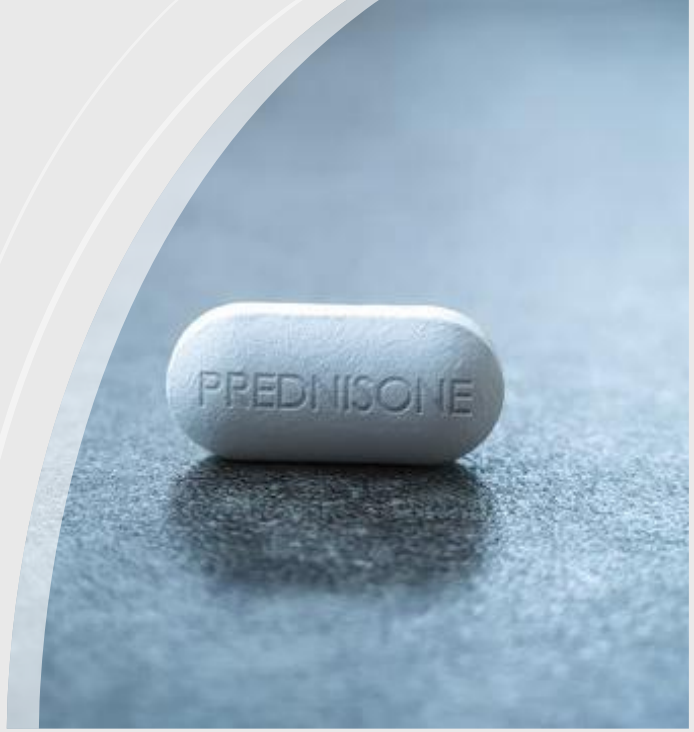
Glukokortikoidi pri sepsi – koristi in škoda

Jernej Berden

KO za intenzivno interno medicino



Glukokortikoidi pri sepsi in septičnem šoku

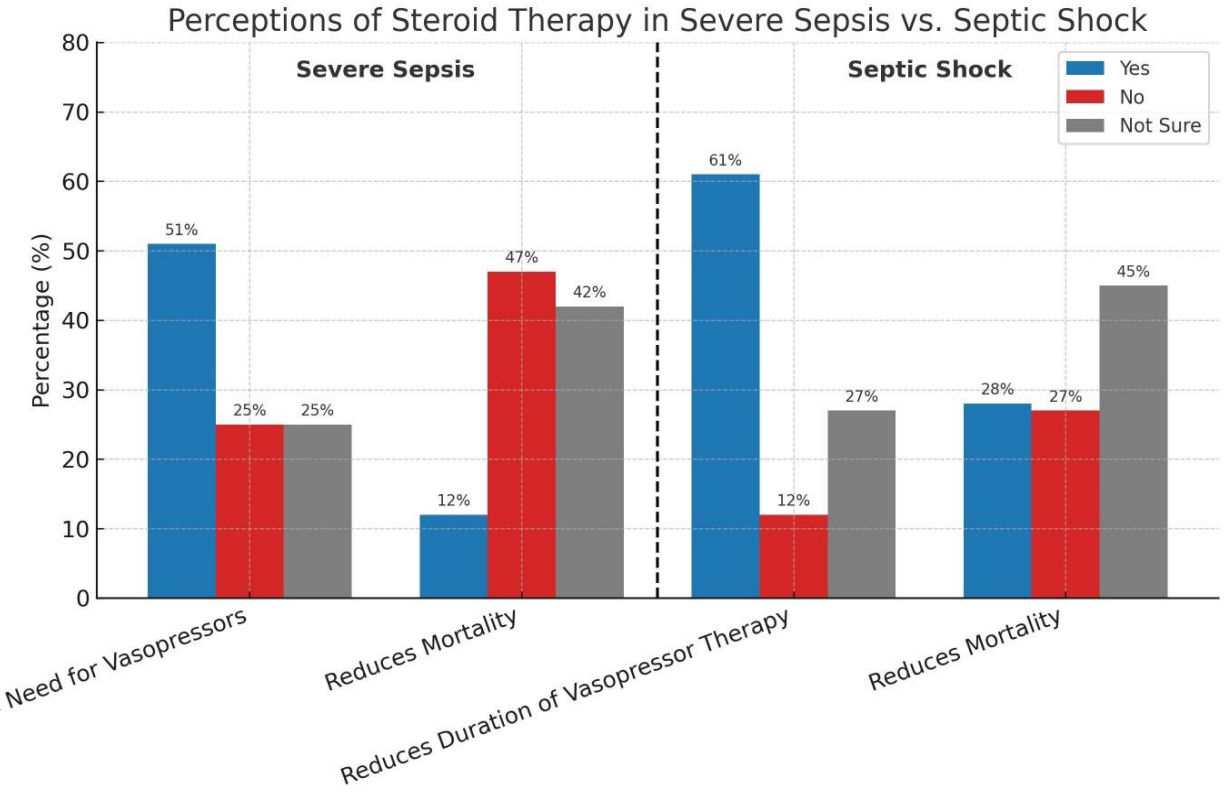
Journal of Critical Care (2012) 27, 351–361

ELSEVIER

Journal of Critical Care

US practitioner opinions and prescribing practices regarding corticosteroid therapy for severe sepsis and septic shock☆,☆☆

Jeffrey J. Bruno PharmD, BCPS, BCNSP[a,*], Brian M. Dee PharmD, BCPS, BCNSP[a],



SSC smernice

CONFERENCE REPORTS AND EXPERT PANEL

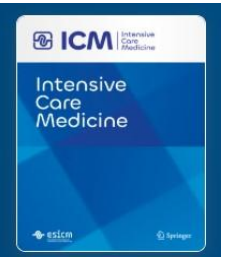
Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016

H. CORTICOSTEROIDS

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).

Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021

Guidelines | Published: 02 October 2021



For adults with septic shock and an ongoing requirement for vasopressor therapy, we suggest using IV corticosteroids.

Quality of evidence: Moderate

Remarks

The typical corticosteroid used in adults with septic shock is IV hydrocortisone at a dose of 200 mg/d given as 50 mg intravenously every 6 hours or as a continuous infusion. It is suggested that this is commenced at a dose of norepinephrine or epinephrine ≥ 0.25 mcg/kg/min at least 4 hours after initiation.

Weak | Additional Therapies | Corticosteroids

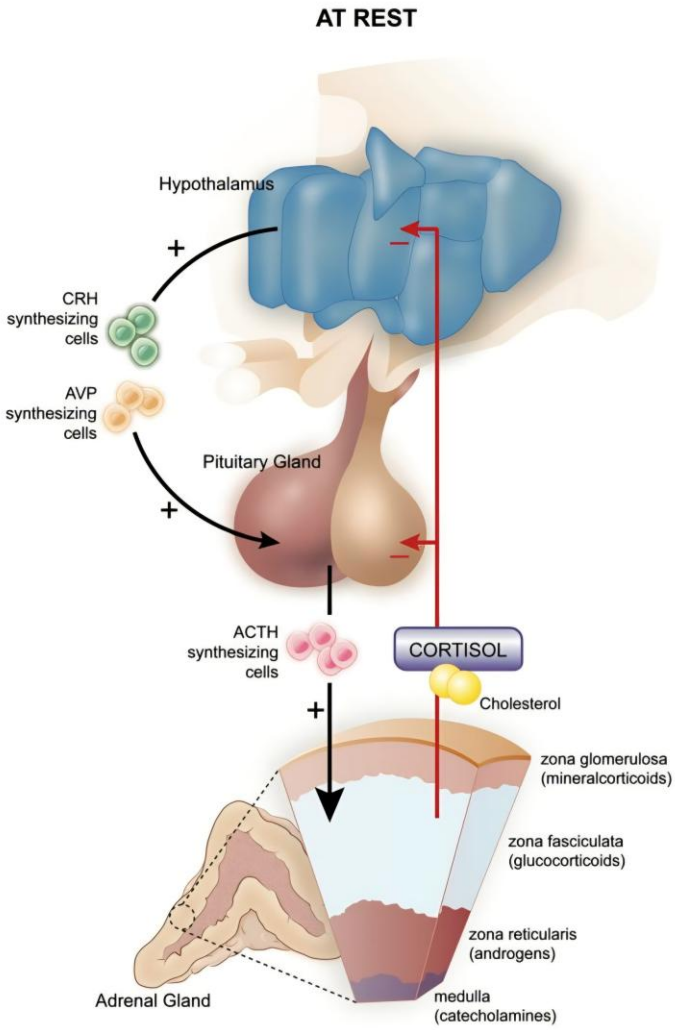
Naravni in sintetični steroidi

Glukokortikoidni učinki:

- glukoneogeneza, Proteoliza, lipoliza
- Inzulinska rezistenca
- Regulacija imunskega in vnetnega odziva
- Ohranjanje homeostaze poškodbi/okužbi

Mineralokortikoidni učinki

- Zadrževanje Na in vode
- Vzdrževanje žilnega tonusa in perfuzije



Compound	Glucocorticoid activity	Mineralocorticoid activity
Natural steroids		
Cortisol	1	1
Corticosterone	0.3	15
Aldosterone	0.3	3,000
Deoxycorticosterone	0.2	100
Synthetic steroids		
Cortisone	0.8	0.8
Fludrocortisone	10	125
Prednisone	4	0.8
Prednisolone	4	0.8
Methylprednisolone	5	0.5
Betamethasone	25	0
Dexamethasone	25	0

Glucocorticoid and mineralocorticoid activity of natural and synthetic steroids, relative to cortisol.

