Corticoïdes et Sepsis

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Conflict Of Interest

- ALL RESEARCH PROGRAMS, INCLUDING APROCCHSS TRIAL, WERE PUBLICLY FUNDED (FRENCH MINISTRY OF HEALTH, EC)
- ACADEMIC COI: CHAIR OF ESICM/SCCM TF FOR 2018 GUIDELINES ON CIRCI, MEMBER OF SSC GUIDELINES PANEL FOR 2008, 2012 & 2016 REVISIONS
- ALL DATA FROM APROCCHSS PRESENTED IN THIS SLIDE-SHOW ARE AVAILABLE @NEJM.ORG

Why I Should Use Corticosteroids?

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)

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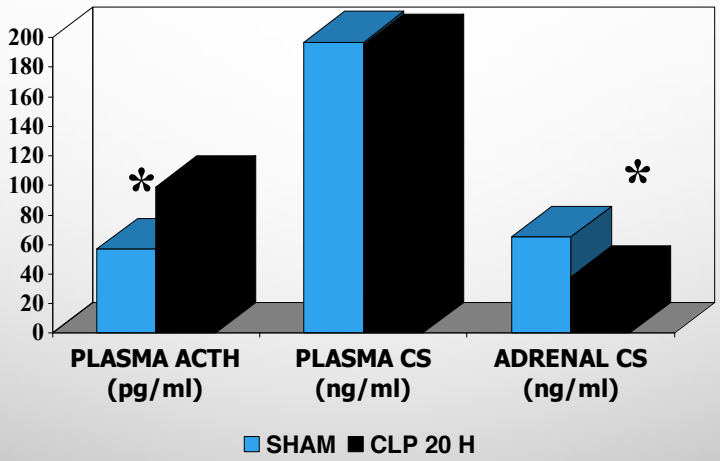
ICM and CCM 2017

DEFINITION OF CIRCI

DEFINED AS DYSREGULATED HOST RESPONSE TO ACUTE INFLAMMATION:

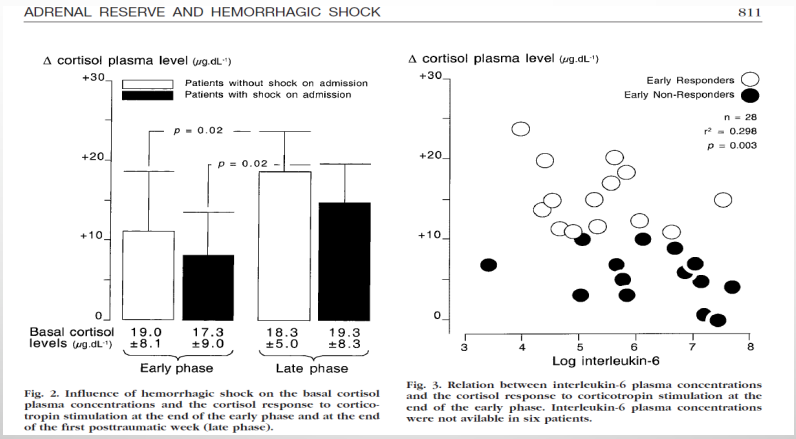
- INADEQUATE CELLULAR CORTICOSTEROID ACTIVITY
- FOR THE SEVERITY OF CRITICAL ILLNESS,
- MANIFESTED BY INSUFFICIENT GC–GR -MEDIATED DOWN-REGULATION OF PRO-INFLAMMATORY TRANSCRIPTION FACTORS.

SEPSIS INDUCED ADRENAL INSUFFICIENCY IN ANIMALS



Koo et al, CCM 2001

Surgical Trauma-Induced Adrenal Insufficiency is Associated with Postoperative Inflammatory Responses


ADRENAL RESERVE AND HEMORRHAGIC SHOCK 811

Δ cortisol plasma level (μg.dL⁻¹)

Patients without shock on admission
Patients with shock on admission

p = 0.02
p = 0.02

+30
+20
+10
0

Basal cortisol levels (μg.dL⁻¹) 19.0 ±8.1 17.3 ±9.0 18.3 ±5.0 19.3 ±8.3

Early phase Late phase

Fig. 2. Influence of hemorrhagic shock on the basal cortisol plasma concentrations and the cortisol response to corticotropin stimulation at the end of the early phase and at the end of the first posttraumatic week (late phase).

Δ cortisol plasma level (μg.dL⁻¹)

