FHU SEPSIS
Personalized Interventions

Sepsis Literature Update
Steroids

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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

11/05/2021

WHY I give corticosteroids?

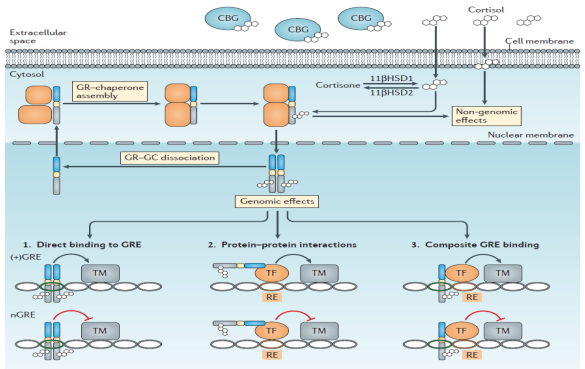
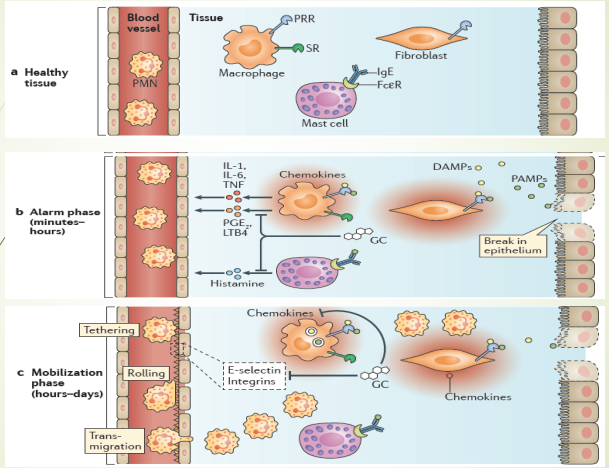
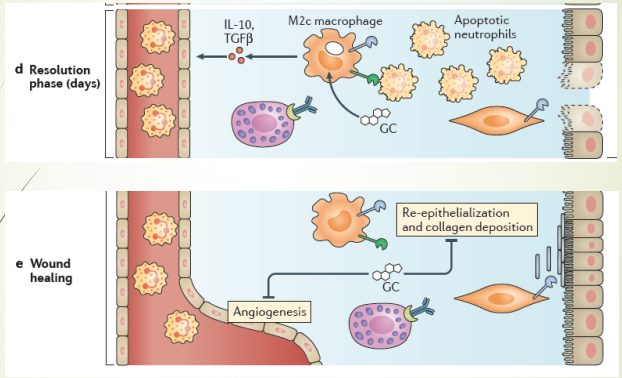


Figure 2 | **Mechanisms of glucocorticoid activity.** In the extracellular space, most endogenous glucocorticoids (GCs)

Nature Rev Immunol 2017



Nature Rev Immunol 2017



Nature Rev Immunol 2017

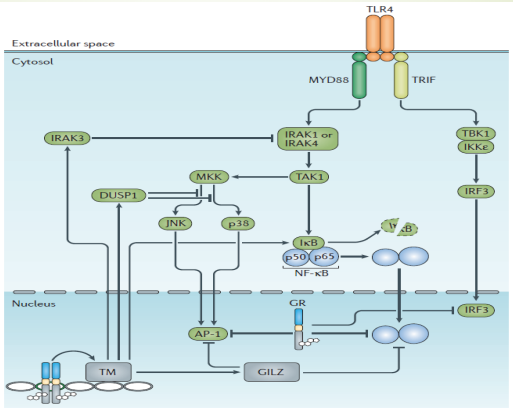
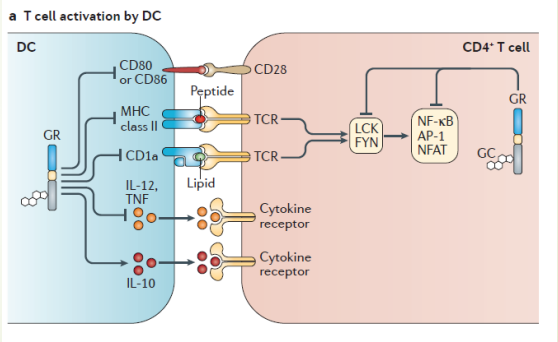


