Immunomodulation des infections graves

Raphaël,
Saint-Georges combattant le dragon,
1503-1505,
Musée du Louvre, Paris

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Liens d'intérêt

Co-financements programme de recherche clinique :

Financements personnels comme consultant :

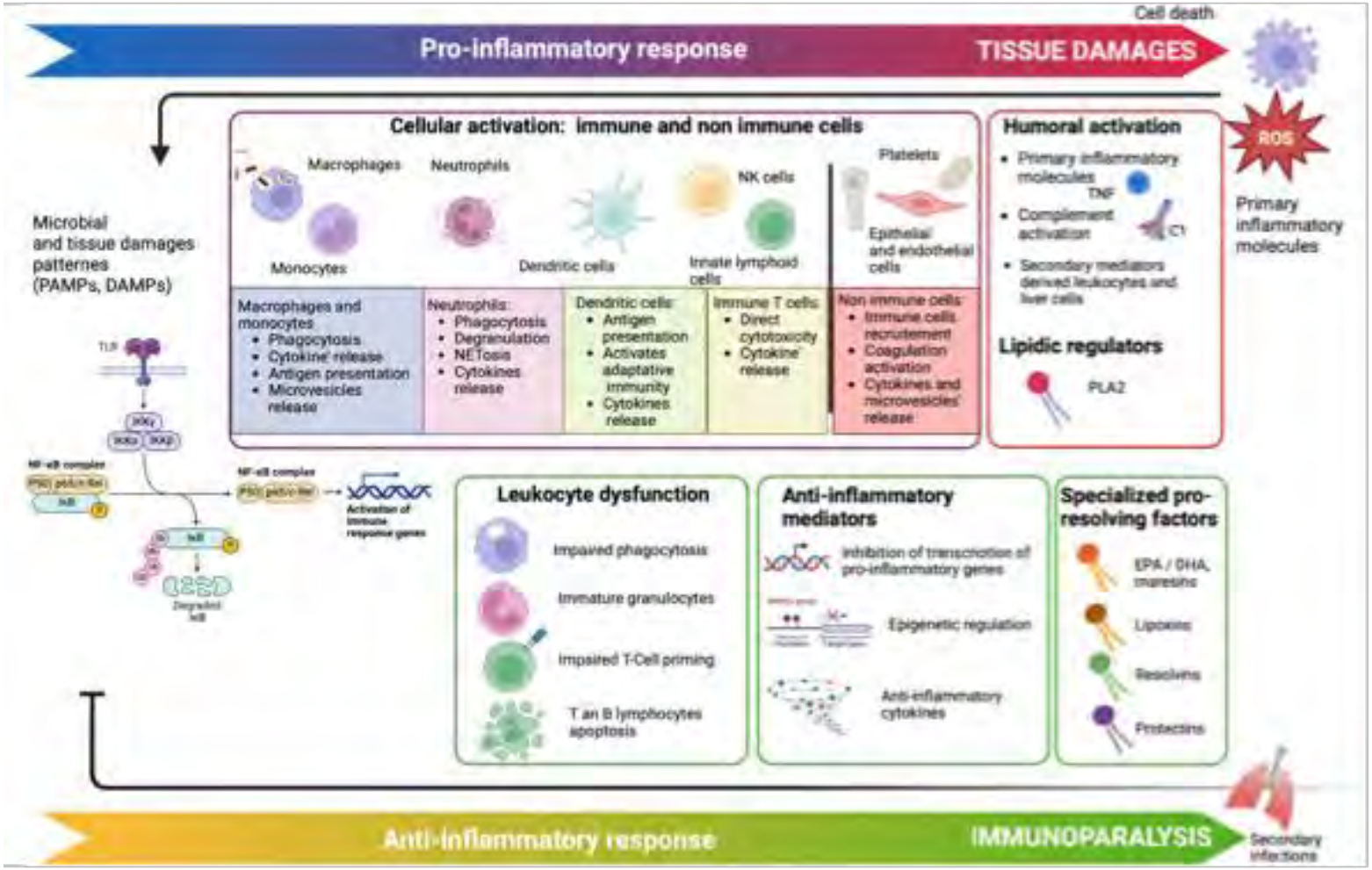
Institutionnels:

Editoriaux :

The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)

- Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection.

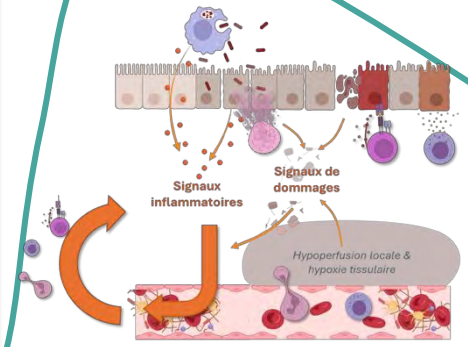
Singer M et al. JAMA 2016;315:801-10.



Stiel L et al. Ann Intensive Care 2024;14:137.

Intensité de la réponse immune

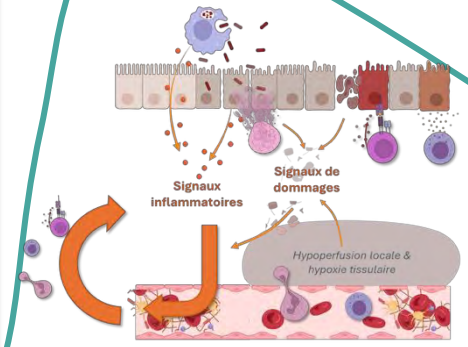
‘Hyperinflammation’



‘Immunoparalysie’