Early Responders
Early Non-Responders

n = 28
r² = 0.298
p = 0.003

+30
+20
+10
0

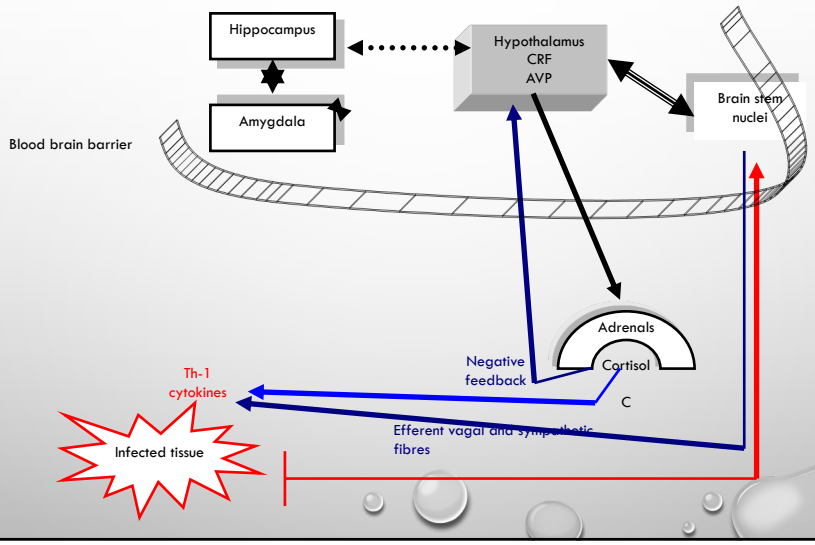
3 4 5 6 7 8

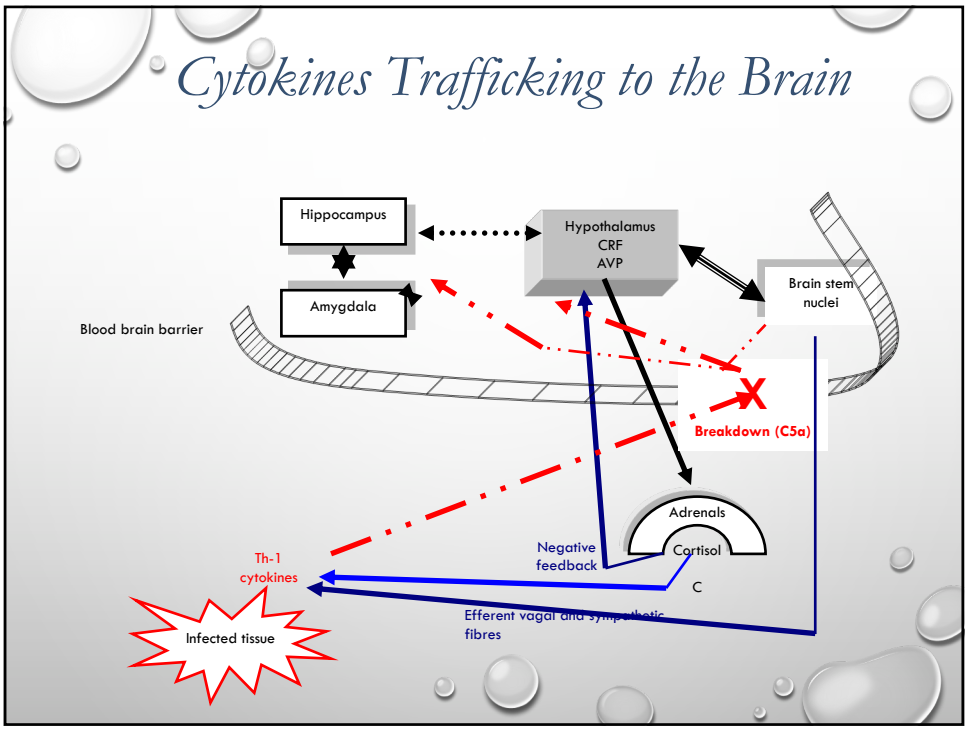
Log interleukin-6

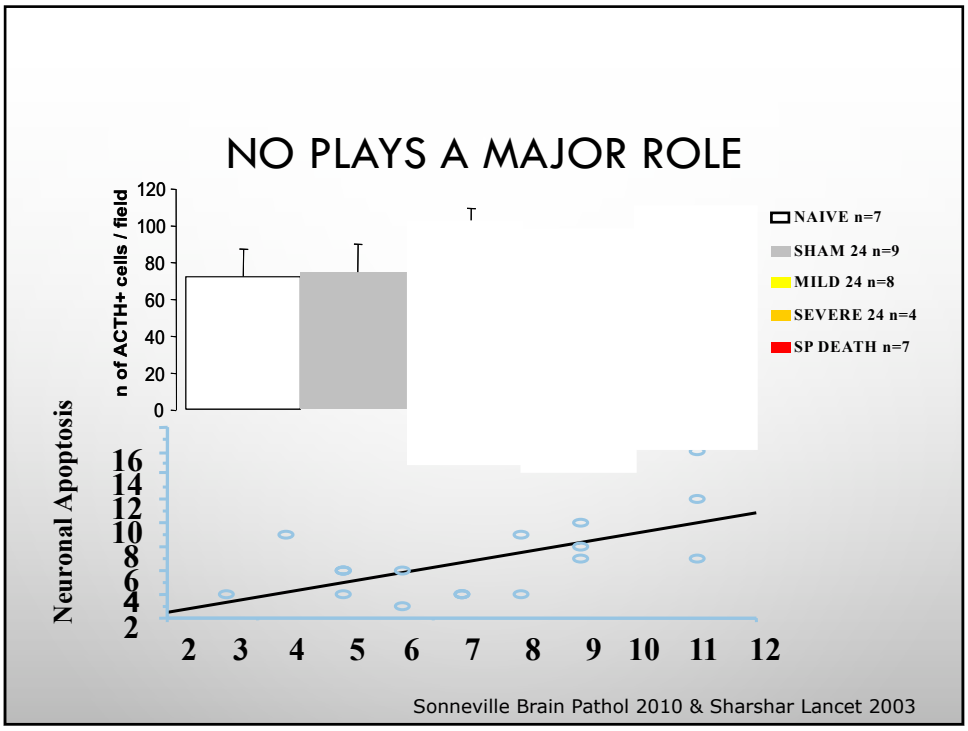
Fig. 3. Relation between interleukin-6 plasma concentrations and the cortisol response to corticotropin stimulation at the end of the early phase. Interleukin-6 plasma concentrations were not avilable in six patients.

Hoen et al, Anesthesiology 2002

Cytokines Trafficking to the Brain

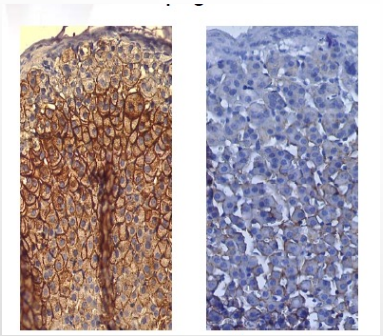



Cytokines Trafficking to the Brain
Hippocampus
Amygdala
Hypothalamus
CRF
AVP
Brain stem nuclei
Blood brain barrier
Breakdown (C5a)
Adrenals
Cortisol
Negative feedback
Th-1 cytokines
Infected tissue
Efferent vagal and sympathetic fibres


NO PLAYS A MAJOR ROLE
n of ACTH+ cells / field
120
100
80
60
40
20
0
NAIVE n=7
SHAM 24 n=9
MILD 24 n=8
SEVERE 24 n=4
SP DEATH n=7
Neuronal Apoptosis
16
14
12
10
8
6
4
2
2 3 4 5 6 7 8 9 10 11 12
Sonneville Brain Pathol 2010 & Sharshar Lancet 2003

PERIPHERAL MECHANISMS MICE STUDIES

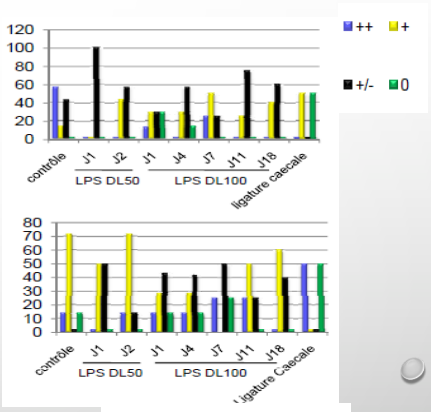
SR-B1



Control

LPS DL50
Day 1

Lipid Depletion

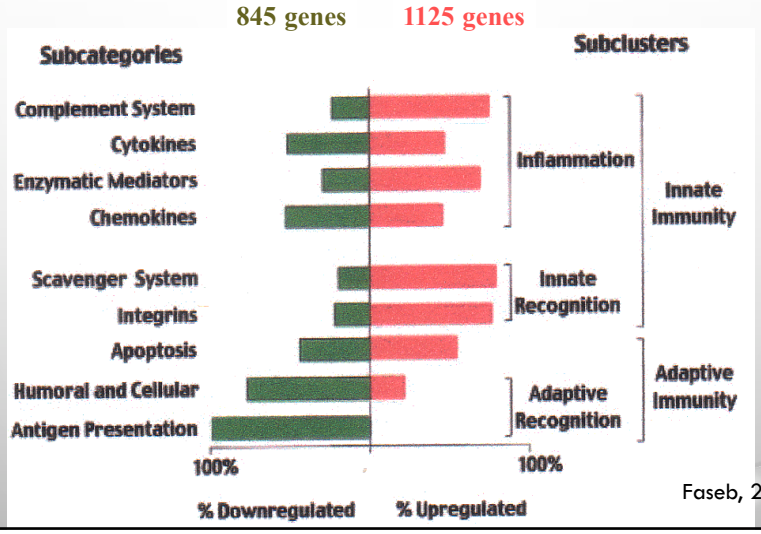


SR-B1 distribution

TABLE 1. Main Mechanisms of Critical Illness-Related Corticosteroid Insufficiency

General defect	Main mechanisms	Key factors
Decrease in cortisol production		
Altered adrenal synthesis of cortisol	Necrosis/hemorrhage	Acute kidney failure; hypo-coagulation; disseminated intravascular coagulation; cardiovascular collapse; tyrosine kinase inhibitors
	Decreased availability of esterified cholesterol	Depletion in adrenal storage regulated by annexin A1–formyl peptide receptors Down regulated scavenger receptor-B1
	Inhibition of steroidogenesis	Immune cells/Toll-like receptors/cytokines
		Drugs (e.g., sedatives, corticosteroids)
		ACTH-like molecules (e.g., corticostatins)
Altered synthesis of CRH/ACTH	Necrosis/hemorrhage	Cardiovascular collapse; disseminated intravascular coagulation; treatment with vasopressor agents
	Inhibition of ACTH synthesis	Glial cells/nitric oxide mediated neuronal apoptosis
		Increased negative feedback from circulating cortisol following up regulation of ACTH-independent mechanisms of cortisol synthesis
		Drugs (e.g., sedatives, anti-infective, psychoactive agents)
		Inappropriate cessation of glucocorticoid treatment
Alteration of cortisol metabolism	Decreased cortisol transport	Down regulation of liver synthesis of cortisol-binding globulins and albumin
	Reduced cortisol breakdown	Decreased expression and activity of the glucocorticoid-inactivating 5-reductase enzymes in the liver with putative role of bile acids; Decreased expression and activity of the hydroxysteroid dehydrogenase in the kidney
Target tissue resistance to cortisol	Inadequate glucocorticoid receptor alpha (GR-α) activity	Multifactorial etiology including reduced GR-α density and transcription and excessive NF-kappa B activation

GC INDUCED IMMUNE CELLS' REPROGRAMMATION RATHER THAN SUPPRESSION!



Faseb, 2002

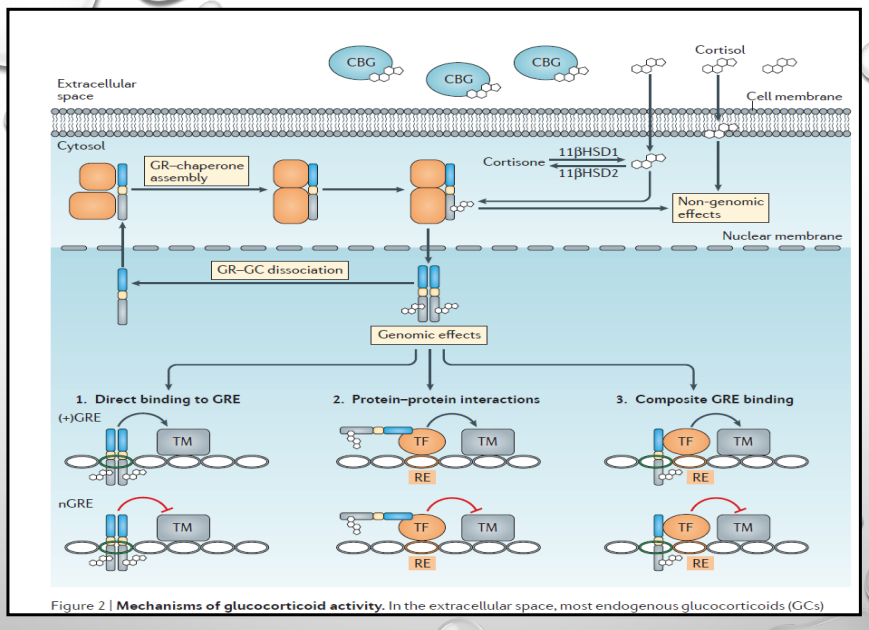


Figure 2 | **Mechanisms of glucocorticoid activity.** In the extracellular space, most endogenous glucocorticoids (GCs)