Figure 4 | **Glucocorticoids inhibit signalling through Toll-like receptors.**

Nature Rev Immunol 2017



Nature Rev Immunol 2017

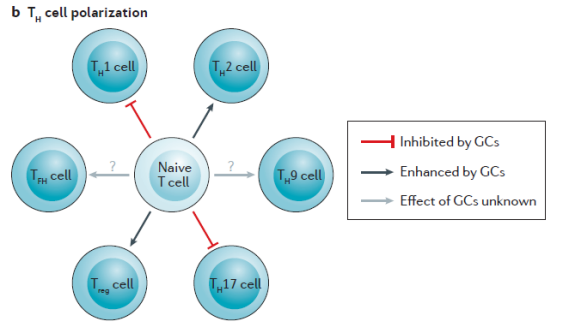
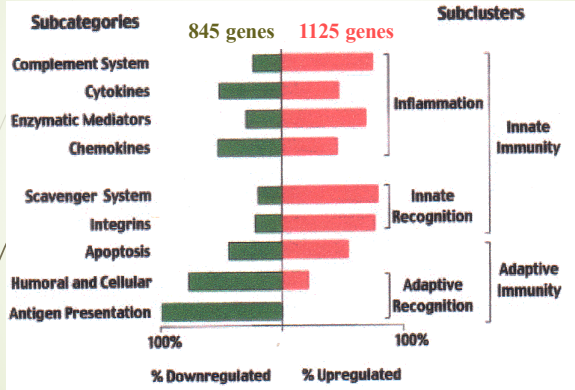


Figure 5 | **Glucocorticoids modulate T cell activity. a** | Glucocorticoids (GCs) suppress

Nature Rev Immunol 2017

Reprograming rather than suppressing!

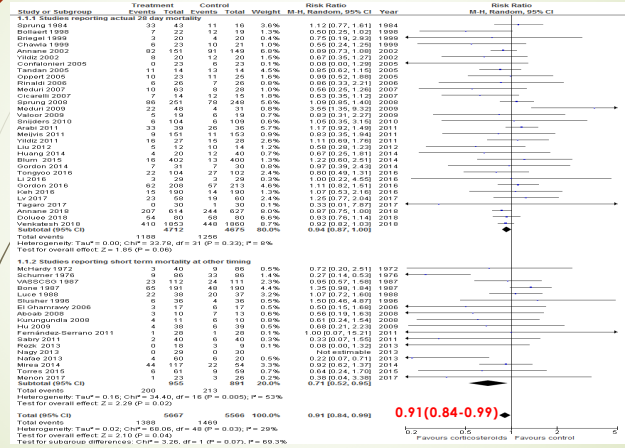


Faseb, 2002

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

Cochrane Library App - January 2020

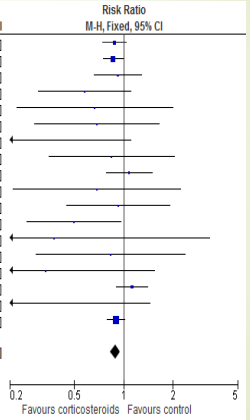
28-Day All Causes Mortality



ICU Mortality

Study or Subgroup	Treatment Events	Treatment Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Annane 2002	90	151	101	149	10.0%	0.88 [0.74, 1.04]
Annane 2018	217	614	257	627	25.0%	0.86 [0.75, 0.99]
Arabi 2011	24	39	24	36	2.5%	0.92 [0.66, 1.30]
Bollaert 1998	8	22	12	19	1.3%	0.58 [0.30, 1.10]
Briegel 1999	4	20	6	20	0.6%	0.67 [0.22, 2.01]
Chawla 1999	6	23	8	21	0.8%	0.68 [0.28, 1.65]
Confalonieri 2005	0	23	7	23	0.7%	0.07 [0.00, 1.10]
Gordon 2014	7	31	8	30	0.8%	0.85 [0.35, 2.04]
Gordon 2016	56	208	53	213	5.1%	1.08 [0.78, 1.50]
Hu 2009	4	38	6	39	0.6%	0.68 [0.21, 2.23]
Keh 2016	13	190	14	190	1.4%	0.93 [0.45, 1.92]
Meduri 2007	11	42	10	19	1.4%	0.50 [0.26, 0.97]
Menon 2017	1	23	3	26	0.3%	0.38 [0.04, 3.38]
Rinaldi 2006	5	26	6	26	0.6%	0.83 [0.29, 2.39]
Sabry 2011	2	40	6	40	0.6%	0.33 [0.07, 1.55]
Sprung 2008	102	251	89	247	8.8%	1.13 [0.90, 1.41]
Torres 2015	1	42	6	46	0.6%	0.18 [0.02, 1.45]
Venkatesh 2018	357	1853	399	1860	39.1%	0.90 [0.79, 1.02]
Total (95% CI)		**3636**		**3631**	**100.0%**	**0.89 [0.83, 0.96]**
Total events	908		1015			

