Pneumonies aiguës communautaires : place des corticoïdes.

Lyon, 21 novembre 2024

AER
ACTUALITÉS EN RÉANIMATION

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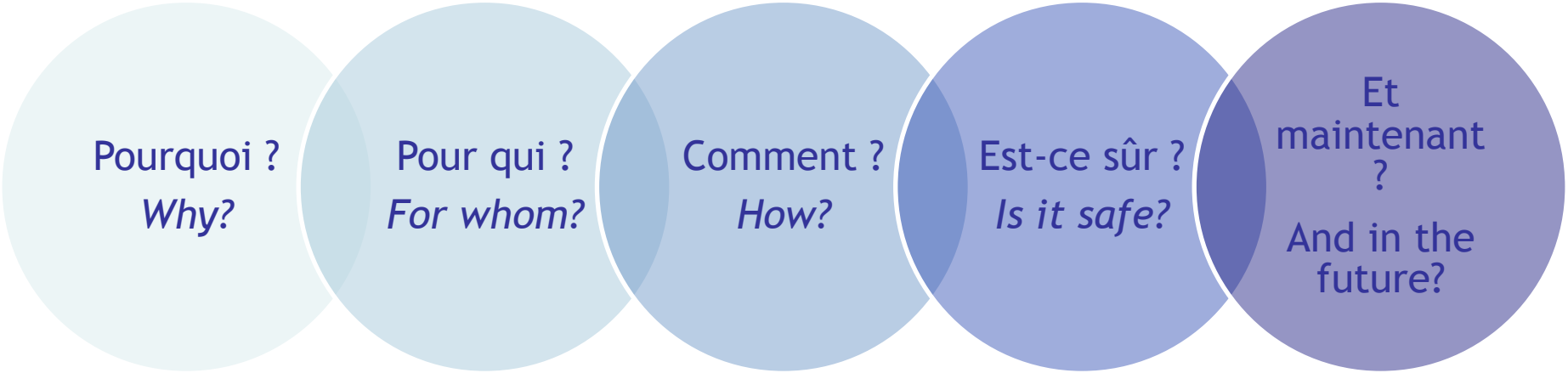
Liens d'intérêt *Links of interest*

Co-financements programme de recherche clinique :
Co-funding of clinical research program:

Financements personnels comme consultant :
Personal fees as a consultant:

Institutionnels :
Institutions:


Pourquoi ?
Why?
Pour qui ?
For whom?
Comment ?
How?
Est-ce sûr ?
Is it safe?
Et maintenant ?
And in the future?

Why? High mortality on D30

2005-2006,
Germany
N=388,406

Ewig et al.
Thorax 2009;64:1062-9.

Comorbidity	Total (%)
Malignancy (other than bronchial)	28.2
Lung cancer	25.21
Pulmonary diseases (other than COPD)	24.45
Dementia	22.36
Renal diseases	20.79
CNS disorders	19.41
Cardiac comorbidity	17.35
Diabetes mellitus	13.66
Liver diseases	12.93
COPD	10.12
Total	17.43
No comorbidity	12.95

432 patients mechanically-ventilated for CAP over a 20-year period (Spain)
Mortality at D-30: **31 %**

TABLE 5 Clinical outcomes

	Non-ARDS patients	ARDS patients	p-value
Subjects	307	125	
Length of hospital stay days	15 [10–27]	16 [9–30]	0.96
ICU mortality	70 [23]	37 [30]	0.14
In-hospital mortality	81 [26]	41 [33]	0.18
30-day mortality	90 [30]	44 [35]	0.25

Data are presented as n, median [interquartile range] or n (%), unless otherwise stated. ARDS: acute respiratory distress syndrome; ICU: intensive care unit. Percentages were calculated for nonmissing data.

Cilloniz et al., Eur Resp J 2018;51 pii:1702215

1,707 ICU-patients (MV 24%), USA
Mortality at D-30: **27 %**

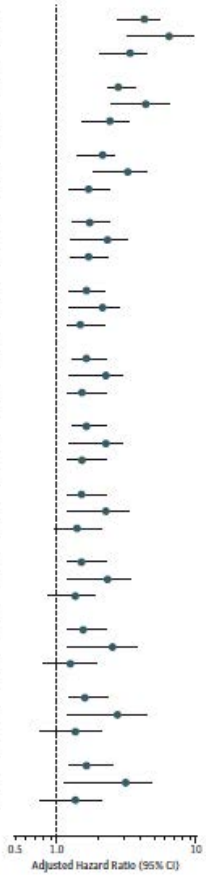
Cavallazzi et al, Chest 2020;158:1008-16.

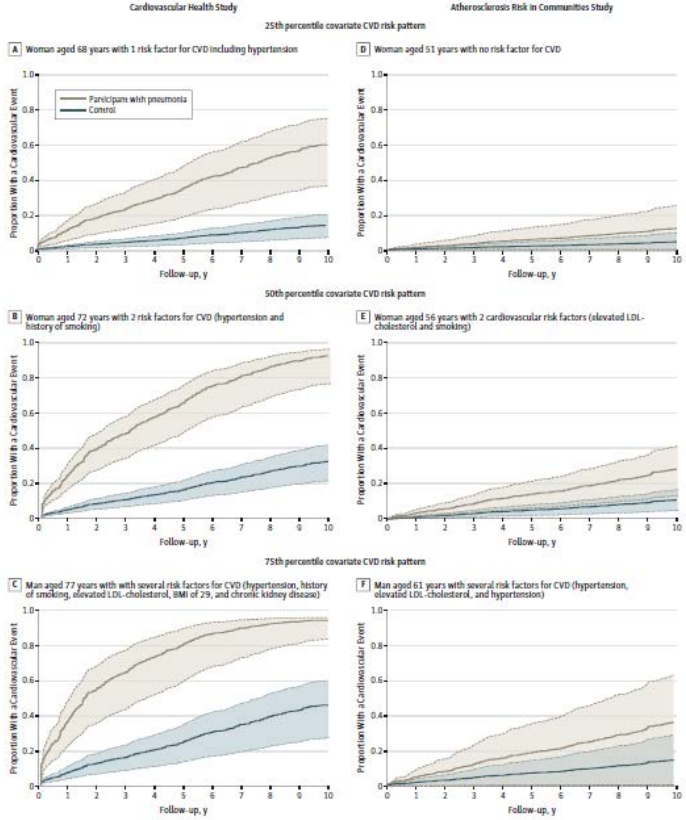
TABLE 3] Number of Deaths in Patients With Community-Acquired Pneumonia Admitted to the ICU in Louisville and the United States

ICU Admissions and Mortality	Louisville, Kentucky[a]			United States of America[b]
	ICU Admission			
	Early	Late	Total	
Adult patients in the ICU with community-acquired pneumonia, No. (%)	1,275	432	1,707	356,326[c]
In-hospital deaths[d]	200 (16)	87 (20)	287 (17)	60,576[c]
15-Day deaths	233 (18)	84 (19)	317 (19)	66,172[c]
30-Day deaths[d]	319 (25)	140 (33)	459 (27)	96,209[c]
6-Month deaths[d]	471 (38)	189 (44)	660 (39)	138,968[c]
1-Year deaths	563 (45)	216 (51)	779 (47)	167,474[c]

