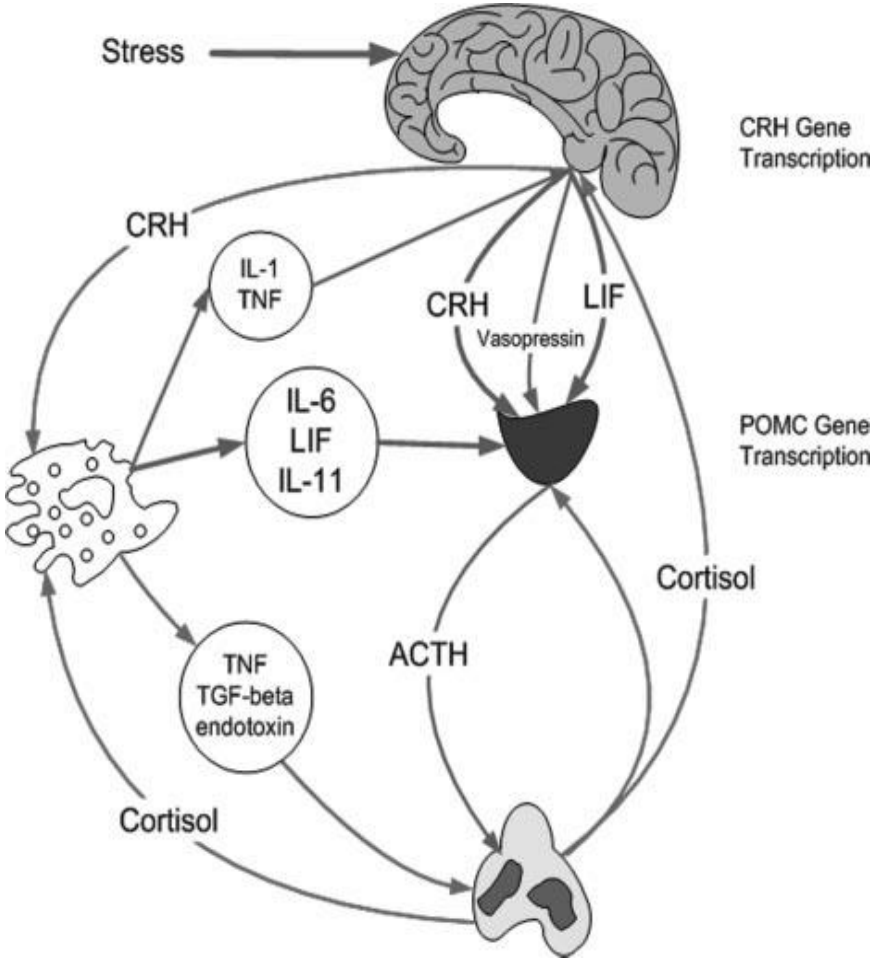
# Η θέση των κορτικοειδών στη σηπτική καταπληξία

*Χριστίνα Ρούτση*
*1η Κλινική Εντατικής Θεραπείας*
*Πανεπιστήμιο Αθηνών, Ιατρική Σχολή,*
*Νοσοκομείο Ευαγγελισμος,*
*Αθήνα*

# Activation of the HPA axis and the interaction with the inflammatory response.



REVIEW ARTICLE

SEMINARS IN MEDICINE

OF THE

BETH ISRAEL HOSPITAL, BOSTON

JEFFREY S. FLIER, M.D., *Editor*

LISA H. UNDERHILL, *Assistant Editor*

# THE HYPOTHALAMIC–PITUITARY–ADRENAL AXIS AND IMMUNE-MEDIATED INFLAMMATION

GEORGE P. CHROUSOS, M.D.

CELSUS described four of the five cardinal signs of inflammation 2000 years ago, and Eustachio discovered the adrenal glands almost 500 years ago, but not until 1936 did Selye note that in rats exposed

reactions, such as tumor necrosis factor $\alpha$, interleukin-1, and interleukin-6.[6-8]

Activation of the stress system heightens arousal, accelerates motor reflexes, improves attention and cognitive function, decreases appetite and sexual arousal, and increases the tolerance of pain.[6,7] The activated system also changes cardiovascular function and intermediary metabolism and inhibits immune-mediated inflammation.

Corticotropin-releasing hormone (CRH) and noradrenergic neurons of the central stress system innervate and stimulate each other.[6-9] Thus, CRH stimulates the secretion of norepinephrine through specific receptors, and norepinephrine stimulates the secretion of CRH primarily through $\alpha_1$-noradrenergic receptors.[6,7,9] By means of autoregulatory, ultrashort negative-feedback loops, CRH and norepinephrine collateral fibers inhibit presynaptic CRH and $\alpha_2$-noradrenergic receptors, respectively. CRH, arginine vasopressin (AVP), and noradrenergic neurons are stimulated by the serotonergic and cholinergic systems and inhibited by the $\gamma$-aminobutyric acid–benzodiazepine and opioid-peptide systems of the brain. Centrally secreted substance P inhibits hypothalamic CRH neurons but not AVP neurons

- **Critical illness-related corticosteroid insufficiency is defined as inadequate corticosteroid activity for the severity of the illness of a patient.**

*J Clin Invest 1951; 30: 274-281*

# 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*)

*Annals of surgery 1976; 184:333-341*

# *Steroids in the Treatment of Clinical Septic Shock*

WILLIAM SCHUMER, M.D.*

## Η χρονική περίοδος της χορήγησης υψηλής δόσης κορτικοστεροειδών στη σηπτική καταπληξία

From 1950 **Steroid success era** to mid 80s

- **Οι 2 μελέτες που εθεσαν τέλος στην χορηγηση υψηλής δοσης κορτικοειδων στην σηπτική καταπληξία**

- **The Effects of High-Dose Corticosteroids in Patients with Septic Shock — A Prospective, Controlled Study**

  ***Charles L. Sprung, et al.***

  ***Engl J Med 1984; 311:1137-1143***

- **A Controlled Clinical Trial of High-Dose Methylprednisolone in the Treatment of Severe Sepsis and Septic Shock**

