CENTRE HOSPITALIER DE VERSAILLES

Traitements adjuvants du sepsis
Les corticoides

JP Bedos, Réanimation, Hôpital Mignot, CH Versailles

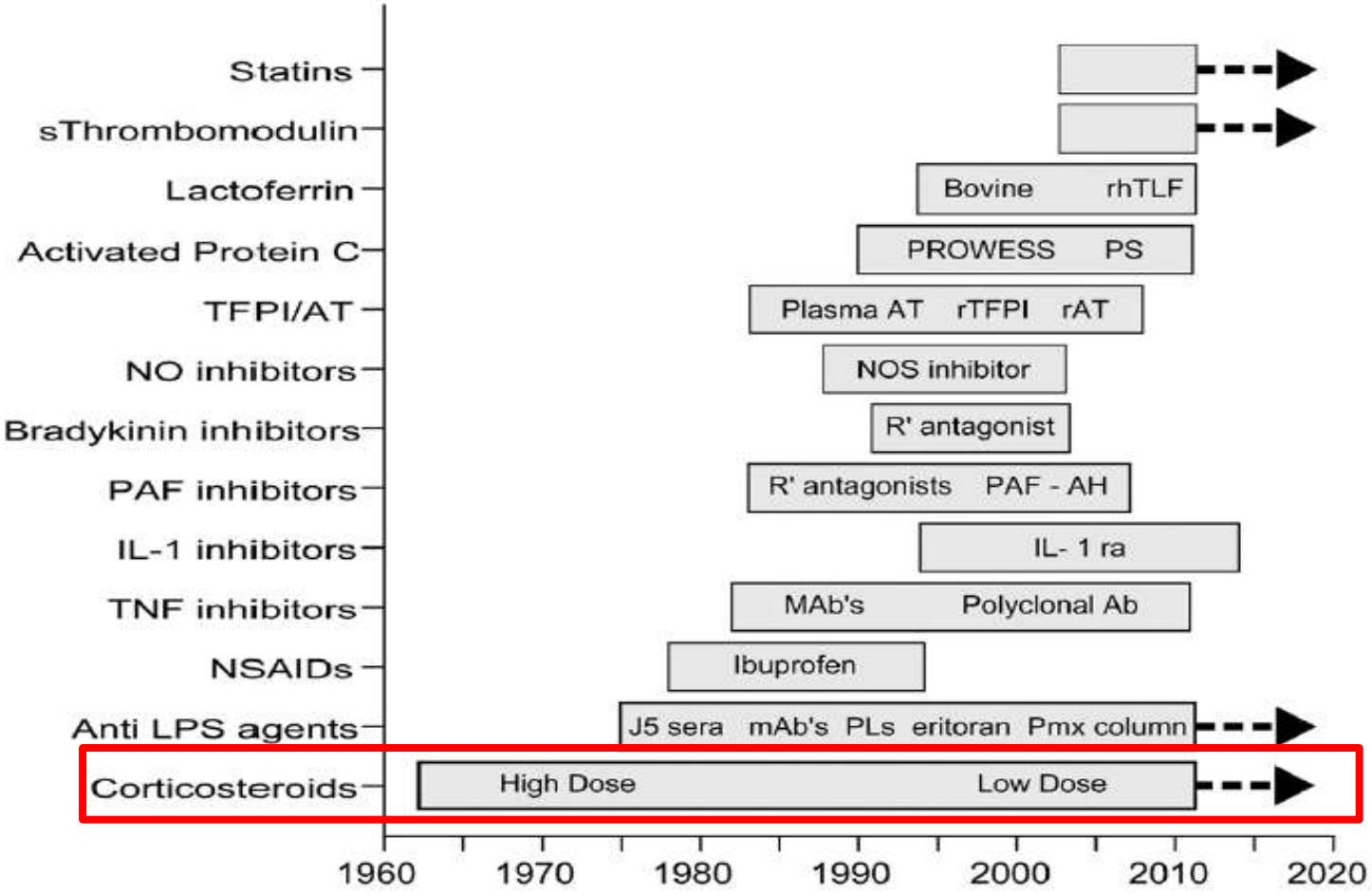
JNI Nantes 2018

AUCUN CONFLIT D’INTERET

POURQUOI DONNER DES CORTICOIDES?

The Next Generation of Sepsis Clinical Trial Designs: What Is Next After the Demise of Recombinant Human Activated Protein C?*

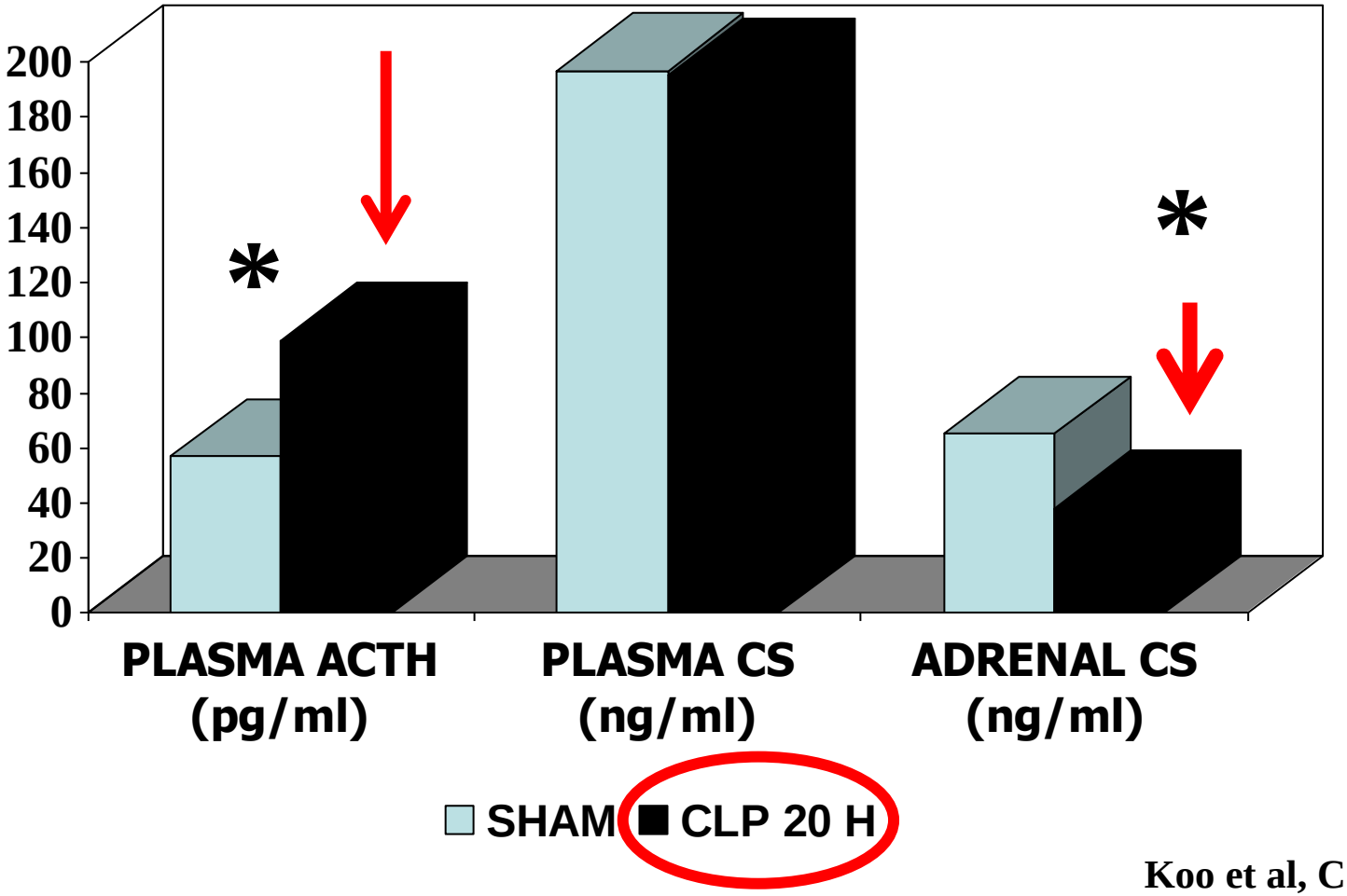
Sepsis and clinical trials with « adjuvants » …….