Annane D. Int Care Med 2017

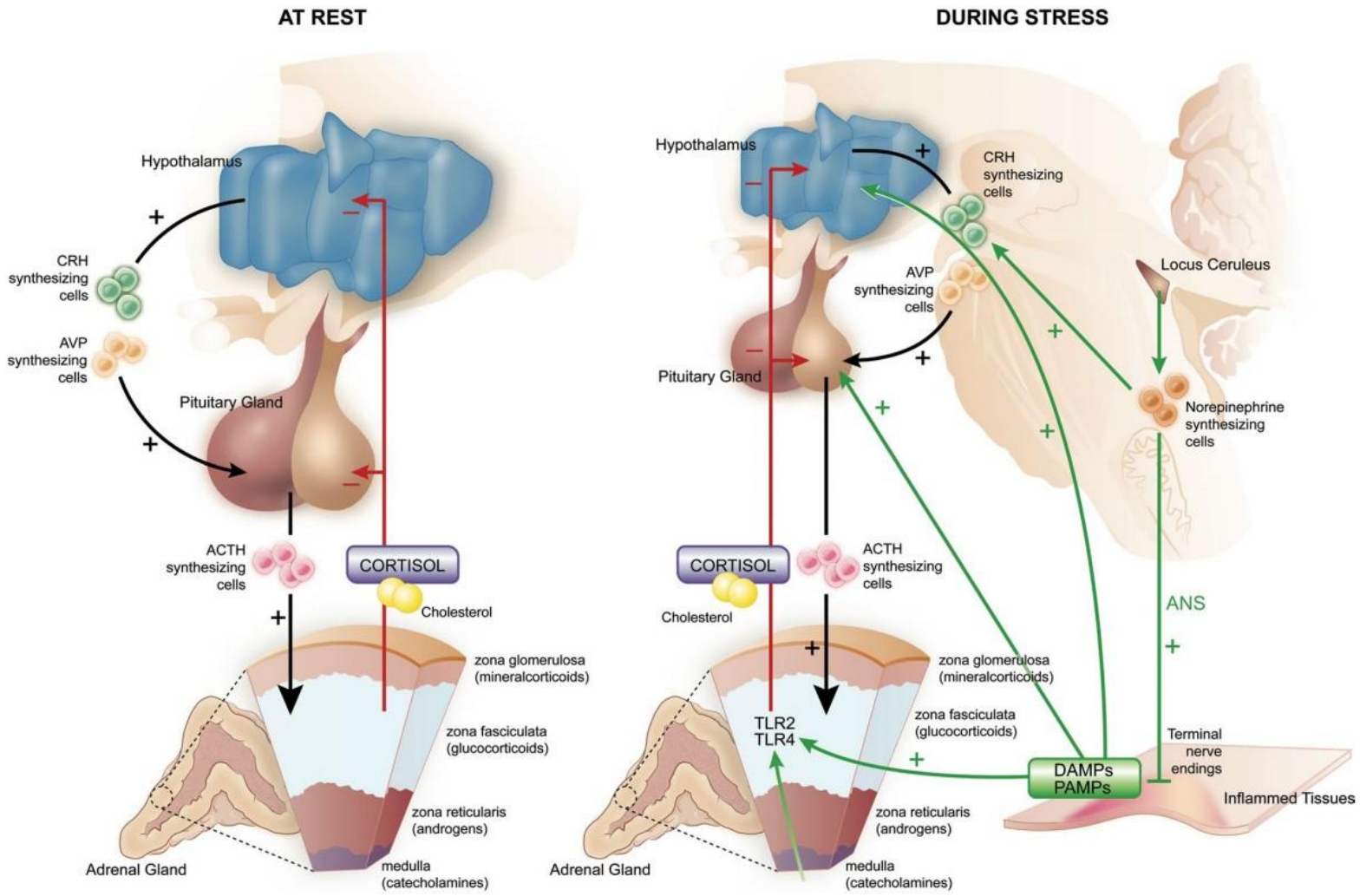
Naravni in sintetični steroidi

Učinki kortizola pri sepsi:

- Zmanjšuje vnetje
- Stabilizacija krvnega tlaka
- Zmanjšuje prepustnost kapilar
- Stabilizacija mikrocirkulacije

Motnja v "sistemu" (CIRCI):

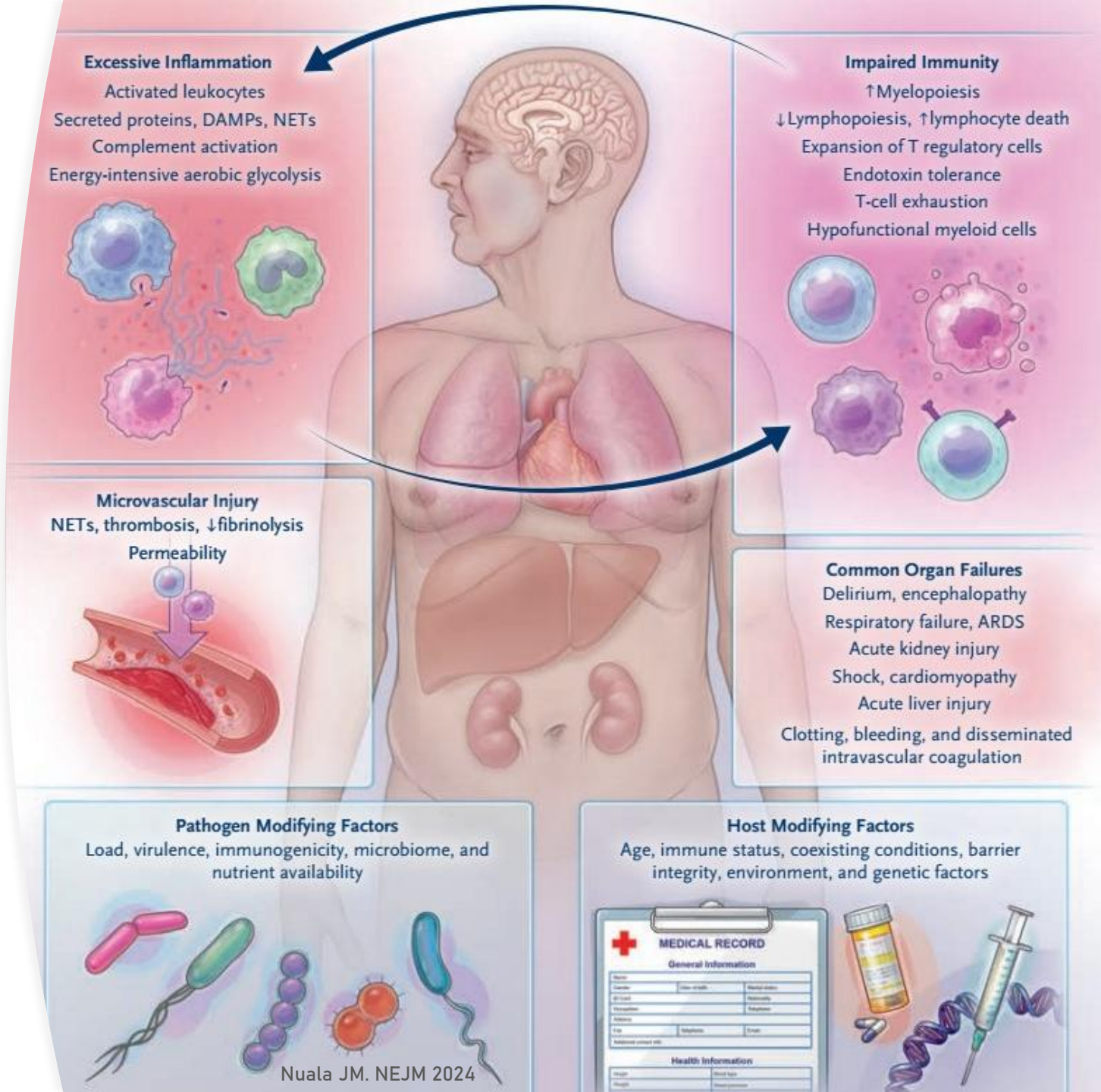
- Disfunkcija osi
- Spremenjena presnova z moteno sintezo
- Zmanjšana občutljivost glukokortikoidnih receptorjev