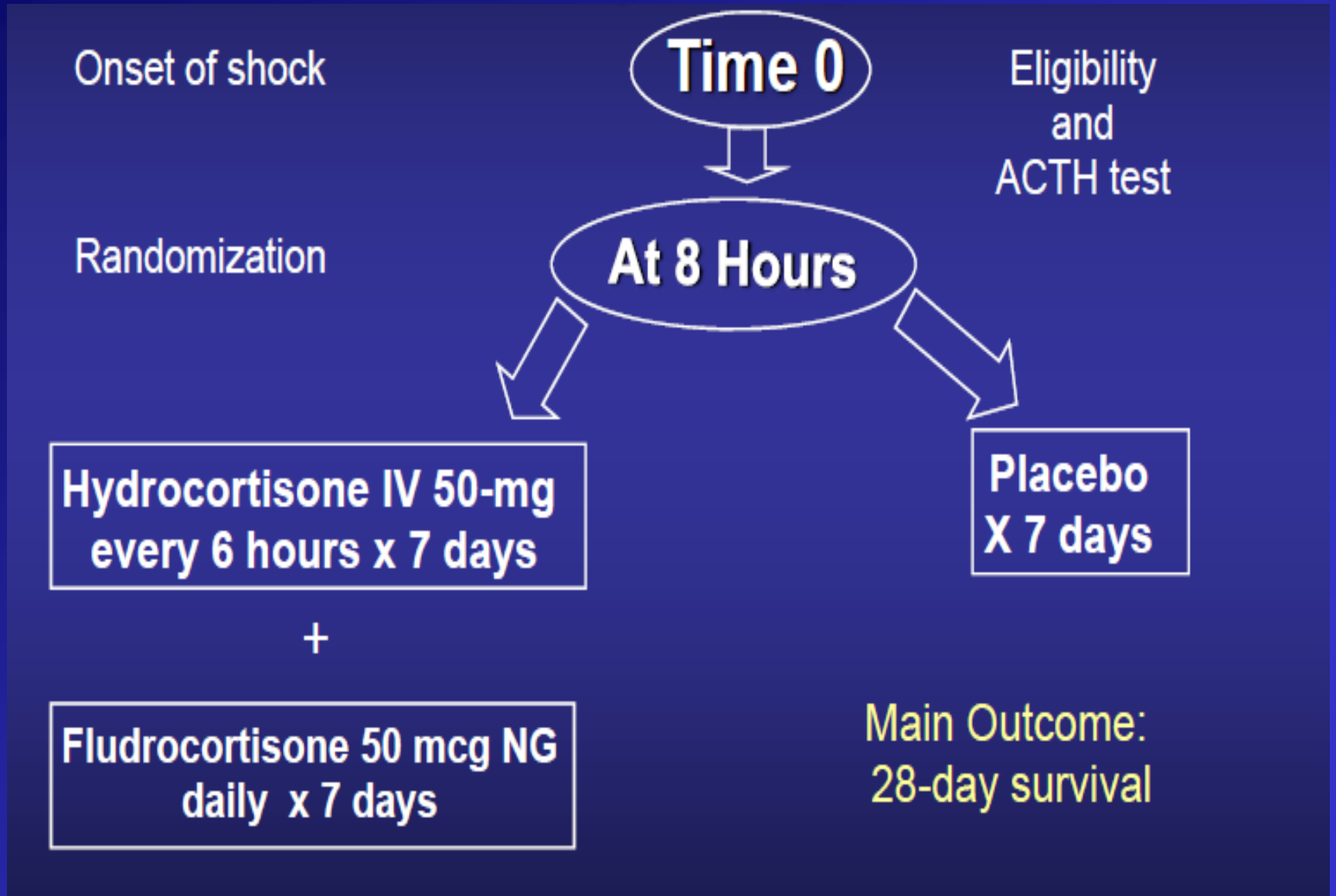
  ***Roger C. Bone,et al. and The Methylprednisolone Severe Sepsis Study Group***

  ***N Engl J Med 1987; 317:653-658***

# High dose steroids for sepsis

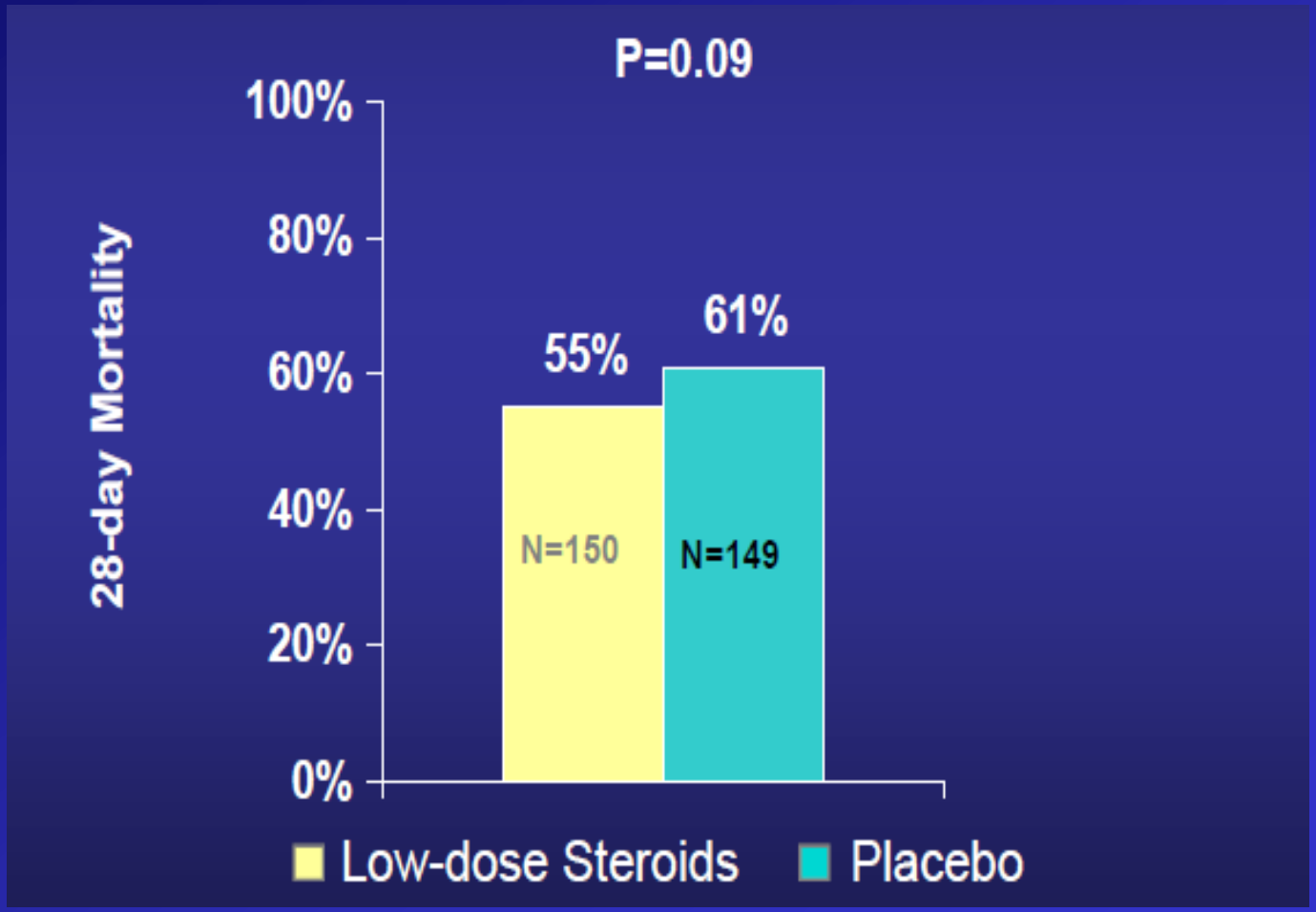
# Low dose steroids in septic shock / study design