Why? High after-CAP morbidity

Time Intervals After Pneumonia	Pneumonia Cases: No. of CVD Events/ No. at Risk (%)	Controls: No. of CVD Events/ No. at Risk (%)	Hazard Ratio (95% CI): Unadjusted	Hazard Ratio (95% CI): Adjusted
0-30 d				
All pneumonia	54/508 (10.6)	6/1092 (0.5)	4.70 (3.42-5.98)	4.07 (2.86-5.27)
With organ dysfunction	28/177 (15.8)	2/396 (0.5)	6.28 (3.46-9.10)	6.23 (3.14-9.33)
Without organ dysfunction	26/331 (7.9)	4/696 (0.6)	3.95 (2.58-5.32)	3.27 (2.03-4.51)
31-90 d				
All pneumonia	11/384 (2.9)	9/1084 (0.8)	3.32 (2.53-4.10)	2.94 (2.18-3.70)
With organ dysfunction	3/122 (2.5)	2/393 (0.5)	4.46 (2.72-6.19)	4.38 (2.46-6.30)
Without organ dysfunction	8/262 (3.1)	7/691 (1.0)	2.80 (1.96-3.65)	2.45 (1.64-3.26)
91 d-1 y				
All pneumonia	22/345 (6.4)	55/1065 (5.2)	2.39 (1.86-2.91)	2.10 (1.59-2.60)
With organ dysfunction	9/113 (8.0)	13/387 (3.4)	3.16 (2.00-4.32)	3.06 (1.80-4.33)
Without organ dysfunction	13/232 (5.6)	42/678 (6.2)	2.03 (1.47-2.60)	1.79 (1.25-2.34)
1-2 y				
All pneumonia	28/272 (10.3)	53/985 (5.4)	2.05 (1.62-2.48)	1.89 (1.46-2.33)
With organ dysfunction	7/87 (8.0)	22/367 (6.0)	2.25 (1.46-3.04)	2.30 (1.39-3.21)
Without organ dysfunction	21/185 (11.4)	31/618 (5.0)	1.96 (1.44-2.47)	1.83 (1.30-2.35)
2-3 y				
All pneumonia	9/209 (4.3)	39/885 (4.4)	1.75 (1.39-2.12)	1.70 (1.32-2.09)
With organ dysfunction	2/68 (2.9)	12/323 (3.7)	1.85 (1.22-2.49)	2.06 (1.26-2.86)
Without organ dysfunction	7/141 (5.0)	27/562 (4.8)	1.70 (1.25-2.14)	1.64 (1.16-2.12)
3-4 y				
All pneumonia	14/182 (7.7)	35/811 (4.3)	1.74 (1.37-2.12)	1.73 (1.32-2.15)
With organ dysfunction	7/63 (11.1)	17/292 (5.8)	1.79 (1.15-2.43)	2.11 (1.25-2.97)
Without organ dysfunction	7/119 (5.9)	18/519 (3.5)	1.72 (1.24-2.19)	1.66 (1.16-2.16)
4-5 y				
All pneumonia	12/143 (8.4)	32/736 (4.3)	1.70 (1.31-2.10)	1.73 (1.30-2.17)
With organ dysfunction	3/54 (5.6)	6/255 (2.4)	1.82 (1.15-2.48)	2.18 (1.27-3.09)
Without organ dysfunction	9/89 (10.1)	26/481 (5.4)	1.64 (1.15-2.13)	1.63 (1.10-2.17)
5-6 y				
All pneumonia	9/113 (8.0)	40/667 (6.0)	1.61 (1.21-2.01)	1.65 (1.20-2.10)
With organ dysfunction	4/45 (8.9)	15/236 (6.4)	1.83 (1.10-2.56)	2.18 (1.19-3.17)
Without organ dysfunction	5/68 (7.4)	25/431 (5.8)	1.46 (0.99-1.94)	1.50 (0.96-2.03)
6-7 y				
All pneumonia	4/90 (4.4)	27/583 (4.6)	1.59 (1.16-2.02)	1.63 (1.15-2.11)
With organ dysfunction	2/35 (5.7)	8/207 (3.9)	1.99 (1.14-2.83)	2.32 (1.20-3.44)
Without organ dysfunction	2/55 (3.6)	19/376 (5.1)	1.35 (0.87-1.83)	1.40 (0.85-1.94)
7-8 y				
All pneumonia	5/75 (6.7)	26/494 (5.3)	1.63 (1.14-2.11)	1.69 (1.15-2.24)
With organ dysfunction	2/27 (7.4)	8/174 (4.6)	2.15 (1.15-3.15)	2.54 (1.20-3.87)
Without organ dysfunction	3/48 (6.3)	18/320 (5.6)	1.32 (0.80-1.84)	1.39 (0.80-1.98)
8-9 y				
All pneumonia	5/58 (8.6)	15/409 (3.7)	1.73 (1.17-2.28)	1.81 (1.18-2.43)
With organ dysfunction	3/22 (13.6)	6/150 (4.0)	2.41 (1.18-3.64)	2.86 (1.23-4.50)
Without organ dysfunction	2/36 (5.6)	9/259 (3.5)	1.33 (0.77-1.89)	1.40 (0.76-2.04)
9-10 y				
All pneumonia	4/39 (10.3)	12/345 (3.5)	1.77 (1.17-2.36)	1.86 (1.18-2.55)
With organ dysfunction	3/17 (17.6)	4/124 (3.2)	2.56 (1.18-3.94)	3.09 (1.23-4.95)
Without organ dysfunction	1/22 (4.5)	8/221 (3.6)	1.32 (0.74-1.90)	1.40 (0.73-2.06)





Corrales-Medina VF et al., JAMA 2015;313:264-74.

Long-term outcome in elderly patients

2009-2017, 39 hospital discharge data bases
Patients ≥80 y discharged alive from ICU for **acute respiratory infection**
Matched w controls (cataract surgery, adjustment for age, sex, comorbidities)
N=1,220 whose 988 matched

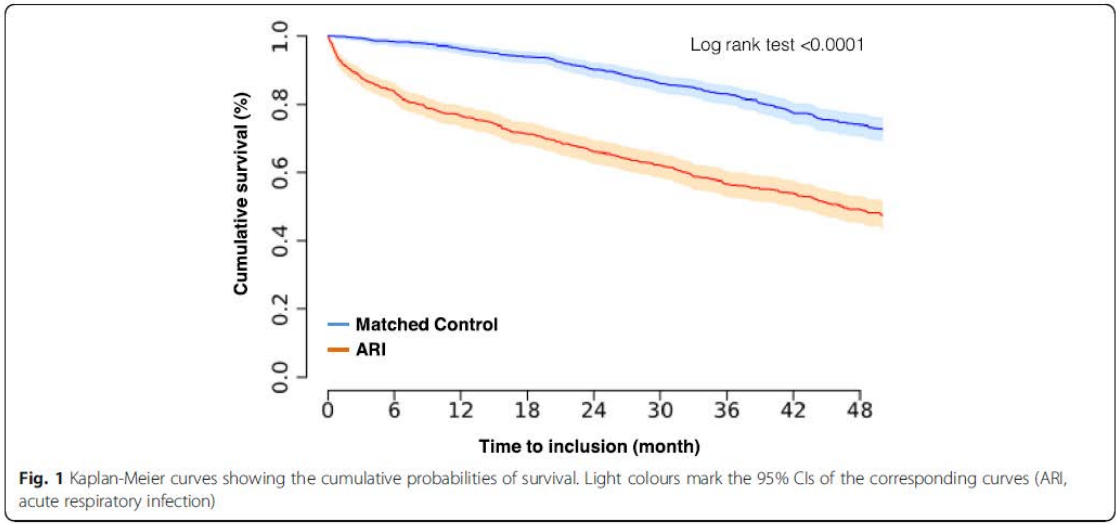
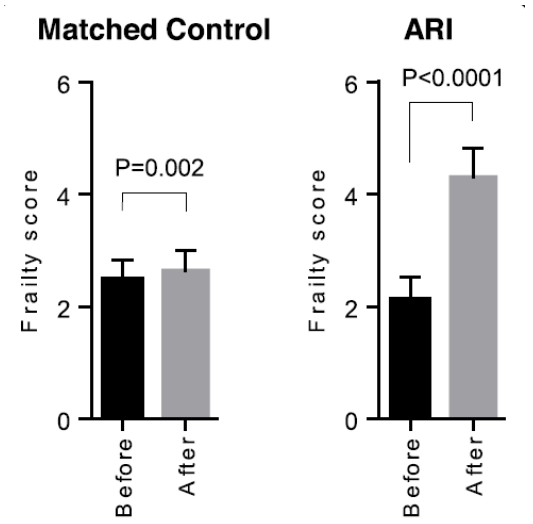


Fig. 1 Kaplan-Meier curves showing the cumulative probabilities of survival. Light colours mark the 95% CIs of the corresponding curves (ARI, acute respiratory infection)



Guillon A et al., Crit Care 2020;24:384.

Lot of (heterogeneous) trials

THE EFFECT OF HYDROCORTISONE UPON THE COURSE OF PNEUMOCOCCAL PNEUMONIA TREATED WITH PENICILLIN*

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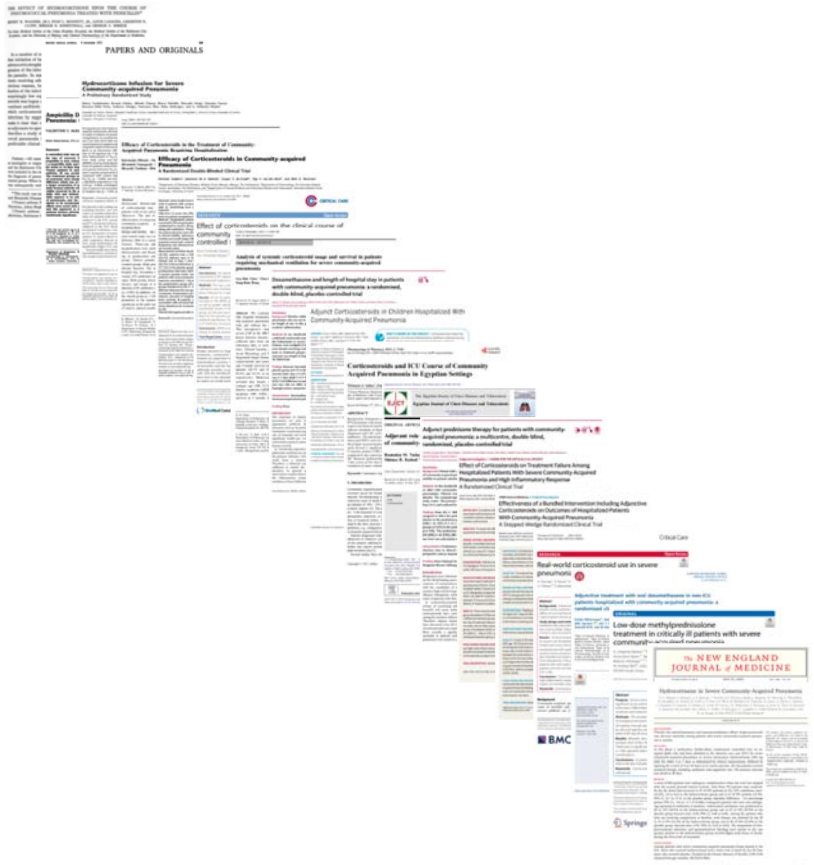
In a number of experimental situations, it has been shown beyond question that initiation of bacterial or viral infection in animals receiving cortisone or adrenocorticotrophic hormone (ACTH) is followed by unusually rapid progression of the infectious process with the outcome overwhelmingly in favor of the parasite. In man as well, the occurrence of a variety of infections in patients receiving adrenal steroids is well documented although it has not, for obvious reasons, been possible to assay with exactness the possible intensification of the infectious process in man by these hormones. On the other hand, surprisingly few experiments have been reported in which administration of steroids was begun *after* infection had been established in animals or where concomitant antibiotic therapy was employed. Furthermore, enough instances in which corticosteroids have appeared to facilitate recovery in severe human infections by suppressing so-called "toxemia" have now been described to make it clear that cautious exploration of the clinical usefulness of these drugs as adjuvants to specific antimicrobial therapy is worthwhile. The present report describes a study of the effect of hydrocortisone upon the course of pneumococcal pneumonia treated with penicillin, a human infection with a rather predictable clinical course.