Annane D. Int Care Med 2017

Patobiologija sepse

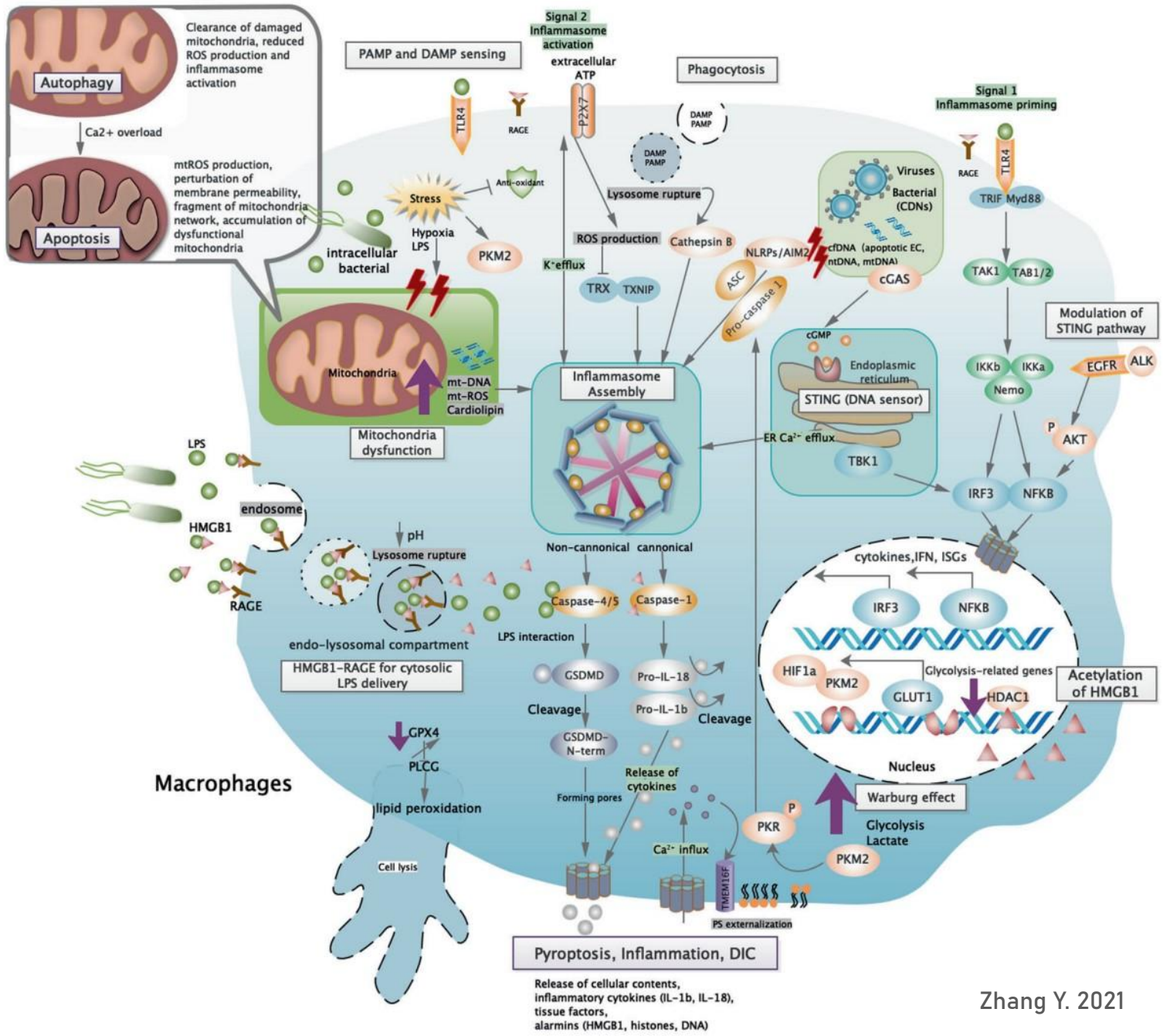
- Moten odziv gostitelja na okužbo
- Disregulacija imunskega odziva
- Poškodba endotela z moteno funkcijo
- Motnje v mikrocirkulaciji
- Kagulopatija
- Hkratna zavora prirojene in pridobljene imunosti
- Vpliv lastnosti patogena in gostitelja



Signalne poti pri sepsi

Ključni koraki:

- Zaznava PAMPs in DAMPS
- Aktivacija ključnih regulatorjev zgodnje faze = IRF3 in NF-kβ
- Tvorba inflamasoma – aktivacija IL-1β in IL-18, indukcija piroptoze
- Disfunkcija mitohondrijev s tvorbo ROS - pospeševanje inflamasoma
- HMGB1 kot pozni alarmin in aktivator inflamasoma - vzdržuje vnetni odziv



Zhang Y. 2021

Protivnetni učinki glukokortikoidov pri sepsi

Negenomska aktivacija (minute):

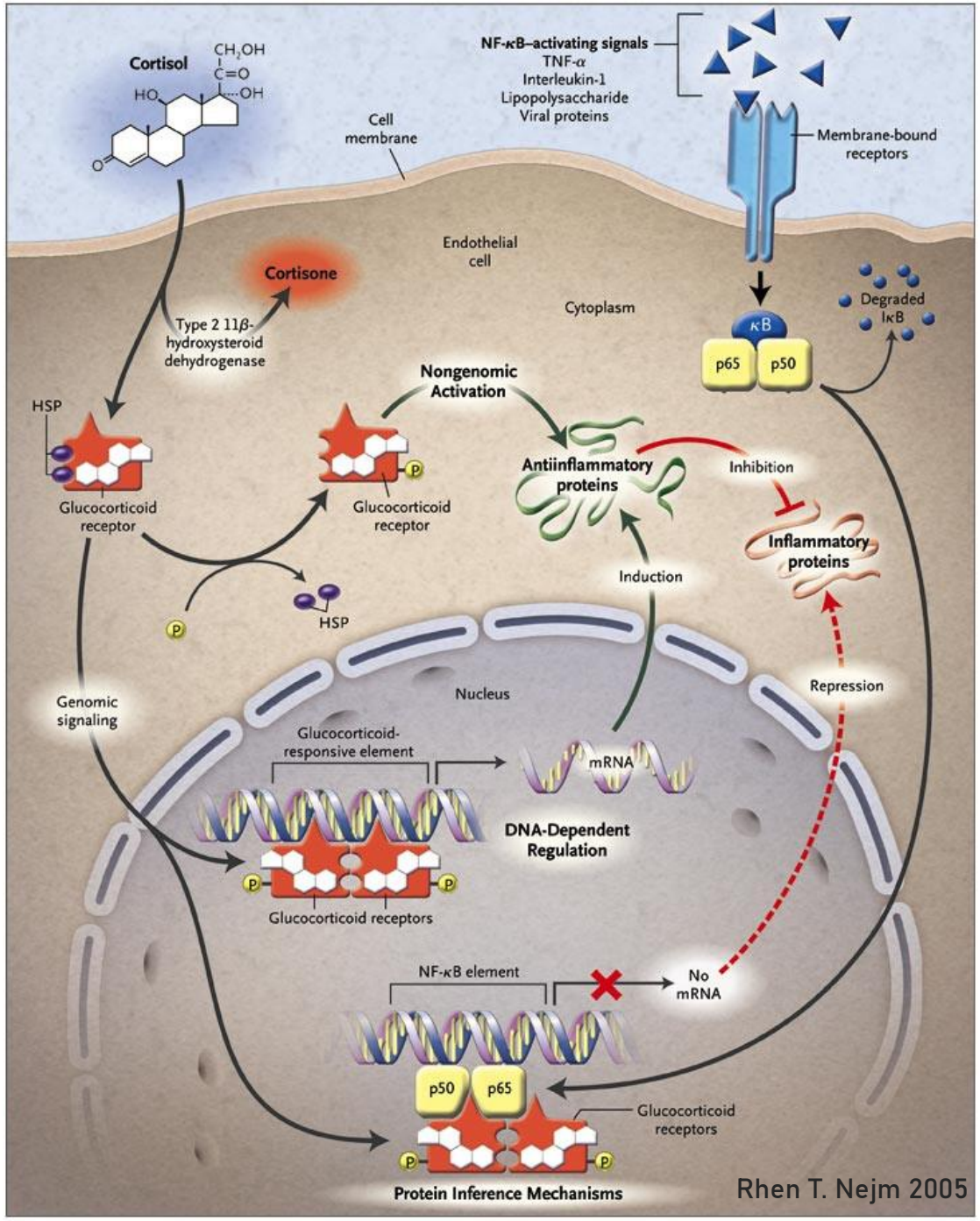
- Stabilizacija membran: npr. zavora signalizacije preko TRL
- Aktivacija signalnih kaskad (protivnetni proteini)
- Aktivacija eNOS - boljša perfuzija tkiv
- Zavora tvorbe ROS

Genomska transrepresija (ure):

- Z neposredno vezavo v jedru zavira transkripcijo, npr. NF-kβ

Genomska transaktivacija (dnevi):