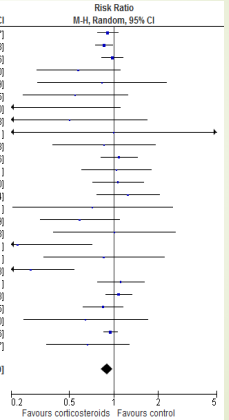
Heterogeneity: Chi² = 19.18, df = 17 (P = 0.32); I² = 11%
Test for overall effect: Z = 3.15 (P = 0.002)



Hospital Mortality

Study or Subgroup	Treatment Events	Treatment Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Annane 2002	95	151	103	149	11.0%	0.91 [0.77, 1.07]
Annane 2018	239	614	284	627	12.4%	0.86 [0.75, 0.98]
Arabi 2011	34	39	32	36	10.8%	0.98 [0.83, 1.16]
Bollaert 1998	8	22	12	19	1.9%	0.58 [0.30, 1.10]
Briegel 1999	5	20	6	20	0.8%	0.83 [0.30, 2.29]
Chawla 1999	6	23	10	21	1.3%	0.55 [0.24, 1.25]
Confalonieri 2005	0	23	7	23	0.1%	0.07 [0.00, 1.10]
El Ghamrawy 2006	3	17	6	17	0.6%	0.50 [0.15, 1.68]
Fernández-Serrano 2011	1	28	1	28	0.1%	1.00 [0.07, 15.21]
Gordon 2014	8	31	9	30	1.3%	0.86 [0.38, 1.93]
Gordon 2016	66	208	62	213	6.5%	1.09 [0.82, 1.46]
Keh 2016	23	190	22	190	2.6%	1.05 [0.60, 1.81]
Luce 1988	22	38	20	37	4.2%	1.07 [0.72, 1.60]
Lv 2017	23	58	19	60	3.1%	1.25 [0.77, 2.04]
McHardy 1972	3	40	9	86	0.6%	0.72 [0.20, 2.51]
Meduri 2007	13	42	10	19	2.1%	0.59 [0.32, 1.09]
Meijvis 2011	8	151	8	153	0.9%	1.01 [0.39, 2.63]
Nafae 2013	4	60	6	20	0.7%	0.22 [0.07, 0.71]
Rinaldi 2006	6	26	7	26	1.0%	0.86 [0.33, 2.21]
Schumer 1976	9	86	33	86	1.8%	0.27 [0.14, 0.53]
Sprung 1984	33	43	11	16	4.7%	1.12 [0.77, 1.61]
Sprung 2008	111	251	100	245	9.3%	1.08 [0.88, 1.33]
Tandan 2005	11	14	13	14	6.0%	0.85 [0.62, 1.15]
Torres 2015	6	61	9	59	0.9%	0.64 [0.24, 1.70]
Venkatesh 2018	478	1853	504	1860	13.4%	0.95 [0.86, 1.06]
Yildiz 2002	8	20	12	20	1.9%	0.67 [0.35, 1.27]
Total (95% CI)		**4109**		**4074**	**100.0%**	**0.90 [0.82, 0.99]**
Total events	1223		1315			

Heterogeneity: Tau² = 0.01; Chi² = 39.58, df = 25 (P = 0.03); I² = 37%
Test for overall effect: Z = 2.18 (P = 0.03)



How I give steroids?

