL designed to test the hypothesis that hydrocortisone-plus-fludrocortisone therapy would improve the clinical outcomes of patients with septic shock.**

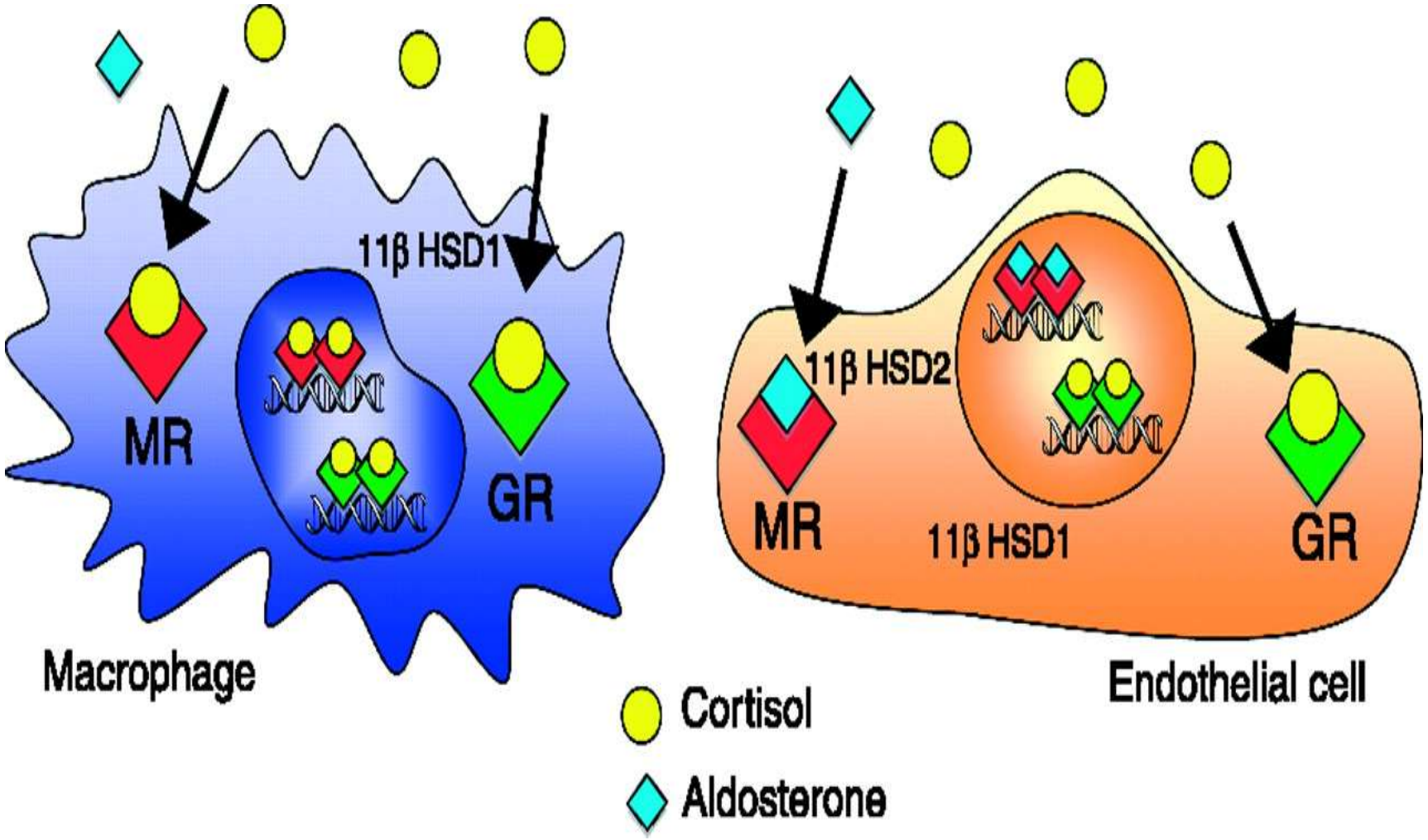
Mineralocorticoid Receptor…



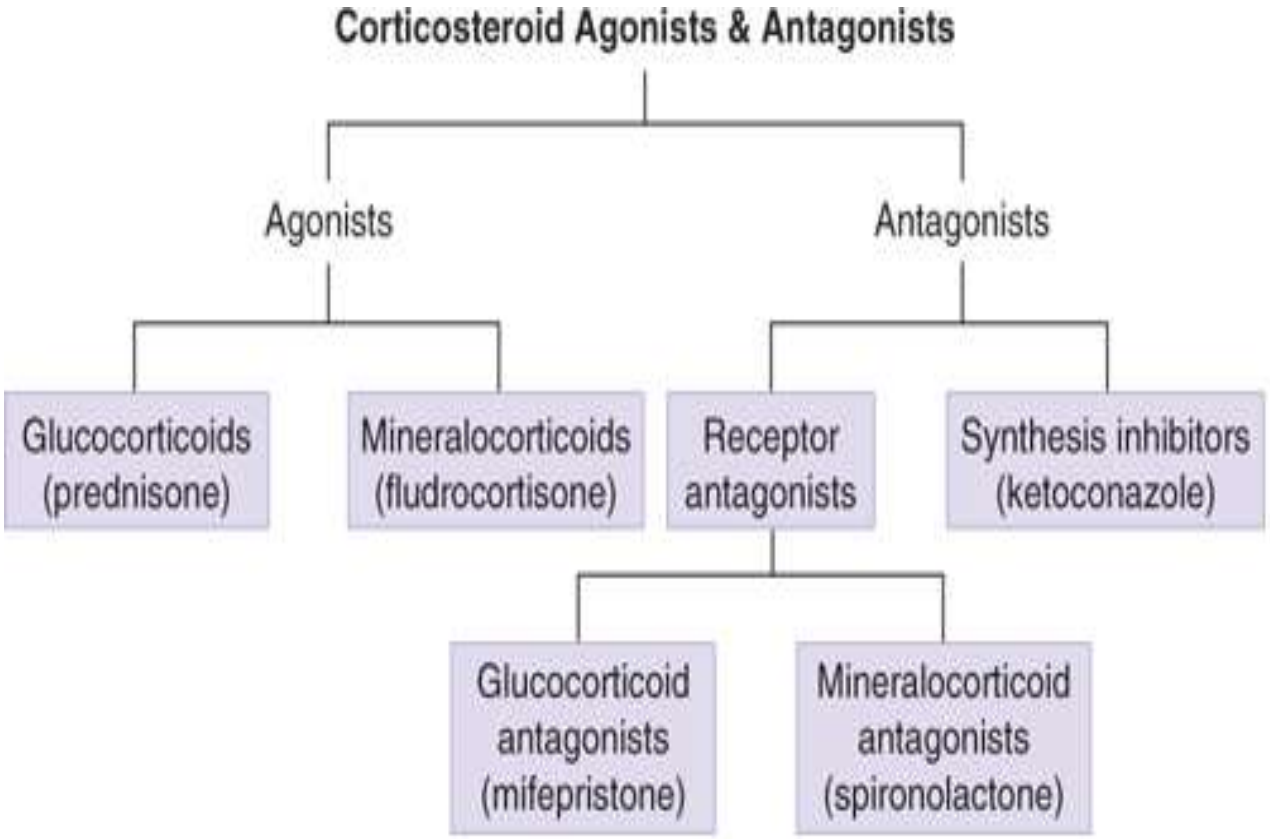
Mineralocorticoid Receptor…



Mineralocorticoid & glucocorticoid Receptor…



Agonist and antagonist…

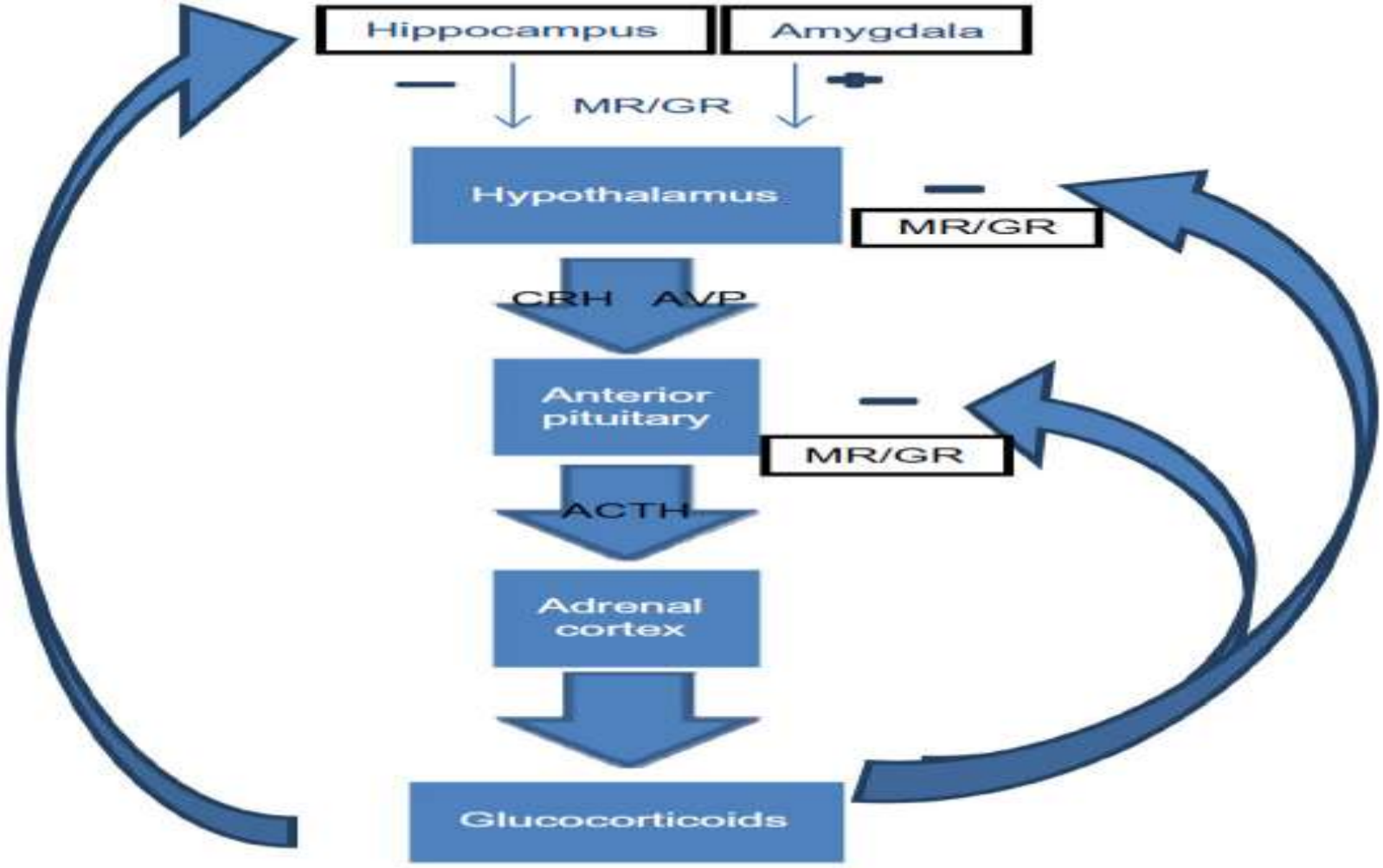


Source: A.J. Trevor, B.G. Katzung, M. Kruidering-Hall: Katzung & Trevor's Pharmacology: Examination & Board Review, 11th Ed.
www.accesspharmacy.com

Functions of the Mineralocorticoids-Aldosterone

1. ⬆ Renal Na+ reabsorption (action on the principal cells of the late distal tubule and collecting duct).
2. ⬆ Renal K+ secretion (action on the principal cells of the late distal tubule and collecting duct).
3. ⬆ Renal H+ secretion (action on the alpha-intercalated cells of the late distal tubule and collecting duct).