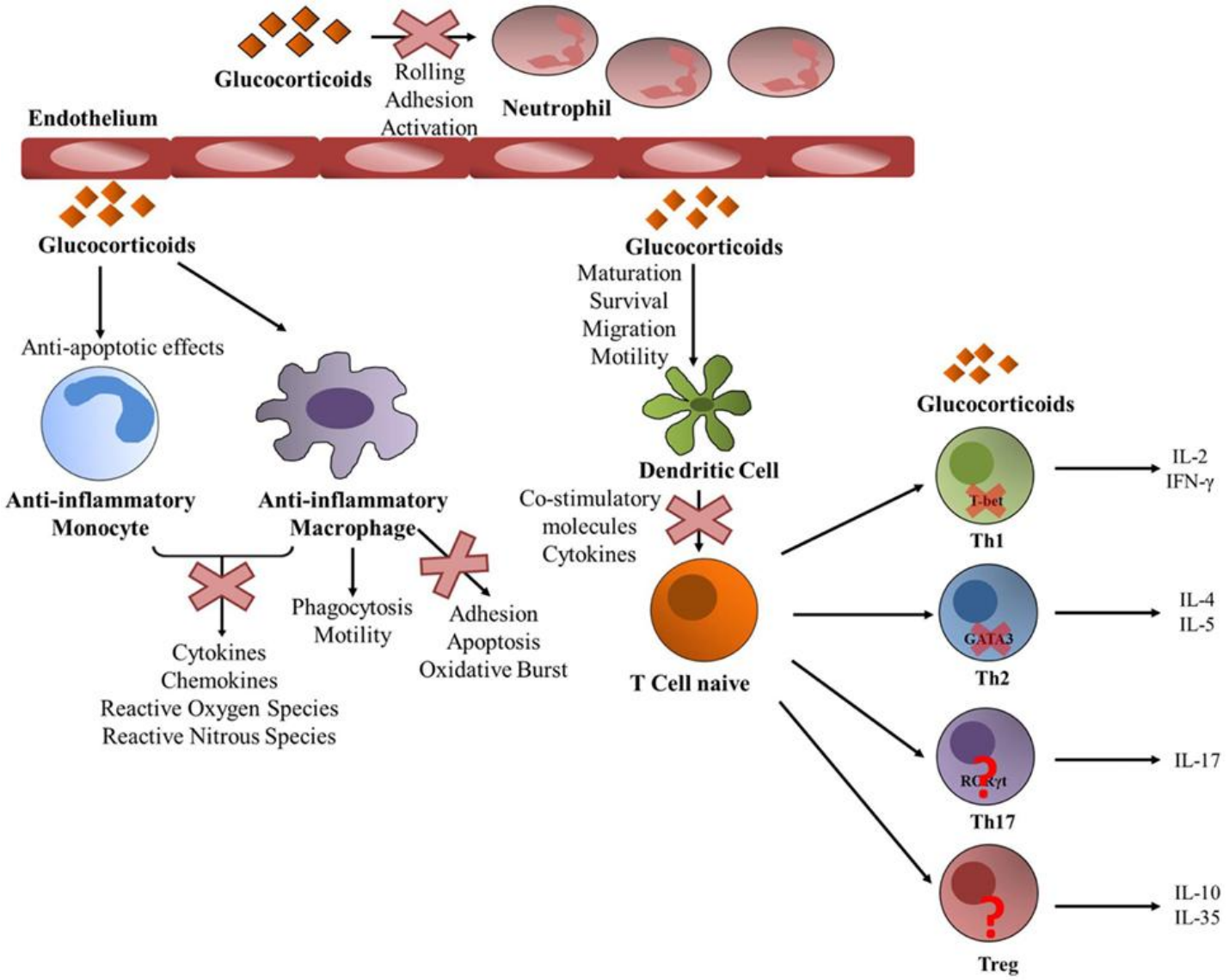
- Aktivacija/represija transkripcije protivnetnih/vnetnih mediatorjev



Rhen T. Nejm 2005

Protivnetni učinki glukokortikoidov pri sepsi

- Preprečujejo apoptozo makrofagov in monocitov + spodbujajo fagocitozo in motiliteto
- Zavirajo adhezijo in oksidativne izbruhe makrofagov in nevtrofilcev
- Pospešujejo zorenje in migracijo dendritičnih celic ob hkratni zavori aktivacije T-celic
- Zavirajo produkcijo citokinov T-celic



Liberman AC. 2018

Neželeni učinki glukokortikoidov pri sepsi

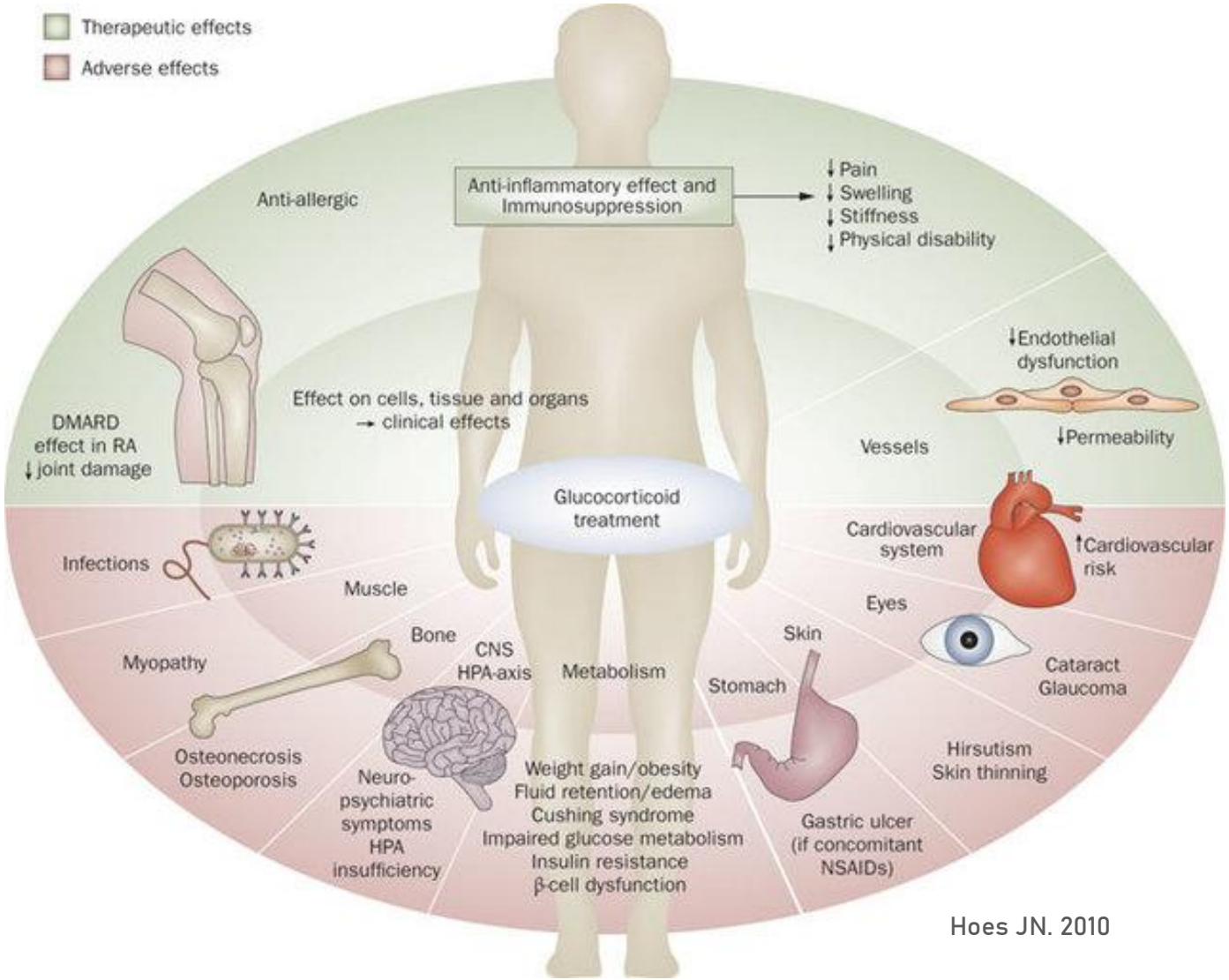
Imunski sistem
- Povečana dovzetnost za sekuindarne okužbe, reaktivacija latentnih okužb, imunoparaliza

Presnovni učinki
- Hiperglikemija, inzulinska rezistenca, katabolizem beljakovin

Gastrointestinalni sistem
- Tveganje za krvavitev, ulkusi

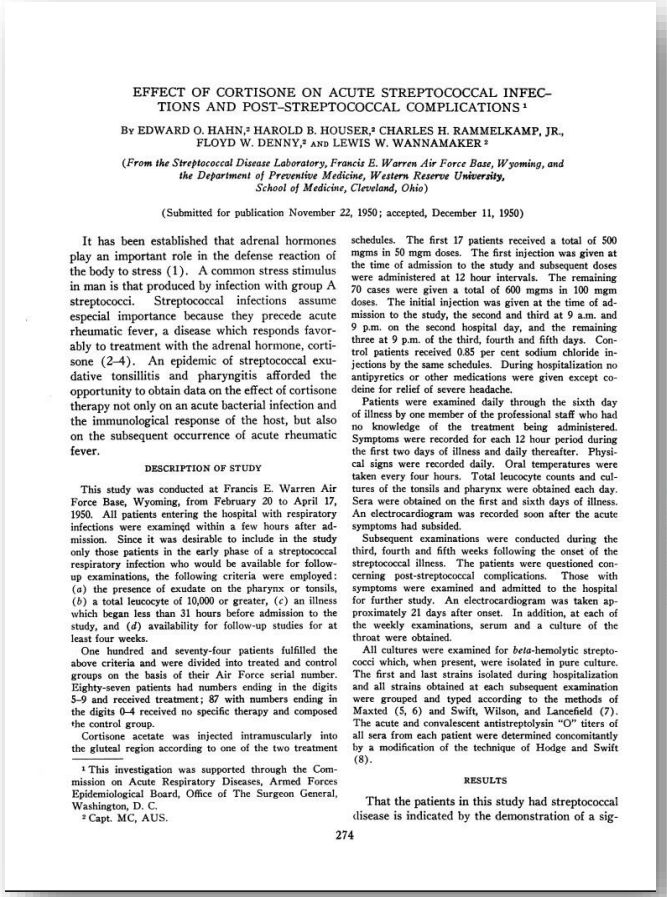
Endokrini sistem
- Supresija osi hipotalamus-hipofiza-nadledvičnici

Nevro-psihiatrični učinki
- Delirij, halucinacije, manija, depresija, motnje spanja



Hoes JN. 2010

Glukokortikoidi pri sepsi



EFFECT OF CORTISONE ON ACUTE STREPTOCOCCAL INFECTIONS AND POST-STREPTOCOCCAL COMPLICATIONS [1]

By EDWARD O. HAHN,[2] HAROLD B. HOUSER,[2] CHARLES H. RAMMELKAMP, JR., FLOYD W. DENNY,[2] AND LEWIS W. WANNAMAKER [2]

(From the Streptococcal Disease Laboratory, Francis E. Warren Air Force Base, Wyoming, and the Department of Preventive Medicine, Western Reserve University, School of Medicine, Cleveland, Ohio)

(Submitted for publication November 22, 1950; accepted, December 11, 1950)

It has been established that adrenal hormones play an important role in the defense reaction of the body to stress (1). A common stress stimulus in man is that produced by infection with group A streptococci. Streptococcal infections assume especial importance because they precede acute rheumatic fever, a disease which responds favorably to treatment with the adrenal hormone, cortisone (2-4). An epidemic of streptococcal exudative tonsillitis and pharyngitis afforded the opportunity to obtain data on the effect of cortisone therapy not only on an acute bacterial infection and the immunological response of the host, but also on the subsequent occurrence of acute rheumatic fever.