Nature Rev Immunol 2017

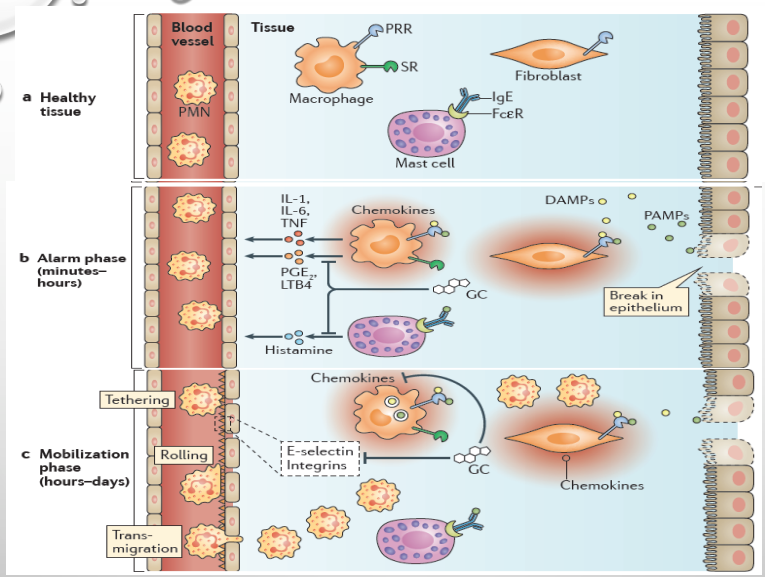
Box 2 | **Cellular targets of glucocorticoid action in animal models of disease**

Mouse studies have revealed the crucial cellular targets for glucocorticoid treatment of various inflammatory and autoimmune models of human disease. In the studies cited in the table below, glucocorticoid efficacy in the indicated disease model was reduced by genetic ablation of glucocorticoid receptor expression in target cells or by *in vivo* depletion of specific cell types.

Animal model	Human disease modelled	Crucial cellular target of glucocorticoids
Contact hypersensitivity	Allergic contact dermatitis	Myeloid cells[99]
Experimental autoimmune encephalomyelitis	Multiple sclerosis	T_H17 cells[56]
Antigen-induced arthritis	Rheumatoid arthritis	T_H17 cells[85]
LPS-induced endotoxaemia	Sepsis	Myeloid cells[50] and dendritic cells[51]
Experimentally induced thrombocytopenia	Immune thrombocytopenia	$CD8^+$ T cells[122]
Doxorubicin-induced renal injury	Focal segmental glomerulosclerosis	Myeloid-derived suppressor cells[123]

LPS, lipopolysaccharide; T_H17, T helper 17.

Nature Rev Immunol 2017



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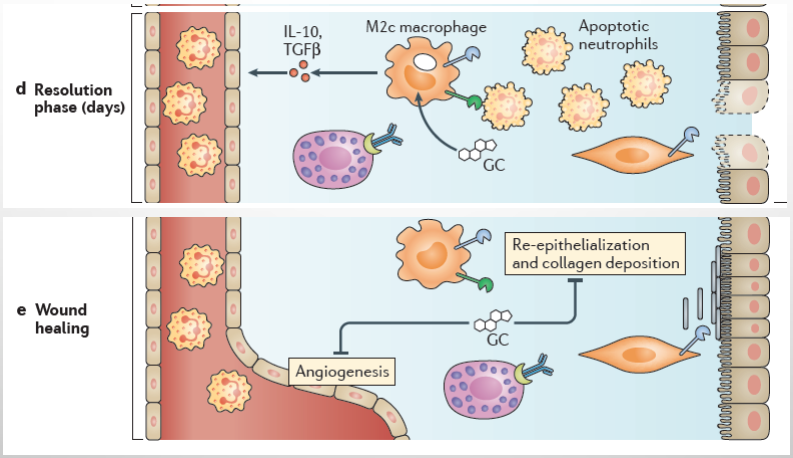

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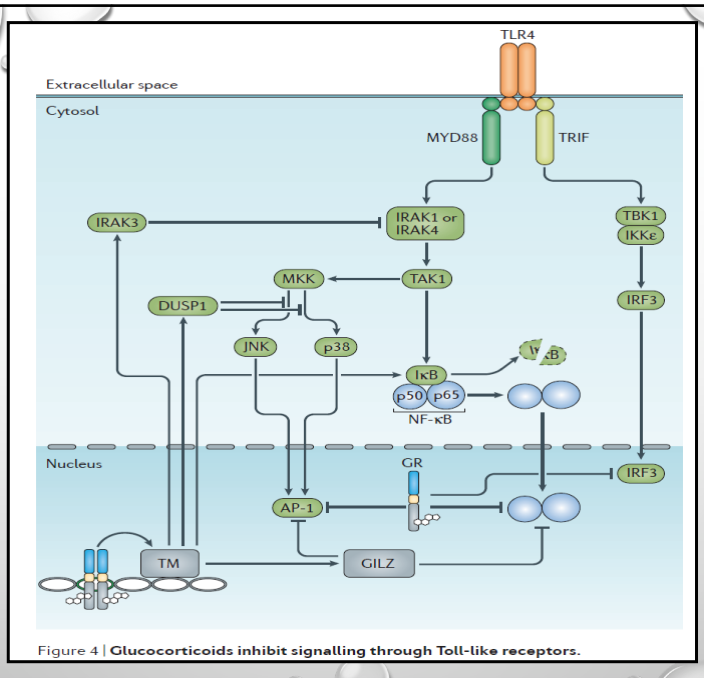
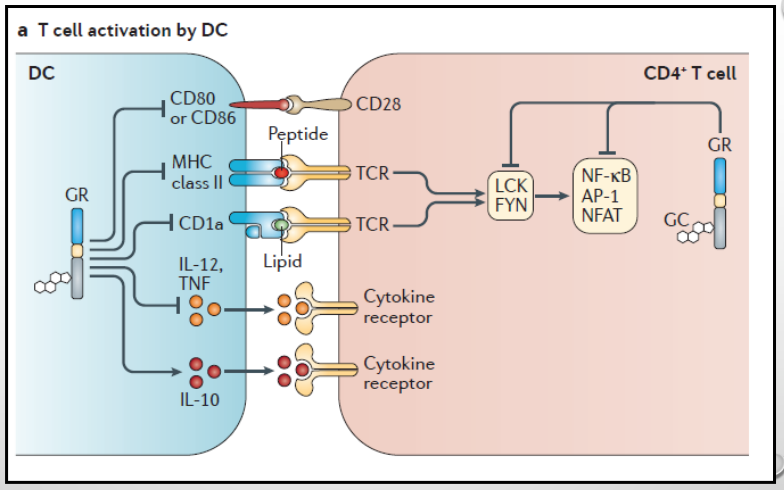