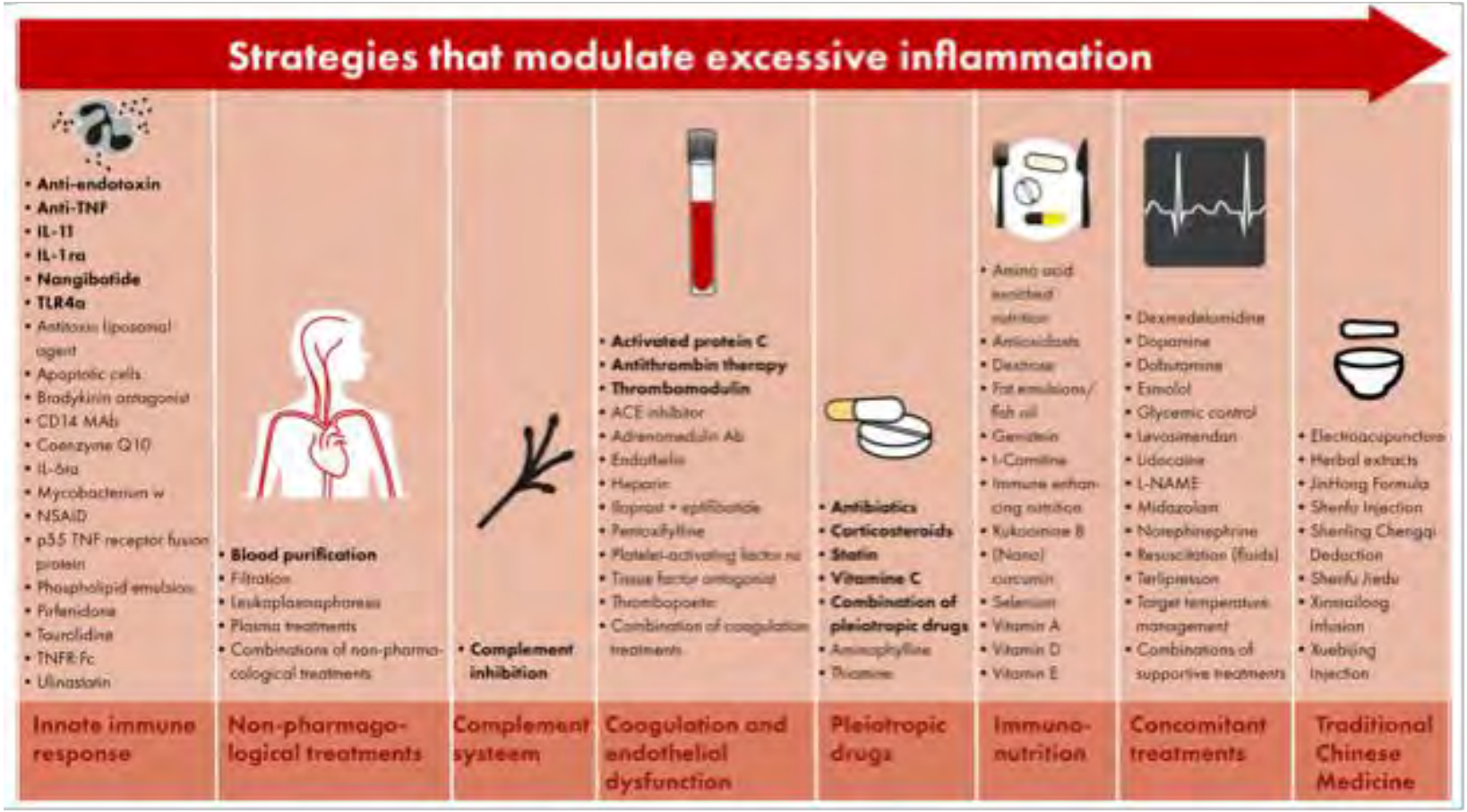
Intensité de la réponse immune

‘Hyperinflammation’



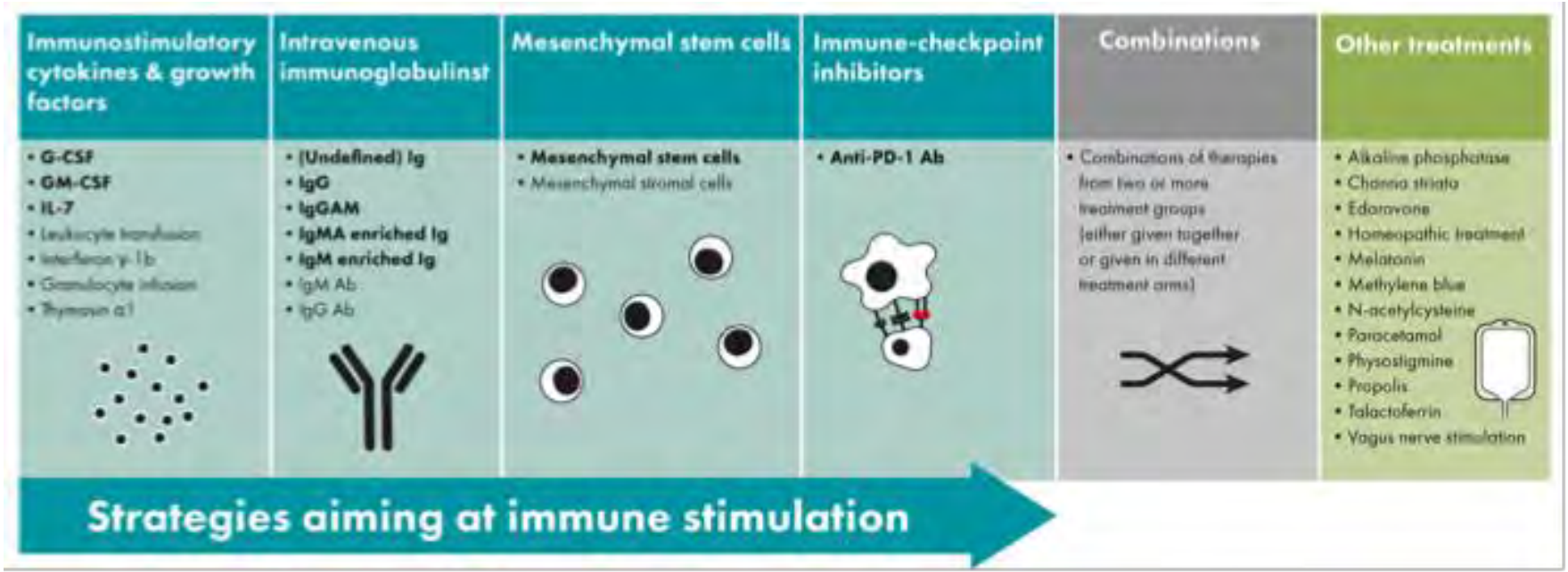
‘Immunoparalysie’