H.P.A. AXIS


Hippocampus
Amygdala
MR/GR
Hypothalamus
MR/GR
CRH AVP
Anterior pituitary
MR/GR
ACTH
Adrenal cortex
Glucocorticoids

Trial Design

- Trial Design and Oversight Information on the design and conduct of **Activated Protein C and Corticosteroids for Human Septic Shock (APROCCHSS)** trial,
- Our placebo-controlled trial, conducted with four parallel groups that were organized in a 2-by-2 factorial design, aimed to evaluate the benefits and risks of **corticosteroids.**
- After the **withdrawal of Activated Protein C from market in october 2011**,trial continued with two parallel groups.

THE INCLUSION CRITERIA

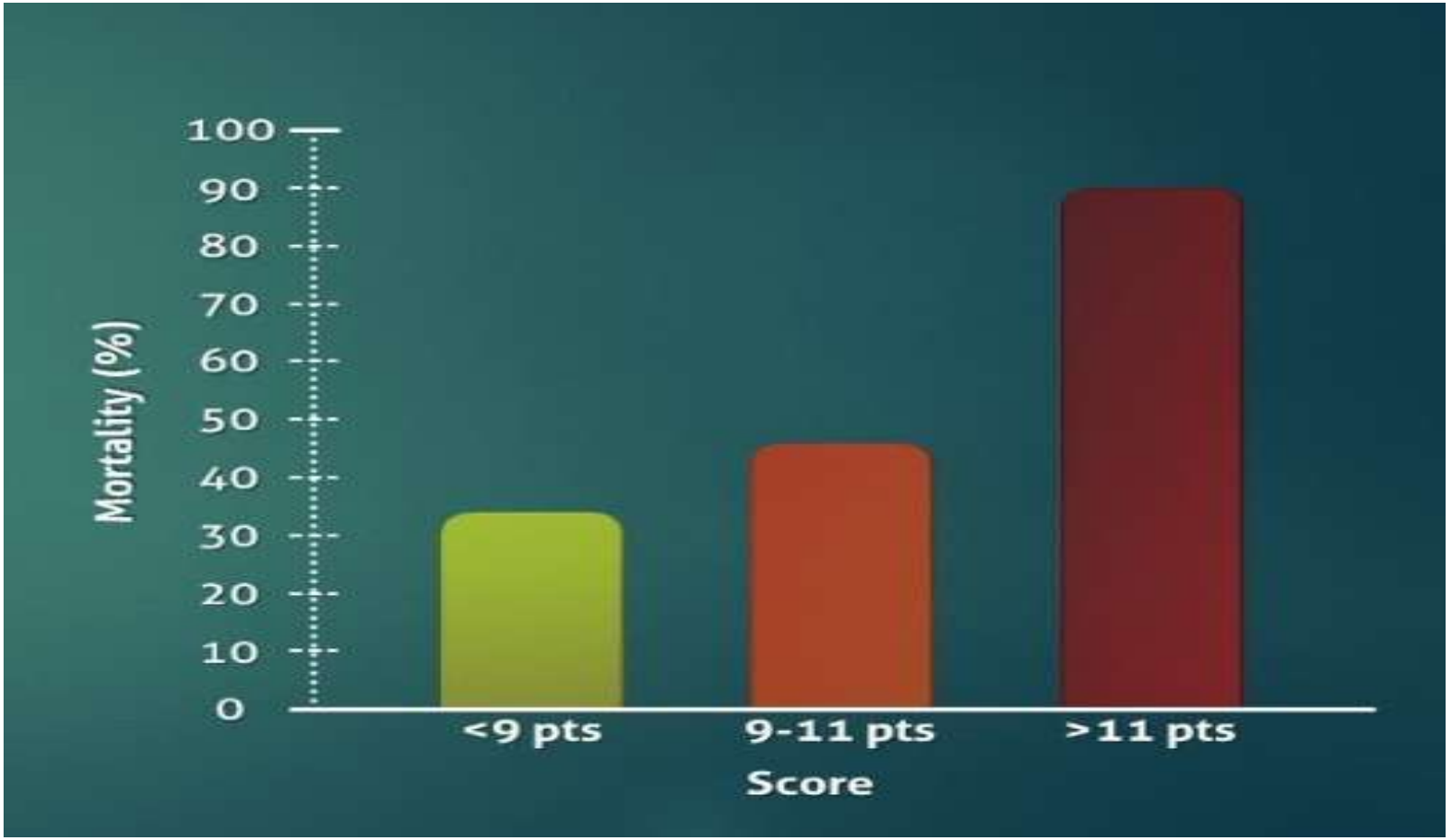
- **Septic shock for less than 24 hours.**
- Septic shock was defined as the presence of a clinically or microbiologically documented infection, a **Sequential Organ Failure Assessment (SOFA)* score > 12 with high requirement** of **vasopressor therapy (norepinephrine, epinephrine, or any other vasopressor at a dose of ≥0.25 µg per kilogram of body weight per minute or ≥1 mg per hour) for at least 6 hours to maintain a systolic blood pressure of at least 90 mm Hg or a mean blood pressure of at least 65 mm Hg.**

THE SEQUENTIAL ORGAN FAILURE ASSESSMENT (SOFA) SCORE

SYSTEM	0	1	2	3	4
Respiration PaO2/FIO2 mm Hg (kPa)	≥400 (53.3)	<400 (53.3)	<300 (40)	<200 (26.7) with respiratory support	<100 (13.3) with respiratory support
Coagulation Platelets ×10³/uL	≥150	<150	<100	<50	<20
Liver Bilirubin mg/dL (umol/L)	<1.2 (20)	1.2-1.9 (20-32)	2.0-5.9 (33-101)	6.0-11.9 (102-204)	>12.0 (204)
Cardiovascular	MAP ≥70mmHg	MAP <70mmHg	Dopamine <5 or Dobutamine (any dose)	Dopamine 5.1 - 15 or Epinephrine ≤ 0.1 or Norepinephrine ≤ 0.1	Dopamine >15 or Epinephrine >0.1 or Norepinephrine >0.1
CNS GCS Score	15	13-14	10-12	6-9	<6
Renal Creatinine, mg/dl (umol/L) **Urine Output, ml/d**	<1.2 (110)	1.2 -1.9 (110-170)	2.0 - 3.4 (171-299)	3.5 - 4.9 (300 -440) <500	> 5.0 (440) <200

Catecholamine Doses = ug/kg/min for at least 1hr

Mortality and SOFA Score



THE INCLUSION CRITERIA…

- **Septic shock for less than 24 hours.**
- **Sequential Organ Failure Assessment (SOFA) score > 12 AND Requirement of higher dosage of inotropic supports** (Dose of ≥0.25 µg per kilogram of body weight per minute)

- **Major exclusion criteria** were the presence of septic shock **for more than 24 hours,** a high risk of bleeding, pregnancy or lactation, previous treatment with corticosteroids.