Figure 4 | **Glucocorticoids inhibit signalling through Toll-like receptors.**

Nature Rev Immunol 2017



Nature Rev Immunol 2017

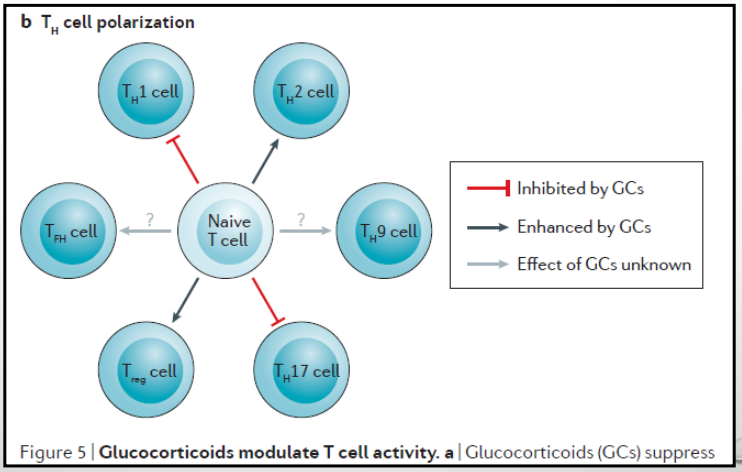


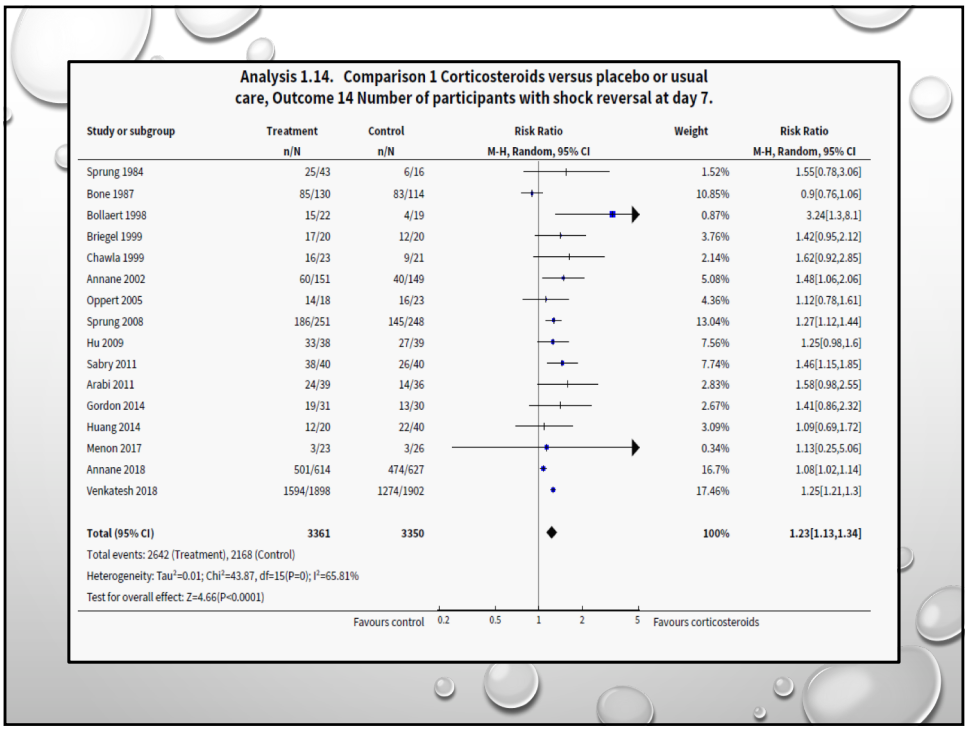
Figure 5 | **Glucocorticoids modulate T cell activity. a** | Glucocorticoids (GCs) suppress

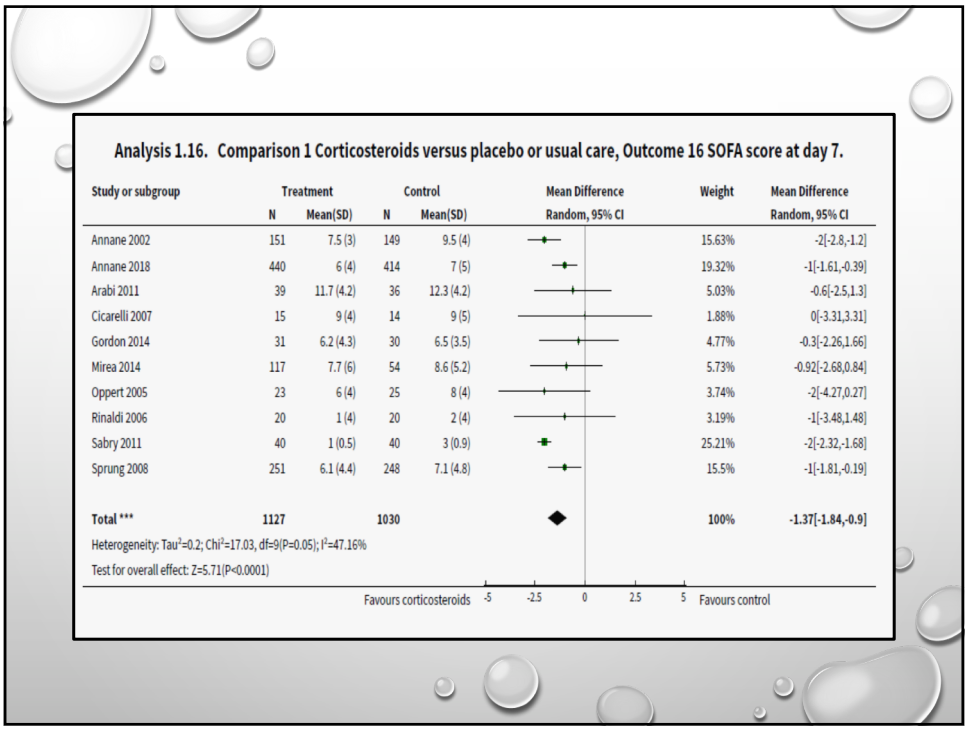
Nature Rev Immunol 2017

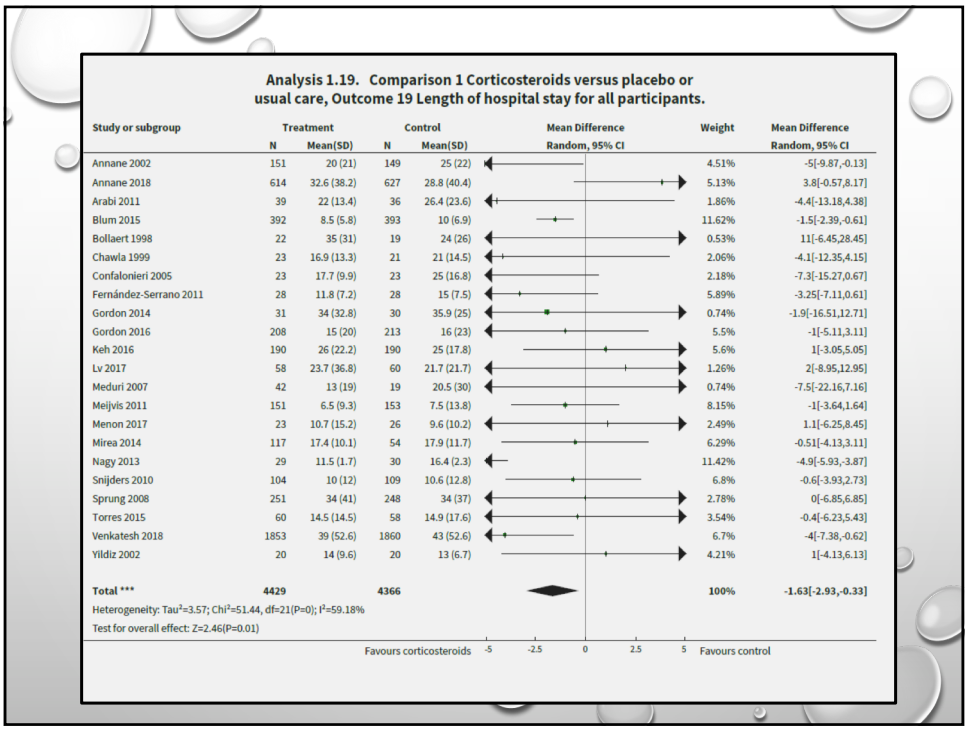
Highlights From The CDSR In December 2019, 'Corticosteroids For Treating Sepsis In Children And Adults'.

Cochrane Library App - January 2020

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 28-Day all-cause mortality	50	11233	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.84, 0.99]
10 90-Day all-cause mortality	7	5934	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.87, 1.00]
11 Long-term mortality	7	6236	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.91, 1.03]
12 Intensive care unit mortality	18	7267	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.83, 0.96]
13 Hospital mortality	26	8183	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.82, 0.99]


Analysis 1.14. Comparison 1 Corticosteroids versus placebo or usual care, Outcome 14 Number of participants with shock reversal at day 7.
Study or subgroup
Treatment n/N
Control n/N
Risk Ratio M-H, Random, 95% CI
Weight
Risk Ratio M-H, Random, 95% CI
Sprung 1984 25/43 6/16 1.52% 1.55[0.78,3.06]
Bone 1987 85/130 83/114 10.85% 0.9[0.76,1.06]
Bollaert 1998 15/22 4/19 0.87% 3.24[1.3,8.1]
Briegel 1999 17/20 12/20 3.76% 1.42[0.95,2.12]
Chawla 1999 16/23 9/21 2.14% 1.62[0.92,2.85]
Annane 2002 60/151 40/149 5.08% 1.48[1.06,2.06]
Oppert 2005 14/18 16/23 4.36% 1.12[0.78,1.61]
Sprung 2008 186/251 145/248 13.04% 1.27[1.12,1.44]
Hu 2009 33/38 27/39 7.56% 1.25[0.98,1.6]
Sabry 2011 38/40 26/40 7.74% 1.46[1.15,1.85]
Arabi 2011 24/39 14/36 2.83% 1.58[0.98,2.55]
Gordon 2014 19/31 13/30 2.67% 1.41[0.86,2.32]
Huang 2014 12/20 22/40 3.09% 1.09[0.69,1.72]
Menon 2017 3/23 3/26 0.34% 1.13[0.25,5.06]
Annane 2018 501/614 474/627 16.7% 1.08[1.02,1.14]
Venkatesh 2018 1594/1898 1274/1902 17.46% 1.25[1.21,1.3]
Total (95% CI) 3361 3350 100% 1.23[1.13,1.34]
Total events: 2642 (Treatment), 2168 (Control)
Heterogeneity: Tau²=0.01; Chi²=43.87, df=15(P=0); I²=65.81%
Test for overall effect: Z=4.66(P<0.0001)
Favours control
0.2
0.5
1
2
5
Favours corticosteroids