*Annane D et al. JAMA 2000;283: 1038-45*



# Low dose steroids in septic shock: 28-day mortality

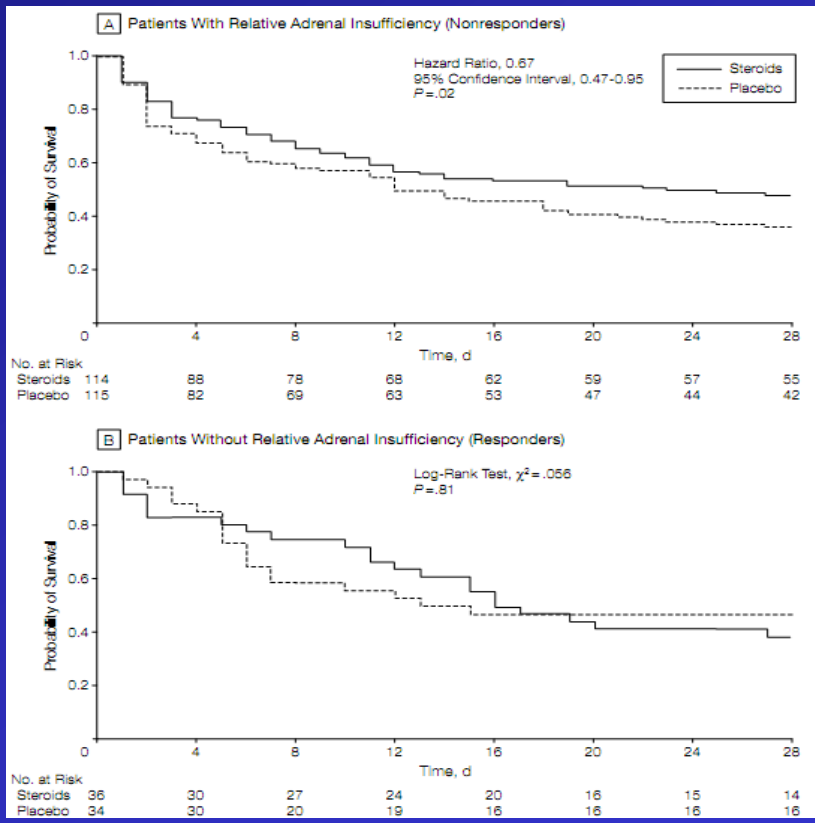
*Annane D et al. JAMA 2000;283: 1038-45*

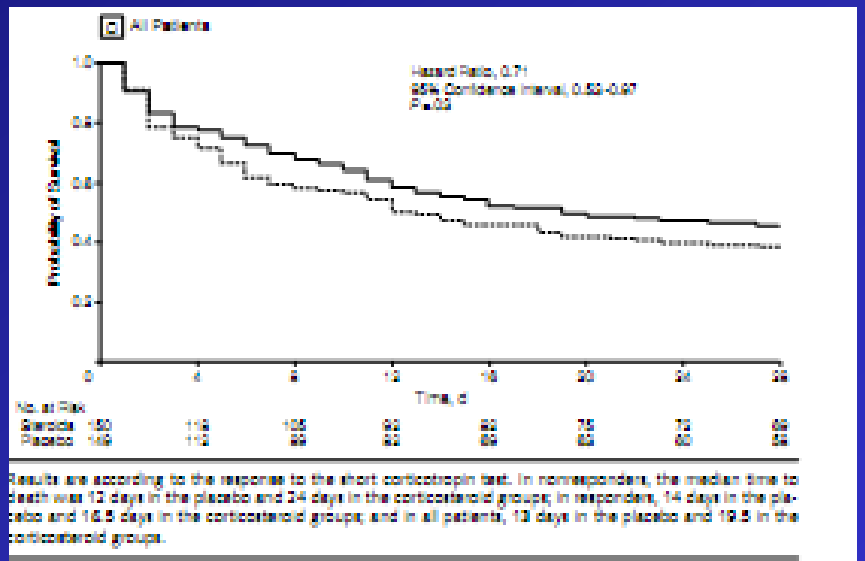


# Effect of treatment with low doses of hydrocortisone on mortality in patients with septic shock

***Annane et al. JAMA 2002; 288:862***

- 300 pts with septic shock
- Hydrocortisone 50mg q 6 h
  + Fludro- 50µg q day , 7 days
- ACTH-*stim* test
- **Non responders:**
  **Mortality 63% (control) vs. 53% (steroids)**
- **Responders:**
  **<u>slightly increased mortality in steroid group</u>**
- **Reduced vasopressor use**




Results are according to the response to the short corticotropin test. In nonresponders, the median time to death was 12 days in the placebo and 24 days in the corticosteroid groups; in responders, 14 days in the placebo and 16.5 days in the corticosteroid groups; and in all patients, 13 days in the placebo and 19.5 in the corticosteroid groups.

# Corticosteroid Therapy of Septic Shock
# CORTICUS Study

*Sprung C et al. NEJM 2008; 358: 111-124*

- **Multicenter, double-blind, RCT**
- **52 ICUs, March 2002 – Nov 2005 (3 ½ yrs)**
- **Pts. > 18 yrs with sepsis and onset of shock within the previous 72h (SBP < 90 despite fluids or need for vasopressors for > 1 hour)**
- **Hydrocortisone or Placebo:**
  - **50 mg IV q 6h x 5 days**
  - **50 mg IV q 12h on days 6 to 8**
  - **50 mg IV q 24h on days 9 to 11 then stopped**

# CORTICUS study
# Sprung et al, NEJM; 2008:111-124

- ACTH 250 µg stimulation test
- Non-responder: < 9 µg/dL
- Intended sample size: 800
  - 500 patients enrolled
  - 499 analyzable

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 10, 2008 VOL. 358 NO. 2

# Hydrocortisone Therapy for Patients with Septic Shock

Charles L. Sprung, M.D., Djillali Annane, M.D., Ph.D., Didier Keh, M.D., Rui Moreno, M.D., Ph.D., Mervyn Singer, M.D., F.R.C.P., Klaus Freivogel, Ph.D., Yoram G. Weiss, M.D., Julie Benbenishty, R.N., Armin Kalenka, M.D., Helmuth Forst, M.D., Ph.D., Pierre-Francois Laterre, M.D., Konrad Reinhart, M.D., Brian H. Cuthbertson, M.D., Didier Payen, M.D., Ph.D., and Josef Briegel, M.D., Ph.D., for the CORTICUS Study Group*

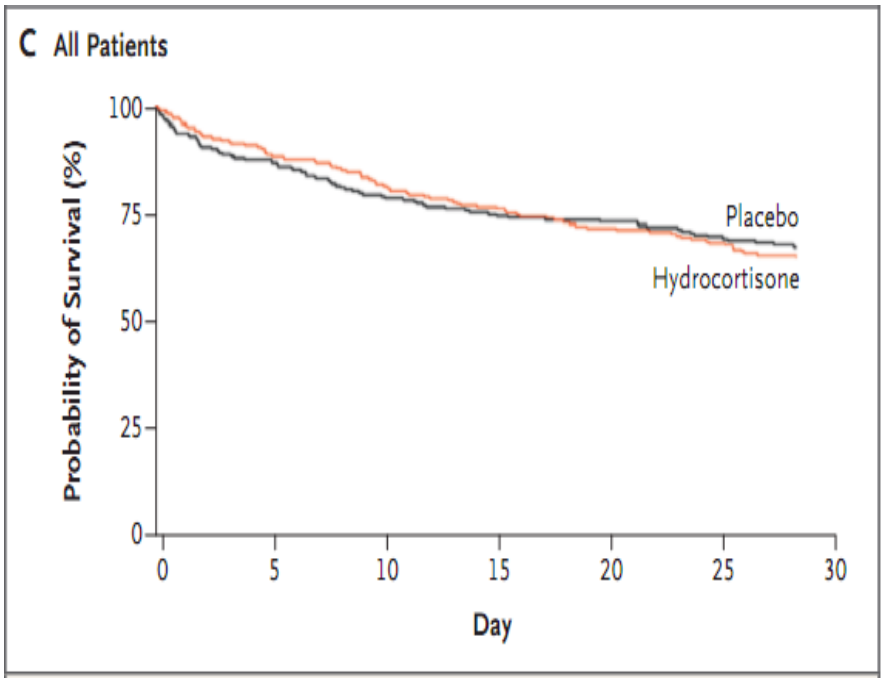



Figure 2. Kaplan–Meier Curves for Survival at 28 Days.