DOSAGE

- **Hydrocortisone was administered as a 50-mg intravenous bolus every 6 hours, and fludrocortisone was given as a 50-µg tablet through a nasogastric tube once daily in the morning.**
- Trial agents were administered for 7 days without tapering.

Steroid	Glucocorticoid potency	Mineralocorticoid potency
cortisol	1	0.054
prednisone	4	0.002
prednisolone	1.7	0.013
dexamethasone	21	0.0094
betamethasone	45	0.0038
triamcinolone	0.35	0.0002
prednylidene	182	0.0011
aldosterone	0.07	1.0

Trial Measurements and Procedures

- **Plasma total cortisol levels** were measured before, and 30 and 60 minutes after, an intravenous bolus of 250 µg of corticotropin (Synacthen test).

- The variables that were investigated at baseline and during the 180-day follow-up have been detailed elsewhere.

BASELINE CHARACTERISTICS

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)

* Plus–minus values are means ±SD. There were no significant differences between the two groups.
† One patient in the placebo group had a missing value for age.
‡ The Simplified Acute Physiology Score II (SAPS II) ranges from 0 to 163, with higher scores indicating greater severity

RESULTS

- Among the 1241 patients included in the trial, the **90-day mortality was 43.0% (264 of 614 patients) in the hydrocortisone-plus-fludrocortisone group** and **49.1%** (308 of 627 patients) in the placebo group (P=0.03).

- The relative risk of death in the hydrocortisoneplus-fludrocortisone group was **0.88** (95% confidence interval, 0.78 to 0.99).

Results..

- **Mortality was significantly lower in the hydrocortisone-plus-fludrocortisone group** than in the placebo group at ICU discharge (35.4% vs. 41.0%, P=0.04), hospital discharge (39.0% vs. 45.3%, P=0.02), and day 180 (46.6% vs. 52.5%, P=0.04)

OUTCOMES

- **The primary outcome was 90-day all-cause mortality**.
- **Secondary outcomes -**

1. **all-cause mortality** at ICU discharge, hospital discharge, day 28, and day 180 ,
2. the percentage of patients **weaned from vasopressors**
3. the percentage of patients **weaned from mechanical ventilation** at day 28 and day 90;
4. **ventilator-free days** up to day 28 and day 90;
5. the **percentage** of patients with a total **SOFA score below 6** (organ-failure–free) at day 28 and day 90;
6. **the time to reaching a SOFA score below 6**; organ-failure–free days up to day 28 and day 90;
7. the percentage of **patients discharged** from the ICU and hospital up to day 28 and day 90

OUTCOMES

- **All-Cause Mortality At day 90,** death had occurred in 264 of 614 patients (43.0%; 95% confidence interval [CI], 39.0 to 47.0) in the hydrocortisone-plus-fludrocortisone group and in 308 of 627 patients (49.1%; 95% CI, 45.1 to 53.1) in the placebo group (P=0.03)

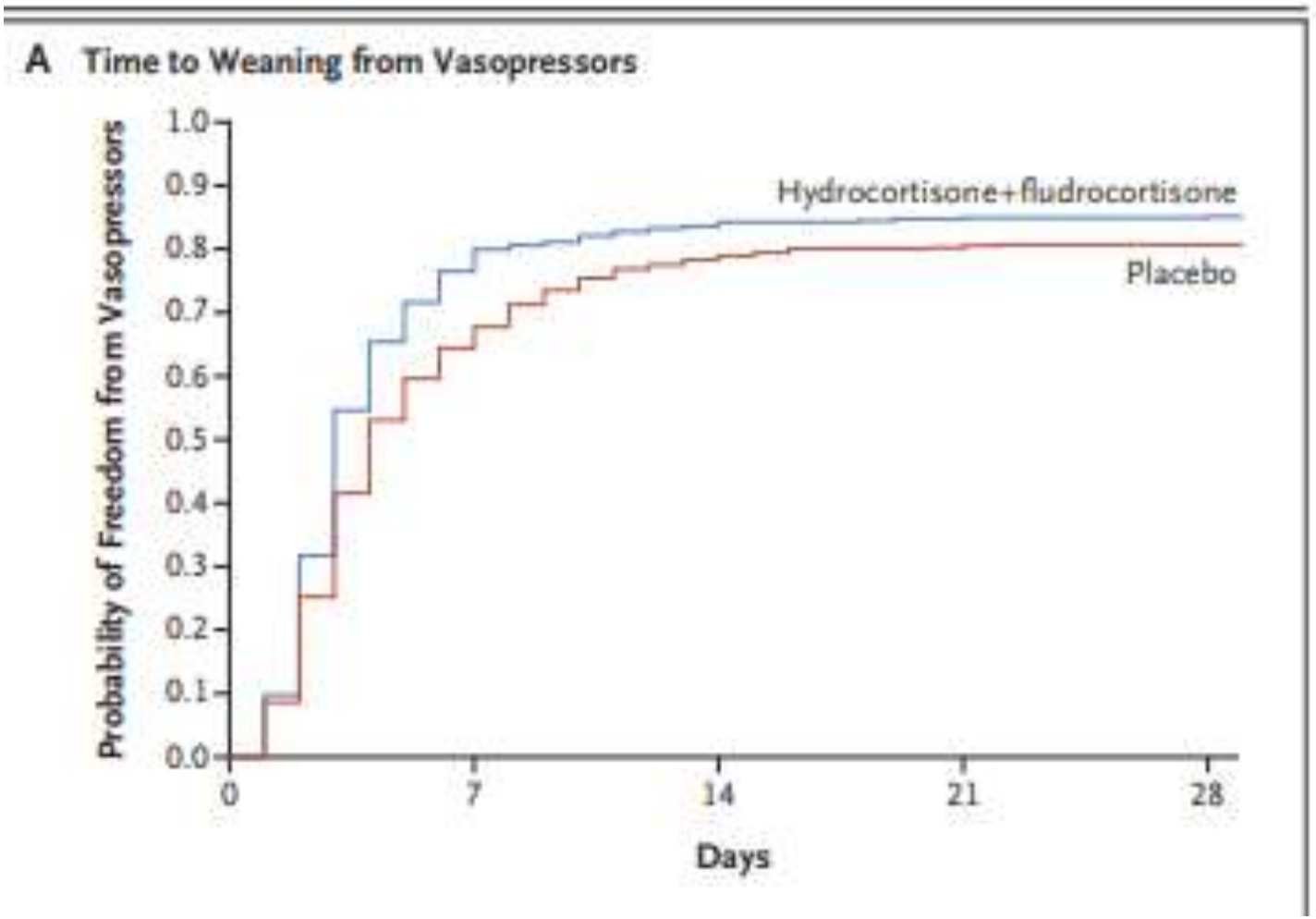
  The relative risk of death was 0.88 (95% CI, 0.78 to 0.99) in favor of hydrocortisone-plus-fludrocortisone therapy.