Different corticosteroids

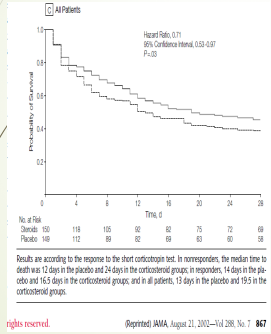
Molecules	Glucocorticoid activity relative to hydrocortisone	Mineralocorticoid activity relative to hydrocortisone	Non-genomic effects relative to hydrocortisone
Hydrocortisone	1	1	1
Prednisone	4	0.8	4
Prednisolone	4	0.8	4
Methylprednisolone	5	0.5	14
Betamethasone	25	0	0
Dexamethasone	25	0	20
Fludrocortisone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

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

Hydrocortisone + Fludrocortisone

TRIAL 1

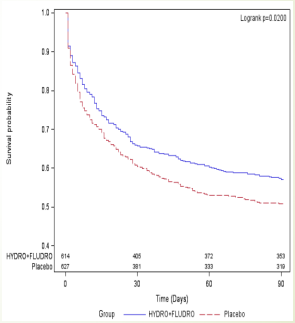
N=300



Annane Jama 2002

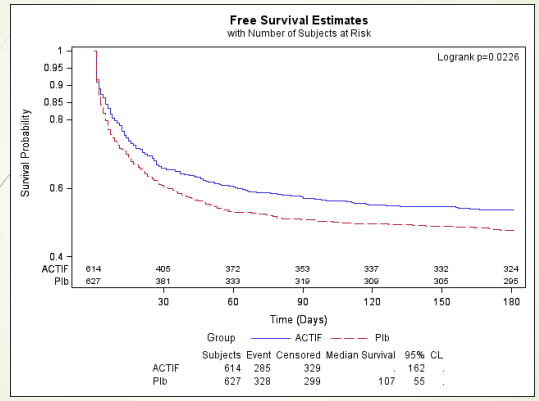
TRIAL 2

N=1241



Annane NEJM 2018

18



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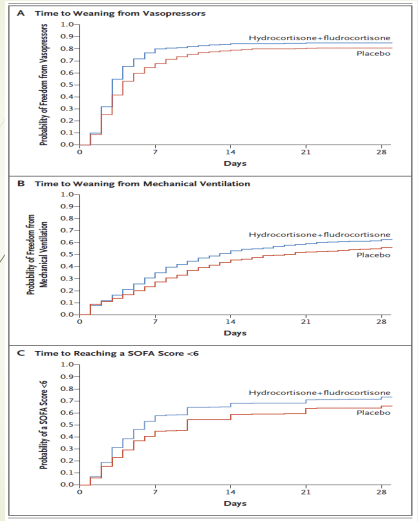
Annane NEJM 2018



P<0.001

P<0.006

P<0.001

11/05/2021

The NEW ENGLAND JOURNAL of MEDICINE

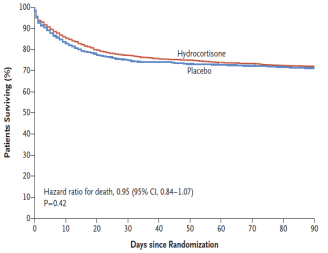
Table 3. Adverse Events.*

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

11/05/2021

Annane et al NEJM 2018

N=3658



- Hydrocortisone :
  - Faster resolution of shock (median, 3d vs 4 days)
  - Shorter duration of initial MV (median, 6 vs 7 days)
  - Fewer blood transfusions 37.0% vs. 41.7%; OR, 0.82; 95% CI, 0.72 to 0.94; P = 0.004

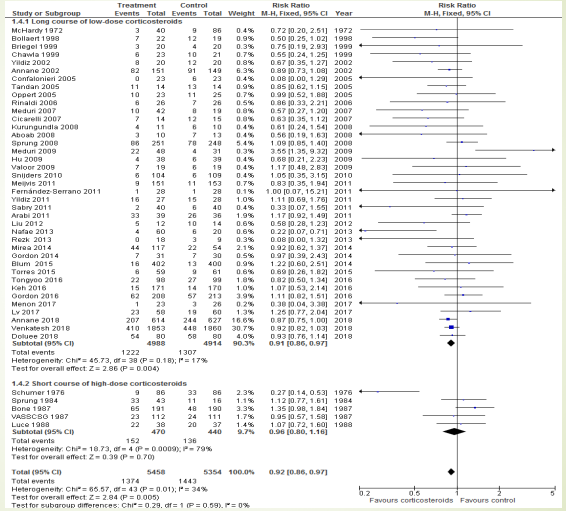
33 ADVERSE EVENTS:
- Hyperglycemia (6 HC vs 3 P)
  Hypernatremia (3 HC vs 0 P)
- - Myopathy (3 HC vs 0 P)

Venkatesh, NEJM 2018

Which Dose & duration, I use?