OPAL S; CCM 2014

Adrenal insufficiency during the late stage of polymicrobial sepsis

- Peritoneal sepsis induced adrenal insufficiency in rats



Koo et al, CCM 2001

The Role of ACTH and Corticosteroids for Sepsis and Septic Shock: An Update

2016

frontiers in Endocrinology

Djillali Annane[1,2]*

SEPSIS ► Réponse inadéquate de l'axe hypothlamique-pituitaire-surrénalien

►Critical illness related corticosteroids insufficiency = **CIRCI**

- RARE = Nécrose ou hémorragie hypothalamus/glande pituitaire ou surrénales

- Diminution de synthèse et de libération CRH – ACTH

- **Diminution de la stéroidogénèse surrénalienne**

  ■ Diminution de la sensibilité des récepteurs surrénaliens à l'ACTH
  ■ Diminution de la délivrance du cortisol aux tissus / Résistance tissulaire aux cortisol / diminution du binding et de l'affinité des récepteurs au cortisol
  ■ Diminution de la « down-regulation » des facteurs de transcription pro-inflammatoire médié par l'interaction GC-GR

Critical Illness-Related Corticosteroid Insufficiency (CIRCI): A Narrative Review from a Multispecialty Task Force of the Society of Critical Care Medicine (SCCM) and the European Society of Intensive Care Medicine (ESICM)

Djillali Annane, MD, PhD[1]; Stephen M. Pastores, MD, FCCM[2], Wiebke Arlt, MD, DSc, FRCP[3]; Robert A. Balk, MD, MCCM[4]; Albertus Beishuizen, MD, PhD[5]; Josef Briegel, MD, PhD[6]; Joseph Carcillo, MD, FCCM[7]; Mirjam Christ-Crain, MD, PhD[8]; Mark S. Cooper, MD[9]; Paul E. Marik, MD, FCCM[10]; Gianfranco Umberto Meduri, MD[11]; Keith M. Olsen, PharmD, FCCM[12]; Bram Rochwerg, MD[13]; Sophia C. Rodgers, RN, MSN, ACNP, FCCM[14]; James A. Russell, MD[15]; Greet Van den Berghe, MD, PhD[16]

ICM and CCM 2017

QUELLES ACTIONS ?

The Role of ACTH and Corticosteroids for Sepsis and Septic Shock: An Update

2016

frontiers in Endocrinology

Djillali Annane[1,2]*

Amélioration de la fonction cardio-vasculaire

-Restoration d'un **volume sanguin** effectif par rétention hydro-sodée
-Restoration de la **résistance vasculaire systémique et de la réponse aux catécholamines** avec vasoconstriction et élévation de la PA
- Amélioration de la microcirculation et de la perfusion tissulaire

Diminution des défaillances d'organes

- **Diminution de l'inflammmation** tissulaire par diminution drastique de l'activité NF k B à différents niveaux
-Inhibition de l'iNOS avec prévention de l'hypoxie tissulaire et meilleure délivrance d'O2
- Amélioration de la fonction glomérulaire, de la Cl de l'eau libre

Les corticoides ne sont pas équivalents ...

COMPOUND	RELATIVE ANTI-INFLAM-MATORY POTENCY	RELATIVE SODIUM-RETAINING POTENCY
HYDROCORTISONE	1	1
PREDNISONE	4	0.8
9α-FLUOROCORTISONE	10	125
METHYLPREDNISOLONE	5	0.5
BETAMETHASONE	25	0
DEXAMETHASONE	25	0

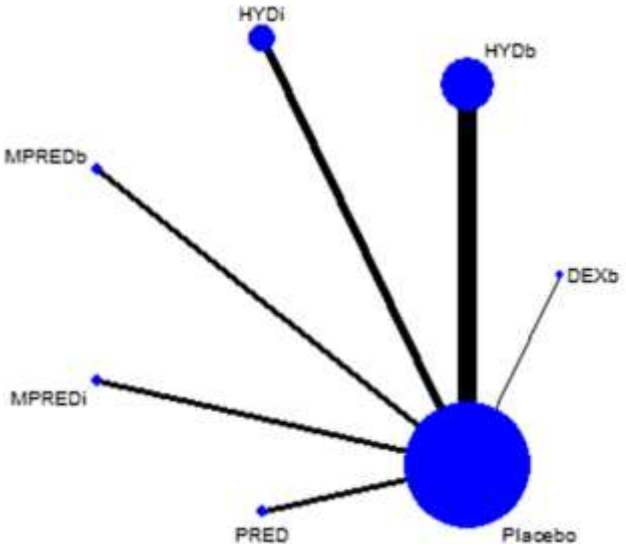
Gibbison *et al. Critical Care* (2017) 21:78
DOI 10.1186/s13054-017-1659-4

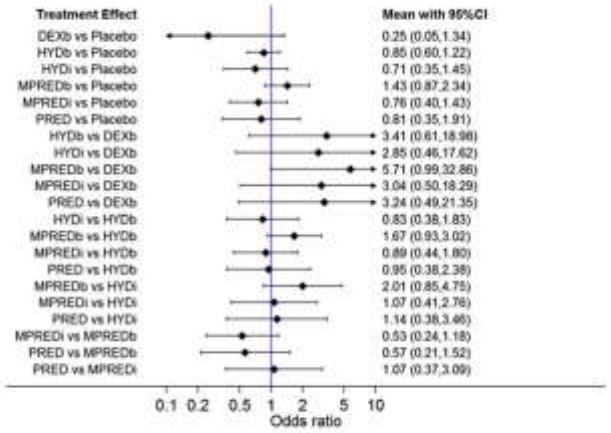
Critical Care

RESEARCH Open Access

Corticosteroids in septic shock: a systematic review and network meta-analysis

Ben Gibbison[1*], José A. López-López[2], Julian P. T. Higgins[3], Tom Miller[1], Gianni D. Angelini[4], Stafford L. Lightman[5] and Djillali Annane[6,7]





Hydrocortisone en <u>bolus ou continue ></u> placebo et Methyprednisolone en termes d'effets **sur la durée du choc**