OUTCOMES..

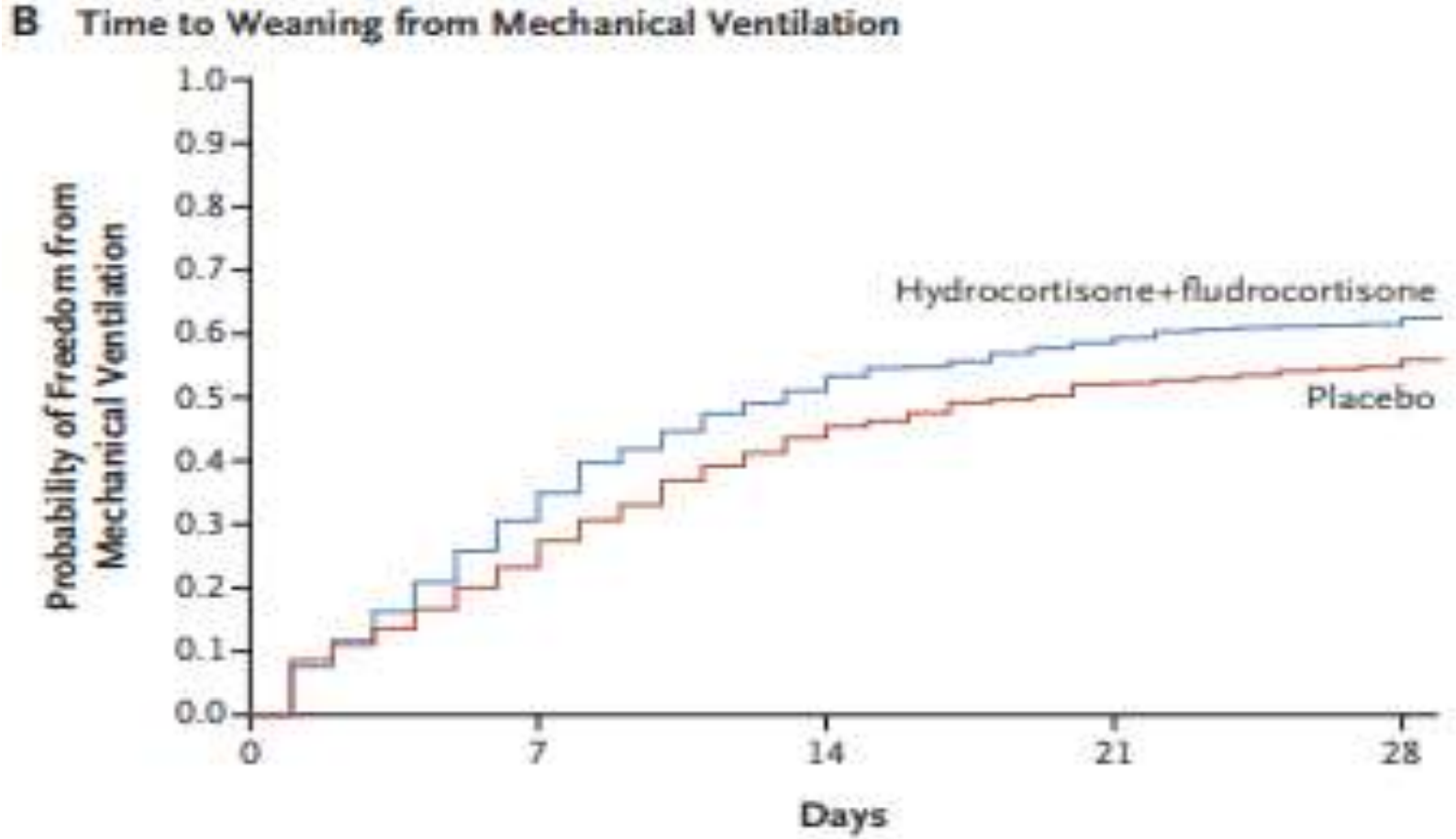
- **Secondary Outcomes** **Mortality was significantly lower** in the hydrocortisone-plus-fludrocortisone group than in theplacebo group