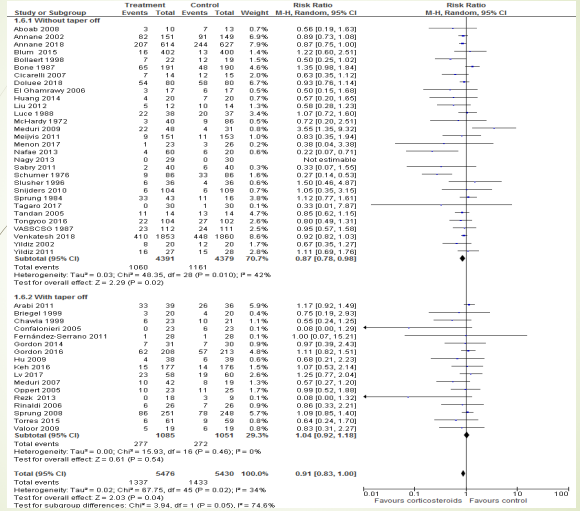
>400 mg/day HC equivalent <24h

<400mg/jday HC equivalent >72 h

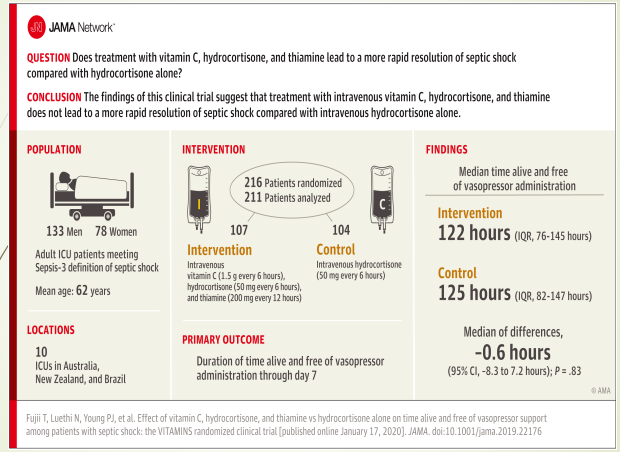


Without tapering off

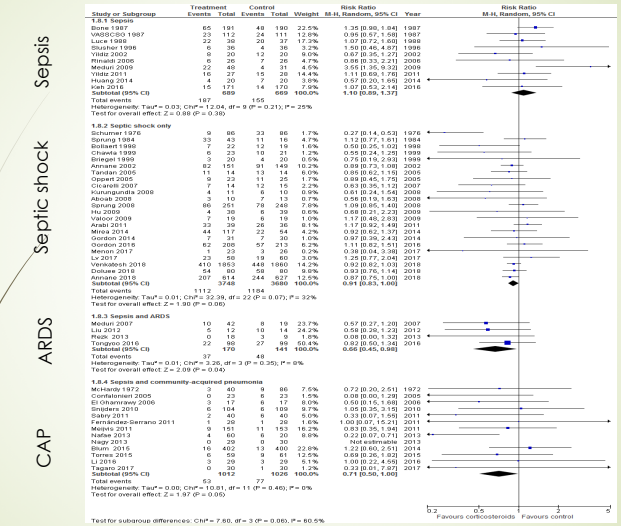
With tapering off



Combined with vitamins?



Who I treat?