Bull Johns Hopkins Hosp 1956;98:197-215.



For whom? General ward patients

Article	N	Intervention	Outcome
Blum, Lancet 2015	785	Prednisone 50mg/d x 7d vs. PLA	Time to clinical stability
Wittermans, ERJ 2021	401	DXM 6mg/d x 4d vs. PLA	LOS

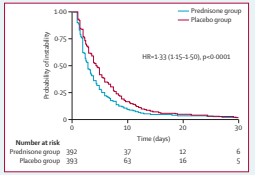
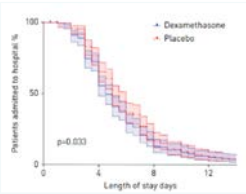
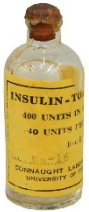


Figure 2: Kaplan-Meier curve of time to clinical stability





For whom? ICU patients? the time of uncertainty

Analysis 1.2. Comparison 1 Corticosteroids versus no treatment or placebo, Outcome 2 Mortality - adults, severe pneumonia, by allocation concealment.

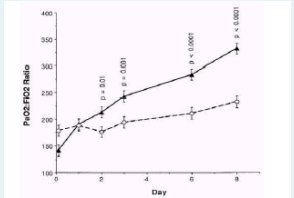
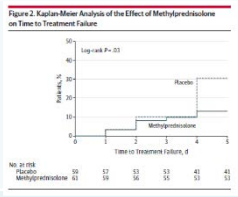
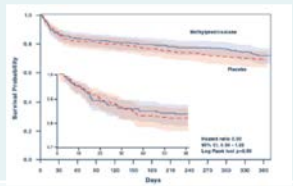
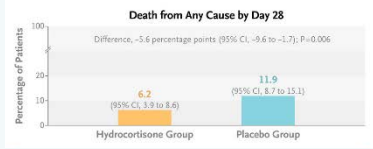
Study or subgroup	Corticosteroids n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.2.1 Low risk of bias					
Blum 2015	15/202	13/184		20.95%	1.05[0.51,2.15]
Confalonieri 2005	0/23	7/23		11.55%	0.07[0,1.1]
McHardy 1972	3/40	9/86		8.8%	0.72[0.2,2.51]
Snijders 2010	5/48	5/45		7.95%	0.94[0.29,3.02]
Torres 2015	6/61	9/59		14.09%	0.64[0.24,1.7]
Subtotal (95% CI)	**374**	**397**		**63.35%**	**0.72[0.46,1.13]**
Total events: 29 (Corticosteroids), 43 (Control)					
Heterogeneity: Tau^2=0; Chi^2=4.08, df=4(P=0.4); I^2=1.93%					
Test for overall effect: Z=1.42(P=0.16)					
1.2.2 Unclear risk of bias					
El-Ghamrawy 2006	3/17	6/17		9.24%	0.5[0.15,1.68]
Marik 1993	1/14	3/16		4.31%	0.38[0.04,3.26]
Nafae 2013	4/60	6/20		13.86%	0.22[0.07,0.71]
Sabry 2011	2/40	6/40		9.24%	0.33[0.07,1.55]
Subtotal (95% CI)	**131**	**93**		**36.65%**	**0.34[0.17,0.68]**
Total events: 10 (Corticosteroids), 21 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.92, df=3(P=0.82); I^2=0%					
Test for overall effect: Z=3.05(P=0)					
Total (95% CI)	**505**	**490**		**100%**	**0.58[0.4,0.84]**
Total events: 39 (Corticosteroids), 64 (Control)					
Heterogeneity: Tau^2=0; Chi^2=9.07, df=8(P=0.34); I^2=11.77%					
Test for overall effect: Z=2.84(P=0)					
Test for subgroup differences: Chi^2=3.17, df=1 (P=0.08), I^2=68.45%					

Stern A et al. Cochrane Database of Systematic Reviews 2017

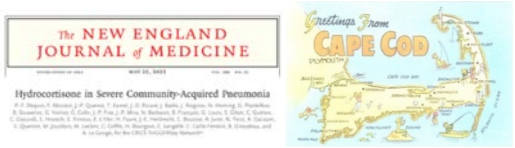
For whom? ICU patients

ICU

-low-risk of bias trials
-clinically relevant outcome

Article		N	Intervention	Outcome	
	Confalonieri, AJRCCM 2005	48	HSHC 240mg/d x 7d vs. PLA	PaO2:FiO2 MODS	
	Torres, JAMA 2015	120	MPD 1mg/kg/d x 5d vs. PLA	Therapeutic failure	
	Meduri, ICM 2022	584	MPD 40mg/d x 7d Tapered till D20 vs. PLA	Mortality Day 60	
	Dequin, NEJM 2023	795	HSHC 200mg/d x 4d Tapered till D7-14 vs. PLA	Mortality Day 28	

For whom? All ICU-patients?

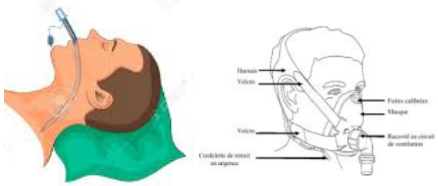


PEEP >5 cmH2O

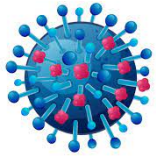
PaO2:FiO2 <300
FiO2 >0.5

estP:F <300

PIS >130 (group 5)



Main non-inclusion criteria



Influenza

For whom? CAP-related septic-shock?

APROCCHSS trial, post-hoc

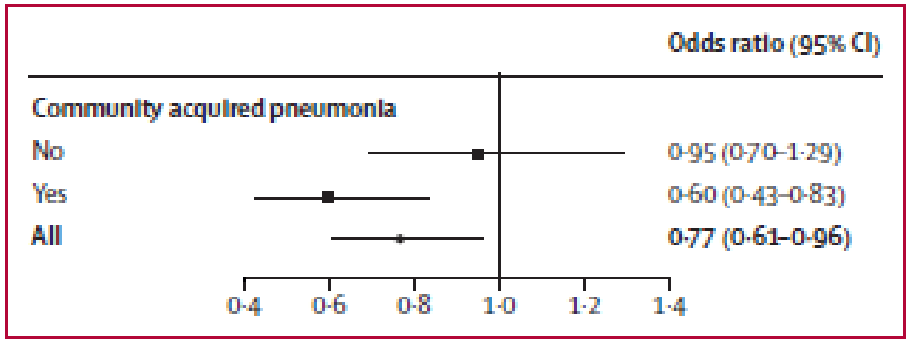


Figure 1: Forest plot of corticosteroid effects across subgroups with or without community acquired pneumonia

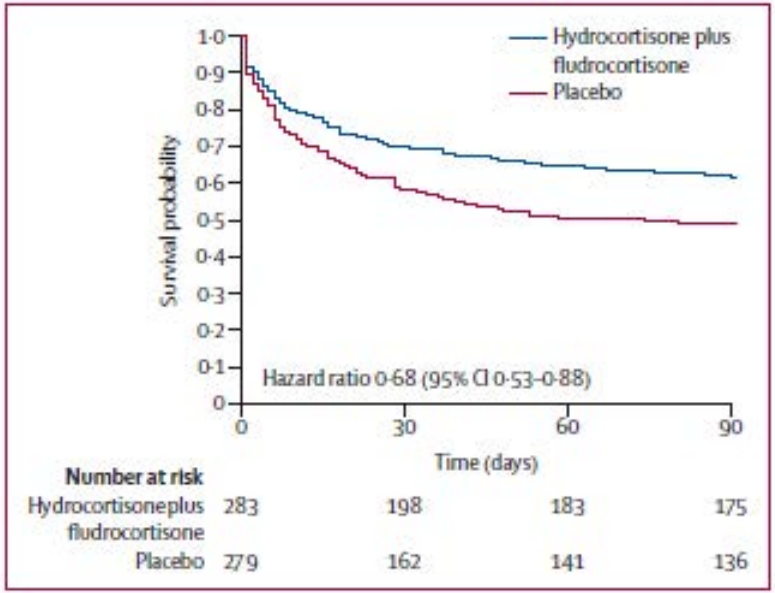


Figure 2: 90-day survival distributions

Heming N et al. Lancet Respir Med 2024;12:366-74.