Un demi-siècle de recherche clinique



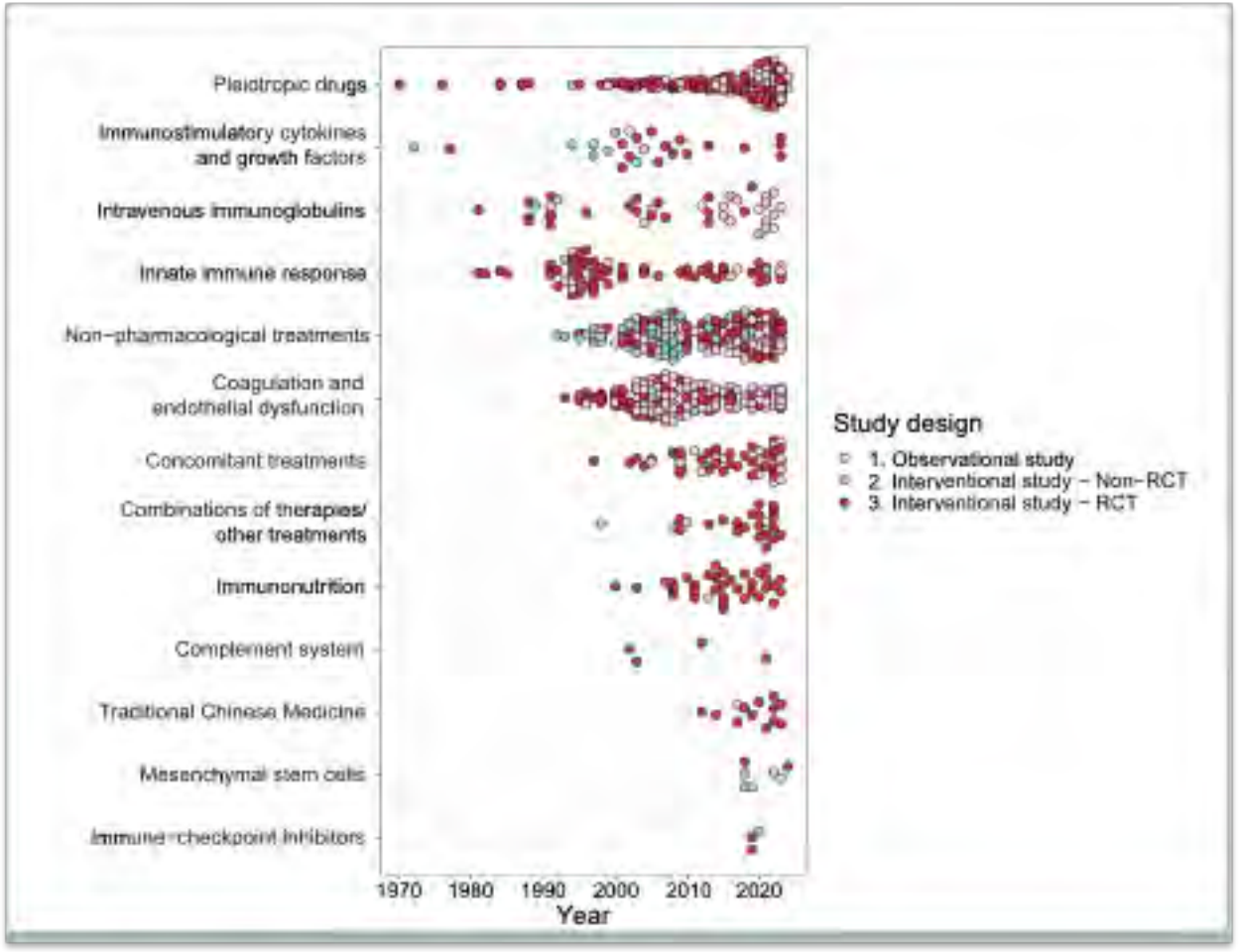
Slim MA et al. Crit Care 2024;28:183.

Un demi-siècle de recherche clinique



Slim MA et al. Crit Care 2024;28:183.