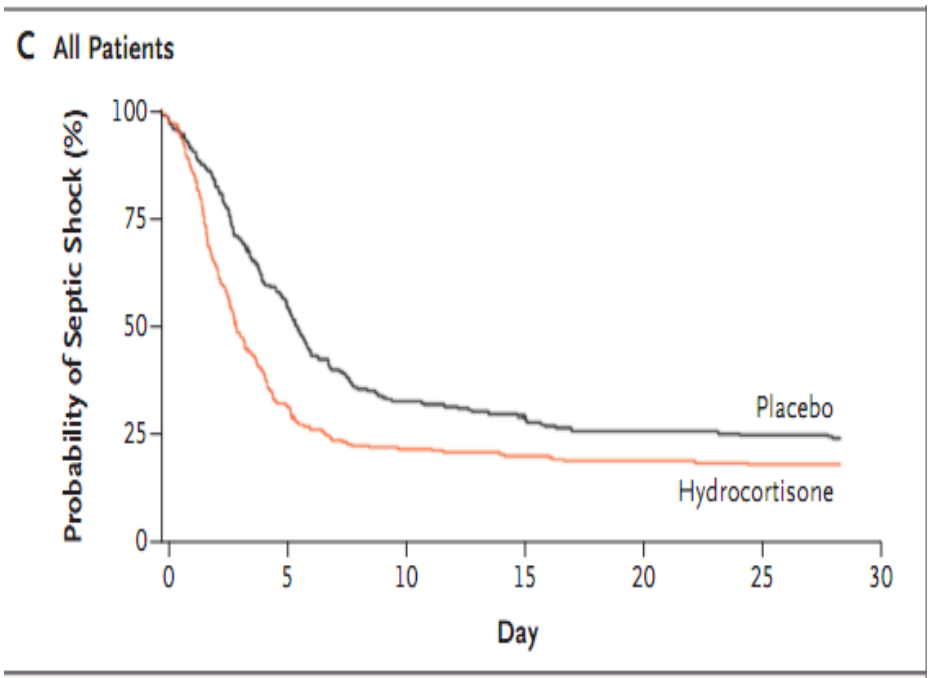



Figure 3. Kaplan–Meier Curves for the Time to Reversal of Shock.

# CORTICUS: Conclusions

- Hydrocortisone RX
  - Did not decrease mortality
  - Deceased time to shock reversal
  - Was associated with an increased incidence of:
    - super infections, including new episodes of sepsis or septic shock
    - Hyperglycemia
    - Hypernatremia

# Annane vs. CORTICUS

| | Annane | CORTICUS |
|---|---|---|
| Treatment start | ≤ 8h of shock | ≤ 72 h of shock |
| Fludrocortisone | Yes | No |
| Steroid taper | No | Yes |
| More medical pts | Yes | No |
| More surg pts | No | Yes |
| More intra-abd'l source of infxn | No | Yes |
| Placebo mortality | 61% | 31% |
| # Nonresponders | 77% | 44% |

# *So, who should get steroids?*

Surviving Sepsis Campaign

# Steroids

Suggest intravenous hydrocortisone be given only to adult septic shock patients after blood pressure is identified to be poorly responsive to fluid resuscitation and vasopressor therapy

Grade 2C

# The GRADE approach

**G**rades of

**R**ecommendation,

**A**ssessment,

**D**evelopment, and

**E**valuation

# Grading quality of evidence

- **GRADE A – high quality**
  **(Randomized controlled trial, RCT)**
- **GRADE B – moderate quality**
  **(Downgraded RCT or upgraded observational)**
- **GRADE C – low quality**
  **(Observational or cohort)**
- **GRADE D – very low quality**
  **(Case series or expert opinion)**

# Grading strength of recommendation

- **GRADE 1 – strong recommendation → do it**

  **“ we recommend ”**

- **GRADE 2 – weak recommendation → probably do it**

  **“ we suggest ”**

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- **Not using intravenous hydrocortisone to treat adult septic shock patients if adequate fluid resuscitation and vasopressor therapy are able to restore hemodynamic stability . In case this is not achievable, we suggest intravenous hydrocortisone alone at a dose of 200 mg per day (grade 2C).**

- **2. Not using the ACTH stimulation test to identify adults with septic shock who should receive hydrocortisone (grade 2B).**

- **3. In treated patients hydrocortisone tapered when vasopressors are no longer required (grade 2D).**

- **4. Corticosteroids not be administered for the treatment of sepsis in the absence of shock (grade 1D).**

- **5. When hydrocortisone is given, use continuous flow (grade 2D).**

ClinicalTrials.gov

ClinicalTrials.gov Identifier: NCT01448109
First received: October 5, 2011
Last updated: June 18, 2013

Study Chair: Balasubramanian Venkatesh

# ADjunctive coRticosteroid trEatment iN criticAlly ilL Patients With Septic Shock (ADRENAL)

- The George Institute
- Collaborators:
- National Health and Medical Research Council, Australia
- Australian and New Zealand Intensive Care Society Clinical Trials Group

# STEROID Randomized Control Trial CHALLENGES

- decline mortality
- timing of steroid use
- duration
- weaning from steroids
- assessing adrenal status
- etomidate use