Analysis 1.16. Comparison 1 Corticosteroids versus placebo or usual care, Outcome 16 SOFA score at day 7.
Study or subgroup
Treatment N
Mean(SD)
Control N
Mean(SD)
Mean Difference Random, 95% CI
Weight
Mean Difference Random, 95% CI
Annane 2002 151 7.5 (3) 149 9.5 (4) 15.63% -2[-2.8,-1.2]
Annane 2018 440 6 (4) 414 7 (5) 19.32% -1[-1.61,-0.39]
Arabi 2011 39 11.7 (4.2) 36 12.3 (4.2) 5.03% -0.6[-2.5,1.3]
Cicarelli 2007 15 9 (4) 14 9 (5) 1.88% 0[-3.31,3.31]
Gordon 2014 31 6.2 (4.3) 30 6.5 (3.5) 4.77% -0.3[-2.26,1.66]
Mirea 2014 117 7.7 (6) 54 8.6 (5.2) 5.73% -0.92[-2.68,0.84]
Oppert 2005 23 6 (4) 25 8 (4) 3.74% -2[-4.27,0.27]
Rinaldi 2006 20 1 (4) 20 2 (4) 3.19% -1[-3.48,1.48]
Sabry 2011 40 1 (0.5) 40 3 (0.9) 25.21% -2[-2.32,-1.68]
Sprung 2008 251 6.1 (4.4) 248 7.1 (4.8) 15.5% -1[-1.81,-0.19]
Total *** 1127 1030 100% -1.37[-1.84,-0.9]
Heterogeneity: Tau²=0.2; Chi²=17.03, df=9(P=0.05); I²=47.16%
Test for overall effect: Z=5.71(P<0.0001)
Favours corticosteroids
-5
-2.5
0
2.5
5
Favours control



How I Give Steroids?

All Corticosteroids Are Not Equivalent

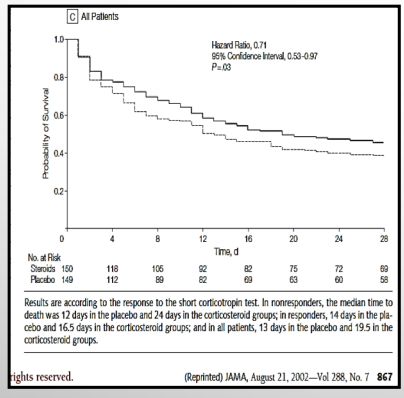
Molecules	Glucocorticoid activity relative to hydrocortisone	Mineralocorticoid activity relative to hydrocortisone	Non-genomic effects relative to hydrocortisone
Hydrocortisone	1	1	1
Prednisone	4	0.8	4
Prednisolone	4	0.8	4
Methylprednisolone	5	0.5	14
Betamethasone	25	0	0
Dexamethasone	25	0	20
Fludrocortisone	10	125	?

Annane, Scientific American – Crit Care of the Surg Patient 2017

Hydrocortisone + Fludrocortisone

TRIAL 1

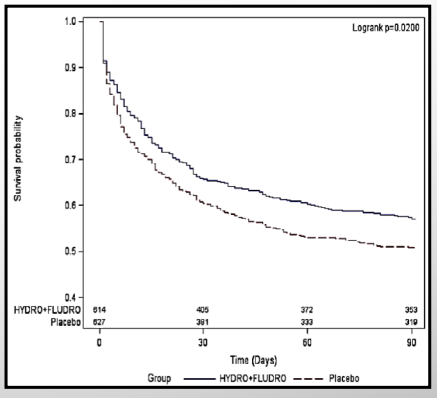
N=300



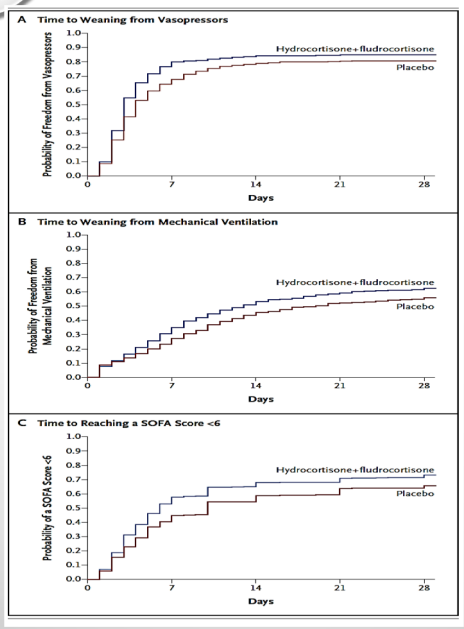
Annane Jama 2002

TRIAL 2

N=1241



Annane NEJM 2018



P<0.001

P<0.006

P<0.001

Annane et al NEJM 2018

06/05/2021

Table 3. Adverse Events.*

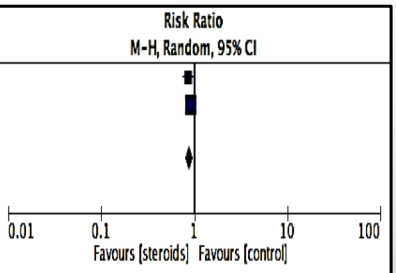
Event	Placebo (N=627)	Hydrocortisone plus Fludrocortisone (N=614)	Relative Risk (95% CI)†	P Value
≥1 Serious event by day 180 — no./total no. (%)	363/626 (58.0)	326/614 (53.1)	0.92 (0.83–1.01)	0.08
≥1 Serious bleeding event by day 28 — no./total no. (%)	119/626 (19.0)	127/614 (20.7)	1.09 (0.87–1.36)	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

Annane et al NEJM 2018

ADRENAL AND APROCCHSS

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Annane 2018	207	614	244	627	38.6%	0.87 [0.75, 1.00]
Venkatesh 2018	410	1841	448	1840	61.4%	0.91 [0.81, 1.03]
Total (95% CI)		**2455**		**2467**	**100.0%**	**0.90 [0.82, 0.98]**
Total events	617		692			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.32$, df = 1 (P = 0.57); $I^2 = 0\%$
Test for overall effect: Z = 2.35 (P = 0.02)



Rochwerg CCM 2018

MC IMMUNE EFFECTS IN SEPSIS

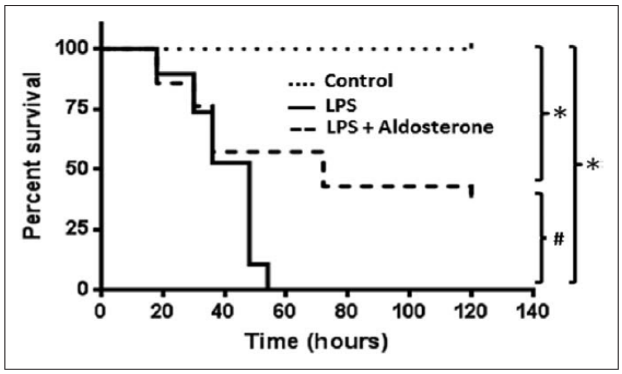
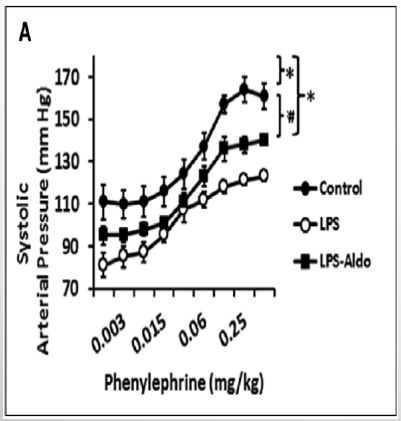
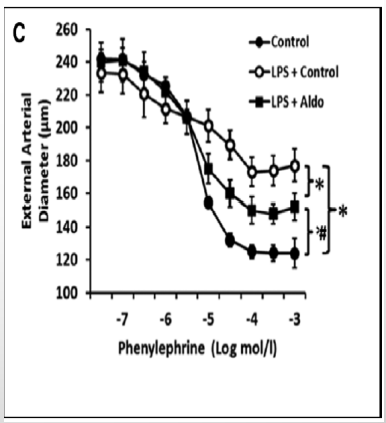


Figure 1. Effects of aldosterone on survival during endotoxic shock—mice were injected intraperitoneally with vehicle or lipopolysaccharide (LPS) (15 mg/kg) with or without aldosterone (1 mg/kg). Survival was monitored for 120 hs $^*p < 0.05$ vs control, $\#p \leq 0.05$ vs LPS, $n = 20$ in all groups).