For whom? Immuno-suppressed patients?

Only data for HIV-related pneumocystosis

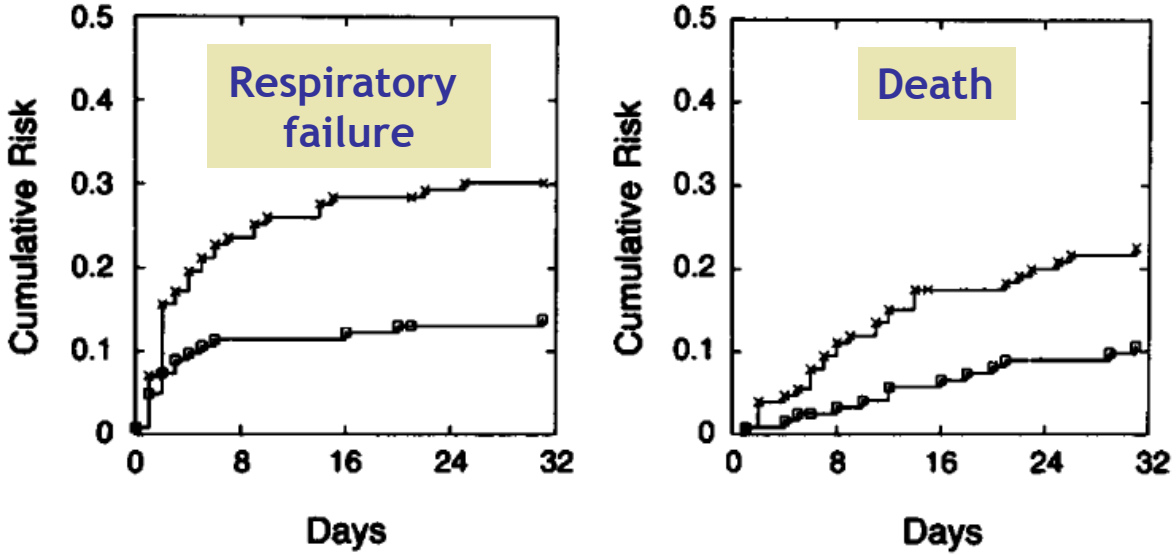


Figure 1. Cumulative Risk of an Unfavorable Outcome over a Period of 31 Days.

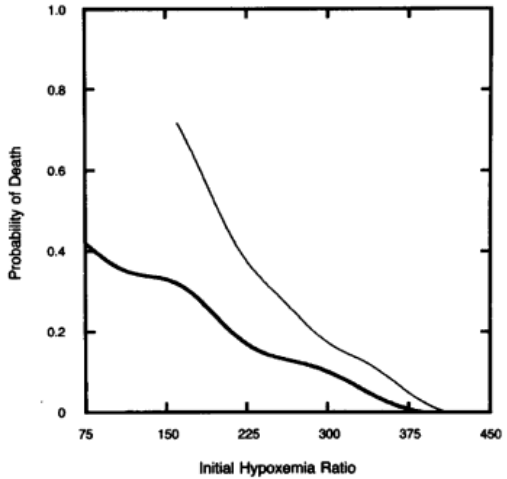
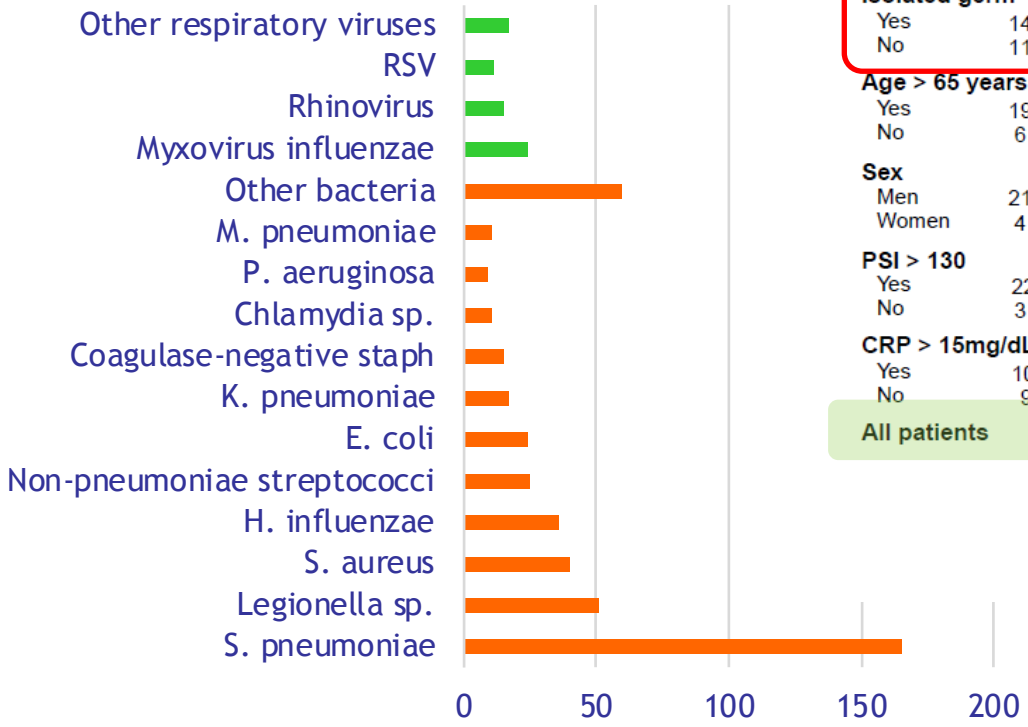


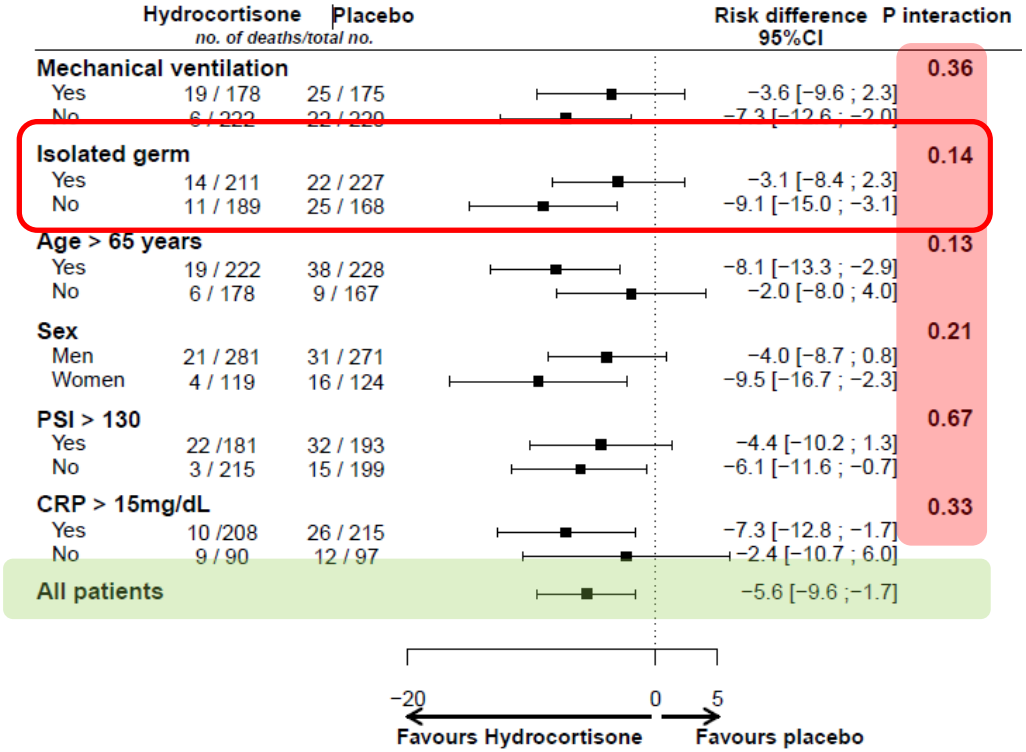
Figure 2. Probability of Death from Respiratory Causes, According to Initial Hypoxemia Ratio.

Bozette et al. New Engl J Med 1990;323:1451-7

For which pathogen?