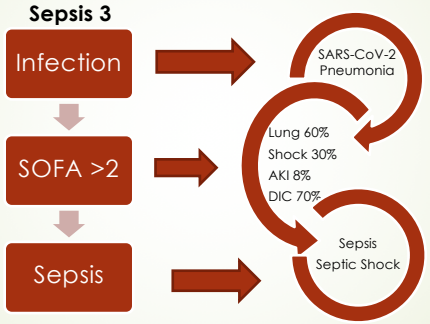
Unprecedented pandemic

144 861 502
Confirmed cases
Updated : 23 April 2021,
3 075 042
Confirmed deaths
Updated : 23 April 2021

Source <John Hopkins

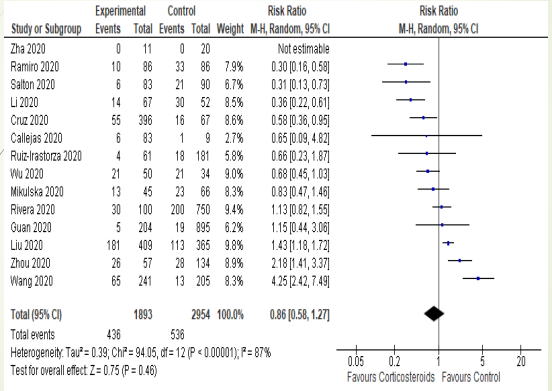
COVID 19 not just infection but viral sepsis

Sepsis is the Clinical Phenotype



NEJM 2019, NEJM 2020, JAMA 2020, Lancet 2020

Corticosteroids – Mortality - observational cohorts



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Zha 2020	0	11	0	20		Not estimable
Ramiro 2020	10	86	33	86	7.9%	0.30 [0.16, 0.58]
Salton 2020	6	83	21	90	6.7%	0.31 [0.13, 0.73]
Li 2020	14	67	30	52	8.5%	0.36 [0.22, 0.61]
Cruz 2020	55	396	16	67	8.6%	0.58 [0.36, 0.95]
Callejas 2020	6	83	1	9	2.7%	0.65 [0.09, 4.82]
Ruiz-Irastorza 2020	4	61	18	181	5.8%	0.66 [0.23, 1.87]
Wu 2020	21	50	21	34	9.0%	0.68 [0.45, 1.03]
Mikulska 2020	13	45	23	66	8.3%	0.83 [0.47, 1.46]
Rivera 2020	30	100	200	750	9.4%	1.13 [0.82, 1.55]
Guan 2020	5	204	19	895	6.2%	1.15 [0.44, 3.06]
Liu 2020	181	409	113	365	9.8%	1.43 [1.18, 1.72]
Zhou 2020	26	57	28	134	8.9%	2.18 [1.41, 3.37]
Wang 2020	65	241	13	205	8.3%	4.25 [2.42, 7.49]
Total (95% CI)		**1893**		**2954**	**100.0%**	**0.86 [0.58, 1.27]**
Total events	436		536			

Heterogeneity: Tau² = 0.39; Chi² = 94.05, df = 12 (P < 0.00001); I² = 87%
Test for overall effect: Z = 0.75 (P = 0.46)

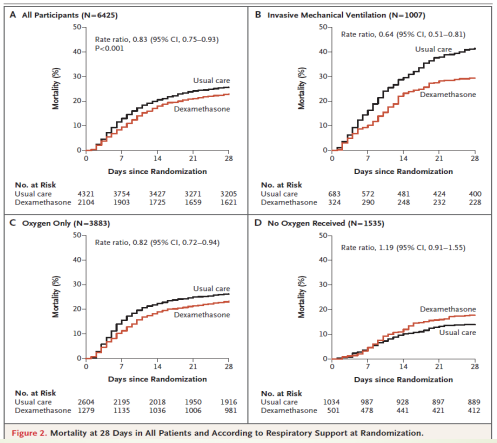
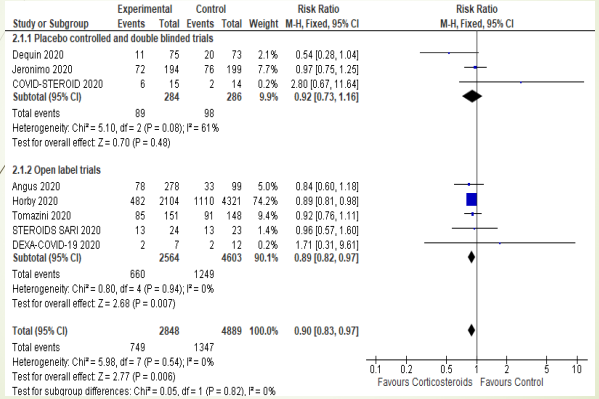


Figure 2. Mortality at 28 Days in All Patients and According to Respiratory Support at Randomization.