CCM 2017

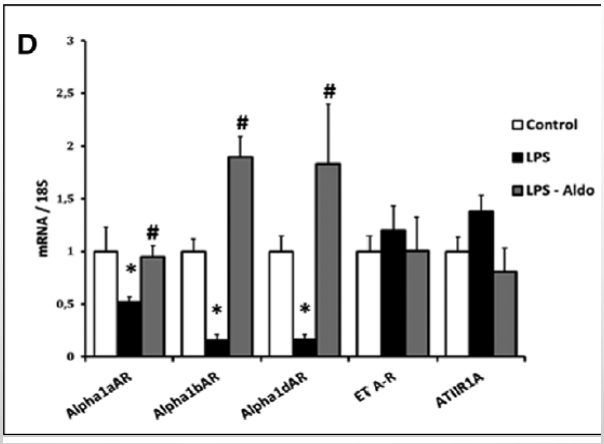
MC IMMUNE EFFECTS IN SEPSIS





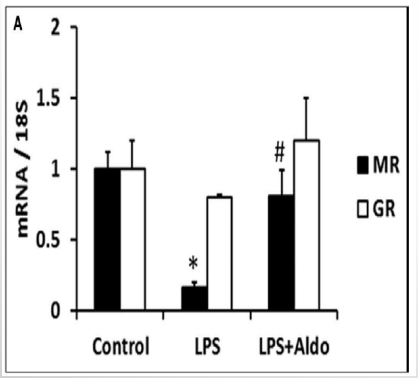
CCM 2017

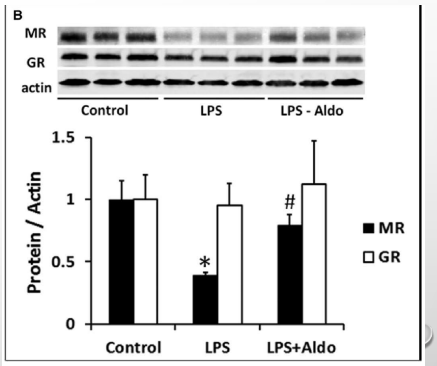
MC IMMUNE EFFECTS IN SEPSIS



CCM 2017

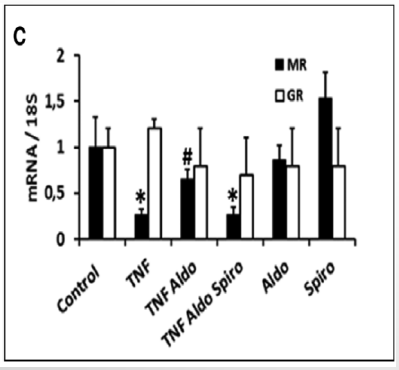
MC IMMUNE EFFECTS IN SEPSIS

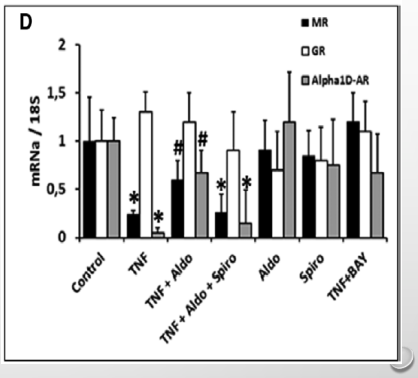




CCM 2017

MC IMMUNE EFFECTS IN SEPSIS



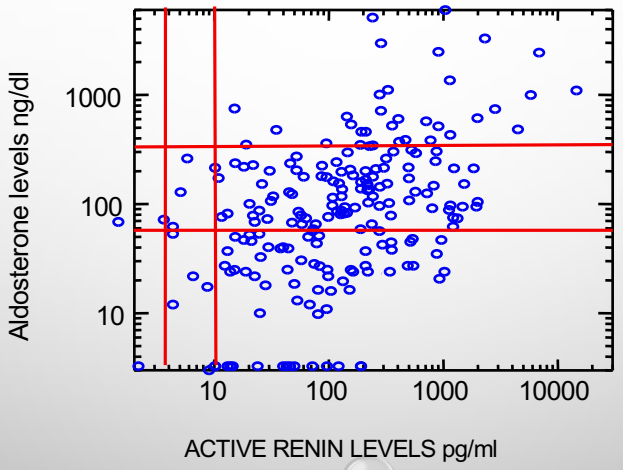


HUVEC experiments

Arterial smooth muscle cells

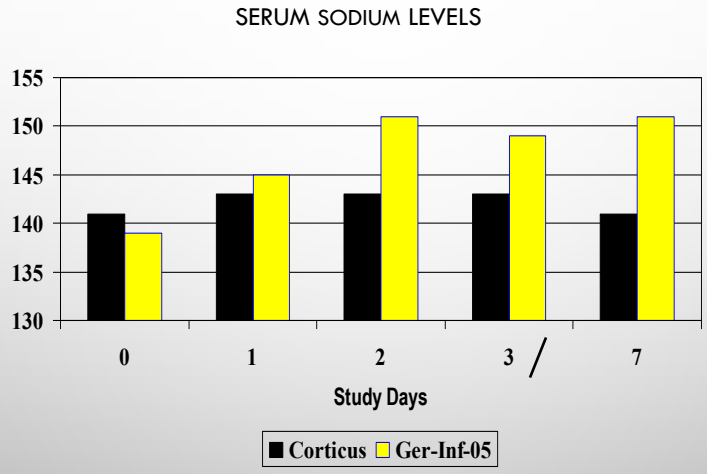
CCM 2017

Mineralocorticoid Insufficiency in Septic Shock

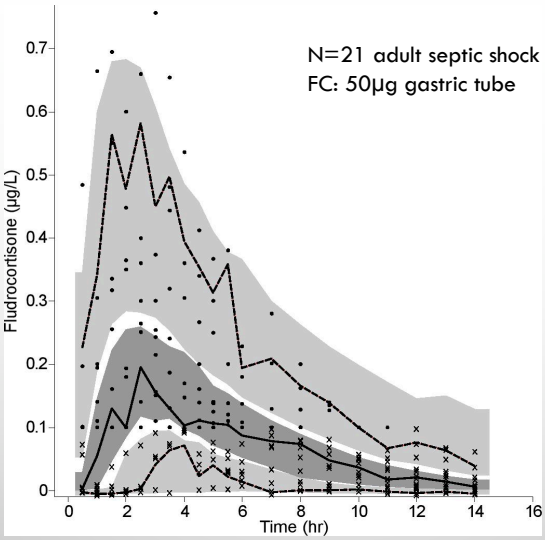


N= 225

Mineralocorticoid effects of HC versus HC+FC



Jama 2002 & NEJM 2008



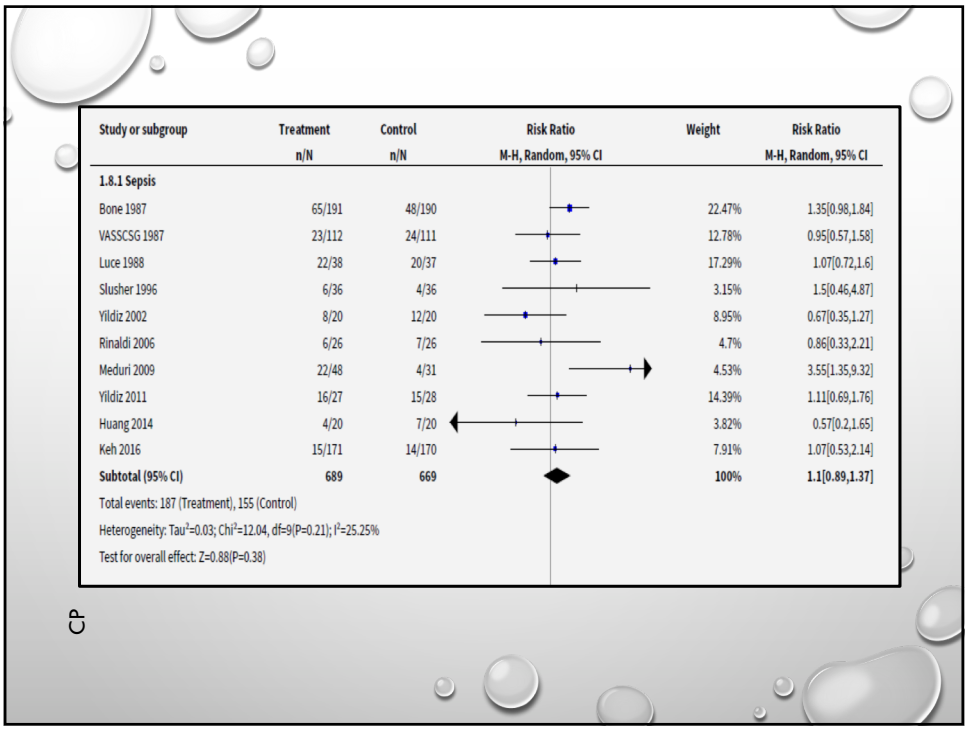
Br J Clin Pharmacol (2016)

Which Dose & Duration ?