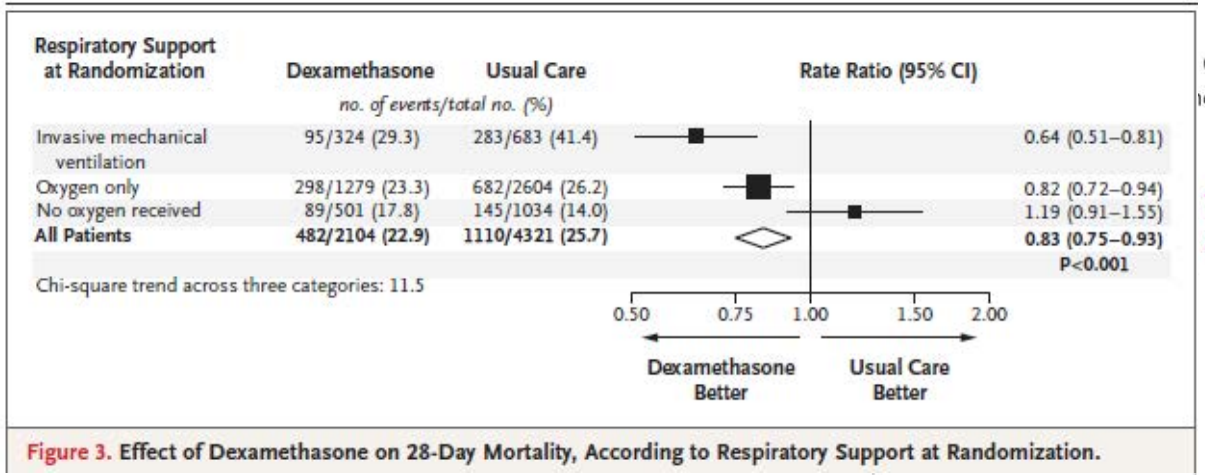
At least 1 identified pathogen:
54%





Even for viruses?! Once upon a time…

Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury *Russell, Lancet 2020;395:473-5.*

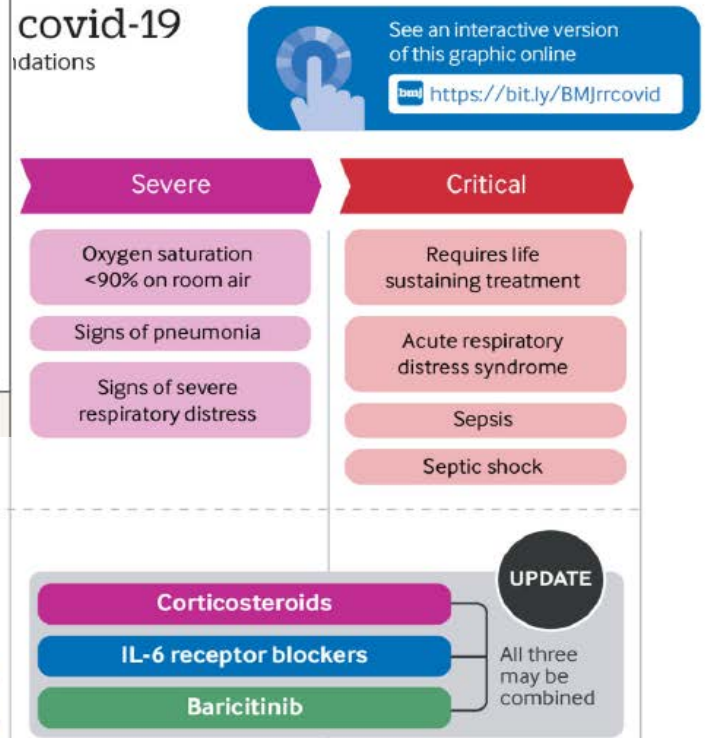


Respiratory Support at Randomization	Dexamethasone	Usual Care	Rate Ratio (95% CI)
	no. of events/total no. (%)		
Invasive mechanical ventilation	95/324 (29.3)	283/683 (41.4)	0.64 (0.51–0.81)
Oxygen only	298/1279 (23.3)	682/2604 (26.2)	0.82 (0.72–0.94)
No oxygen received	89/501 (17.8)	145/1034 (14.0)	1.19 (0.91–1.55)
All Patients	**482/2104 (22.9)**	**1110/4321 (25.7)**	**0.83 (0.75–0.93)**
			P<0.001

Chi-square trend across three categories: 11.5

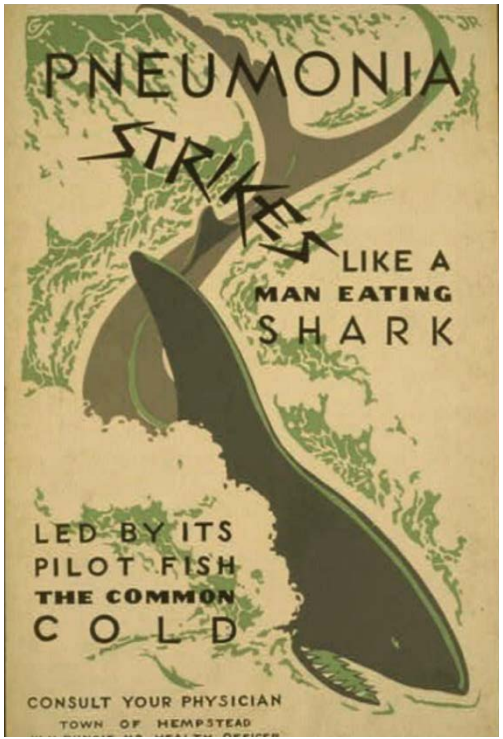
Figure 3. Effect of Dexamethasone on 28-Day Mortality, According to Respiratory Support at Randomization.

Recovery Collaborative Group, New Engl J Med 2021;384:693-704.



BMJ 2020;370:m3379 (actualisation septembre 2022)

For flu? No to date!



Analysis 1.1. Comparison 1 Corticosteroid therapy versus no corticosteroid therapy, Outcome 1 Mortality following admission, hospitalised participants - studies reporting odds ratios.

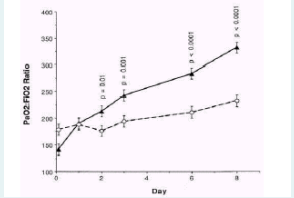
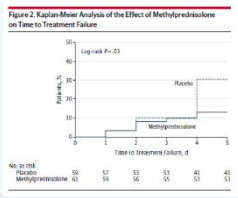
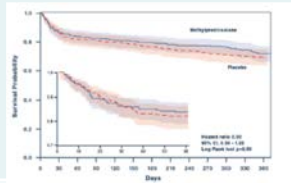
Study or subgroup	Corticos-teroid group N	No corti-costeroid group N	log[Odds Ratio] (SE)	Odds Ratio IV, Random, 95% CI	Weight	Odds Ratio IV, Random, 95% CI
1.1.1 Unadjusted mortality						
Balaganesakumar 2013	70	210	3.2 (0.354)		9.37%	23.75[11.87,47.52]
Chawla 2013	38	39	2.5 (1.083)		3.96%	11.79[1.41,98.41]
Huang 2017	29	19	0.2 (0.658)		6.69%	1.26[0.35,4.57]
Kinikar 2012	21	71	2.1 (0.614)		7.06%	8.12[2.44,27.05]
Li 2012	27	19	1.6 (1.127)		3.76%	5.14[0.56,46.82]
Mady 2012	43	43	1.1 (0.473)		8.3%	2.87[1.14,7.25]
Patel 2013	39	24	1 (0.712)		6.25%	2.75[0.68,11.11]
Sertogullarindan 2011	7	13	0.8 (0.953)		4.64%	2.13[0.33,13.81]
Viasus 2011	37	129	1 (0.788)		5.69%	2.76[0.59,12.92]
Yu 2011a	54	74	1.8 (0.601)		7.17%	6.13[1.89,19.88]
Subtotal (95% CI)					**62.87%**	**4.79[2.35,9.79]**
Heterogeneity: Tau^2=0.81; Chi^2=27.1, df=9(P=0); I^2=66.79%						
Test for overall effect: Z=4.31(P<0.0001)						
1.1.2 Adjusted mortality						
Delaney 2016	280	327	0.6 (0.256)		10.16%	1.85[1.12,3.06]
Kim 2011	107	138	0.8 (0.387)		9.07%	2.2[1.03,4.7]
Liem 2009	29	38	1.4 (0.654)		6.72%	4.11[1.14,14.82]
Linko 2011	72	60	1.2 (0.963)		4.58%	3.3[0.5,21.78]
Xi 2010	52	103	1.3 (0.669)		6.6%	3.67[0.99,13.6]
Subtotal (95% CI)					**37.13%**	**2.23[1.54,3.24]**

Favours corticosteroid 0.01 0.1 1 10 100 Favours no corticosteroid

Lansbury L et al. Cochrane Database of Systematic Reviews 2019, Issue 2. Art. No.: CD010406.

How? Are all corticosteroids equal?

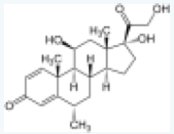
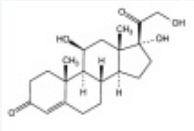
ICU

Article		N	Intervention	Outcome	
	Confalonieri, AJRCCM 2005	48	HSHC 240mg/d x 7d vs. PLA	PaO2:FiO2 MODS	
	Torres, JAMA 2015	120	MPD 1mg/kg/d x 5d vs. PLA	Therapeutic failure	
	Meduri, ICM 2022	584	MPD 40mg/d x 7d Tapered till D20 vs. PLA	Mortality Day 60	
	Dequin, NEJM 2023	795	HSHC 200mg/d x 4d Tapered till D7-14 vs. PLA	Mortality Day 28	

How? Two recent and discordant trials

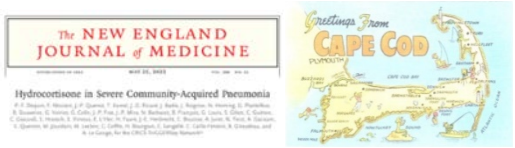
	ESCAPe (N=584/1,406)	CAPE COD (N=795/1,200)
MV	33.0%	44.4%
Vasopressors	13.0%	11.6%
PIS class IV or V	82.0%	82.6%
Sex ratio	26.8	2.27
Age (y)	69	67
Death on D 28		6.2% P=0.006 11.9%
Death on D60	16.0% P=0.61 18.0%	
Death on D90		9.3% P=0.02 14.7%

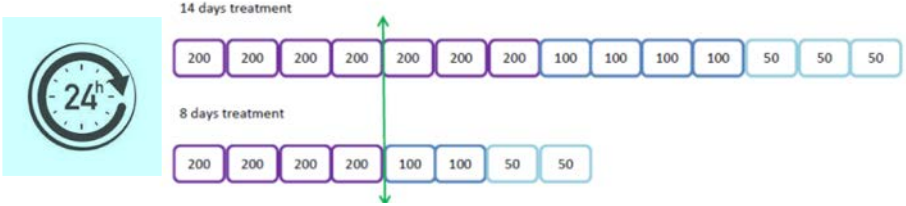
Why these discrepansies?