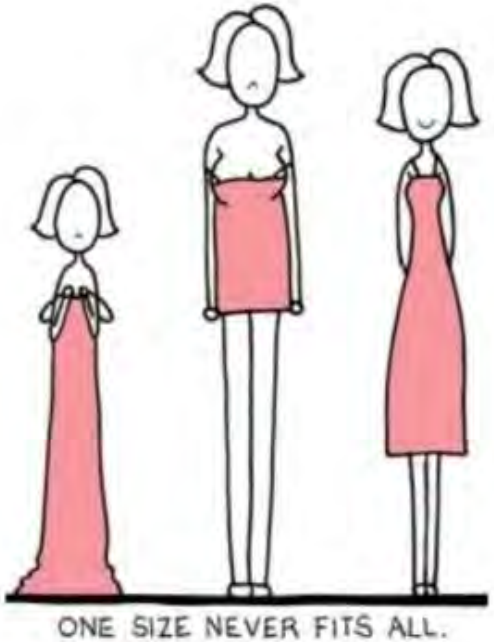
Un demi-siècle de recherche clinique

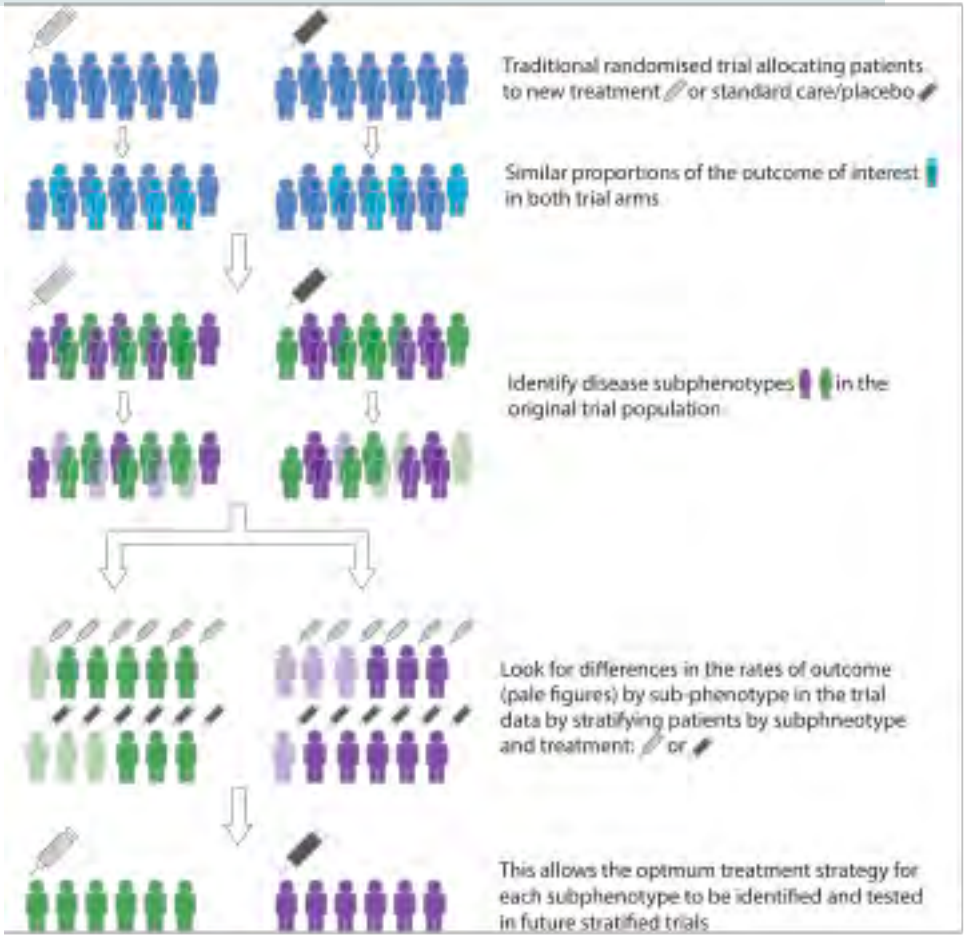


Très peu de résultats probants

Slim MA et al. Crit Care 2024;28:183.

Des essais pas assez ciblés





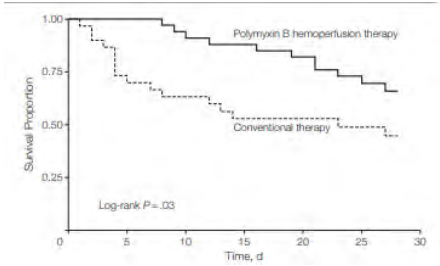
Antcliffe DB et al., Intensive Care Med 2025;51:756-68.

Phénotypes cliniques ? e.g. Polymyxin B hemoperfusion

CARING FOR THE CRITICALLY ILL PATIENT

Early Use of Polymyxin B Hemoperfusion in Abdominal Septic Shock
The EUPHAS Randomized Controlled Trial

n=62, 6 center



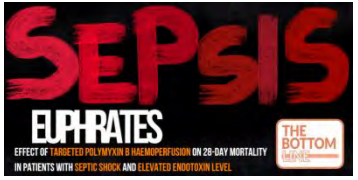
D28 mortality: 32.0 vs. 53.0 %
HR 0.43 [0.20-0.94]
(secondary outcome)

EUPHAS, Cruz DN et al. JAMA 2009;301:2445-52.

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Effect of Targeted Polymyxin B Hemoperfusion on 28-Day Mortality in Patients With Septic Shock and Elevated Endotoxin Level
The EUPHRATES Randomized Clinical Trial

n=450, 55 center



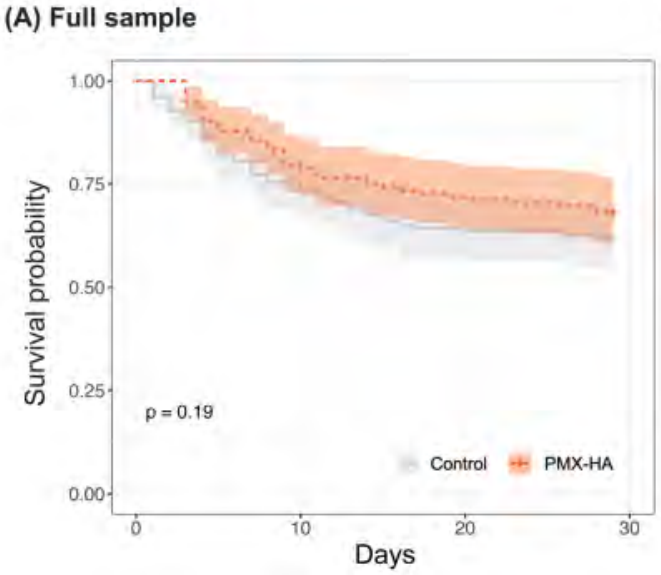
D28 mortality: 37.7 vs. 34.5 %
RR 1.09 [0.85-1.39] p=0.49