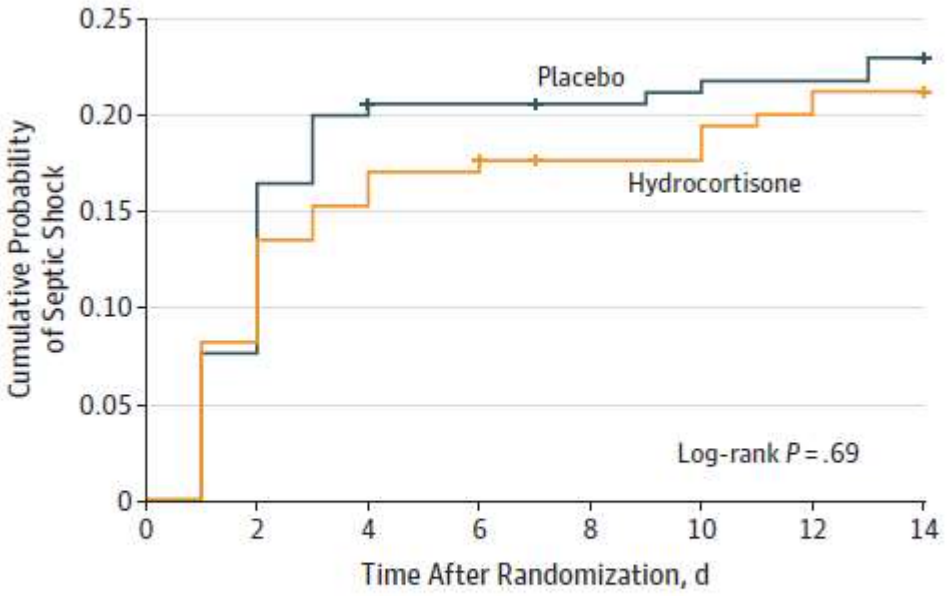
QUELS PATIENTS?
Des concepts à la maladie ....

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

Figure 2. Time to Septic Shock



No. at risk

Placebo	176	161	139	136	134	131	130	128
Hydrocortisone	177	163	146	142	138	138	134	130

- N = 380, 2009-2013
- HC 200 mg continuous infusion x 5 days then taper until day 11

RESULTS:

- No difference in:
  - dev't of septic shock w/in 14 d,
  - time to septic shock, ICU & hospital, and 180-d mortality.
- Higher incidence of hyperglycemia
- No diff in infections, weaning failure, muscle weakness & hypernatremia

JAMA 2016;316:1775-85

Guidelines for the Diagnosis and Management of Critical Illness-Related Corticosteroid Insufficiency (CIRCI) in Critically Ill Patients (Part I): Society of Critical Care Medicine (SCCM) and European Society of Intensive Care Medicine (ESICM) 2017

Djillali Annane, MD, PhD[1]; Stephen M. Pastores, MD, FCCM[2]; Bram Rochwerg, MD[3]; Wiebke Arlt, MD, DSc, FRCP[4]; Robert A. Balk, MD, MCCM[5]; Albertus Beishuizen, MD, PhD[6]; Josef Briegel, MD, PhD[7]; Joseph Carcillo, MD, FCCM[8]; Mirjam Christ-Crain, MD, PhD[9]; Mark S. Cooper, MD[10]; Paul E. Marik, MD, FCCM[11]; Gianfranco Umberto Meduri, MD[12]; Keith M. Olsen, PharmD, FCCM[13]; Sophia C. Rodgers, RN, MSN, ACNP, FCCM[14]; James A. Russell, MD[15]; Greet Van den Berghe, MD, PhD[16]

Should corticosteroids be administered among hospitalized adult patients with sepsis without shock?

Recommendation: We suggest **against corticosteroid administration in adult patients with sepsis without shock** (conditional recommendation, moderate level).

Crit Care Med December 2017;45:2078-88

Intensive Care Med December 2017;43:1751-63

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

- 19 ICU; 300 Pts; choc septique avec TAsyst < 90 avec > 5 gammaKg/mn de catécholamine
- 151 Pts CS versus 149 placebo;
- **229 NON répondeurs au test au Synacthène (réponse < 9microg/dl): 115 Placebo vs 114 CS**

► *Mortalité à J28 des NON répondeurs*: **63%** placebo versus **53%** CS (95% CI 0,4-0,95; p: 0,02)

(1) Hydrocortisone (50-mg intravenous bolus every 6 h for 7 d plus fludrocortisone, 50 µg orally every 24 h for 7 d); (2) respective placebos
Treatment had to be initiated ≤8 h after shock onset.

Annane JAMA 2002

Hydrocortisone Therapy for Patients with Septic Shock

- 52 ICU; 499 Pts, choc septique avec TAsyst < 90 avec > 5 gammaKg/mn de catécholamine
- 251 Pts CS versus 248 placebo
- **233 NON répondeurs: 108 placebo vs 125 CS**
- *Mortalité à J28 des NON répondeurs*: **36,1%** placebo vs **39,2%** CS (P: 0,65)

► Pas de différence de mortalité chez les répondeurs: 28,7% placebo vs 28,8% CS

- Plus d'épisodes de superinfections ...

1) Hydrocortisone (50 mg every 6 h for 5 d, then 50 mg every 12 h for 3 d, then 50 mg every 24 h for 3 d);
(2) placebo