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 1, 2018 VOL. 378 NO. 9

# Adjunctive Glucocorticoid Therapy in Patients with Septic Shock

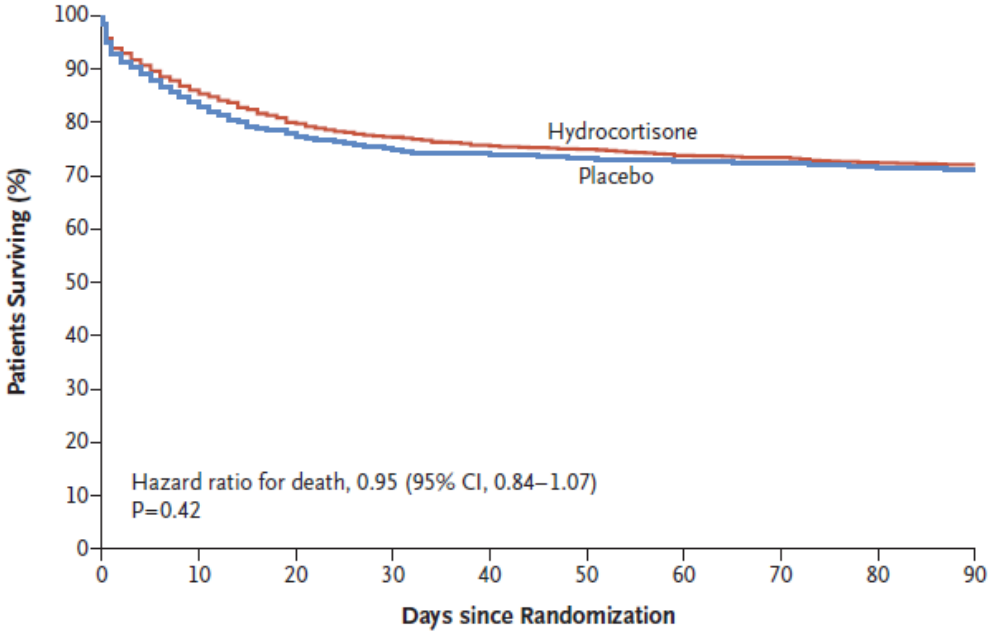
B. Venkatesh, S. Finfer, J. Cohen, D. Rajbhandari, Y. Arabi, R. Bellomo, L. Billot, M. Correa, P. Glass, M. Harward, C. Joyce, Q. Li, C. McArthur, A. Perner, A. Rhodes, K. Thompson, S. Webb, and J. Myburgh, for the ADRENAL Trial Investigators and the Australian–New Zealand Intensive Care Society Clinical Trials Group*

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 MARCH 1, 2018 VOL. 378 NO. 9

# Adjunctive Glucocorticoid Therapy in Patients with Septic Shock



**A Survival**




**No. at Risk**

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Hydrocortisone | 1832 | 1591 | 1481 | 1418 | 1388 | 1374 | 1356 | 1348 | 1328 | 1321 |
| Placebo | 1826 | 1546 | 1433 | 1376 | 1354 | 1337 | 1330 | 1322 | 1312 | 1300 |

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 1, 2018 VOL. 378 NO. 9

# Adjunctive Glucocorticoid Therapy in Patients with Septic Shock

**CONCLUSIONS**

Among patients with septic shock undergoing mechanical ventilation, a continuous infusion of hydrocortisone did not result in lower 90-day mortality than placebo. (Funded by the National Health and Medical Research Council of Australia and others; ADRENAL ClinicalTrials.gov number, NCT01448109.)

*Intensive Care Med (2018) 44:1470–1482*
https://doi.org/10.1007/s00134-018-5332-4

**ORIGINAL**

# Corticosteroid treatment in critically ill patients with severe influenza pneumonia: a propensity score matching study

Gerard Moreno[1], Alejandro Rodríguez[1*], Luis F. Reyes[2,17] Josep Gomez[1], Jordi Sole-Violan[3], Emili Díaz[4], María Bodí[1], Sandra Trefler[1], Juan Guardiola[5], Juan C. Yébenes[6], Alex Soriano[7], José Garnacho-Montero[8], Lorenzo Socias[9], María del Valle Ortíz[10], Eudald Correig[11], Judith Marín-Corral[12], Montserrat Vallverdú-Vidal[13], Marcos I. Restrepo[14], Antoni Torres[15] and Ignacio Martín-Loeches[16] on behalf of the GETGAG Study Group