1. **at ICU discharge** (35.4% [217 of 613 patients] vs. 41.0% [257 of 627 patients], P=0.04),
2. **Hospital discharge** (39.0% [239 of 613 patients] vs. 45.3% [284 of 627 patients], P=0.02), and day 180 (46.6% [285 of 611 patients] vs. 52.5% [328 of 625 patients], P=0.04
3. Patients in the hydrocortisone-plus-fludrocortisone group had a significantly **shorter time** than those in the placebo group to **weaning from vasopressor therapy and mechanical ventilation**

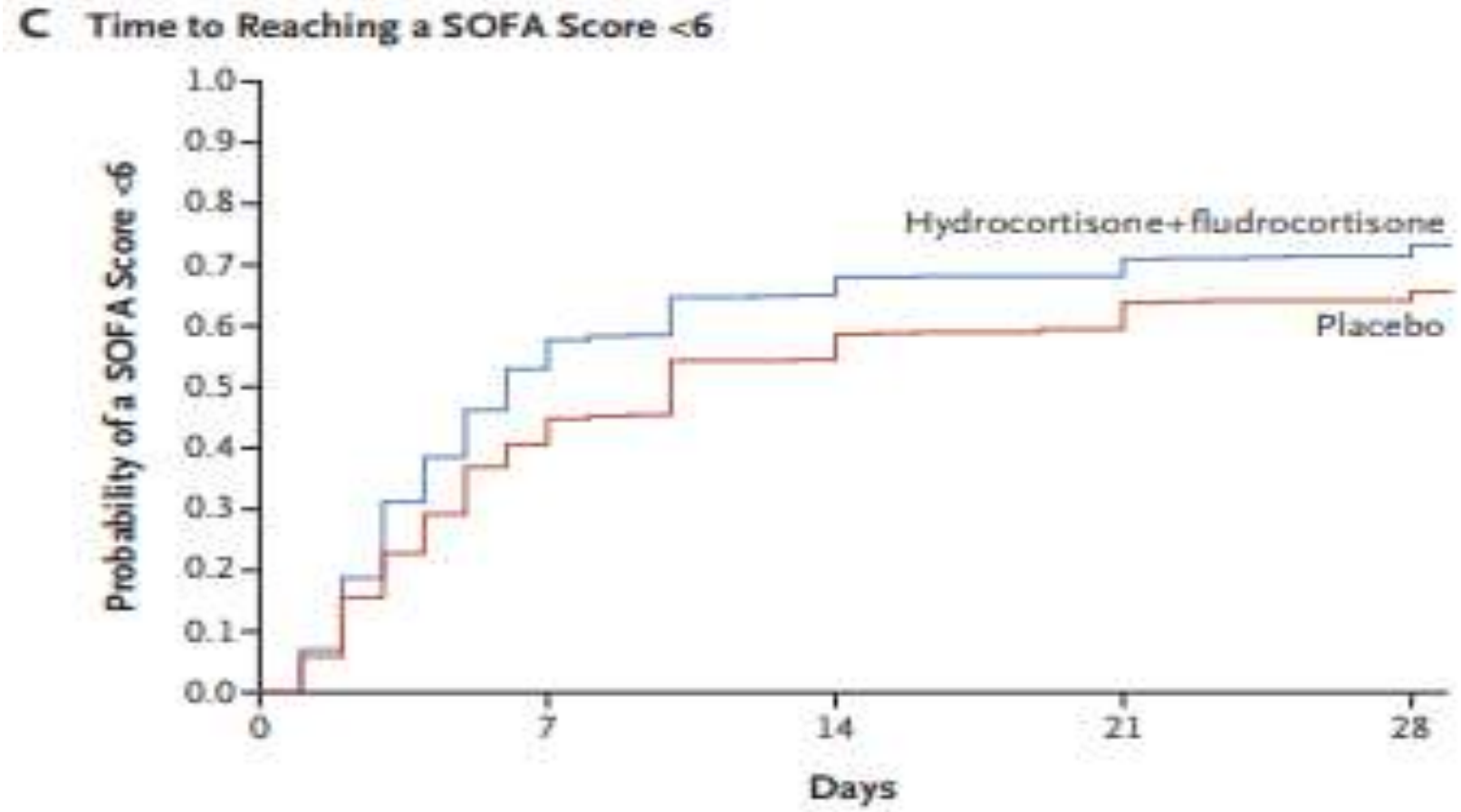
WEANING FROM VASOPRESSORS



WEANING FROM VENTILATION



TIME TO REACH SOFA<6



Serious Adverse Events

- A total of 326 of 614 patients **(53.1%)** in the hydrocortisone-plus-fludrocortisone group and 363 of 626 patients **(58.0%)** in the placebo group had at least one serious adverse event by day 180 (P=0.08)
- The risk of **gastroduodenal bleeding** was **not significantly higher** with hydrocortisone plus fludrocortisone than with placebo (relative risk, 0.88; 95% CI, 0.58 to 1.34; P=0.56),
- **nor** was the **risk of superinfection** (relative risk, 1.09; 95% CI, 0.92 to 1.30; P=0.30).
- However, the **risk of hyperglycemia was significantly higher** with hydrocortisone plus fludrocortisone (relative risk, 1.07; 95% CI, 1.03 to 1.12; P=0.002).

Serious Adverse Events

- **Risk of gastroduodenal bleeding – NOT HIGHER**
- **Risk of superinfection – NOT HIGHER**
- **Risk of hyperglycemia - Significantly higher**