DESCRIPTION OF STUDY

This study was conducted at Francis E. Warren Air Force Base, Wyoming, from February 20 to April 17, 1950. All patients entering the hospital with respiratory infections were examined within a few hours after admission. Since it was desirable to include in the study only those patients in the early phase of a streptococcal respiratory infection who would be available for follow-up examinations, the following criteria were employed: (*a*) the presence of exudate on the pharynx or tonsils, (*b*) a total leucocyte of 10,000 or greater, (*c*) an illness which began less than 31 hours before admission to the study, and (*d*) availability for follow-up studies for at least four weeks.

One hundred and seventy-four patients fulfilled the above criteria and were divided into treated and control groups on the basis of their Air Force serial number. Eighty-seven patients had numbers ending in the digits 5-9 and received treatment; 87 with numbers ending in the digits 0-4 received no specific therapy and composed the control group.

Cortisone acetate was injected intramuscularly into the gluteal region according to one of the two treatment schedules. The first 17 patients received a total of 500 mgms in 50 mgm doses. The first injection was given at the time of admission to the study and subsequent doses were administered at 12 hour intervals. The remaining 70 cases were given a total of 600 mgms in 100 mgm doses. The initial injection was given at the time of admission to the study, the second and third at 9 a.m. and 9 p.m. on the second hospital day, and the remaining three at 9 p.m. of the third, fourth and fifth days. Control patients received 0.85 per cent sodium chloride injections by the same schedules. During hospitalization no antipyretics or other medications were given except codeine for relief of severe headache.

Patients were examined daily through the sixth day of illness by one member of the professional staff who had no knowledge of the treatment being administered. Symptoms were recorded for each 12 hour period during the first two days of illness and daily thereafter. Physical signs were recorded daily. Oral temperatures were taken every four hours. Total leucocyte counts and cultures of the tonsils and pharynx were obtained each day. Sera were obtained on the first and sixth days of illness. An electrocardiogram was recorded soon after the acute symptoms had subsided.

Subsequent examinations were conducted during the third, fourth and fifth weeks following the onset of the streptococcal illness. The patients were questioned concerning post-streptococcal complications. Those with symptoms were examined and admitted to the hospital for further study. An electrocardiogram was taken approximately 21 days after onset. In addition, at each of the weekly examinations, serum and a culture of the throat were obtained.

All cultures were examined for *beta*-hemolytic streptococci which, when present, were isolated in pure culture. The first and last strains isolated during hospitalization and all strains obtained at each subsequent examination were grouped and typed according to the methods of Maxted (5, 6) and Swift, Wilson, and Lancefield (7). The acute and convalescent antistreptolysin "O" titers of all sera from each patient were determined concomitantly by a modification of the technique of Hodge and Swift (8).

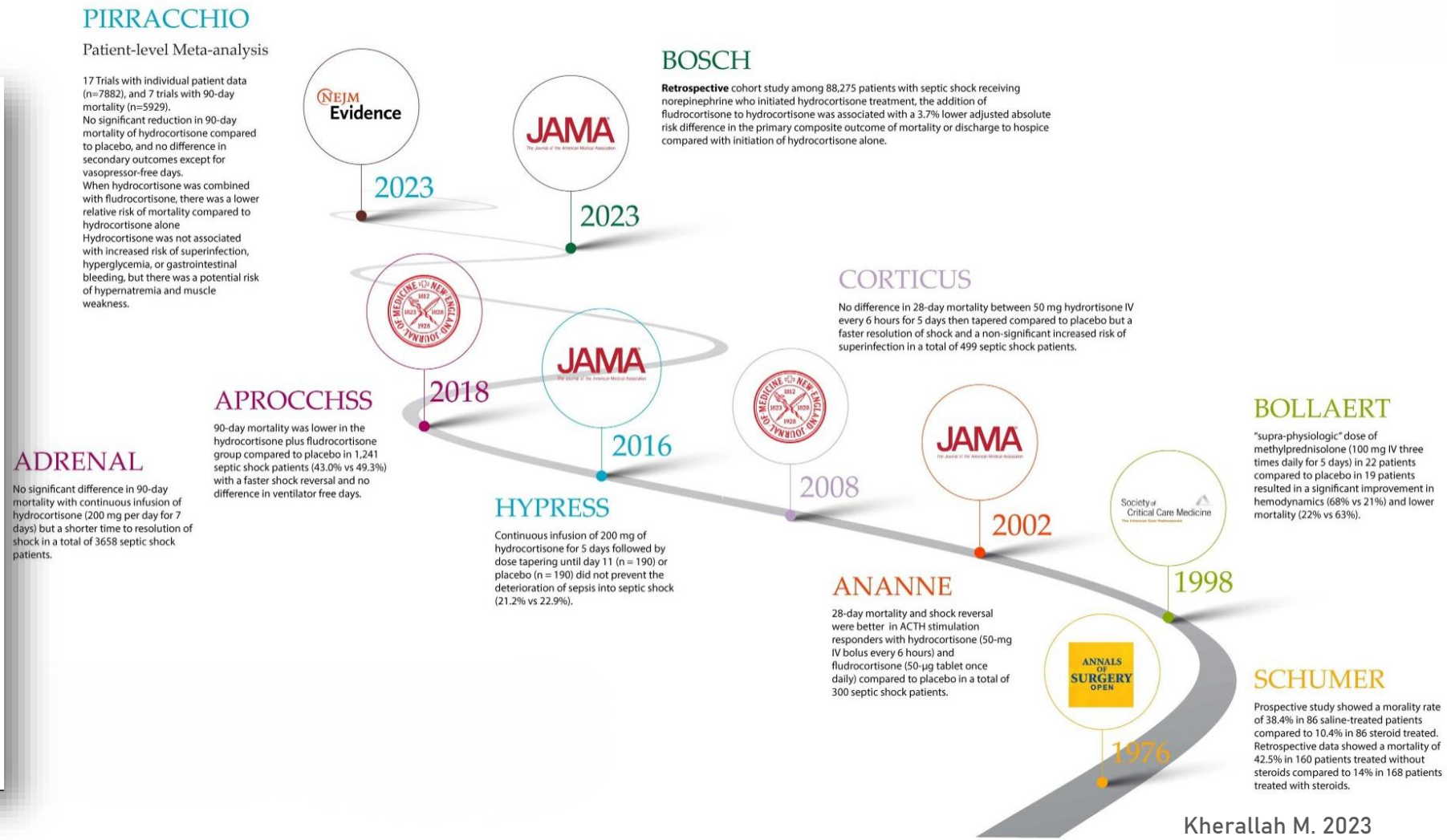
RESULTS

That the patients in this study had streptococcal disease is indicated by the demonstration of a sig-

[1] This investigation was supported through the Commission on Acute Respiratory Diseases, Armed Forces Epidemiological Board, Office of The Surgeon General, Washington, D. C.

[2] Capt. MC, AUS.

274



Kherallah M. 2023

Glukokortikoidi pri sepsi

Francija, RCT 2002:

- Nižja 28-dnevna mortaliteta pri bolnikih z insuficienco nadledvičnice
- Hitrejša resolucija šoka

Annane Trial

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

Annane D, Sébille V, Charpentier C, et al. Effect of Treatment With Low Doses of Hydrocortisone and Fludrocortisone on Mortality in Patients With Septic Shock. *JAMA*. 2002;288(7):862–871.

Methods

- Double blinded
- Randomized
- Parallel-groups (corticotropin test responders vs non-responders)
- 19 French ICUs

Intervention

50 mg IV boluses of hydrocortisone q6hrs **AND** one 50 ug fludrocortisone tablet QD **OR** placebo for 7 days

RESULTS

28 day mortality in septic shock patients with relative adrenal insufficiency (non-responders to corticotropin test)

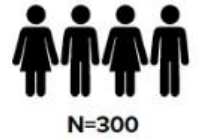
Hydrocortisone+Fludrocortisone: 60/114 deaths (53%)

Placebo: 73/115 deaths (63%)

Secondary Outcomes	Steroid	Placebo
Mortality at end of ICU stay	58%	70%
Mortality at 1 year follow up	68%	77%
Vasopressor Therapy discontinuation at 28 days	57%	40%
Median time to Vasopressor Therapy Discontinuation	7 days	10 days

THE BOTTOM LINE

There was no significant effect of steroids on mortality in responders, but among nonresponders (patients with septic shock and adrenal insufficiency) low dose steroids do reduce 28 day mortality and vasopressor dependence time. The number needed to treat to save one life at 28 days was 7 people.