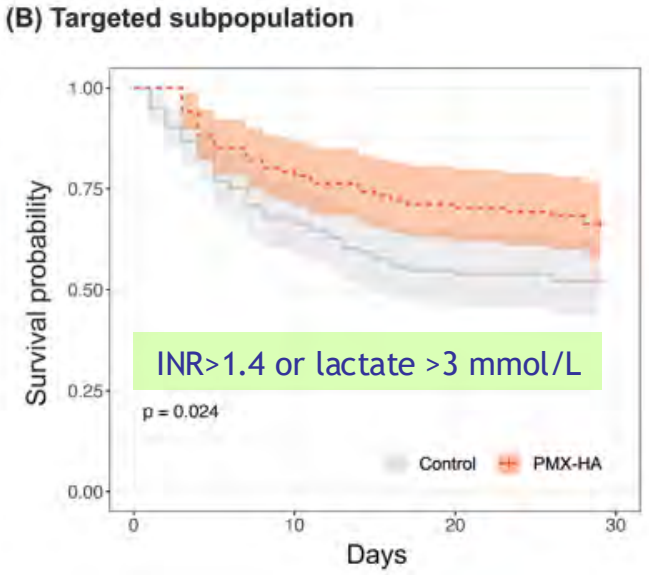
EUPHRATES, Dellinger RP et al. JAMA 2018;320:1455-63.

Phénotypes cliniques ? e.g. Polymyxin B hemoperfusion

JSEPTIC-DIC
Japanese retrospective cohort, n=1911
(350 treated w/ PXM-HA)
Machine-learning causal forest model
(Heterogeneity in Treatment Effect)

EUPHRATES
n=286 w/ high endotoxin activity on 450
(132 randomized to PXM-HA)
Validation.



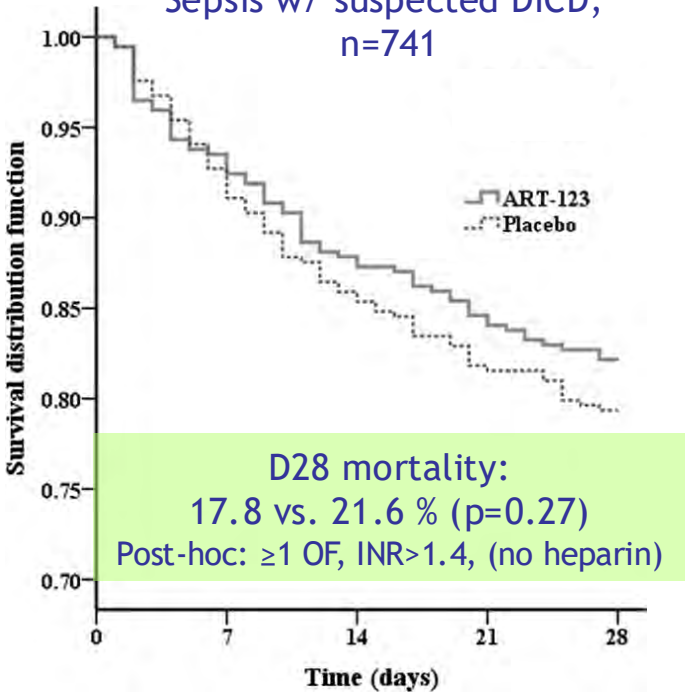


Okawa I et al. Crit Care 2023;27:245.

Phénotypes cliniques ? e.g. Thrombomoduline

A Randomized, Double-Blind, Placebo-Controlled, Phase 2b Study to Evaluate the Safety and Efficacy of Recombinant Human Soluble Thrombomodulin, ART-123, in Patients With Sepsis and Suspected Disseminated Intravascular Coagulation*

Sepsis w/ suspected DICD, n=741



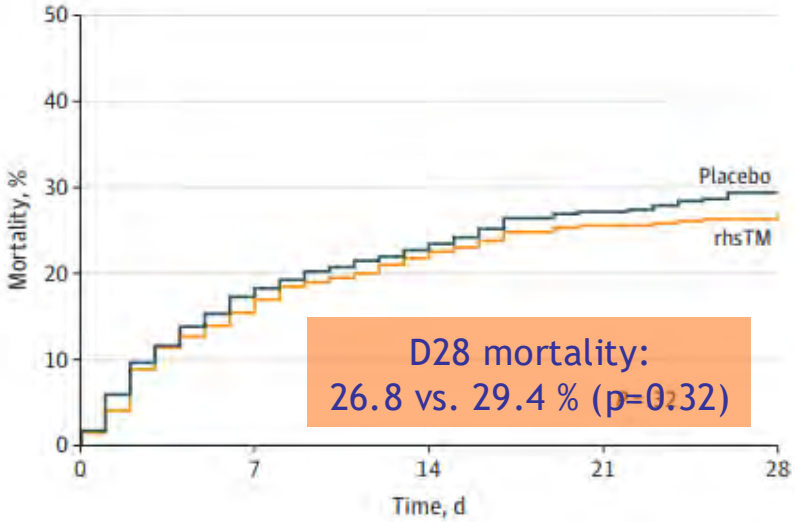
D28 mortality:
17.8 vs. 21.6 % (p=0.27)
Post-hoc: ≥1 OF, INR>1.4, (no heparin)

ART-123, Vincent JL et al. CCM 2013;41:2069-79.

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Effect of a Recombinant Human Soluble Thrombomodulin on Mortality in Patients With Sepsis-Associated Coagulopathy
The SCARLET Randomized Clinical Trial

Sepsis w/ DICD, n=800, 159 center



D28 mortality:
26.8 vs. 29.4 % (p=0.32)

SCARLET, Vincent JL et al. JAMA 2019;321:1993-2002.