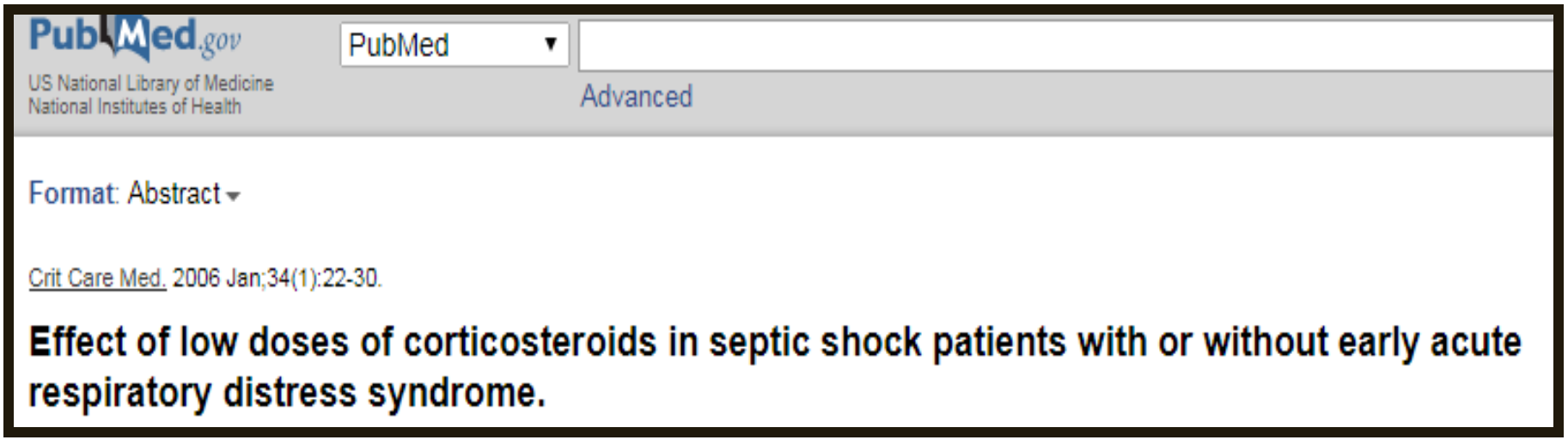
Adverse Events

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

* Plus–minus values are means ±SD.
† Shown is the relative risk for hydrocortisone plus fludrocortisone versus placebo.
‡ Neurologic sequelae were assessed according to the score on the Muscular Disability Rating Scale (MDRS), with a score of 1 indicating no deficit, 2 minor deficit with no functional disability, 3 distal motor deficit, 4 mild-to-moderate proximal motor deficit, and 5 severe proximal

OTHER TRIALS-**The first trial (Ger-Inf-05)**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Format: Abstract

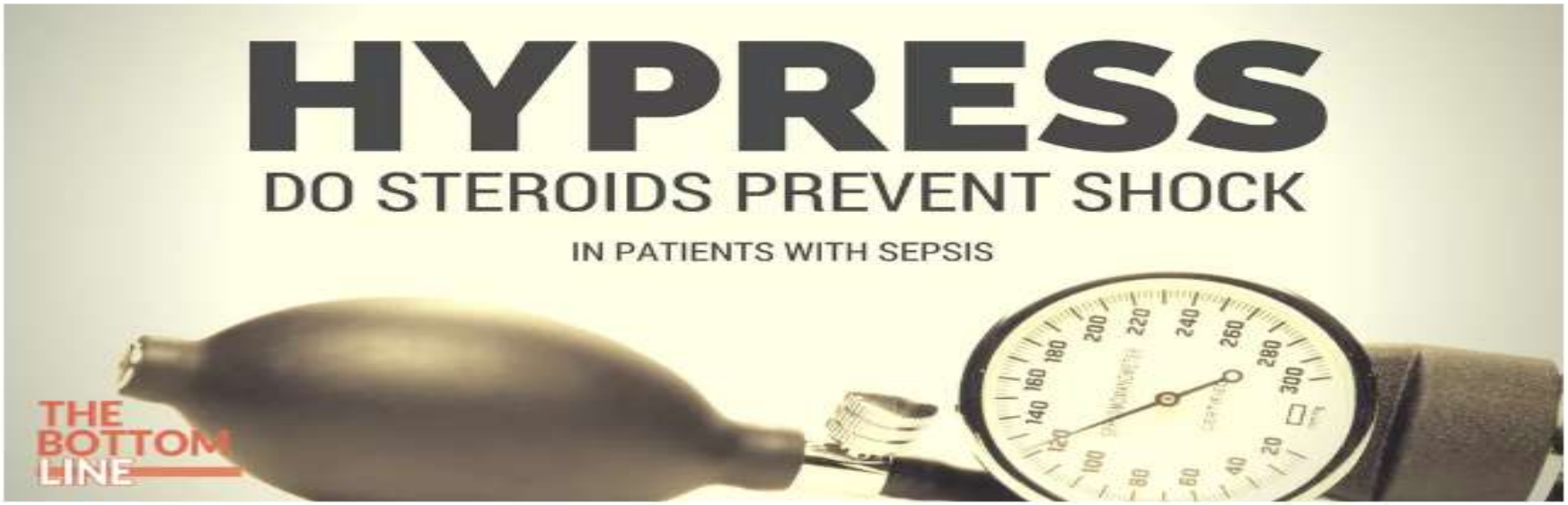
Crit Care Med. 2006 Jan;34(1):22-30.

Effect of low doses of corticosteroids in septic shock patients with or without early acute respiratory distress syndrome.

The first trial (Ger-Inf-05), in which patients received hydrocortisone plus fludrocortisone or matching placebos for 7 days, showed an absolute difference of 6 percentage points in 28-day mortality **in favor of hydrocortisone plus fludrocortisone.**

CORTICUS TRIAL…

Corticosteroid Therapy of Septic Shock [CORTICUS TRIAL] showed no significant survival benefit from an 11-day course of hydrocortisone alone.