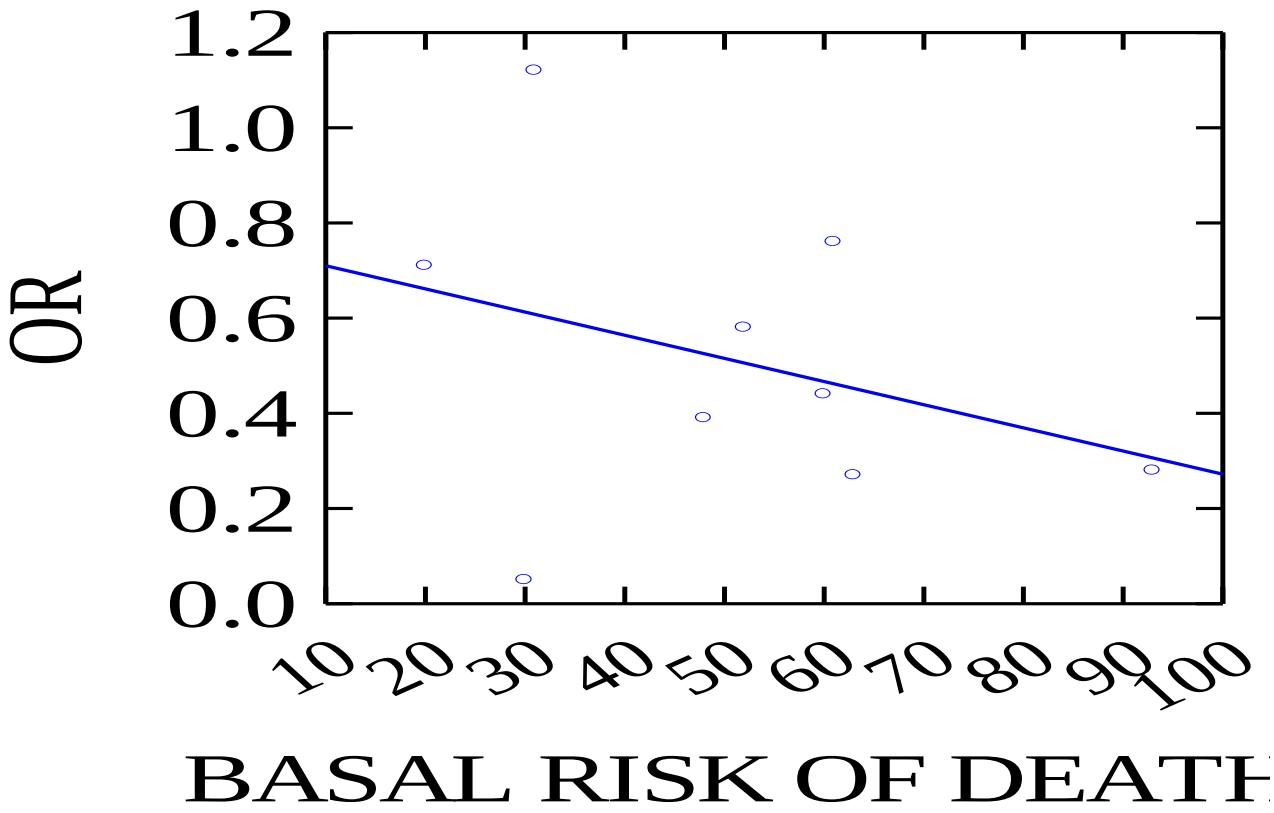
Sprung NEJM 2008

Quelles différences entre Etude française et CORTICUS ???

Baseline Risk of Death

	Annane	Corticus
Placebo	91/149 (61%)	77/248 (31%)

EFFECTS OF STEROIDS ON MORTALITY ACCORDING TO BASAL RISK OF DEATH



OTHER STUDY DIFFERENCES

	France	Corticus
Randomisation	8 hours	72 hours
SBP < 90 mmHg	> 1 hour	< 1 hour
Treatment	FC	None
SAPS II	59 ± 21	49 ± 17

Profil des patients

	France	Corticus
Medical	60%	35%
Emergency surgery	37%	54%
Elective surgery	3%	10%

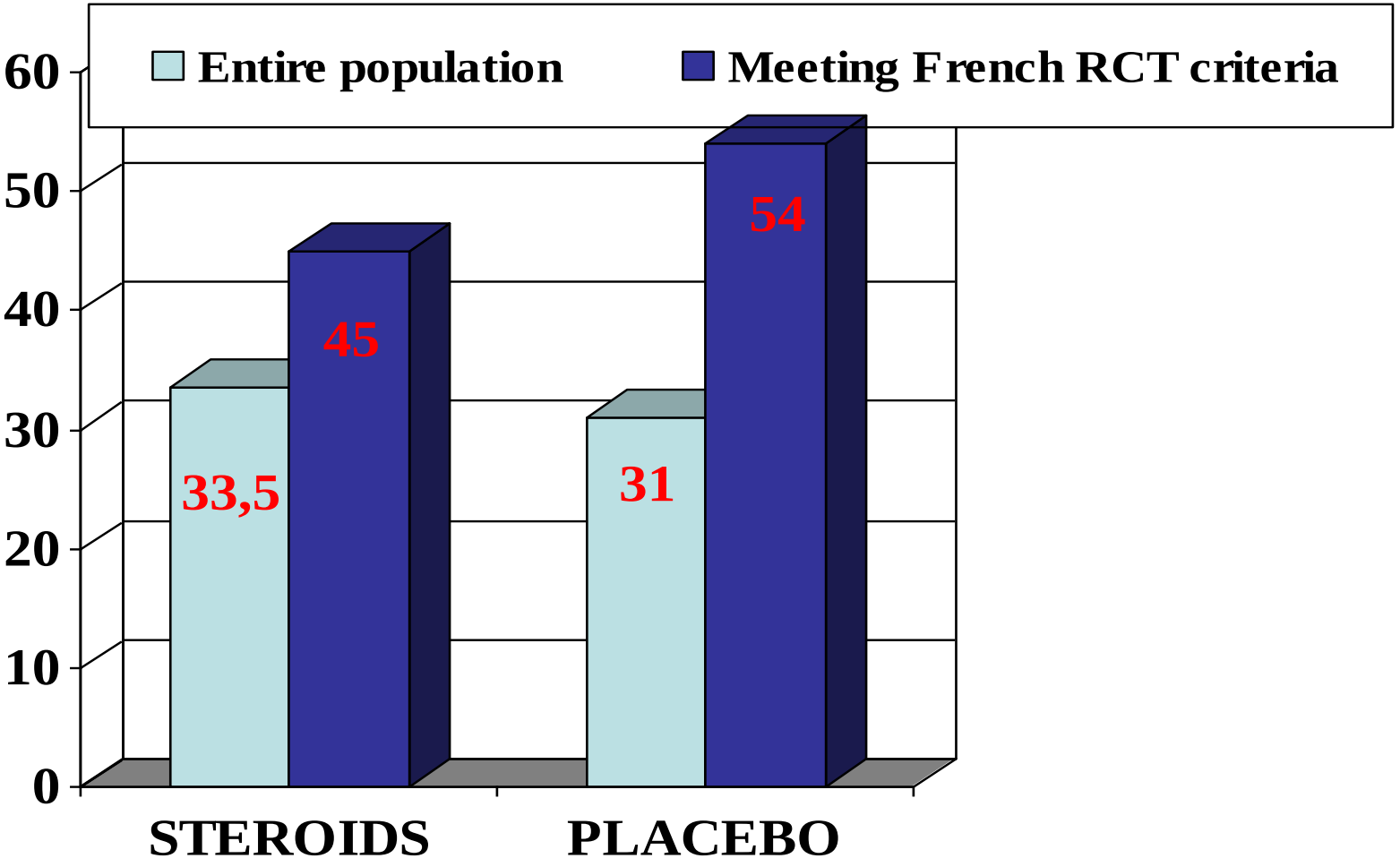
SITE OF INFECTION

	Annane	Corticus
Lung	59%	34%
Abdomen	19%	48%
Urinary tract	9%	7%
Wound/Soft tissue	12%	7%
Other	28%	19%