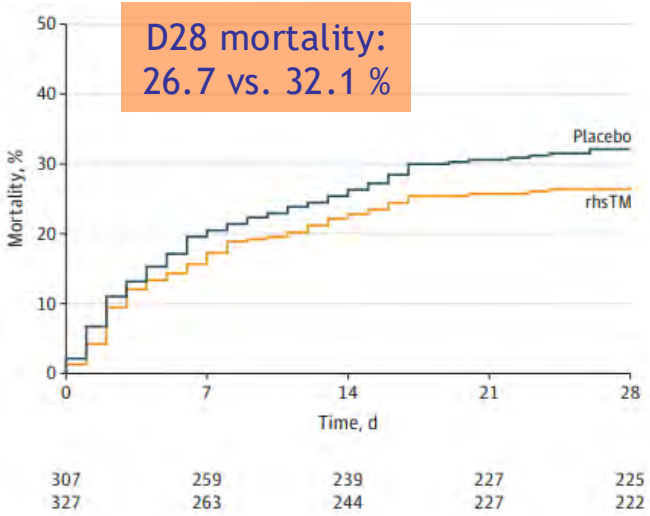
Phénotypes cliniques ? e.g. Thrombomoduline

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Effect of a Recombinant Human Soluble Thrombomodulin on Mortality in Patients With Sepsis-Associated Coagulopathy
The SCARLET Randomized Clinical Trial

INR still >1.4 at baseline, n=634/800 (post-hoc)

B Baseline coagulopathy subgroup



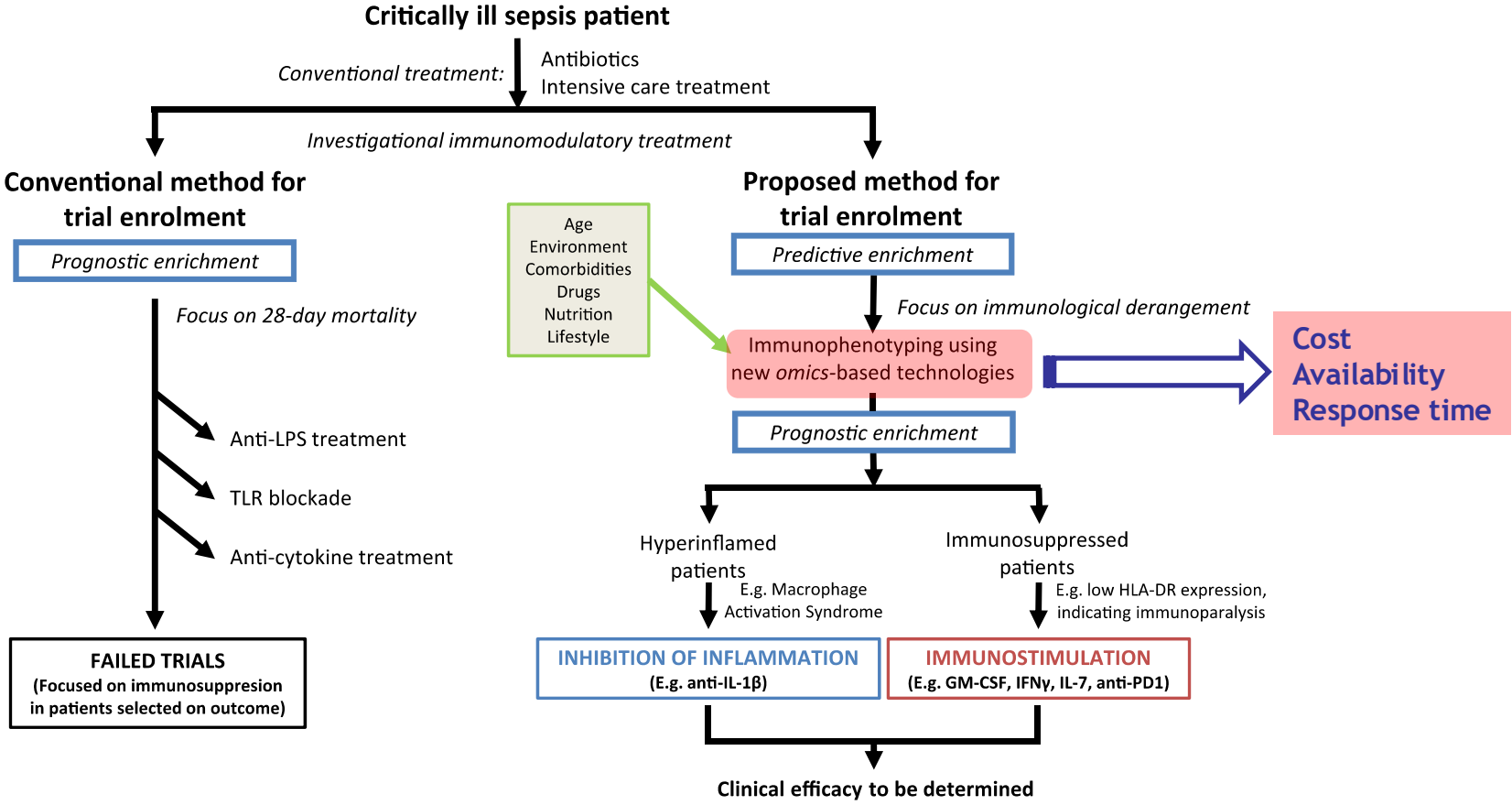
RESEARCH Open Access

Efficacy and safety of human soluble thrombomodulin (ART-123) for treatment of patients in France with sepsis-associated coagulopathy: post hoc analysis of SCARLET

D28 mortality:
All patients: 26.8 vs. 29.4 % (p=0.32)
French patients: 17.3 vs 25.7%
French Patients w/o baseline heparin:
13.0 vs. 29.5% (ARR 12.6 [0.4-32.8])

SCARLET, Vincent JL et al. JAMA 2019;321:1993-2002. *SCARLET post-hoc, François B et al. Ann Intensive Care 2021;11:53.*