Nonresponders
Placebo 115
Steroid 114

Responders
Placebo 34
Steroid 36

Glukokortikoidi pri sepsi

Multicentrična RTC, 2008:

- Ni razlike v 28-dnevni mortaliteti
- Hitrejša hemodinamska stabilizacija in resolucija šoka
- Neznačilen porast sekundarnih okužb in hiperglikemije

CORTICUS Trial

Hydrocortisone Therapy for Patients with Septic Shock

Sprung CL, Annane D, Keh D, et al. Hydrocortisone therapy for patients with septic shock. *N Engl J Med.* 2008;358(2):111-124

Methods

- 52 medical and surgical ICUs in 9 countries
- Randomized, Double-blind, Placebo controlled
- Intention to treat, interim, and post hoc subgroup analyses

Intervention

50 mg of IV hydrocortisone q6hrs **THEN** tapered **OR** placebo

RESULTS

No significant difference in 28-day mortality in patients who did not have a response to corticotropin was identified.

Hydrocortisone: 49 of 125 died (39.2%)

Placebo: 39 of 108 died (36.1%)

Secondary Outcome	Steroid	Placebo
Time to Reversal of Shock (all patients)	3.3 days	5.8 days
Time to Reversal of Shock (response to corticotropin)	2.8 days	5.8 days
Time to Reversal of Shock (no response to corticotropin)	3.9 days	6.0 days

N=500 | **N=252 Steroid** | **N=248 Placebo**

THE BOTTOM LINE

Hydrocortisone did not improve survival or reversal of shock in patients with septic shock, although reversal of shock was faster in those who received hydrocortisone. There was a non-statistically significant increase in the number of episodes of superinfection and hyperglycemia in the hydrocortisone group as compared to placebo.

Glukokortikoidi pri sepsi

Multicentrična RTC, 2016:

- Bolniki brez šoka in hipotenzije
- Ni razlike v razvoju šoka
- Ni razlike v mortaliteti
- Ni razlike v zapletih

HYPRESS Trial

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

Keh D, Trips E, Marx G, et al. Effect of Hydrocortisone on Development of Shock Among Patients With Severe Sepsis: The HYPRESS Randomized Clinical Trial. *JAMA*. 2016;316(17):1775-1785.

Methods

- Multicenter; 34 ICUs in German Community and University Hospitals
- Placebo-controlled
- Double-blind, randomized controlled trial

Intervention

IV hydrocortisone 200 mg/day for 5 days **THEN** sequentially tapered for 5 days **OR** placebo

RESULTS

No significant difference in development of septic shock within 14 days of treatment initiation was identified.

Hydrocortisone: 36 of 170 developed septic shock (21.2%)

Placebo: 39 of 170 developed septic shock (22.9%)

ADVERSE EVENTS

Hyperglycemia (Insulin administration was not significantly different between two groups)

***Secondary infections, weaning failure, muscle weakness, hypernatremia, or other adverse events were not significantly different between treatment groups*

THE BOTTOM LINE

A continuous infusion followed by tapering of hydrocortisone did not prevent severe sepsis to septic shock progression within 14 days of treatment initiation when compared to placebo.

Glukokortikoidi pri sepsi

Multicentrična RTC, 2018:

- Ni razlike v 90-dnevni mortaliteti
- Hitrejša hemodinamska stabilizacija in resolucija šoka
- Krajši čas ventilacije in zdravljenja v EIT

ADRENAL Trial

Adjunctive Glucocorticoid Treatment in Critically Ill Patients with Septic Shock

Venkatesh B, Finfer S, Cohen J, et al. Adjunctive Glucocorticoid Therapy in Patients with Septic Shock. *N Engl J Med.* 2018;378(9):797-808.

Methods

- International, pragmatic, double-blind, parallel-group RCT
- Intention to treat, subgroup, and sensitivity analysis

Intervention

Continuous IV hydrocortisone 200 mg/ day **OR** placebo

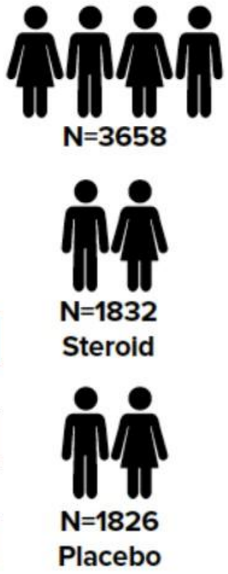
RESULTS

No significant difference in 90-day mortality was identified in the 6 prespecified subgroup analyses (sex, admission type—medical/surgical, catecholamine dose, site of sepsis, APACHE II score, and time from shock onset to randomization)

Hydrocortisone: 511 of 1832 died (27.9%)

Placebo: 526 of 1826 died (28.8%)

Secondary Outcomes	Steroid	Placebo
Time to Resolution of Shock	3 days	4 days
Time to Discharge from ICU	10 days	12 days
Duration of Mechanical Ventilation	6 days	7 days
Blood Transfusion	37%	41.7%



THE BOTTOM LINE

Continuous infusion of hydrocortisone did NOT result in lower 90-day mortality. Steroid use led to more rapid resolution of shock, shorter inpatient ICU time, and lower incidence of blood transfusion.

Glukokortikoidi pri sepsi

Francija, RTC 2018:

- Nižja 90-dnevna mortaliteta
- Manj večorganske odpovedi, hitrejša hemodinamska stabilizacija
- Hiperglikemija je najpogostejši zaplet

APROCCHSS Trial

Hydrocortisone Plus Fludrocortisone for Adults with Septic Shock

Annane D, Renault A, Brun-Buisson C, et al. Hydrocortisone Plus Fludrocortisone for Adults with Septic Shock. *N Engl J Med.* 2018;378:809-818.

Methods

- Multi-centered, pragmatic, double-blind, parallel study in France.
- Intention to treat, subgroup, and sensitivity analysis.
- 1241 patients in 69 medical and surgical ICUs in 69 countries

Intervention

IV hydrocortisone 50 mg q6hrs **AND** PO fludrocortisone 50 µg **OR** placebo

RESULTS

A significant difference in 90-day mortality was identified with an absolute risk reduction of 6.1%, P=.03, NNT of 17.

Steroid: 264 of 614 died (43%)

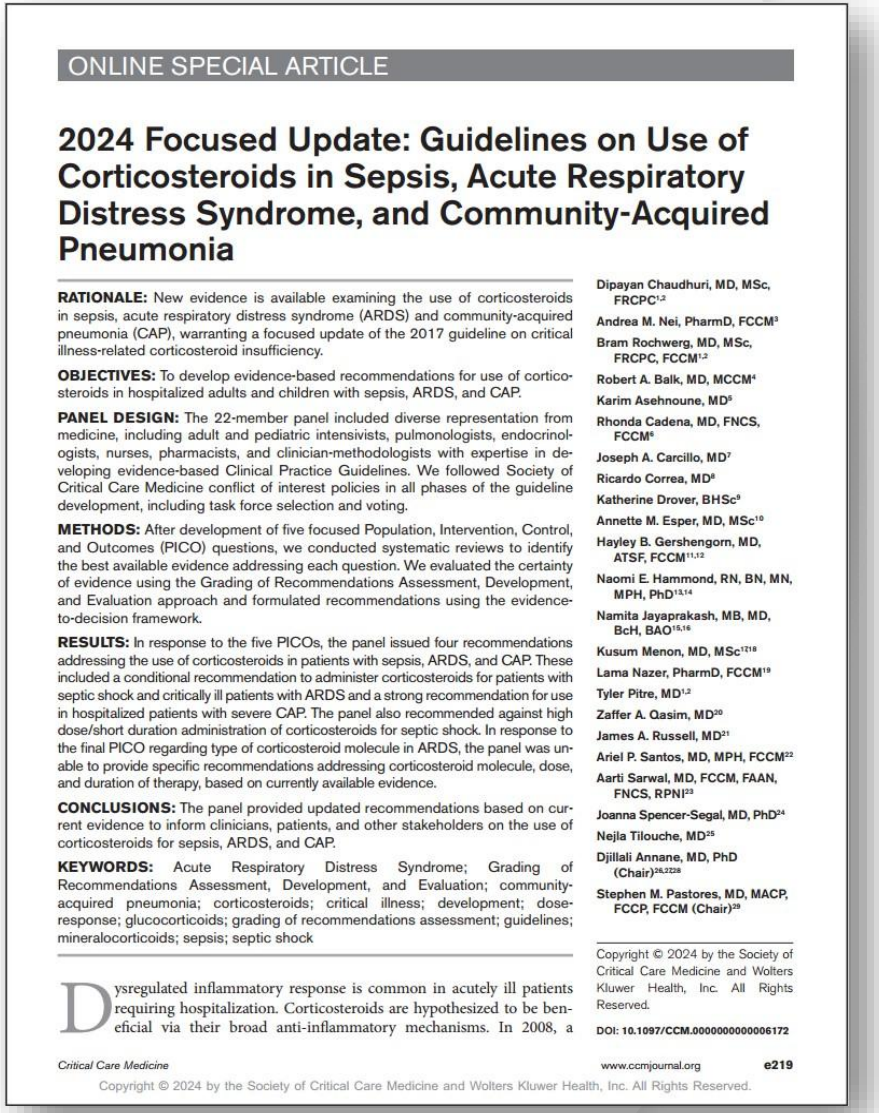
Placebo: 308 of 627 died (49.1%)

Secondary Outcomes	Steroid	Placebo
Vasopressor Free Days	15 days	17 days
Vasopressor Free Days	10 days	11 days
Organ Failure Free Days	12 days	14 days
Hyperglycemic Days	3.4 days	4.3 days

THE BOTTOM LINE

Hydrocortisone and fludrocortisone combination showed both a mortality and resolution to shock benefit. The steroid regimen was shown to be safe, with hyperglycemia noted as the most common adverse reaction.