# Corticosteroid treatment in critically ill patients with severe influenza pneumonia: a propensity score matching study

*Intensive Care Medicine 2018; 44: 2070*

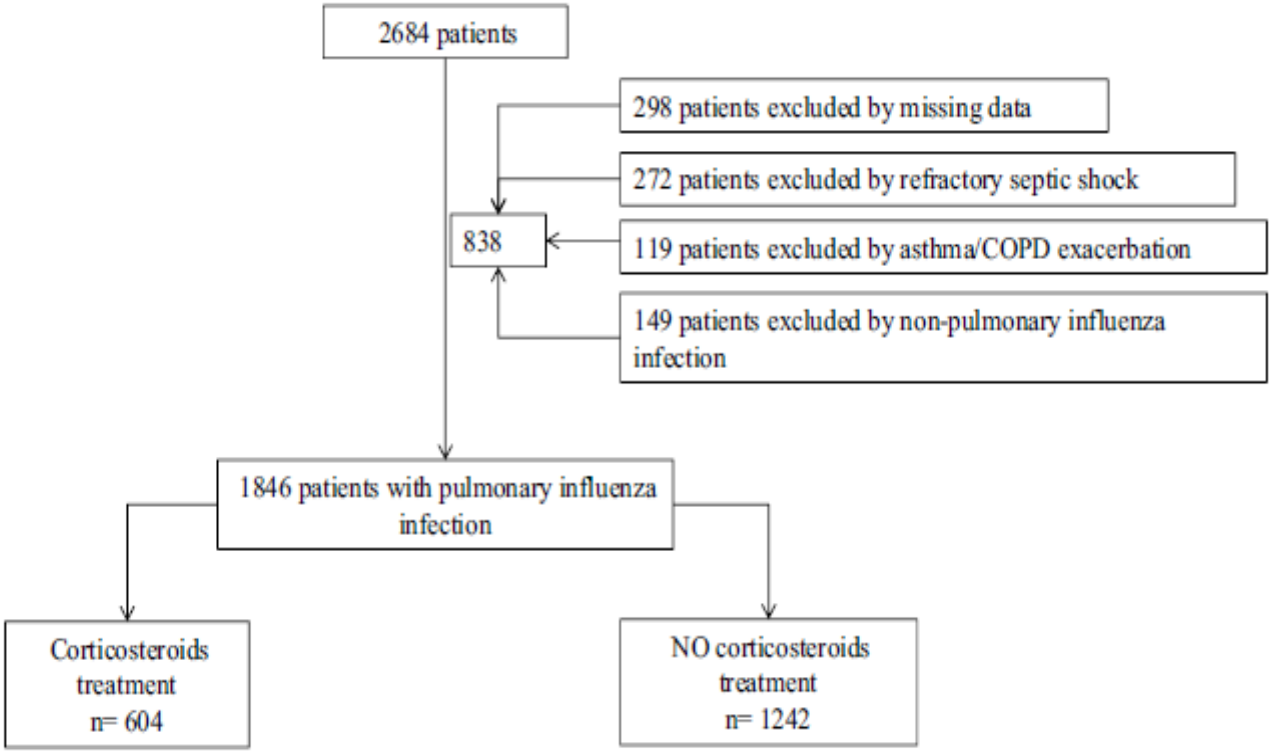



**Fig. 1** Flowchart of all excluded and included patients

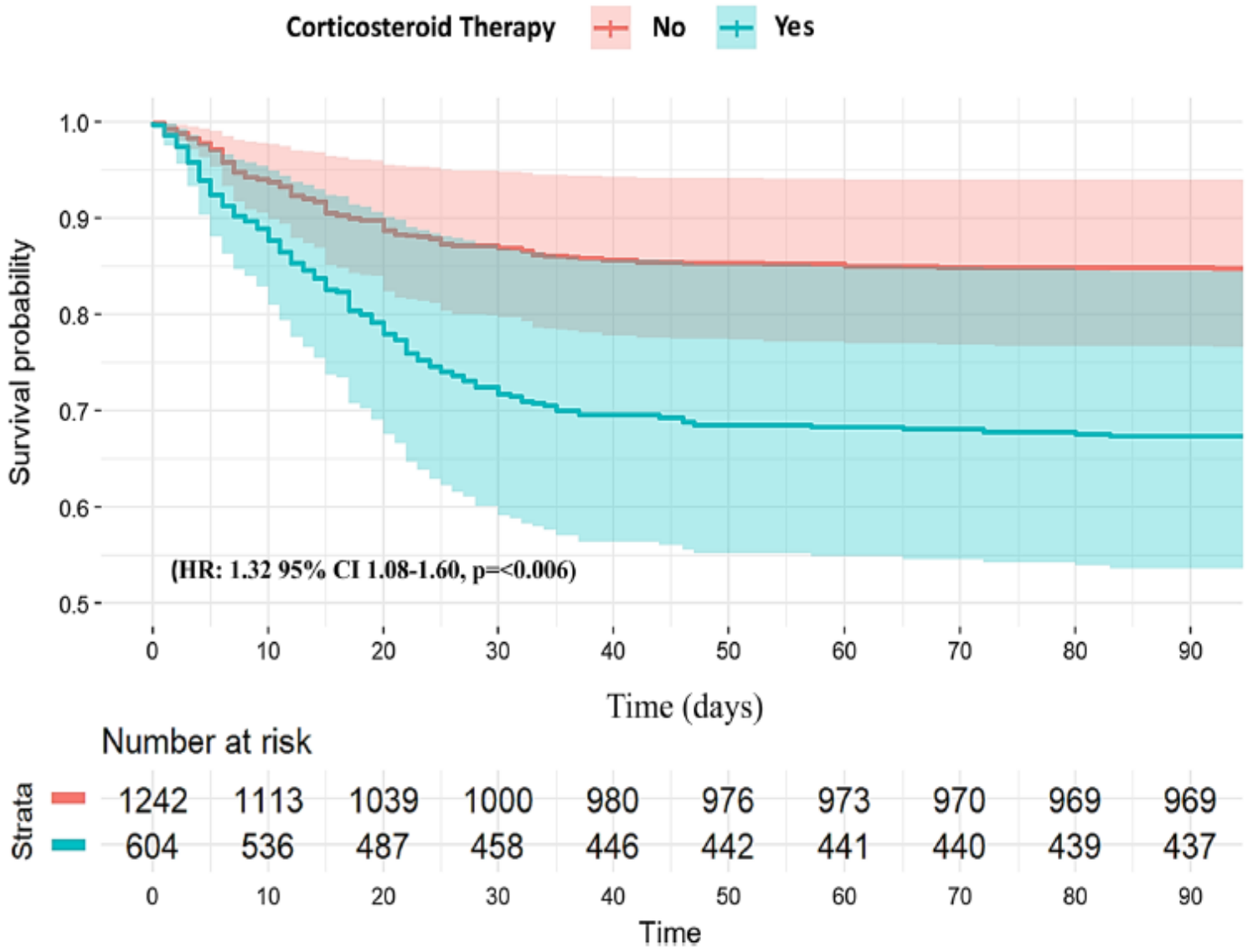



**Fig. 3** Cox regression survival plot during ICU admission according to corticosteroid therapy

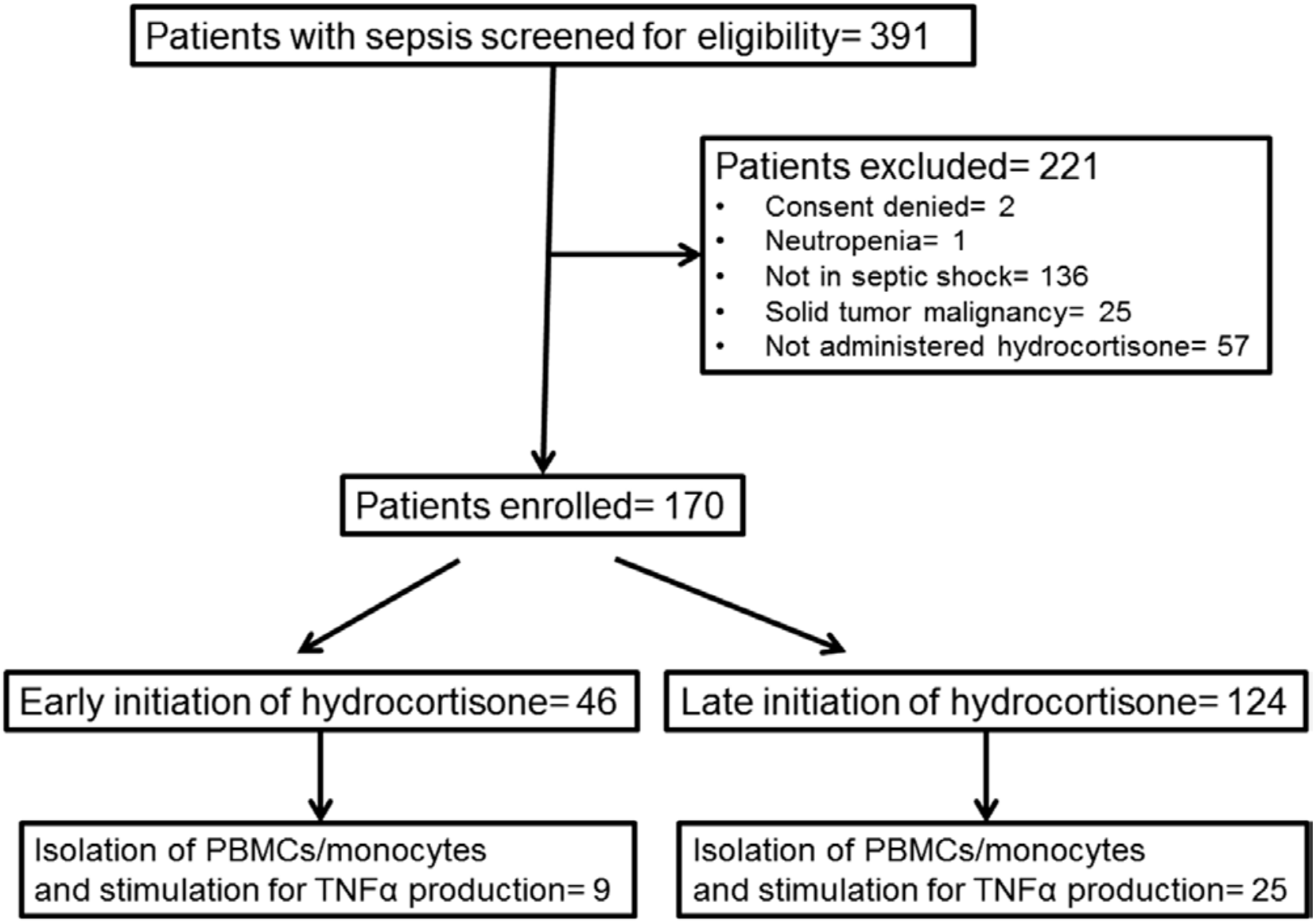
*Crit Care Med 2014, in press*

**Published Ahead-of-Print - Last Updated: March 26, 2014**

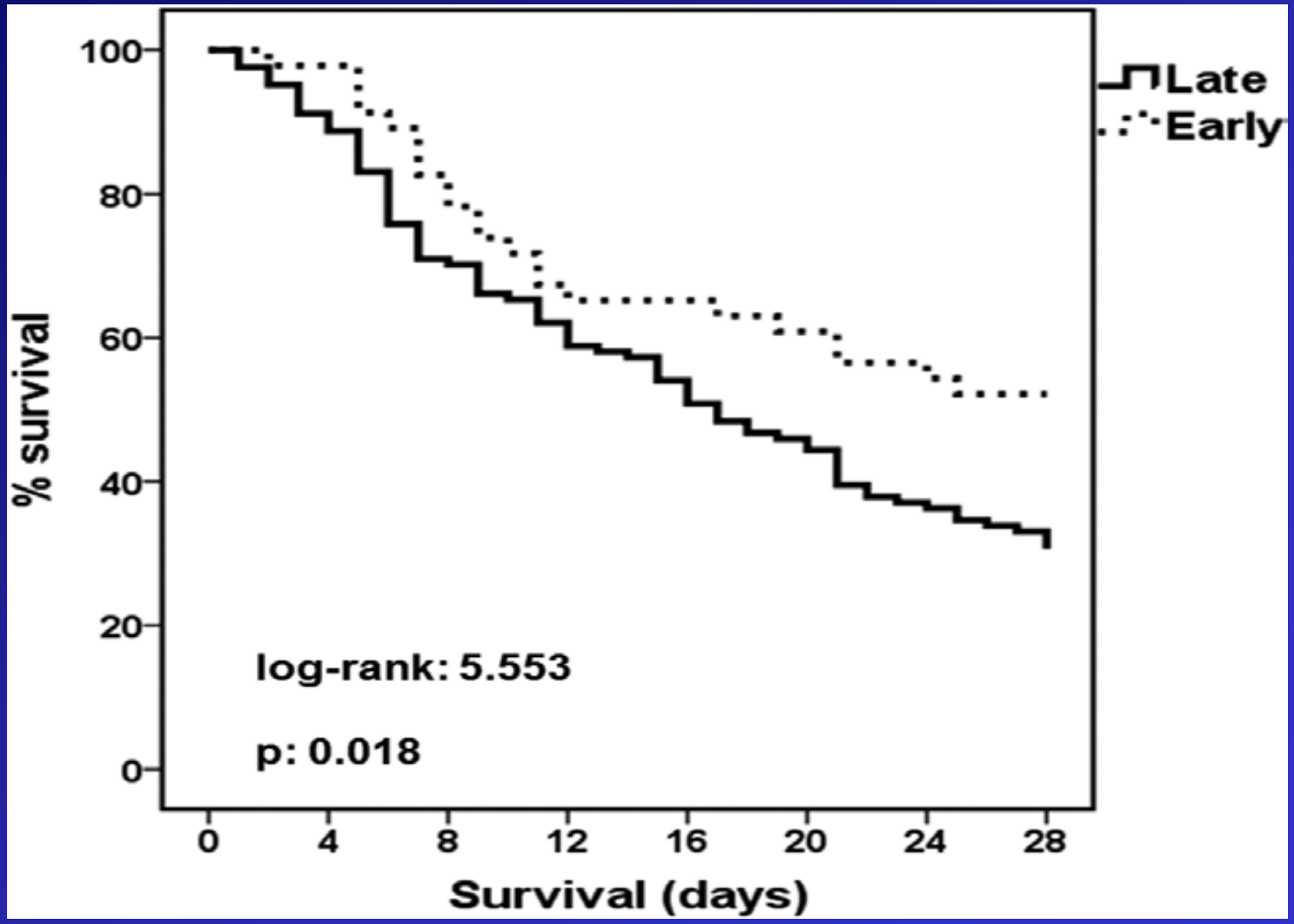
# Early Administration of Hydrocortisone Replacement After the Advent of Septic Shock: Impact on Survival and Immune Response

Chrysostomos S. Katsenos, MD[1]; Anastasia N. Antonopoulou, MD, PhD[2]; Efterpi N. Apostolidou, MD, PhD[3]; Aikaterini Ioakeimidou, MD[4]; Georgia Th. Kalpakou, MD[5]; Metaxia N. Papanikolaou, MD, PhD[6]; Aikaterini C. Pistiki, MD[7]; Margarita C. Mpalla, MD[6]; Michael D. Paraschos, MD[1]; Maria A. Patrani, MD[1]; Maria E. Pratikaki, MD, PhD[8]; Theodoros A. Retsas, MD[9]; Athina A. Savva, MD[7]; Spyridoula D. Vassiliagkou, MD, MSc[10]; Alexandra A. Lekkou, MD, PhD[11]; Ioanna Dimopoulou, MD[2]; Christina Routsi, MD, PhD[8]; Konstantinos E. Mandragos, MD, PhD[1]; on behalf of the Hellenic Sepsis Study Group