Immune status as a biomarker

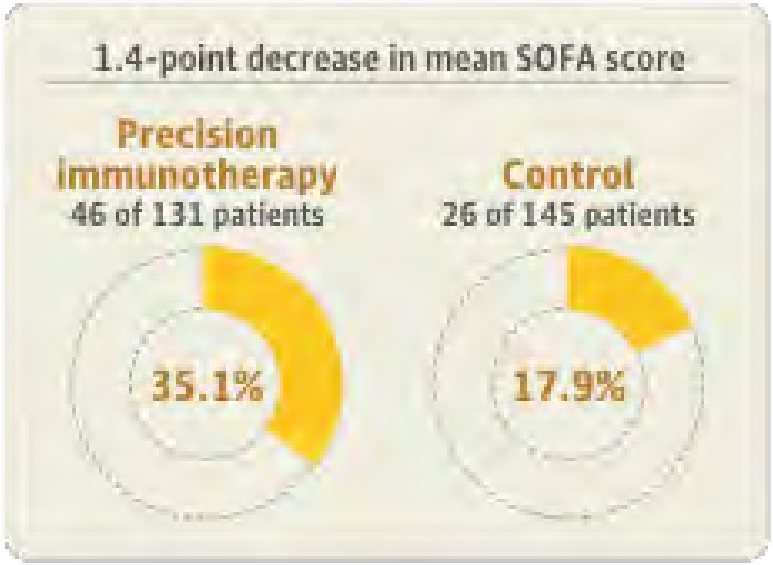


Pickkers P, Van der Poll T, Intensive Care Med 2019;45:110-2.

Preuve de concept ?

Precision Immunotherapy to Improve Sepsis Outcomes
The ImmunoSep Randomized Clinical Trial

Ferritine >4420 ng/mL	Anakina (N=25)
	Placebo (N=23)
Ferritine ≤4420 ng/mL ET HLA-DR <5000	rhIFNγ (N=106)
	Placebo (N=122)



p=0,002

Giamarellos-Bourboulis EJ et al. JAMA 2026;335:775-86.

Immunostimulation ?

IFN-gamma-1b

Interferon gamma-1b for the prevention of hospital-acquired pneumonia in critically ill patients: a phase 2, placebo-controlled randomized clinical trial

109 patients (200 planned) under MV
w/ at least 1 organ failure
IFN gamma-1b 100 μg x 5 vs. PLA
Stopped for safety.

D28 mortality and/or HAP:
47.3 vs. 30.2 % (p=0.06)
(non-septic patients, CTx)

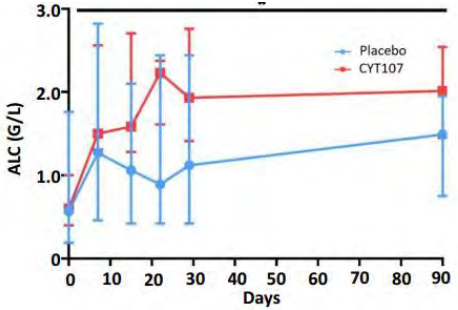
Roquilly A et al. Intensive Care Med 2023;49:530-44.

iv IL-7

RESEARCH Open Access

Intravenously administered interleukin-7 to reverse lymphopenia in patients with septic shock: a double-blind, randomized, placebo-controlled trial

21 patients (40 planned)
Septic shock w/ lymphopenia
(ALCs ≤900/mm^3 x 2)
Stopped for safety.



Unexpected high [CYT107]
3/15 ARF following administration

Daix T et al. Ann Intensive Care 2023;13:17.

Du phénotype à l'endotype

Phénotype clinique

regroupement clinique *ex: Sepsis sur pneumonie à pneumocoque*

Sous-groupes

Appartenance **définis par des variables avec *cut-offs*** faisant basculer d'un sous-groupe à l'autre.

Ex: gravité basée sur le score SOFA

Sous-phénotypes

Classement et fiabilité du classement optimisés par **analyses multi-dimensionnelles.**

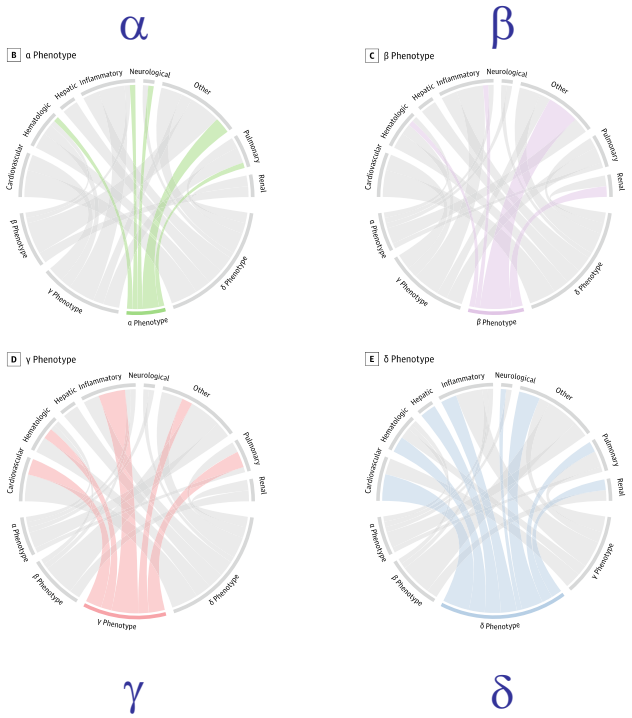
Ex: sous-phénotypes anti- ou hyper- inflammatoires

'Endotypes'

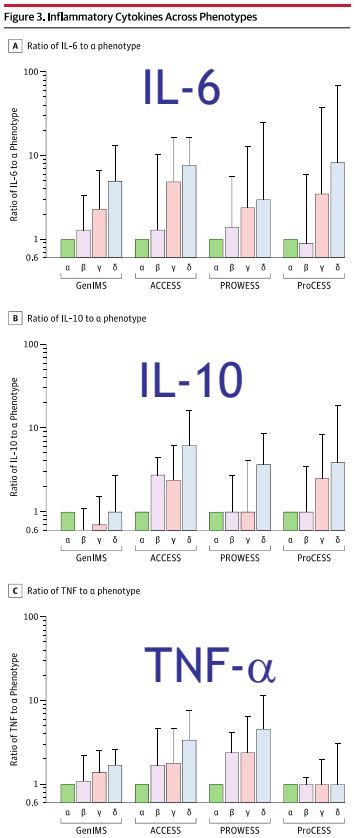
Regroupement selon par des **caractéristiques physiopathologiques communes**