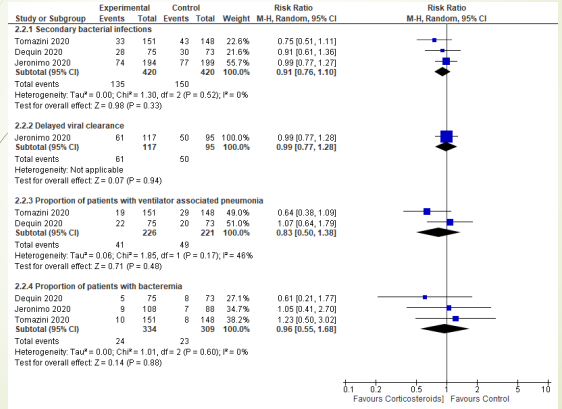
RECOVERY, NEJM 2021

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



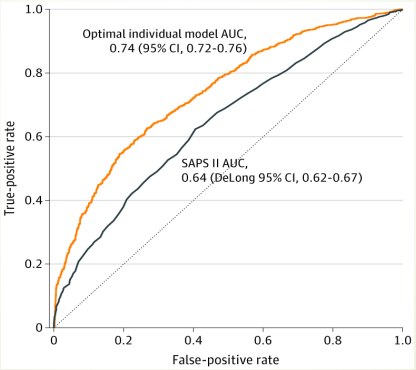
Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
2.2.1 Secondary bacterial infections						
Tomazini 2020	33	151	43	148	22.6%	0.75 [0.51, 1.11]
Dequin 2020	28	75	30	73	21.6%	0.91 [0.61, 1.36]
Jeronimo 2020	74	194	77	199	55.7%	0.99 [0.77, 1.27]
Subtotal (95% CI)		**420**		**420**	**100.0%**	**0.91 [0.76, 1.10]**
Total events	135		150			
Heterogeneity: Tau² = 0.00; Chi² = 1.30, df = 2 (P = 0.52); I² = 0%						
Test for overall effect: Z = 0.98 (P = 0.33)						
2.2.2 Delayed viral clearance						
Jeronimo 2020	61	117	50	95	100.0%	0.99 [0.77, 1.28]
Subtotal (95% CI)		**117**		**95**	**100.0%**	**0.99 [0.77, 1.28]**
Total events	61		50			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.07 (P = 0.94)						
2.2.3 Proportion of patients with ventilator associated pneumonia						
Tomazini 2020	19	151	29	148	49.0%	0.64 [0.38, 1.09]
Dequin 2020	22	75	20	73	51.0%	1.07 [0.64, 1.79]
Subtotal (95% CI)		**226**		**221**	**100.0%**	**0.83 [0.50, 1.38]**
Total events	41		49			
Heterogeneity: Tau² = 0.06; Chi² = 1.85, df = 1 (P = 0.17); I² = 46%						
Test for overall effect: Z = 0.71 (P = 0.48)						
2.2.4 Proportion of patients with bacteremia						
Dequin 2020	5	75	8	73	27.1%	0.61 [0.21, 1.77]
Jeronimo 2020	9	108	7	88	34.7%	1.05 [0.41, 2.70]
Tomazini 2020	10	151	8	148	38.2%	1.23 [0.50, 3.02]
Subtotal (95% CI)		**334**		**309**	**100.0%**	**0.96 [0.55, 1.68]**
Total events	24		23			
Heterogeneity: Tau² = 0.00; Chi² = 1.01, df = 2 (P = 0.60); I² = 0%						
Test for overall effect: Z = 0.14 (P = 0.88)						