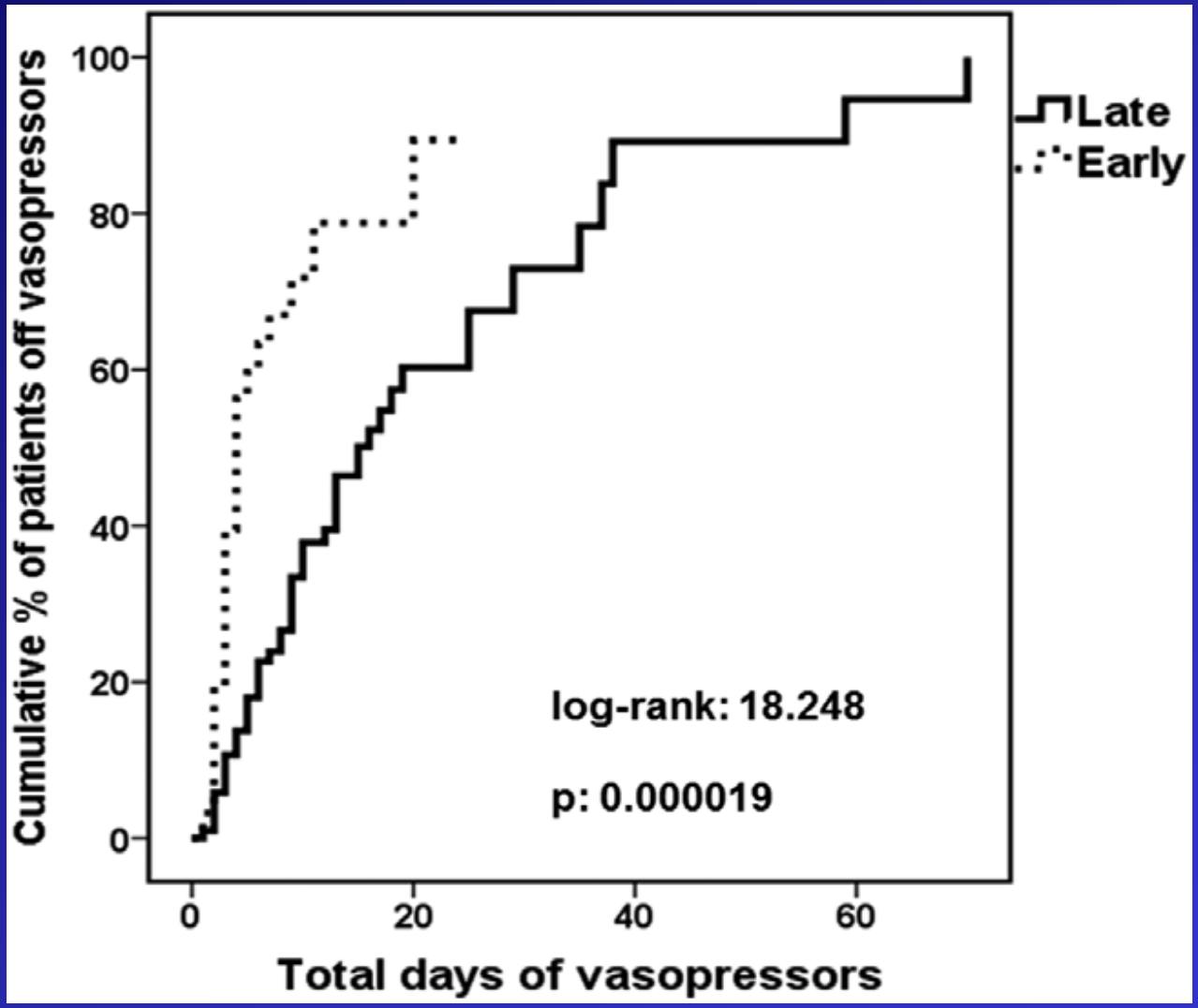
# Study flowchart



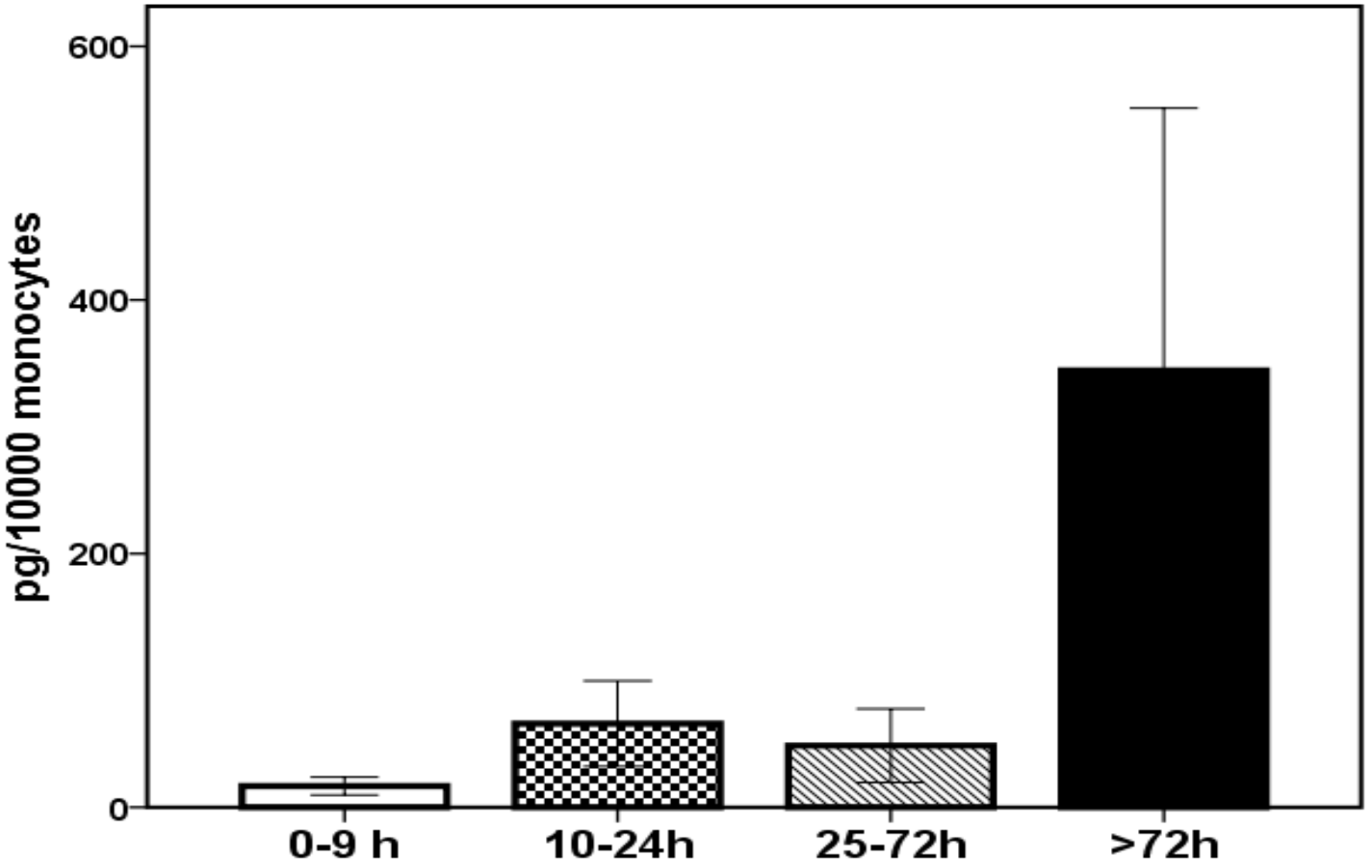
# Impact of early initiation of hydrocortisone on clinical outcome



# Impact of early initiation of hydrocortisone on the total time on vasopressors



# Επίδραση της πρώιμης έναρξης χορήγησης υδροκορτιζόνης στην παραγωγή TNF-α από τα κυκλοφορούντα μονοκύτταρα



# Early Administration of Hydrocortisone Replacement After the Advent of Septic Shock: Impact on Survival and Immune Response*

***Katsenos et al, Critical Care Med 2014; 42:1651***

- **Η πρώιμη (εντός 9 ωρών από την έναρξη αγγειοσυσπαστικών) χορήγηση δόσεων υποκατάστασης υδροκορτιζόνης παρατείνει την επιβίωση των ασθενών με σηπτική καταπληξία.**

- **Η θεραπεία αυτή επίσης έχει αντιφλεγμονώδη δράση.**

Surviving Sepsis Campaign

# www.survivingsepsis.org

♦ ♦ ♦

# www.IHI.org

*Intensive Care Med (2020) 46:2067–2070*
https://doi.org/10.1007/s00134-020-06223-y

**EDITORIAL**

# The ten reasons why corticosteroid therapy reduces mortality in severe COVID-19

Yaseen M. Arabi[1*], George P. Chrousos[2] and G. Umberto Meduri[3,4]

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# **Fig. 1** Hypothalamic–pituitary–adrenal (HPA) response in COVID-19.