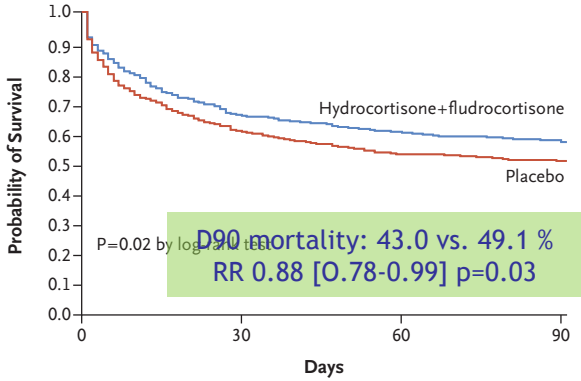
	ESCAPe (N=584/1,406)	CAPE COD (N=795/1,200)
Sex ratio	26.8	2.27
Corticosteroid	 MPD 40 mg/d x 7d then tapered	 HC 200 mg/d x 4-7d then tapered
Inclusion window	<96h post hospital admission	<24h post 1st severity criterion
Treatment course	20 d	8-14 d (median: 5 d)

Heterogeneity in the treatment effect ?

Hydrocortisone as a panacea?



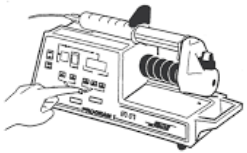




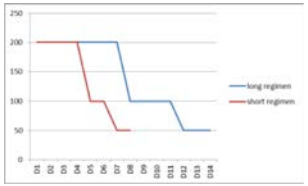
D90 mortality: 43.0 vs. 49.1 %
RR 0.88 [0.78-0.99] p=0.03

Annane et al. NEJM 2018;378:809-18.

Scheme adapted to evolution on day 4
Experimental treatment stopped at ICU discharge
(median HC infusion: 5 days)

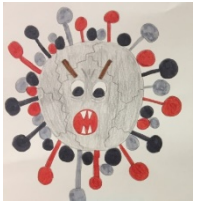


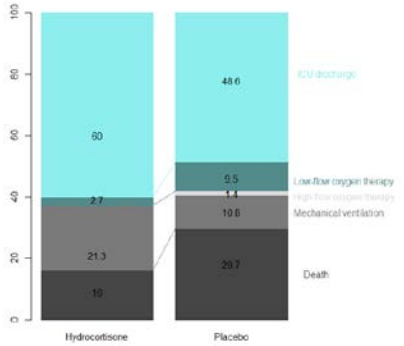
Continuous infusion



Gradual tapering

?

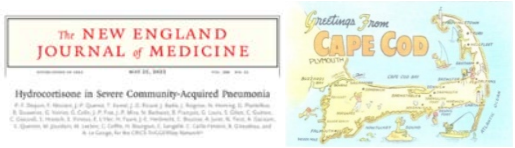


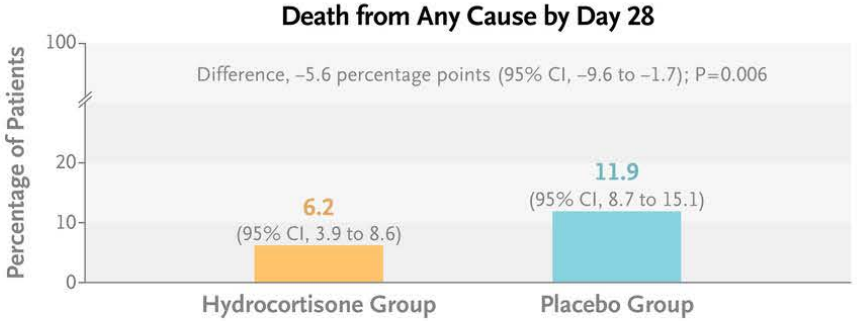


Day 28 status, p=0.025
CAPE-COVID trial, post-hoc analysis

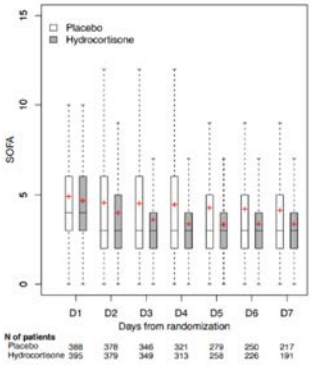
Dequin PF et al. JAMA 2020;324:1298-306.

How? How it works?

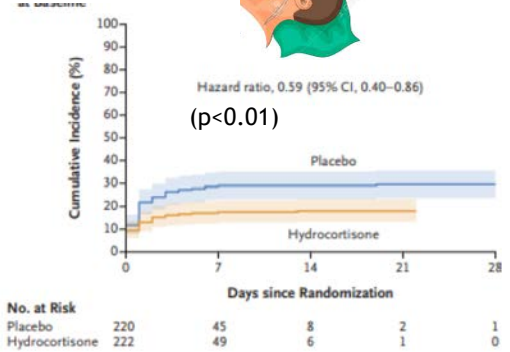




SOFA score

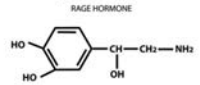


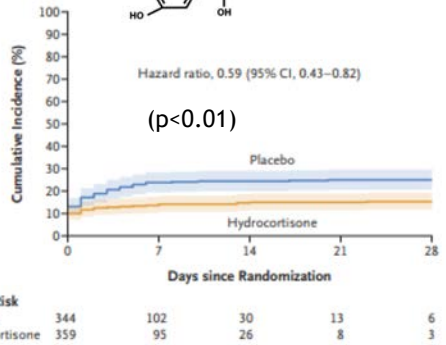
(p=0.003)



(p<0.01)

Norepinephrine





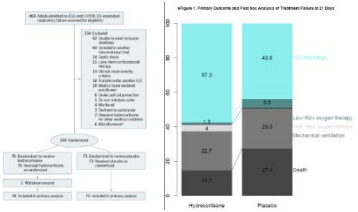
(p<0.01)

Anti-inflammatory hypothesis?

- 20 patients **w COVID-19**
- Co-included in IMPACT study and CAPE-COVID RCT

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

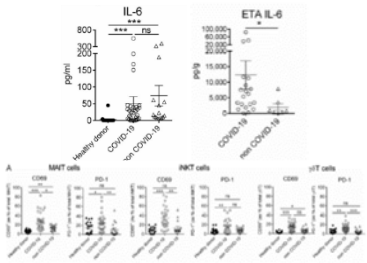
Effect of Hydrocortisone on 21-Day Mortality or Respiratory Support Among Critically Ill Patients With COVID-19
A Randomized Clinical Trial