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
4 28-Day all-cause mortality by subgroups based on treatment dose/duration	44	10812	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.86, 0.97]
4.1 Long course of low-dose cor-ticosteroids	39	9902	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.86, 0.97]
4.2 Short course of high-dose corticosteroids	5	910	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.80, 1.16]

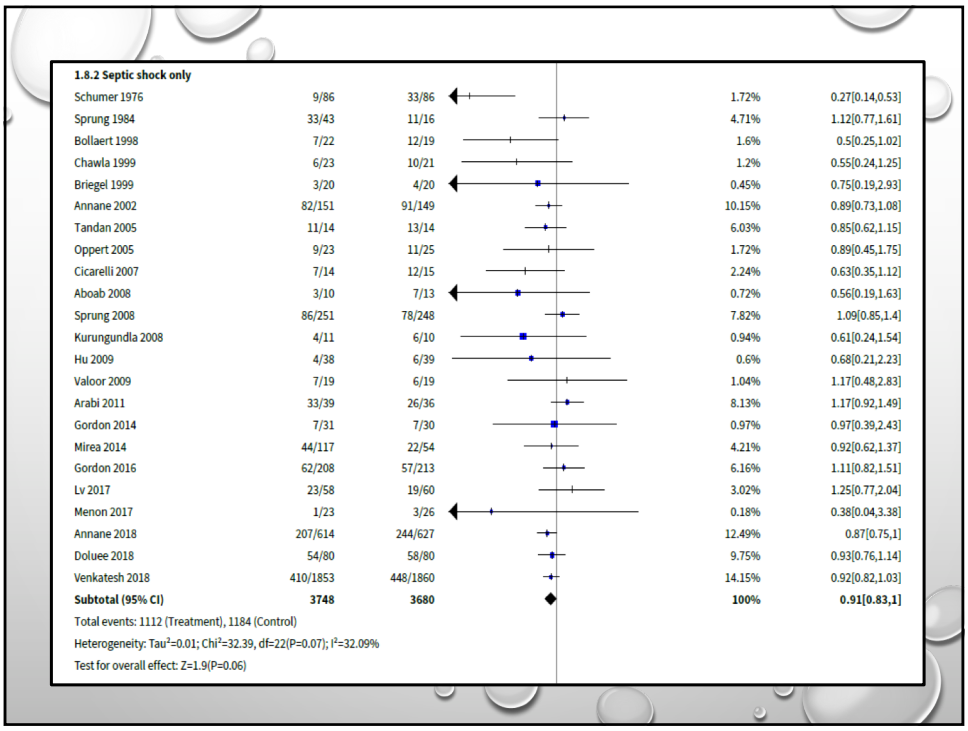
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
5 28-Day all-cause mortality based on mode of drug adminis-tration	45	9978	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.82, 0.99]
5.1 Intravenous bolus	27	4749	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.83, 1.02]
5.2 Continuous infusion	18	5229	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.66, 1.07]
6 28-Day all-cause mortality based on mode of drug termina-tion	47	10906	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.83, 1.00]
6.1 Without taper off	30	8770	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.78, 0.98]
6.2 With taper off	17	2136	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.92, 1.18]

Who I Treat?



Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.8.1 Sepsis					
Bone 1987	65/191	48/190		22.47%	1.35[0.98,1.84]
VASSCSG 1987	23/112	24/111		12.78%	0.95[0.57,1.58]
Luce 1988	22/38	20/37		17.29%	1.07[0.72,1.6]
Slusher 1996	6/36	4/36		3.15%	1.5[0.46,4.87]
Yildiz 2002	8/20	12/20		8.95%	0.67[0.35,1.27]
Rinaldi 2006	6/26	7/26		4.7%	0.86[0.33,2.21]
Meduri 2009	22/48	4/31		4.53%	3.55[1.35,9.32]
Yildiz 2011	16/27	15/28		14.39%	1.11[0.69,1.76]
Huang 2014	4/20	7/20		3.82%	0.57[0.2,1.65]
Keh 2016	15/171	14/170		7.91%	1.07[0.53,2.14]
Subtotal (95% CI)	**689**	**669**		**100%**	**1.1[0.89,1.37]**
Total events: 187 (Treatment), 155 (Control)					
Heterogeneity: Tau^2=0.03; Chi^2=12.04, df=9(P=0.21); I^2=25.25%					
Test for overall effect: Z=0.88(P=0.38)					

CP



1.8.2 Septic shock only				
Schumer 1976	9/86	33/86	1.72%	0.27[0.14,0.53]
Sprung 1984	33/43	11/16	4.71%	1.12[0.77,1.61]
Bollaert 1998	7/22	12/19	1.6%	0.5[0.25,1.02]
Chawla 1999	6/23	10/21	1.2%	0.55[0.24,1.25]
Briegel 1999	3/20	4/20	0.45%	0.75[0.19,2.93]
Annane 2002	82/151	91/149	10.15%	0.89[0.73,1.08]
Tandan 2005	11/14	13/14	6.03%	0.85[0.62,1.15]
Oppert 2005	9/23	11/25	1.72%	0.89[0.45,1.75]
Cicarelli 2007	7/14	12/15	2.24%	0.63[0.35,1.12]
Aboab 2008	3/10	7/13	0.72%	0.56[0.19,1.63]
Sprung 2008	86/251	78/248	7.82%	1.09[0.85,1.4]
Kurungundla 2008	4/11	6/10	0.94%	0.61[0.24,1.54]
Hu 2009	4/38	6/39	0.6%	0.68[0.21,2.23]
Valoor 2009	7/19	6/19	1.04%	1.17[0.48,2.83]
Arabi 2011	33/39	26/36	8.13%	1.17[0.92,1.49]
Gordon 2014	7/31	7/30	0.97%	0.97[0.39,2.43]
Mirea 2014	44/117	22/54	4.21%	0.92[0.62,1.37]
Gordon 2016	62/208	57/213	6.16%	1.11[0.82,1.51]
Lv 2017	23/58	19/60	3.02%	1.25[0.77,2.04]
Menon 2017	1/23	3/26	0.18%	0.38[0.04,3.38]
Annane 2018	207/614	244/627	12.49%	0.87[0.75,1]
Doluee 2018	54/80	58/80	9.75%	0.93[0.76,1.14]
Venkatesh 2018	410/1853	448/1860	14.15%	0.92[0.82,1.03]
Subtotal (95% CI)	**3748**	**3680**	**100%**	**0.91[0.83,1]**

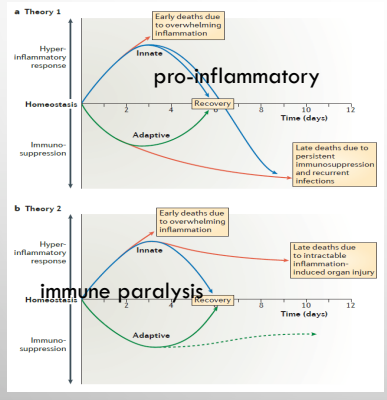
Total events: 1112 (Treatment), 1184 (Control)

Heterogeneity: Tau^2=0.01; Chi^2=32.39, df=22(P=0.07); I^2=32.09%

Test for overall effect: Z=1.9(P=0.06)

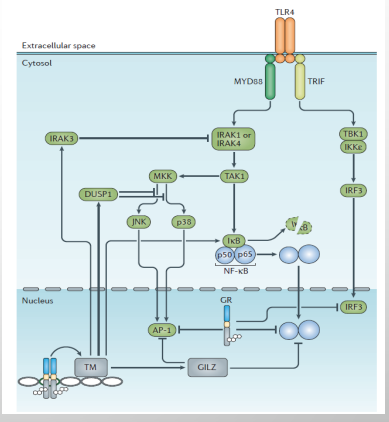
CORTICOSTEROID SENSITIVITY IN SEPSIS REQUIRES

1. A PRO-INFLAMMATORY RESPONSE TO INFECTION AND NOT IMMUNE PARALYSIS



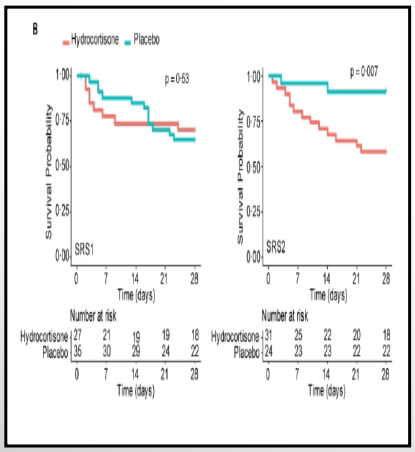
Nat Rev Immunol 2013

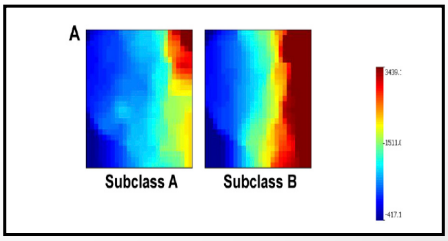
2. Intact CS molecular mechanisms of action



Nat Rev Immunol 2017

Omics Corticosteroids Response Signature





CS:52/120 CS:104/180

OR death: 4.1 (1.4-12) OR death: 3.9 (0.8-18)

Subclass A: immune suppressed
Subclass B: immune competent

SRS1: immune suppressed
SRS2: immune competent

Antcliffe AJRCCM 2018

Wong AJRCCM 2014

JAMA Network

From: **Assessment of Machine Learning to Estimate the Individual Treatment Effect of Corticosteroids in Septic Shock**

JAMA Netw Open. 2020;3(12):e2029050. doi:10.1001/jamanetworkopen.2020.29050

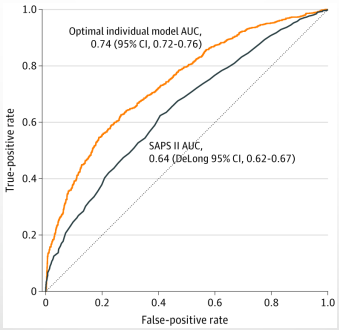


Figure Legend:

Model DiscriminationAUC indicates area under the receiver operating characteristic curve; SAPS II, Simplified Acute Physiology Score.