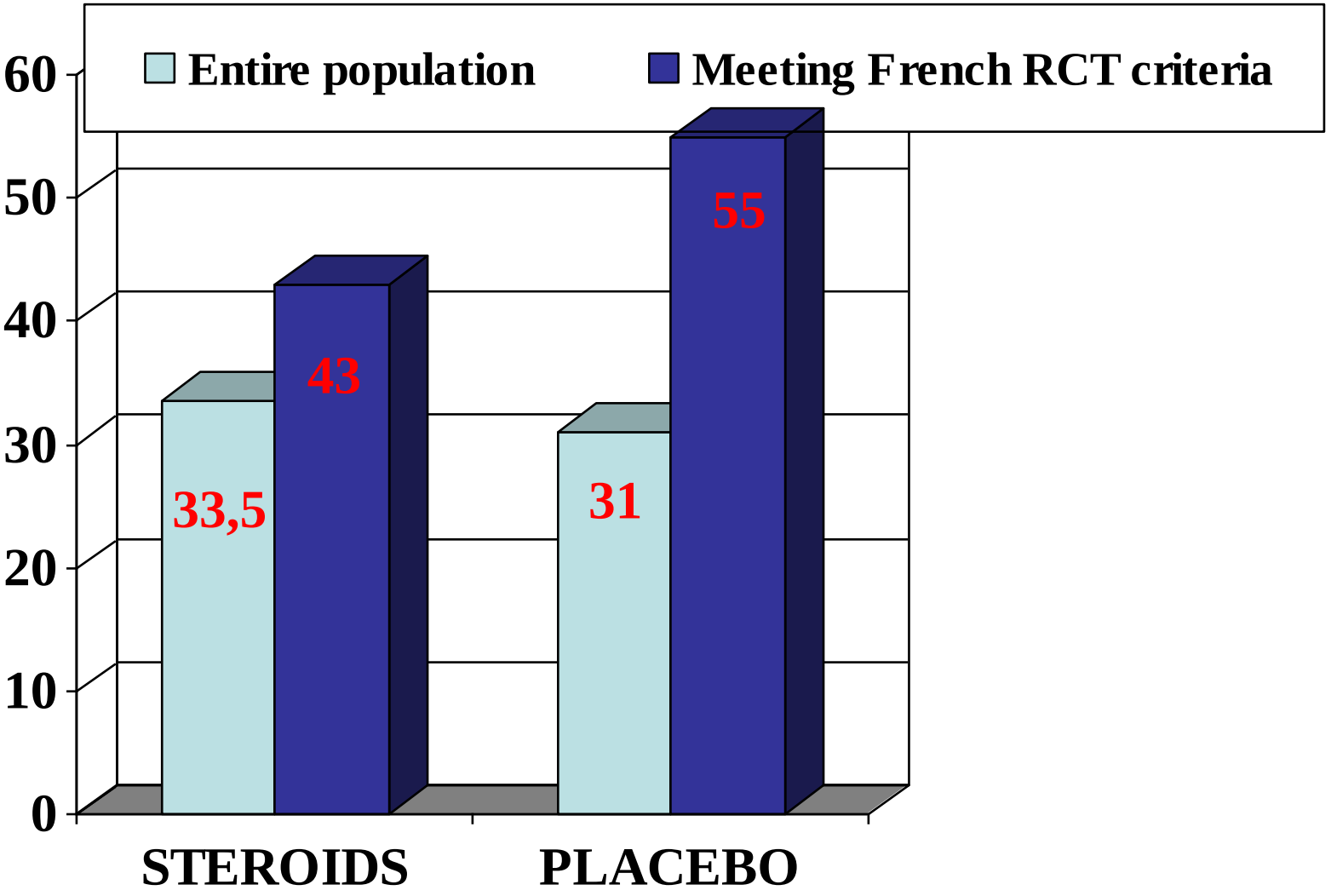
Non-responders to ACTH (delta cortisol ≤ 9 µg/dl)

	Annane	Corticus
Non-responders	77%	47%
Responders	23%	51%
Total	100%	96%

CORTICUS: 28-day mortality
all patients



CORTICUS: 28-day mortality
Non responders



CONTROVERSIES IN CORTICOSTEROID USE FOR SEPSIS

Brit Long, MD* and Alex Koyfman, MD†

J Emerg Med 2017

ICM 2017

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

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).

WHAT’S NEW ?

NEJM 2018

Adjunctive Glucocorticoid Therapy in Patients with Septic Shock

« ADRENALtrial » **Venkatesh**

Hydrocortisone plus Fludrocortisone for Adults with Septic Shock

« APROCCHS trial » Annane

Adjunctive Glucocorticoid Therapy in Patients with Septic Shock

NEJM 2018

« ADRENALtrial » Venkatesh

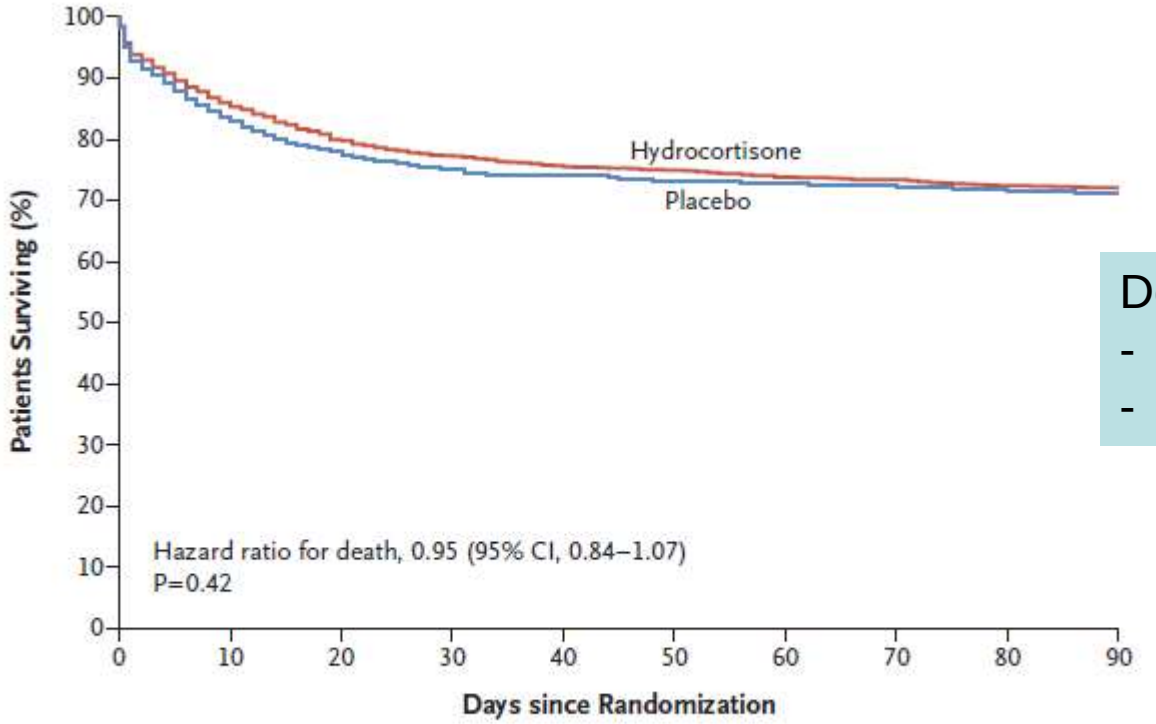
- **3638 Pts/ 69 ICU** med et chir/Australie (45 centres), Gr Bretagne (12); New Zealand (8), Arabie saoudite (3), Danemark (1)
- Patients VM+ sous vasopresseurs ou inotropes > 4h
- HSHC: 1832 Pts: 200 mg IVSE /j maximum 7 jours
- Placebo: 1826 Pts
- Sexe masculin: 60% / Age : 63 ans
- APACHE II: 23 (APACHE II > 25: 45%)
- Admission médical: 69% (Pulm: 35% et Abdo: 25%)
- Hémoc + : 17%
- Catécholamines > 1 mg/h: 54%
- Time from shock to randomization: 21h

Time from shock onset to randomization		
<6 hr	357/1842 (19.4)	349/1851 (18.9)
6 to <12 hr	516/1842 (28.0)	495/1851 (26.7)
12 to <18 hr	441/1842 (23.9)	427/1851 (23.1)
18 to 24 hr	528/1842 (28.7)	580/1851 (31.3)

Adjunctive Glucocorticoid Therapy in Patients with Septic Shock

NEJM 2018

« ADRENALtrial » Venkatesh



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

Décès J 90:

- HSHC: 27,9%
- Placebo: 28,8%

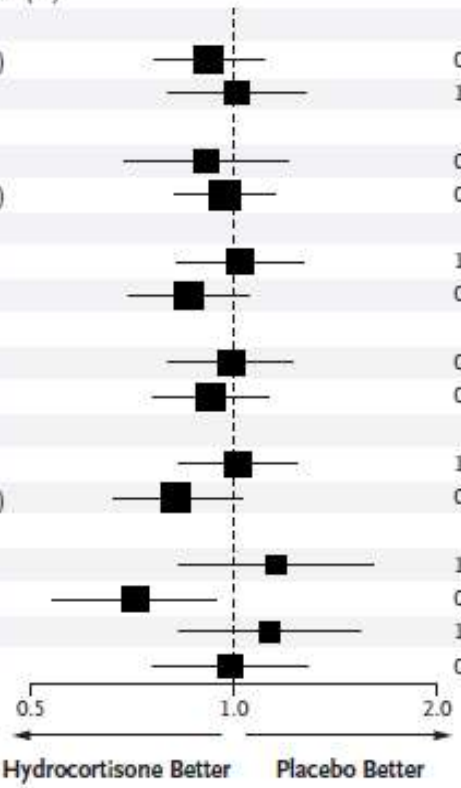
Adjunctive Glucocorticoid Therapy in Patients with Septic Shock

NEJM 2018

« ADRENALtrial » Venkatesh

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)	



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*

- Hydrocortisone group:
  - **Faster resolution of shock (median, 3d vs 4 days)**
  - **Shorter duration of initial mechanical ventilation (median, 6 d vs 7 days)**
  - **Fewer blood transfusions**

    37.0% vs. 41.7%; OR, 0.82; 95% CI, 0.72 to 0.94; P = 0.004

33 ADVERSE EVENTS:

- Hyperglycemia (6 HC vs 3 P)
- Hypernatremia (3 HC vs 0 P)
- Myopathy (3 HC vs 0 P)

NEJM January 2018

Hydrocortisone plus Fludrocortisone for Adults with Septic Shock

APROCCHS Trial Annane

- **1241 Pts dans 34 ICU**; admission « médicale »: 82%
- Patients VM + : 92% sous vasopresseurs > 1mg/h au moins 6h pour TA $\geq$ 90 ou PAM $\geq$ 65
- Randomisation dans les 24h du début du choc
- HSHC: 50 mg /6h bolus + fludrocortisone 50 Micro g/j PO pendant 7 jours
- Sexe masculin: 67%; Age: 66 ans
- SAPS II: 56
- SOFA score: 12
- Infections communautaires: 77%; Pulm: 59%; Urines: 18%; Abdo/ 11%
- Hémoc+ : 37%
- Adéquate Abpie initiale: 96%

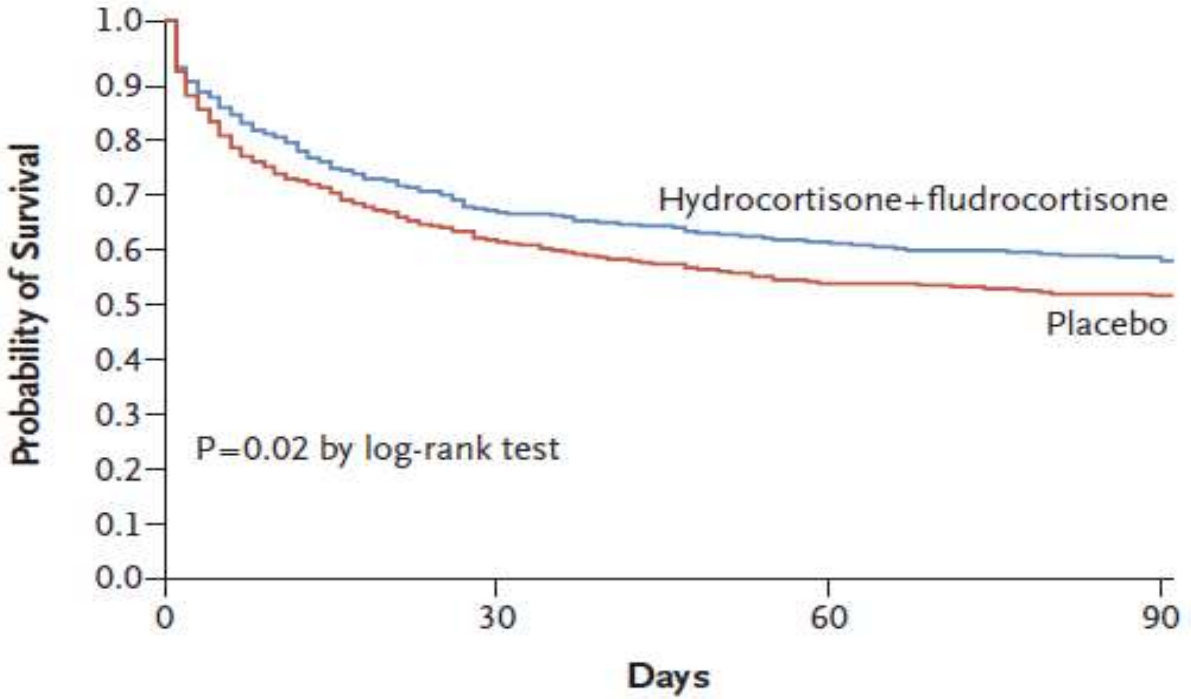
Population

	All patients N=1241
SOFA on ICU admission	10 ± 4
SOFA 12h-6h prior randomisation	11 ± 3
SOFA 6h-0h prior randomisation	12 ± 3
SAPSS II	56 ± 19
Lactates (mmol/l)	4.4 ± 4.9

Annane et al NEJM 2018

Hydrocortisone plus Fludrocortisone for Adults with Septic Shock

APROCCHS Trial Annane



No. at Risk

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

Décès à J90:

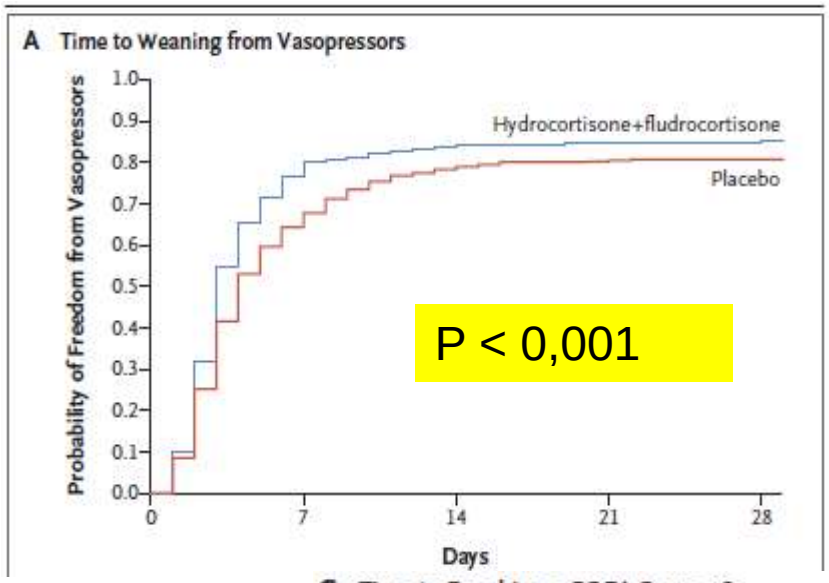
- CS: 43% vs 49,1% placebo p: 0,03
- RR de DC: 0,88 (95% CI, 0,78-0,99) = 12%