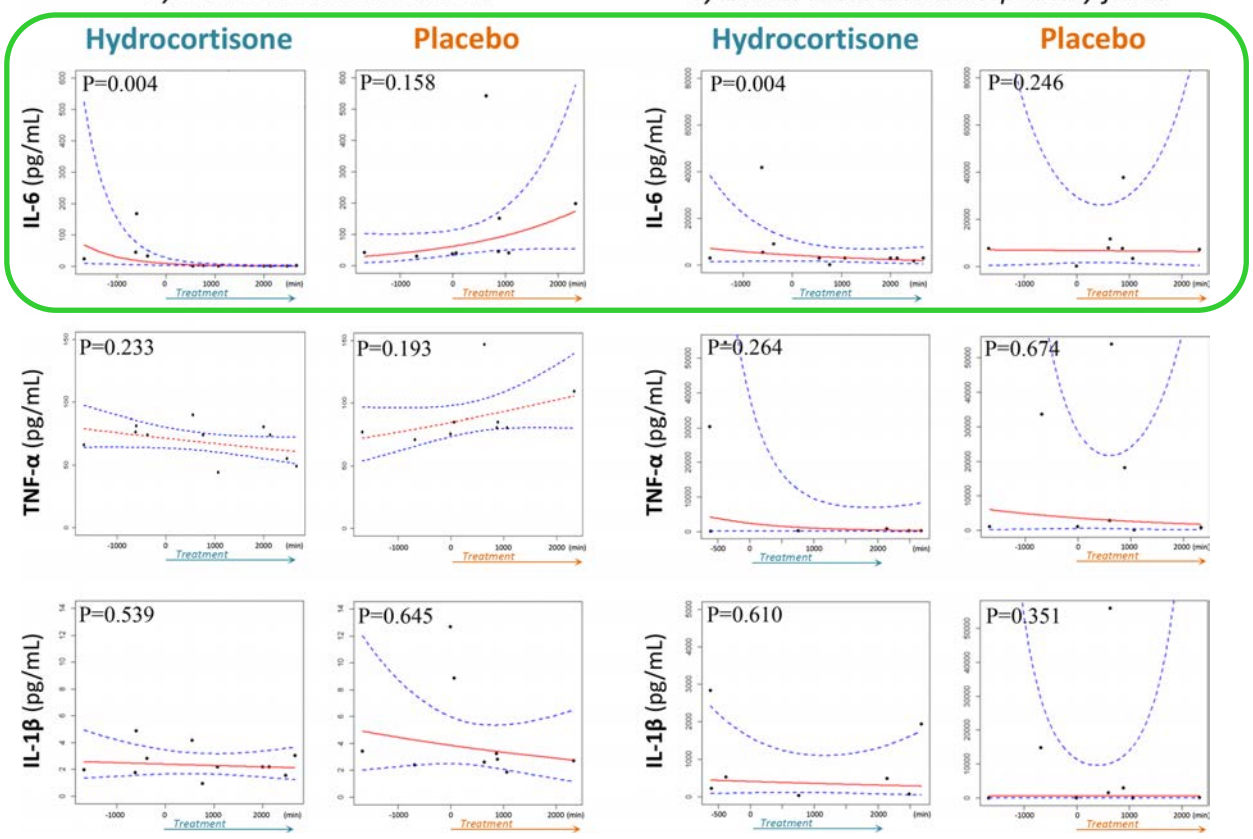


Phenotypical and functional alteration of unconventional T cells in severe COVID-19 patients

Youenn Jouan[1,2,3,4], Antoine Guillon[1,2,3]*, Loic Gonzalez[1,2]*, Yonatan Perez[1,2,3], Chloé Boisseau[1,2], Stephan Ehrmann[1,2,3], Marion Ferreira[2,5], Thomas Daix[6,7,8], Robin Jeannet[6,7,8], Bruno François[6,7,8], Pierre-François Dequin[1,2,3], Mustapha Si-Tahar[1,2], Thomas Baranek[1,2]*, and Christophe Paget[1,2]**

JEM Journal of Experimental Medicine

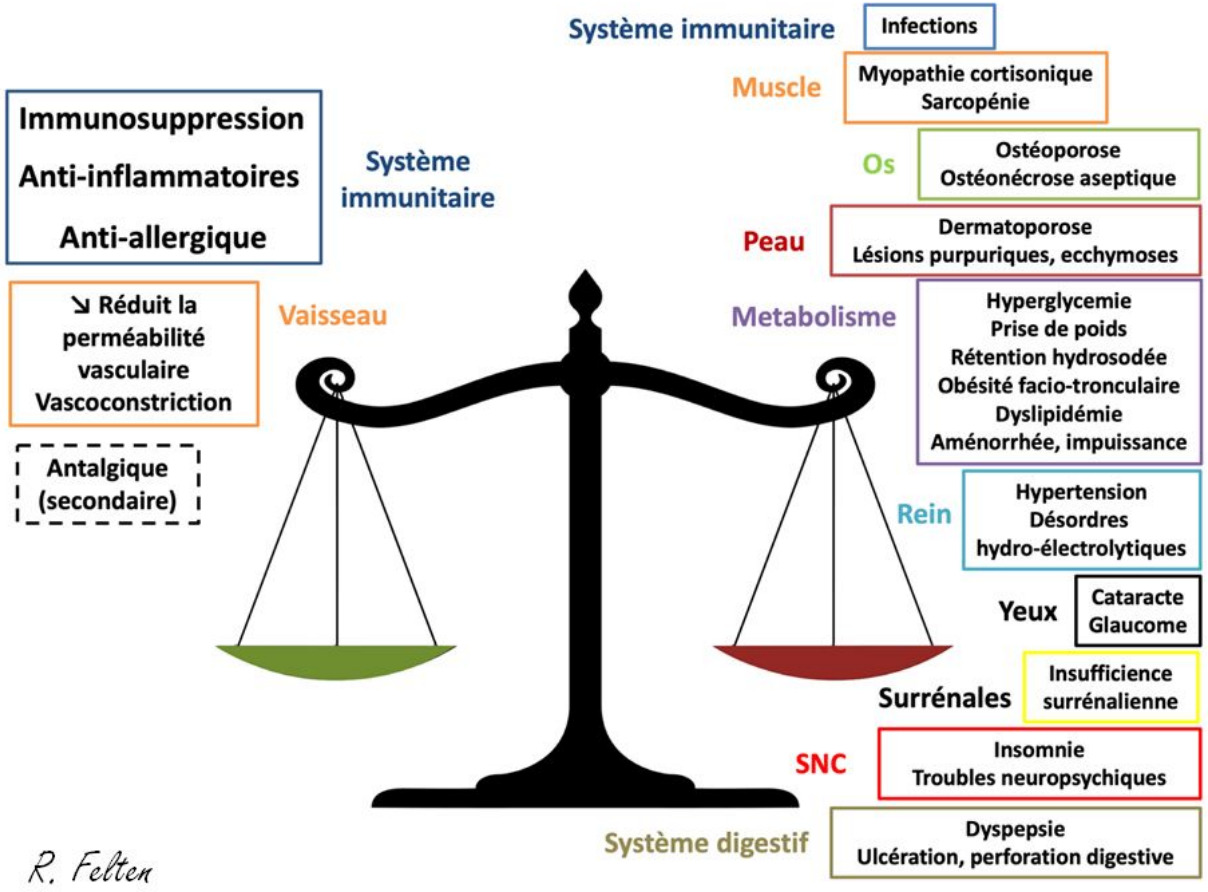




Guillon A et al. Crit Care 2024;28:101.

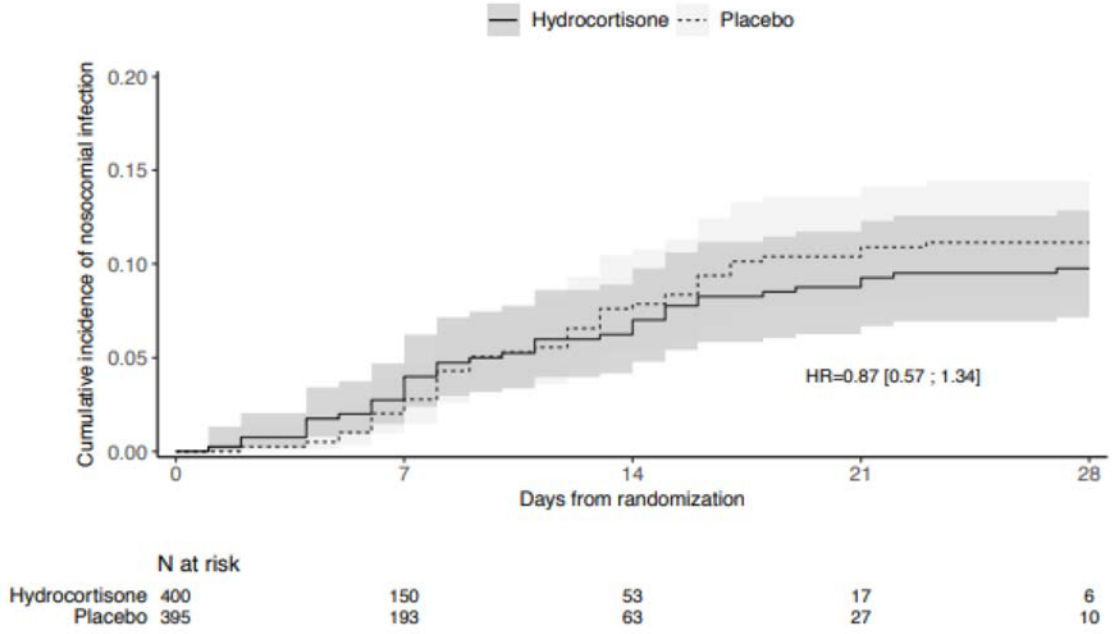
Is it safe?