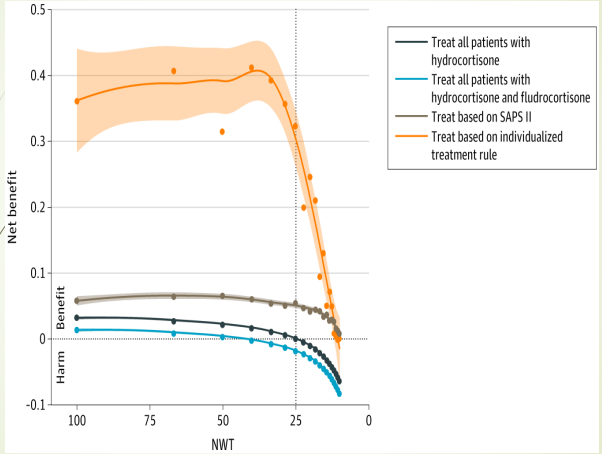
JAMA Network | Open

Original Investigation | Critical Care Medicine

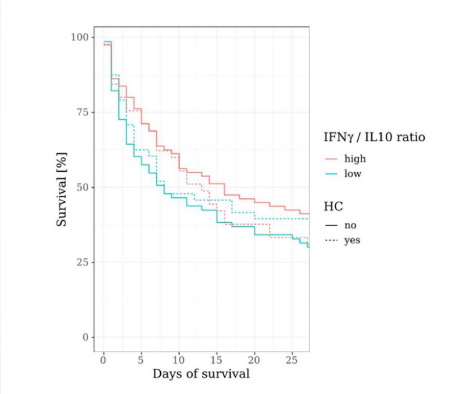
Assessment of Machine Learning to Estimate the Individual Treatment Effect of Corticosteroids in Septic Shock

Romain Pirracchio, MD, PhD; Alan Hubbard, PhD; Charles L. Sprung, MD; Sylvie Chevret, MD, PhD; Djillali Annane, MD, PhD; for the Rapid Recognition of Corticosteroid Resistant or Sensitive Sepsis (RECORDS) Collaborators





IMMUNE STATUS



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IMMUNE STATUS

König et al. IFNγ/IL10 Ratio Stratifies Hydrocortisone Therapy

Study	Number of patients	Odds Ratio	P	CI (lower,	upper)
CORTICUS	83	6.97	1.3e-03	1.79	40.50
HSSG	246	1.83	2.5e-02	1.05	3.22
SISPCT	118	2.36	1.4e-01	0.74	8.99
Crossover	20	6.07	1.6e-01	0.49	353.00
Pooled	467	2.42	6.9e-05	1.58	3.72

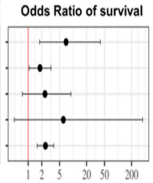

FIGURE 1 | Forest plot showing the outcome in the investigated cohorts depending on hydrocortisone administration according to the theranostic marker. Odds ratios including confidence intervals and thresholds between low and high ratios are shown regarding the IFNγ/IL10 prediction rule for the sub-cohorts of CORTICUS (discovery set), HSSG (validation set), SISPCT (validation set) and the crossover study (validation set).

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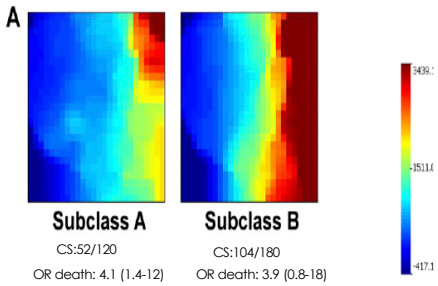
Omics corticosteroids response signature

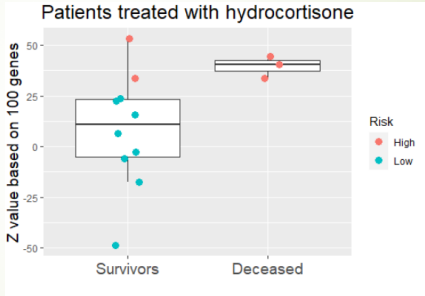


Subclass A: immune suppressed
Subclass B: immune competent

Wong AJRCCM 2014

Testing Hector Wong's 100-genes signature

- Pediatric sepsis
- 2 endotypes
  - A is high-risk : Z > 0
  - B is low-risk : Z < 0



For Practice

- Give
  - hydrocortisone (50mg q6) +
  - fludrocortisone (50µg q24)
- For
  - 7 days
  - No need to taper off
- To
  - Septic shock,
  - Sepsis + ARDS,
  - Sepsis + CAP
  - COVID -19 requiring oxygen supplementation
- Not TO
  - ACTH responders, ie delta cortisol>9µg/dl