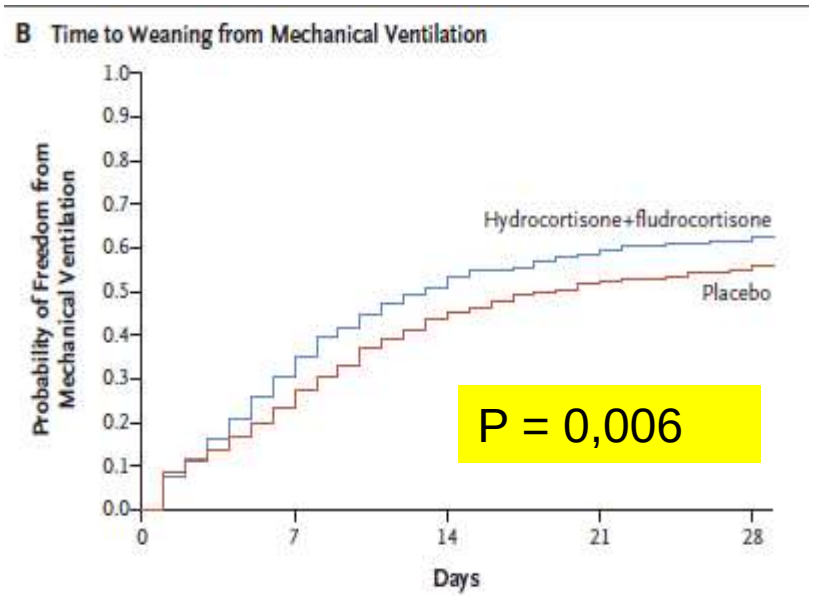
Hydrocortisone plus Fludrocortisone for Adults with Septic Shock

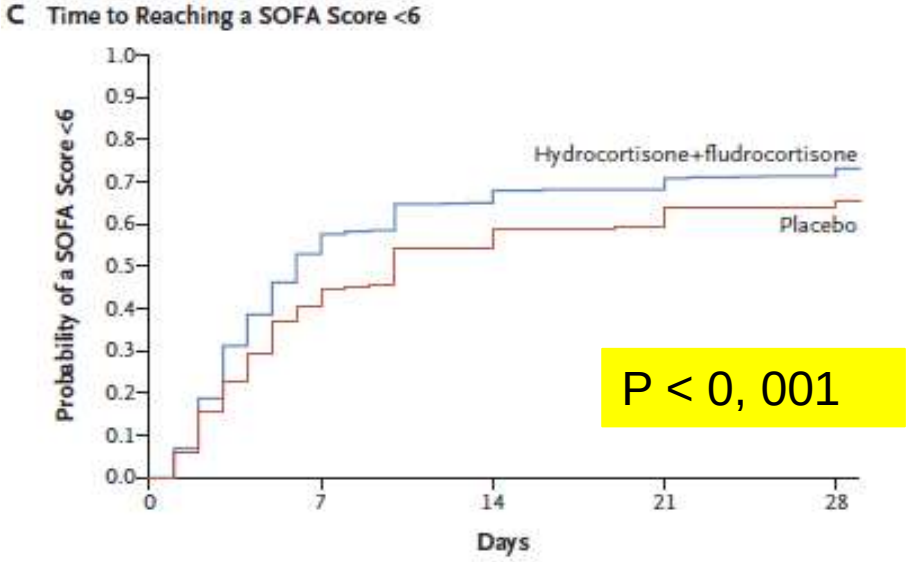
APROCCHS Trial Annane

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
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)		

Hydrocortisone plus Fludrocortisone for Adults with Septic Shock







APROCCHS Trial Annane

Différences entre ADRENAL et APROCCHSS

- HC given as 50 mg IV bolus q 6h + PO fludro 50 mcg tablet once daily x 7 days in APROCCHSS vs HC continuous infusion 200 mg/day x 7 days or until death or ICU discharge in ADRENAL

- **ADRENAL**: higher rate of surgical admissions, lower rate of RRT, lower rates of lung infection and UTI and higher rate of abdominal infections, less Hc +

A Role for Hydrocortisone Therapy in Septic Shock?

Edito NEJM 2018, Suffredini

- Les 2 études ont inclus des patients graves avec des scores de gravité élevés… mais non comparables: SOFA et SAPS II versus APACHE II

- **Patients plus instables APROCHSS**: Noradrenaline > 1mg/h plus de 6h

- **Mortalité des Gr contrôles très différentes** et plus importantes dans l'etude APROCCHS: 49,1% versus 28,8% = Pts PLUS SEVERES

- ***Fludrocortisone dans l'étude APROCCHS***: activité minéralocorticoide augmentée: restoration de l'expression des alpha1-recepteurs par l'aldostérone → amélioration de la réponse contractile à la noradrénaline et survie augmentée des souris en choc endotoxinique(CCM 2017, Fadel F)

- Absorption de la fludrocortisone oral correcte chez 2/3 des patients en choc septique (Br J Clin Pharmacol 2016, Polito A)

►Bénéfice chez les patients les plus sévères au moment du Ttr

A Role for Hydrocortisone Therapy in Septic Shock?

Edito NEJM 2018, Suffredini

Quels patients ?

It is likely that some practitioners caring for a patient with a deteriorating condition who is receiving escalating doses of vasopressors, in whom other core interventions have been instituted (i.e., appropriate antibiotics and adequate volume resuscitation and source control), will consider that the short-term benefits of low-dose hydrocortisone may exceed any risks (e.g., anti-inflammatory effects) as an added therapy in selected patients.

EN PRATIQUE

- Hydrocortisone SANS dose de charge: 50 mg IV bolus/ 6h pendant 7 jours

- Avec Fludrocortisone 50 µg per os 1 fois/j pendant 7 jours (2 études randomisées +)

- PAS de décroissance


Bon vent breton !!

Drugs Related Adrenal Insufficiency

Mechanisms	**Drugs**
Primary adrenal insufficiency	
Haemorrhage	Anticoagulant therapy (heparin, warfarin)
Cortisol synthesis enzyme inhibition	Aminogluthethimide Ketoconazole, Fluconazole Etomidate, Dexmedetomidine
Cortisol metabolism activation	Phenobarbital, Phenytoin Rifampin
Secondary adrenal insufficiency	
Suppression of CRH and ACTH synthesis	Glucocorticoid therapy (systemic or topical) Megestrol acetate, Medroxyprogesterone Ketorolac tromethamine Antidepressant drugs (e.g. imipramine) Opiate drugs
Peripheral resistance to GC	
Interaction with GC receptor	Mifepristone
inhibition of the GC-induced gene transcription	Antipsychotic drugs (e.g. chlorpromazine) Antidepressant drugs (e.g. imipramine)