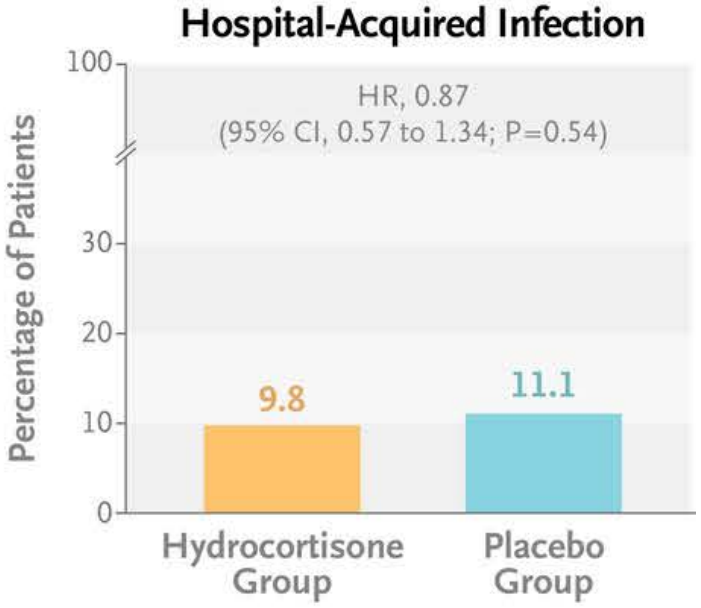
SIDE EFFECTS


Immunosuppression
Anti-inflammatoires
Anti-allergique
Système immunitaire
↘ Réduit la perméabilité vasculaire
Vascoconstriction
Vaisseau
Antalgique (secondaire)
Système immunitaire
Infections
Muscle
Myopathie cortisonique
Sarcopénie
Os
Ostéoporose
Ostéonécrose aseptique
Peau
Dermatoporose
Lésions purpuriques, ecchymoses
Metabolisme
Hyperglycemie
Prise de poids
Rétention hydrosodée
Obésité facio-tronculaire
Dyslipidémie
Aménorrhée, impuissance
Rein
Hypertension
Désordres hydro-électrolytiques
Yeux
Cataracte
Glaucome
Surrénales
Insufficience surrénalienne
SNC
Insomnie
Troubles neuropsychiques
Système digestif
Dyspepsie
Ulcération, perforation digestive
R. Felten

Are corticosteroids safe in critically-ill patients?

sCAP





VAP	
HC (n=152)	Placebo (n=171)
32.0 (21.0%)	38.0 (22.2%)

Cumulative incidence of hospital-acquired infection

Are corticosteroids safe in critically-ill patients?

The NEW ENGLAND JOURNAL of MEDICINE

Hydrocortisone in Severe Community-Acquired Pneumonia

sCAP

	HC (n=231)	Placebo (n=177)	Median of difference	p
Insulin therapy, from inclusion to D7 Median (IQR), IU/day	35.5 [15.0; 57.5]	20.5 [9.4;48.5]	8.7 [4.0; 13.8]	0.0002

Are corticosteroids safe in critically-ill patients?

Sepsis and septic shock

Adverse events				
Superinfection	10	6970	1.04	0.95 to 1.15
Hyperglycemia	10	7017	1.05	0.98 to 1.12
Hypernatremia	6	5033	2.01	1.56 to 2.60
Gastroduodenal bleeding	8	2748	1.11	0.83 to 1.48
Muscle weakness	5	2647	1.73	1.49 to 1.99

Pirrachio R et al. NEJM Evidence 2023;2(6).

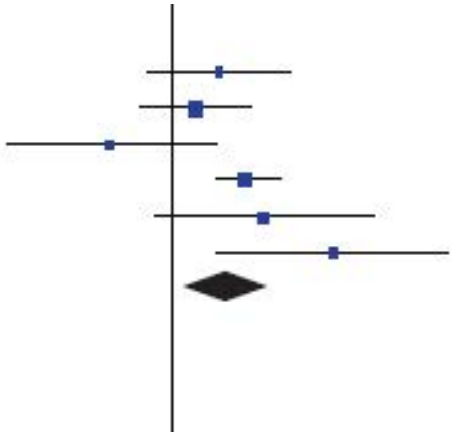
Are corticosteroids safe in critically-ill patients?

Influenza-associated pulmonary aspergillosis

1.3.5 Corticosteroids						
Duan *et al.* 2021	10	72	6	84	17.8%	2.10 [0.72, 6.09]
Huang *et al.* 2019	23	63	13	46	22.0%	1.46 [0.64, 3.32]
Nyga *et al.* 2020	3	10	13	25	11.5%	0.40 [0.08, 1.89]
Schauwvlieghe *et al.* 2018	46	83	99	349	28.2%	3.14 [1.92, 5.13]
Waldeck *et al.* 2020	7	9	33	72	10.8%	4.14 [0.80, 21.29]
Wauters 2012	7	9	7	31	9.6%	12.00 [2.02, 71.36]
Subtotal (95% CI)		**246**		**607**	**100.0%**	**2.28 [1.18, 4.39]**
Total events	96		171			

Heterogeneity: Tau^2=0.33; Chi^2=11.26, df=5 (P=0.05); I^2=56%

Test for overall effect: Z=2.47 (P=0.01)



Effect of administration regimen?

Chong WH et al. J Hosp Infect 2022;120:98-109.

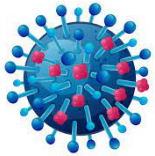
And in the future?

Biobank
Long-term effects?

CRP treshold?
IPDMA, CAP and sCAP
Smit JM et al. (submitted)

CAP-MA
IPDMA
(CAP, sCAP, CAP-related ARDS and CAP-related septic shock)

REMAP-CAP


?

Influenza

GUARDS

Here and now

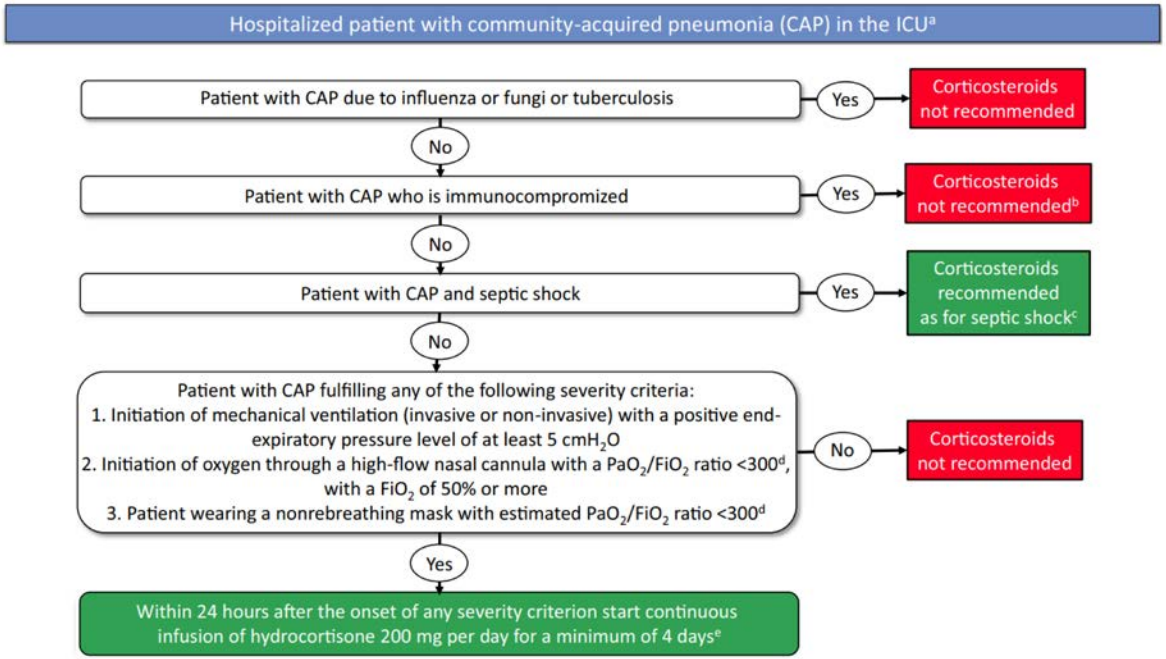
Hydrocortisone for almost everyone w/ sCAP

Whatever the pathogen

(But not (yet) for flu!)

So-called “low-dose”
Early start
Short-time
Add 9α-FC if septic shock

CRP treshold?



Dequin PF, Ramirez JA, Waterer G, Intensive Care Med 2023;49:1397-9.

merci
thank you
danke
gracias
obrigado
grazie
dankie
bedankt
dakujem
mochchakkeram
sukriya
ngiyabonga
dank je
terima kasih
matondo
dhanyavadagalu
dziękuję
sagolun
chokrane
謝謝
go raibh maith agat
спасибо
barka
arigatô
grazzi
мерси
tanemirt
mersi
diolch
dhanyavad
shukriya
teşekkü ederim
welalin
enkosi
gratias ago
misaotra
kop khun
najis tuke
hvala
rahmet
kop khun krap
mercé
leat
nandri
krap
gracie
tapadh
takk
didi madloba
mahalo
manana
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sobodi
tenki
murakoze
kiitos
vinaka
xièxie
ευχαριστώ
Баярлалаа
mauruuru
asante
taiku
nanni
teşekkür ederim
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kam sah hamnida
blagodaram
хвала
köszönöm
akun
acīū
sulpay
tack
bayarlalaa
djere dieuf
dékuji
rahmat
chnorakaloutioun
dhanyavad
shukriya
spas
grâcies
entosi
misaotra
matondo
dhanyavadagalu
dziękuję
chokrane
sagolun
tapadh
takk
mesi
gracie
krap
leat
nandri
mahalo
manana
dankon
sobodi
tenki
murakoze
kiitos
vinaka
xièxie
ευχαριστώ
Баярлалаа
mauruuru
asante
taiku
nanni
teşekkür ederim
trugarez
paldies
faafetai lava
kam sah hamnida
blagodaram
хвала
köszönöm
akun
acīū
sulpay
tack
bayarlalaa
djere dieuf
dékuji
rahmat
chnorakaloutioun
dhanyavad
shukriya
spas
grâcies
entosi
gratias ago