Piracchio et al

JAMA Network

From: **Assessment of Machine Learning to Estimate the Individual Treatment Effect of Corticosteroids in Septic Shock**

JAMA Netw Open. 2020;3(12):e2029050. doi:10.1001/jamanetworkopen.2020.29050

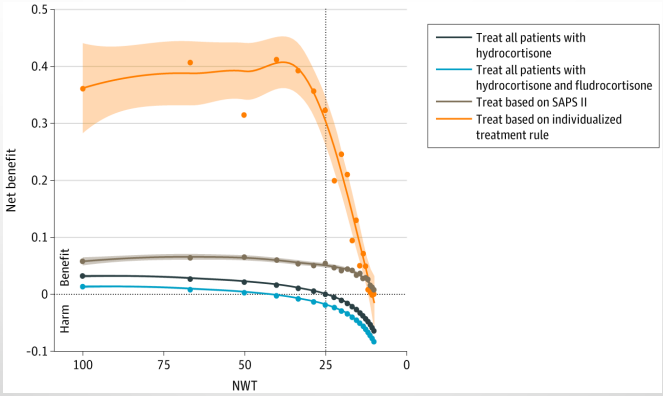


Figure Legend:

Expected Net Benefit Based on the Number Willing to Treat (NWT)The y-axis is the net benefit for each treatment strategy compared with treating no one. Treating no one served as a reference and is equal to zero. For treat all patients and treat based on the Simplified Acute Physiology Score (SAPS II), the treatment considered is either hydrocortisone alone or hydrocortisone with fludrocortisone. For the optimal individual model, the treatment is the one expected to produce the maximal effect at the individual level. The x-axis is the NWT, which is equal to 1/decision threshold. Shading indicates 95% CI.

Date of download: 2/10/2021

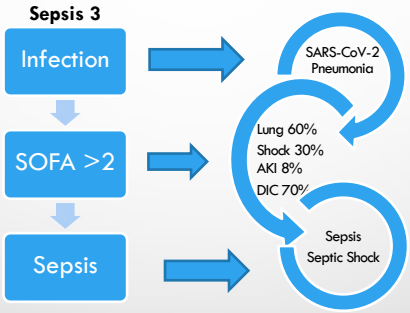
Unprecedented pandemic

106 921 304
Confirmed cases
Updated : 10 Fev 2021,
2 341 425
Confirmed deaths
Updated : 10 Fev 2021,

Source <john Hopkins

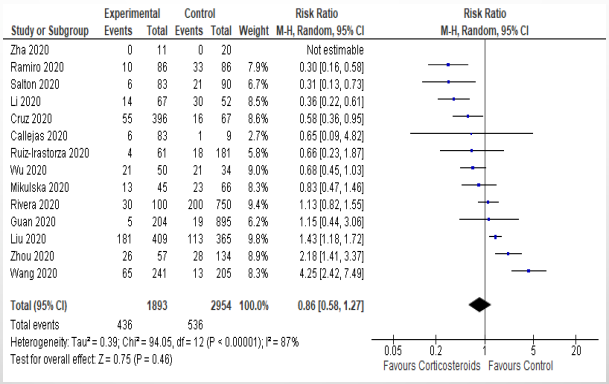
COVID 19 not just infection but viral sepsis

SEPSIS IS THE CLINICAL PHENOTYPE



NEJM 2019, NEJM 2020, JAMA 2020, Lancet 2020

CORTICOSTEROIDS – MORTALITY - OBSERVATIONAL COHORTS



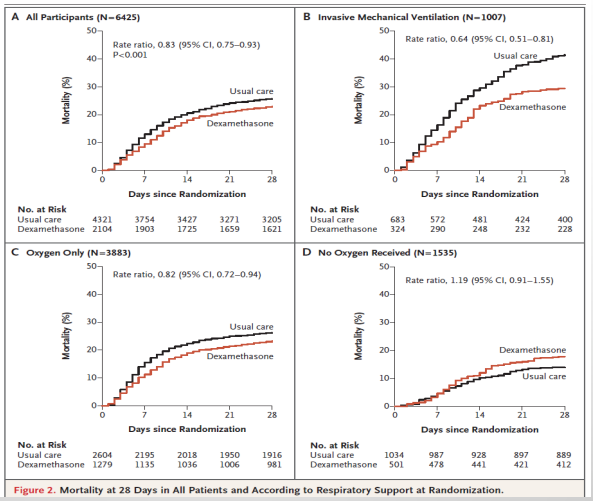
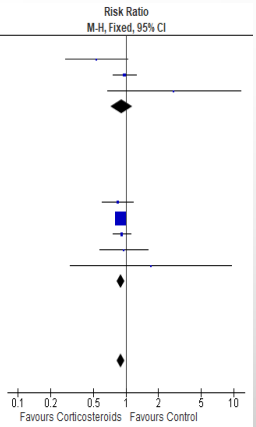


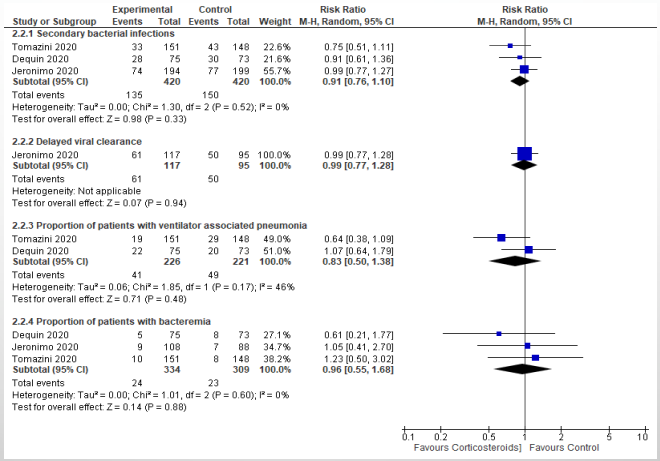
Figure 2. Mortality at 28 Days in All Patients and According to Respiratory Support at Randomization.

Corticosteroids – Mortality- RCTs

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.1.1 Placebo controlled and double blinded trials						
Dequin 2020	11	75	20	73	2.1%	0.54 [0.28, 1.04]
Jeronimo 2020	72	194	76	199	7.7%	0.97 [0.75, 1.25]
COVID-STEROID 2020	6	15	2	14	0.2%	2.80 [0.67, 11.64]
Subtotal (95% CI)		**284**		**286**	**9.9%**	**0.92 [0.73, 1.16]**
Total events	89		98			
Heterogeneity: Chi² = 5.10, df = 2 (P = 0.08); I² = 61%						
Test for overall effect: Z = 0.70 (P = 0.48)						
2.1.2 Open label trials						
Angus 2020	78	278	33	99	5.0%	0.84 [0.60, 1.18]
Horby 2020	482	2104	1110	4321	74.2%	0.89 [0.81, 0.98]
Tomazini 2020	85	151	91	148	9.4%	0.92 [0.76, 1.11]
STEROIDS SARI 2020	13	24	13	23	1.4%	0.96 [0.57, 1.60]
DEXA-COVID-19 2020	2	7	2	12	0.2%	1.71 [0.31, 9.61]
Subtotal (95% CI)		**2564**		**4603**	**90.1%**	**0.89 [0.82, 0.97]**
Total events	660		1249			
Heterogeneity: Chi² = 0.80, df = 4 (P = 0.94); I² = 0%						
Test for overall effect: Z = 2.68 (P = 0.007)						
Total (95% CI)		**2848**		**4889**	**100.0%**	**0.90 [0.83, 0.97]**
Total events	749		1347			
Heterogeneity: Chi² = 5.98, df = 7 (P = 0.54); I² = 0%						
Test for overall effect: Z = 2.77 (P = 0.006)						
Test for subgroup differences: Chi² = 0.05, df = 1 (P = 0.82), I² = 0%						



Corticosteroids – SAEs- RCTs



In Practice

- GIVE
  - HYDROCORTISONE (50MG Q6) +
  - FLUDROCORTISONE (50□G Q24)
- FOR
  - 7 DAYS
  - NO NEED TO TAPER OFF
- TO
  - SEPTIC SHOCK,
  - SEPSIS + ARDS,
  - SEPSIS + CAP
- NOT TO
  - ACTH RESPONDERS, IE DELTA CORTISOL>9□G/DL