Glukokortikoidi pri sepsi



ONLINE SPECIAL ARTICLE

2024 Focused Update: Guidelines on Use of Corticosteroids in Sepsis, Acute Respiratory Distress Syndrome, and Community-Acquired Pneumonia

RATIONALE: New evidence is available examining the use of corticosteroids in sepsis, acute respiratory distress syndrome (ARDS) and community-acquired pneumonia (CAP), warranting a focused update of the 2017 guideline on critical illness-related corticosteroid insufficiency.

OBJECTIVES: To develop evidence-based recommendations for use of corticosteroids in hospitalized adults and children with sepsis, ARDS, and CAP.

PANEL DESIGN: The 22-member panel included diverse representation from medicine, including adult and pediatric intensivists, pulmonologists, endocrinologists, nurses, pharmacists, and clinician-methodologists with expertise in developing evidence-based Clinical Practice Guidelines. We followed Society of Critical Care Medicine conflict of interest policies in all phases of the guideline development, including task force selection and voting.

METHODS: After development of five focused Population, Intervention, Control, and Outcomes (PICO) questions, we conducted systematic reviews to identify the best available evidence addressing each question. We evaluated the certainty of evidence using the Grading of Recommendations Assessment, Development, and Evaluation approach and formulated recommendations using the evidence-to-decision framework.

RESULTS: In response to the five PICOs, the panel issued four recommendations addressing the use of corticosteroids in patients with sepsis, ARDS, and CAP. These included a conditional recommendation to administer corticosteroids for patients with septic shock and critically ill patients with ARDS and a strong recommendation for use in hospitalized patients with severe CAP. The panel also recommended against high dose/short duration administration of corticosteroids for septic shock. In response to the final PICO regarding type of corticosteroid molecule in ARDS, the panel was unable to provide specific recommendations addressing corticosteroid molecule, dose, and duration of therapy, based on currently available evidence.

CONCLUSIONS: The panel provided updated recommendations based on current evidence to inform clinicians, patients, and other stakeholders on the use of corticosteroids for sepsis, ARDS, and CAP.

KEYWORDS: Acute Respiratory Distress Syndrome; Grading of Recommendations Assessment, Development, and Evaluation; community-acquired pneumonia; corticosteroids; critical illness; development; dose-response; glucocorticoids; grading of recommendations assessment; guidelines; mineralocorticoids; sepsis; septic shock

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DOI: 10.1097/CCM.0000000000006172

Dysregulated inflammatory response is common in acutely ill patients requiring hospitalization. Corticosteroids are hypothesized to be beneficial via their broad anti-inflammatory mechanisms. In 2008, a

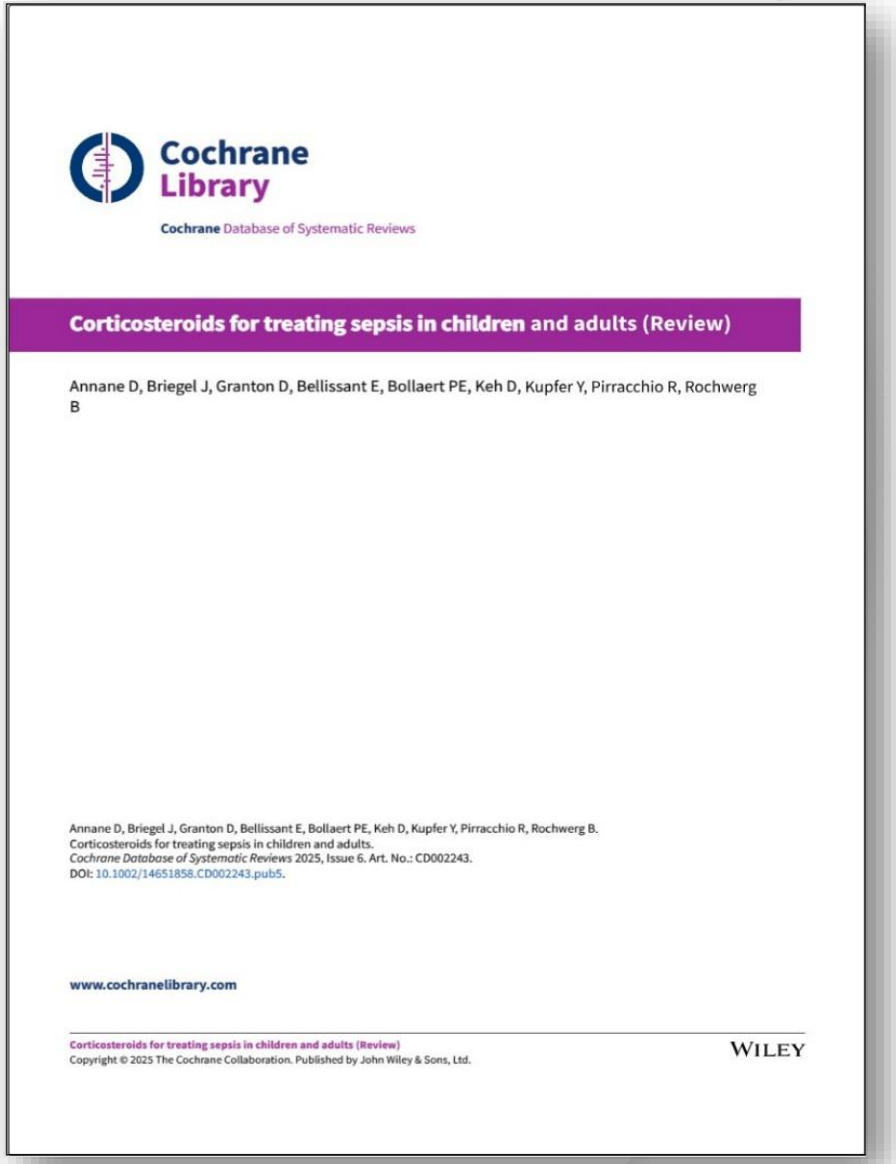
TABLE 3.
Summary of Recommendations[a]

Recommendation 2024	Recommendation Strength, Quality of Evidence	Comparison to 2017 Recommendations
Sepsis and septic shock		
1A. We "suggest" administering corticosteroids to adult patients with septic shock	Conditional recommendation, low certainty evidence	We suggest against corticosteroid administration in adult patients with sepsis without shock (conditional recommendation, moderate quality of evidence)
1B. We "recommend against" administration of high dose/short duration corticosteroids (> 400 mg/d hydrocortisone equivalent for less than 3 d) for adult patients with septic shock (strong recommendation, low certainty)	Strong recommendation, moderate certainty evidence	We suggest using corticosteroids in patients with septic shock that is not responsive to fluid and moderate- to high-dose vasopressor therapy (conditional recommendation, low quality of evidence)

46 RCTs: 7 s sepso, 5 CAP + sepsa, 4 ARDS + sepsa, ostale septični šok

- ICU mortaliteta/30 dnevna: RR 0.93; 95% CI, 0.88-0.98
- Bolnišnična/1-letna mortaliteta: RR 0.94; 95% CI, 0.89-1.00
- Krajši ICU in bolnišnični čas
- Več mišične šibkosti, hipernatremije in hiperglikemije
- Nejasno glede krvavitve iz GIT, sekundarnih okužb, kapi, miokardnega infarkta

Glukokortikoidi pri sepsi



Cochrane Library

Cochrane Database of Systematic Reviews

Corticosteroids for treating sepsis in children and adults (Review)

Annane D, Briegel J, Granton D, Bellissant E, Bollaert PE, Keh D, Kupfer Y, Pirracchio R, Rochwerg B

Annane D, Briegel J, Granton D, Bellissant E, Bollaert PE, Keh D, Kupfer Y, Pirracchio R, Rochwerg B.
Corticosteroids for treating sepsis in children and adults.
Cochrane Database of Systematic Reviews 2025, Issue 6. Art. No.: CD002243.
DOI: 10.1002/14651858.CD002243.pub5.

www.cochranelibrary.com

Corticosteroids for treating sepsis in children and adults (Review)
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87 RCTs (24300 bolnikov):

Summary of findings 1. Summary of findings table - Corticosteroids versus placebo or usual care

Corticosteroids versus placebo or usual care

Patient or population: sepsis in children and adults
Setting: in-hospital
Intervention: corticosteroids
Comparison: placebo or usual care

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo or usual care	Risk with corticosteroids				
28-day all-cause mortality assessed with: vital status follow-up: range 14 days to 30 days	257 per 1000	**229 per 1000** (216 to 245)	**RR 0.89** (0.84 to 0.95)	22915 (72 RCTs)	⊕⊕⊕⊖ Moderate[g]	Treatment probably reduces 28-day all-cause mortality. The number needed to treat is 36, suggesting that treatment with corticosteroids would save one additional life every 36 treated patients.
Long-term mortality assessed with: vital status follow-up: range 6 months to 12 months	352 per 1000	**342 per 1000** (321 to 363)	**RR 0.97** (0.91 to 1.03)	8468 (12 RCTs)	⊕⊕⊖⊖ Low[b,c]	Treatment may result in little to no difference in long-term mortality.
Hospital mortality assessed with: vital status	332 per 1000	**299 per 1000** (279 to 322)	**RR 0.90** (0.84 to 0.97)	17459 (40 RCTs)	⊕⊕⊕⊖ Moderate[d]	Treatment probably reduces hospital mortality. The number needed to treat is 30, suggesting that treatment with corticosteroids would save one additional life every 30 treated patients.
Number of participants with adverse events - superinfection (Superinfection) assessed with: clinical and laboratory variables	182 per 1000	**175 per 1000** (157 to 195)	**RR 0.96** (0.86 to 1.07)	7961 (36 RCTs)	⊕⊕⊖⊖ Low[h,i]	Treatment may result in little to no difference in the number of participants with adverse events (superinfection).
Number of participants with adverse events - muscle weakness (Muscle weakness) assessed with: clinical and laboratory variables	55 per 1000	**60 per 1000** (43 to 84)	**RR 1.09** (0.78 to 1.53)	6729 (7 RCTs)	⊕⊖⊖⊖ Very low[h,i,j]	The evidence is very uncertain about the effect of treatment on the number of participants with adverse events (muscle weakness).