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

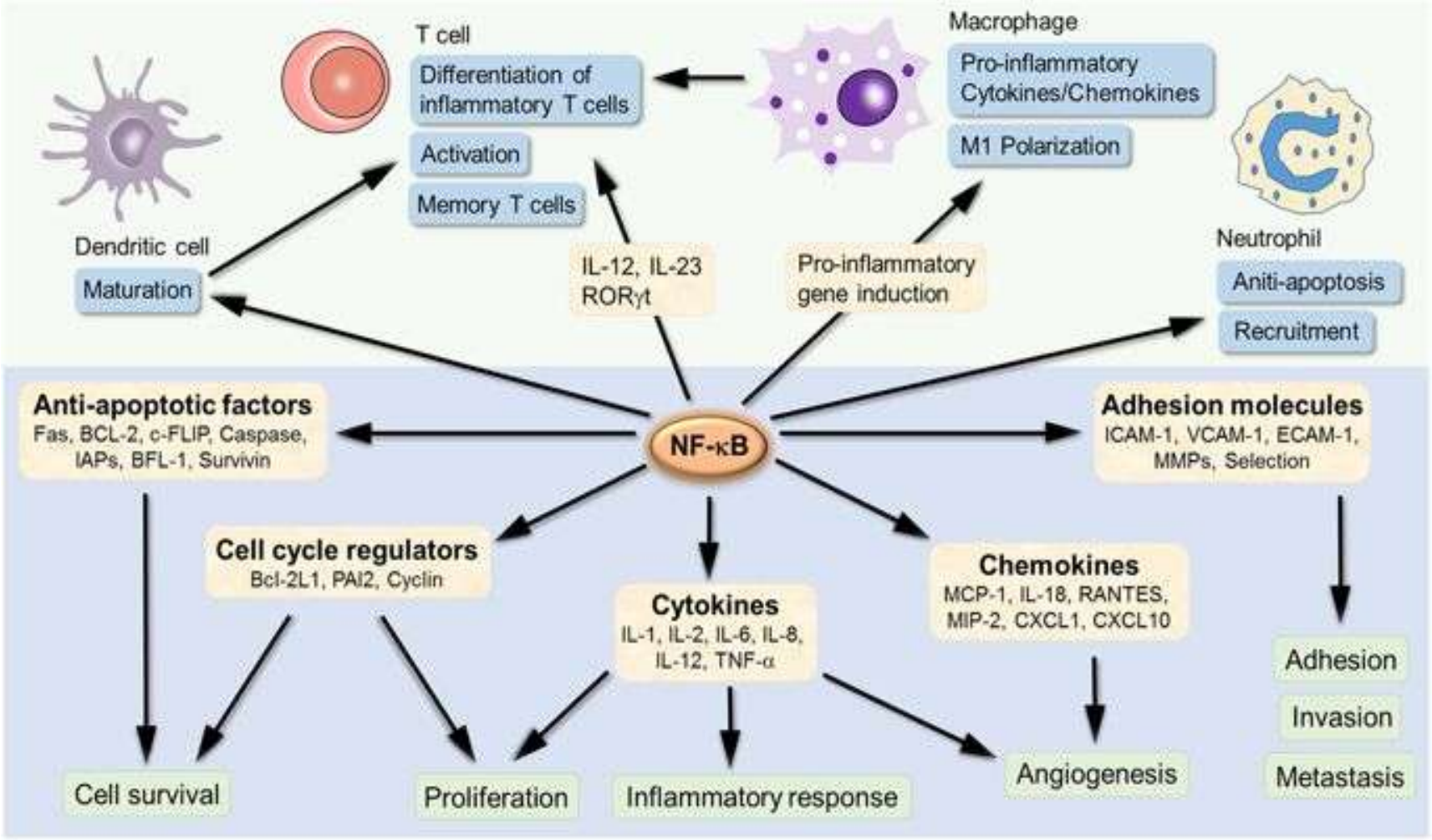
Keh. JAMA 2016. Published online October 3, 2016.doi:10.1001/jama.2016.14799

- In a more recent trial involving 380 adults with severe sepsis (Hydrocortisone for Prevention of Septic Shock [HYPRESS]), **hydrocortisone alone failed to prevent /reverse septic shock.**

OTHER TRIALS…

- There are two main differences between trials that showed a survival benefit from corticosteroid therapy (APROCCHSS and Ger-Inf-05) and those that did not (CORTICUS and HYPRESS).
- First, in the APROCCHSS and Ger-Inf-05 trials, **fludrocortisone was added to hydrocortisone to provide additional mineralocorticoid potency.**
- **The rationale for adding mineralocorticoid treatment is that an experimental sepsis study showed marked nuclear factor κB (NF-κB) –mediated down-regulation of vascular mineralocorticoid receptors.**

Nuclear factor kappa-B (NF-κB)



OTHER TRIALS

- Patients in the **APROCCHSS trial were sicker** than those in the CORTICUS trial, as evidenced by higher SOFA scores (by approximately 1.5 points) and higher SAPS II values (by approximately 7 points), and were more likely to be admitted from medical wards.
- Hence, the **Ger-Inf-05 and APROCCHSS trials independently showed a survival benefit with hydrocortisone plus fludrocortisone in adults** with septic shock and persistent vasopressor dependency and organ failures

DISCUSSION :

The mechanisms by which corticosteroids may favorably affect the outcome of patients with septic shock

In brief, corticosteroids improve cardiovascular function **by restoring effective blood volume through increased mineralocorticoid activity and by increasing systemic vascular resistance, an effect that is partly related to endothelial glucocorticoid receptors.**

This might explain why in our trial there was less need for vasopressors with hydrocortisone plus fludrocortisone than with placebo.

DISCUSSION

Corticosteroids **attenuate inflammation** in various organs in both animals and humans with sepsis, an effect partly related **to inhibition of nuclear factor κB (NF-κB)**.

In our trial, hydrocortisoneplus-fludrocortisone therapy accelerated the resolution of organ failure in adults with septic shock.

DISCUSSION

- Treatment with FLUDROCORTISONE , a mineralocorticoid, **restore α1-adrenoceptor expression**, **improved contractile response to phenylephrine, and improved survival in mice with endotoxic shock.**
- In a recent pharmacokinetic study involving adults with septic shock, **enteral administration** **of 50 µg of fludrocortisone resulted in plasma concentrations of the drug that exerted significant mineralocorticoid effects.**

THE TAKE-HOME MESSAGE

- 7-day treatment with a **50-mg intravenous bolus of hydrocortisone every 6 hours and a daily dose of 50 µg of oral fludrocortisone** resulted in **lower mortality at day 90** and at ICU and hospital discharge than placebo among adults with septic shock.

BUT BOTH

thank you!

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