Mineralocorticoids in sepsis

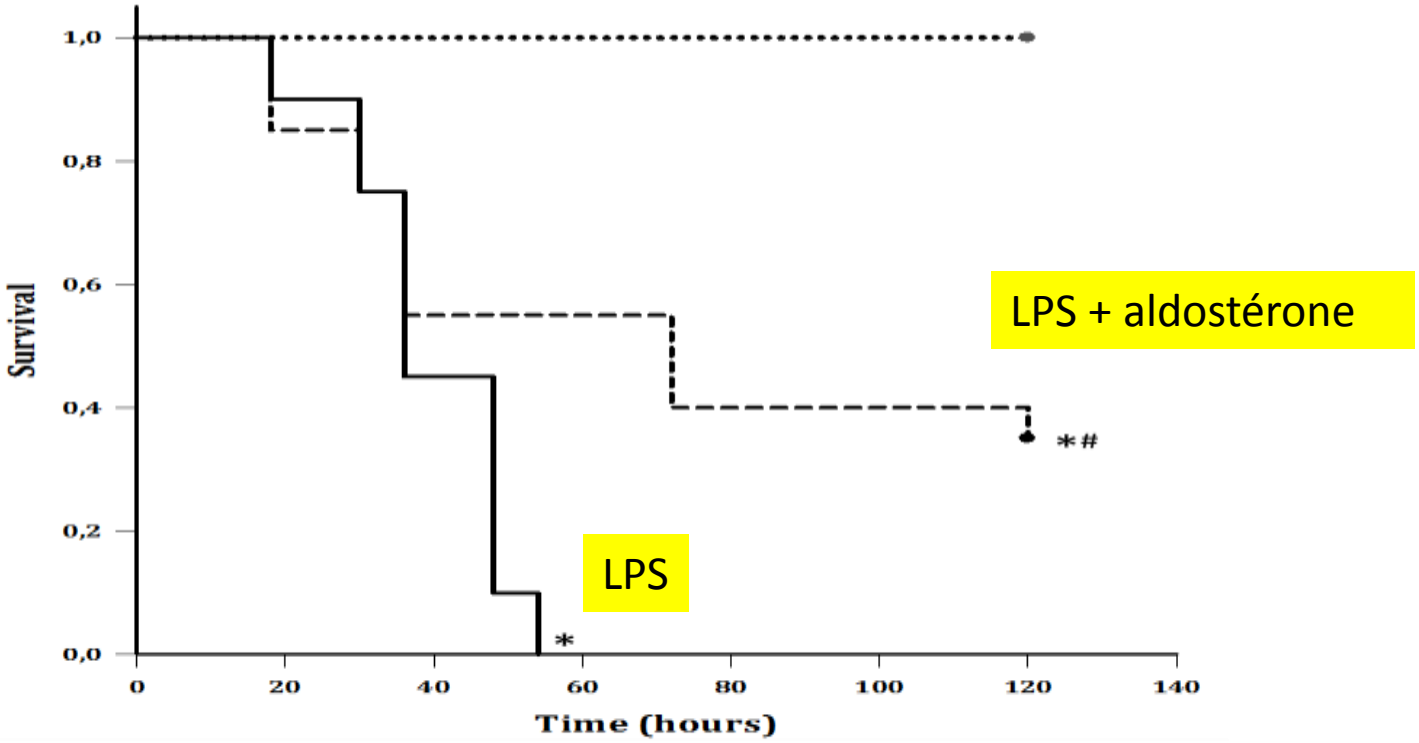


Figure 1 –Effects of Aldosterone on survival in Endotoxinic Shock – Mice were injected intra-peritoneally with vehicle, LPS or LPS and aldosterone (1 mg/kg)
** p<0,05 vs Control, # p<0,05 vs LPS (n=20 in all groups)*

Mineralocorticoids in sepsis

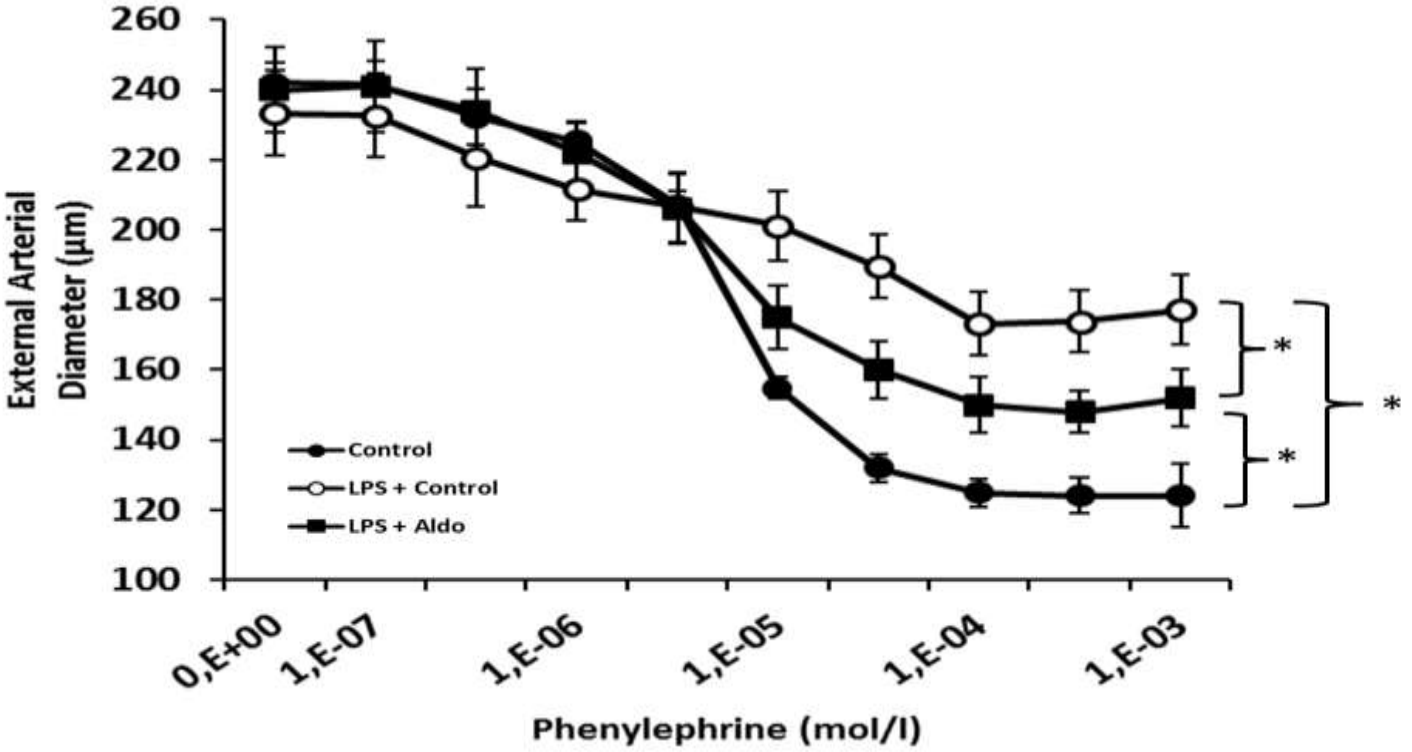


Figure 3 –Influence of treatment with Aldosterone on contraction response to phenylephrine in mesenteric arteries ex vivo – First order mesenteric arteries from control or endotoxinic mice, treated or not with aldosterone were studied in a pressure myograph chamber *(n=7 in all groups)* ** p<0,05*