- Krajši čas ICU zdravljenja (–0.9 dni, 95% CI –1.7 do –0,1 dni)
- Manj organske prizadetosti (SOFA –1.3, 95% CI –1.6 do –0.9)
- Ni razlike med kontinuirano infuzijo in bolusnimi odmerki.
- Več hiperglikemije, hipernatremije
- Brez razlike glede GIT krvavitev, nevropsihiatričnih epizod, MI

Endotipi

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EXTERNAL CORROBORATION THAT CORTICOSTEROIDS MAY BE HARMFUL TO SEPTIC SHOCK ENDOTYPE A PATIENTS

Hector R. Wong, MD[1,2], Kimberly W. Hart, MA[3], Christopher J. Lindsell, PhD[3], Timothy E. Sweeney, MD, PhD[4]

Variable	O.R.	95% C.I.	P value
Endotype B, Hydrocortisone	0.8	0.2 – 3.3	0.80
Endotype A, Placebo	1.0	0.5 – 4.1	0.98
Endotype A, Hydrocortisone	3.1	1.0 – 9.6	0.05
Hydrocortisone	0.8	0.2 – 3.3	0.80
Endotype A	1.9	0.7 – 5.1	0.18
Endotype A x Hydrocortisone	3.6	0.5 – 24.6	0.20

ORIGINAL ARTICLE

Transcriptomic Signatures in Sepsis and a Differential Response to Steroids

From the VANISH Randomized Trial

David B. Antcliffe[1,2*], Katie L. Burnham[3*], Farah Al-Beidh[1], Shalini Santhakumaran[4], Stephen J. Brett[2], Charles J. Hinds[5], Deborah Ashby[4], Julian C. Knight[3], and Anthony C. Gordon[1,2]

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Abstract

Rationale: There remains uncertainty about the role of corticosteroids in sepsis with clear beneficial effects on shock duration, but conflicting survival effects. Two transcriptomic sepsis response signatures (SRSs) have been identified. SRS1 is relatively immunosuppressed, whereas SRS2 is relatively immunocompetent.

Objectives: We aimed to categorize patients based on SRS endotypes to determine if these profiles influenced response to either norepinephrine or vasopressin, or to corticosteroids in septic shock.

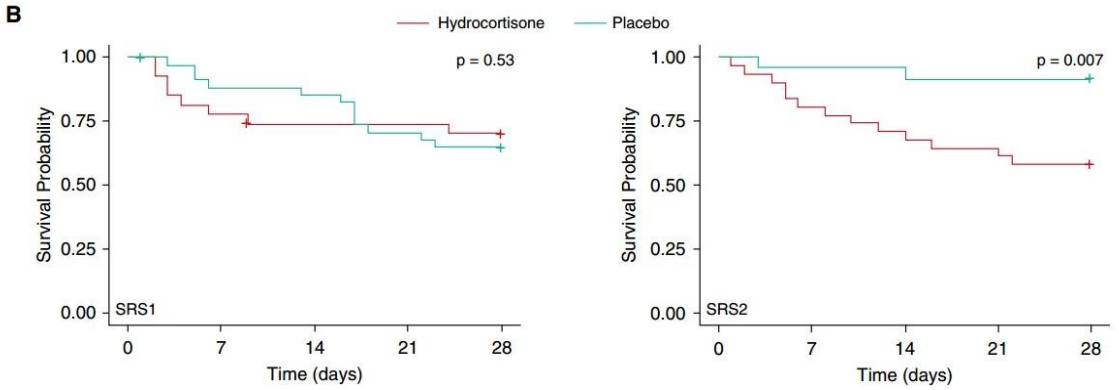
Methods: A *post hoc* analysis was performed of a double-blind, randomized clinical trial in septic shock (VANISH [Vasopressin vs. Norepinephrine as Initial Therapy in Septic Shock]). Patients were included within 6 hours of onset of shock and were randomized to receive norepinephrine or vasopressin followed by hydrocortisone or placebo. Genome-wide gene expression profiling was performed and SRS endotype was determined by a previously established model using seven discriminant genes.

Measurements and Main Results: Samples were available from 176 patients: 83 SRS1 and 93 SRS2. There was no significant interaction between SRS group and vasopressor assignment ($P = 0.50$). However, there was an interaction between assignment to hydrocortisone or placebo, and SRS endotype ($P = 0.02$). Hydrocortisone use was associated with increased mortality in those with an SRS2 phenotype (odds ratio = 7.9; 95% confidence interval = 1.6–39.9).

Conclusions: Transcriptomic profile at onset of septic shock was associated with response to corticosteroids. Those with the immunocompetent SRS2 endotype had significantly higher mortality when given corticosteroids compared with placebo.

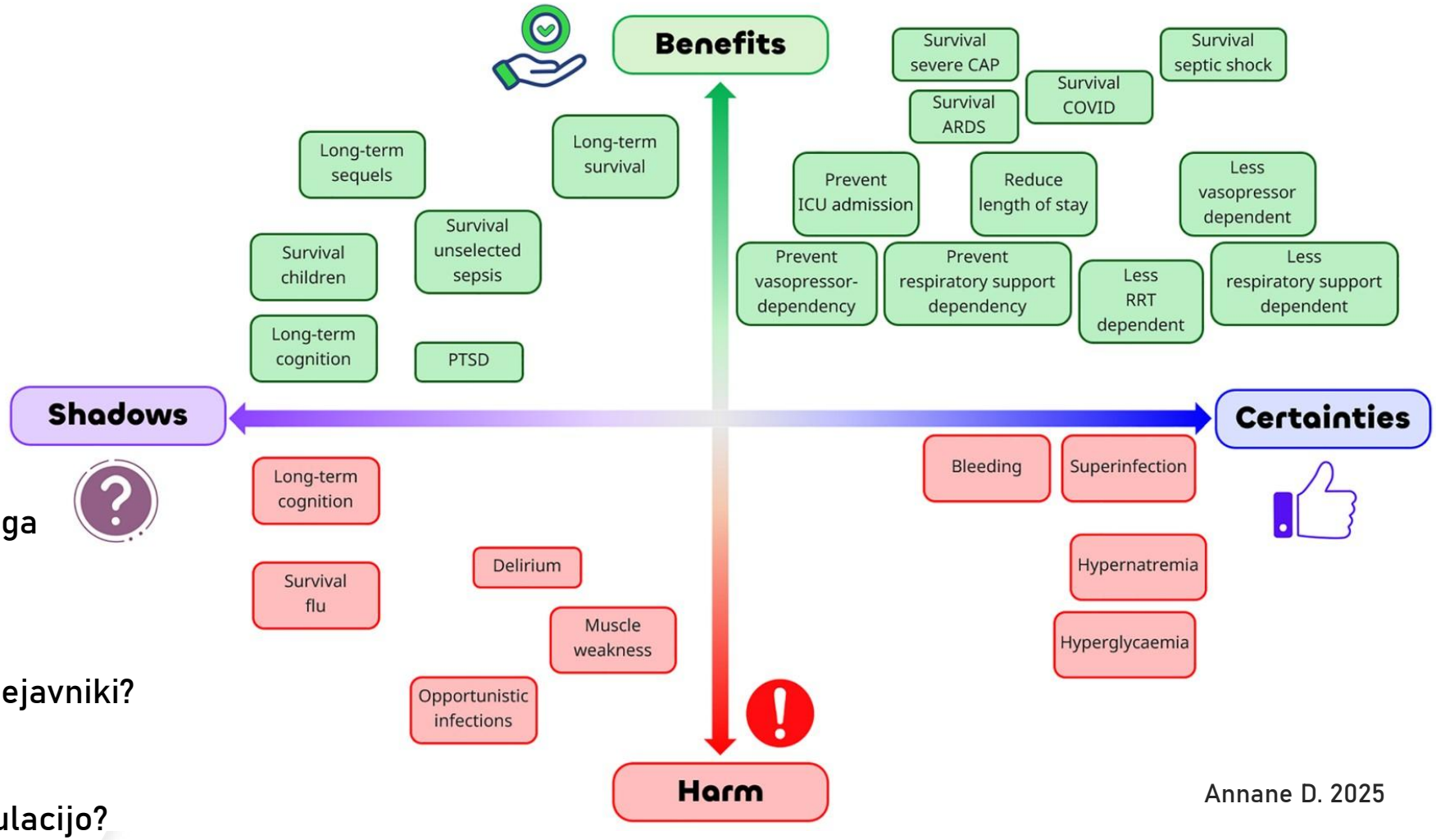
Clinical trial registered with www.clinicaltrials.gov (ISRCTN 20769191).

Keywords: sepsis; norepinephrine; vasopressin; corticosteroids; transcriptomics



Povzetek

- Učinkovitost odvisna od origa spese?
- Steroidi pri virusni sepsi?
- Genomski in negenomski dejavniki?
- Dodatek fludrokortizona?
- Podatki za pediatrično populacijo?



Annane D. 2025

Hvala!