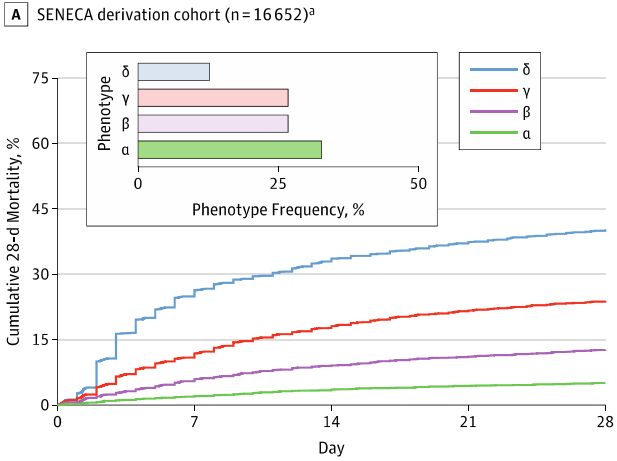
→ **Profils immunitaires du sepsis**

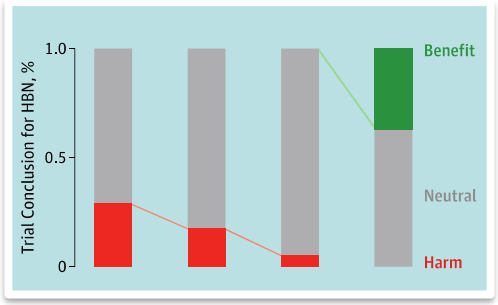
L'aide de l'IA et la variabilité de la réponse



N=20189

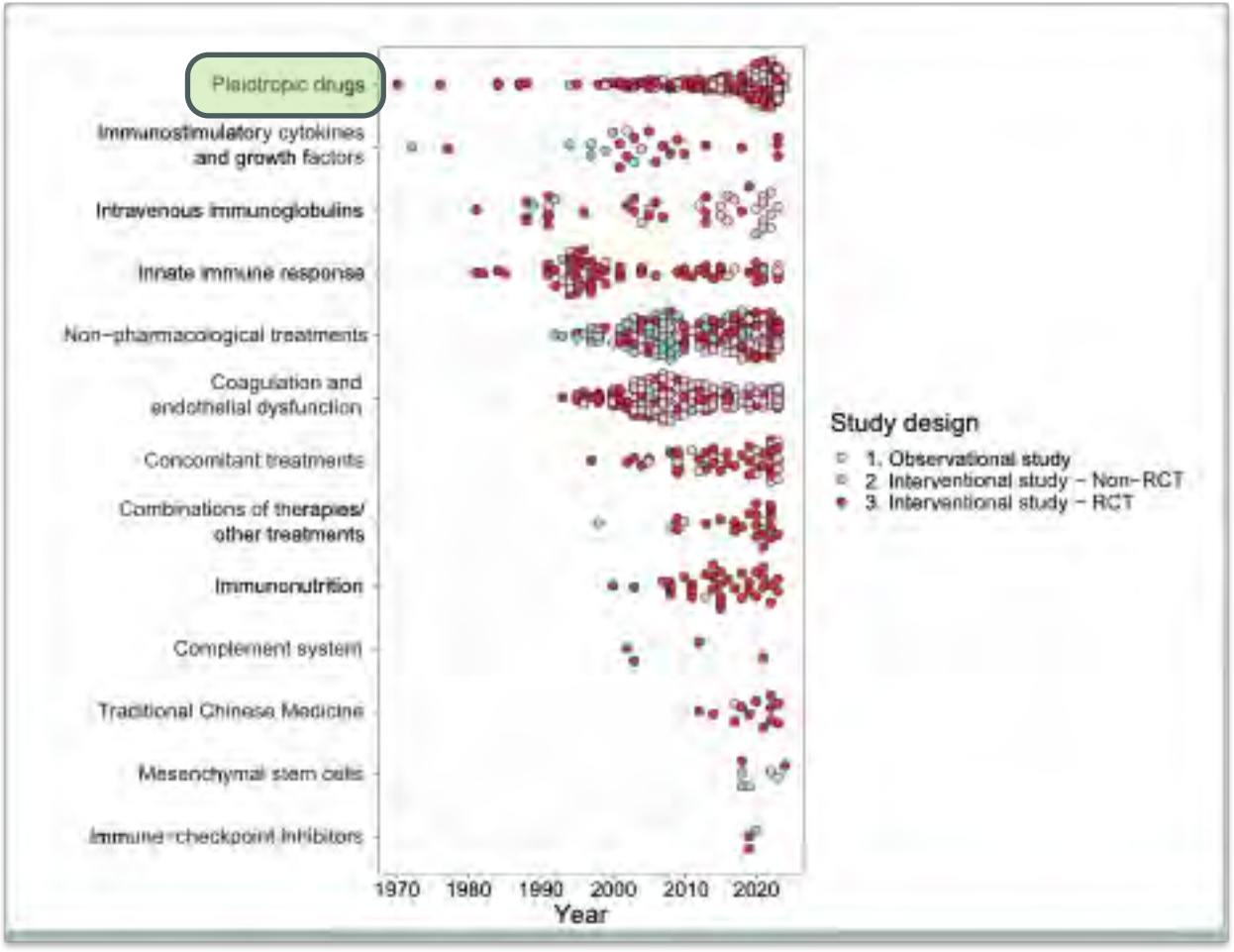






Seymour CW et al. JAMA 2019;321:2003-17.

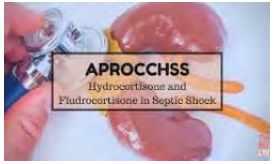
Un demi-siècle de recherche clinique



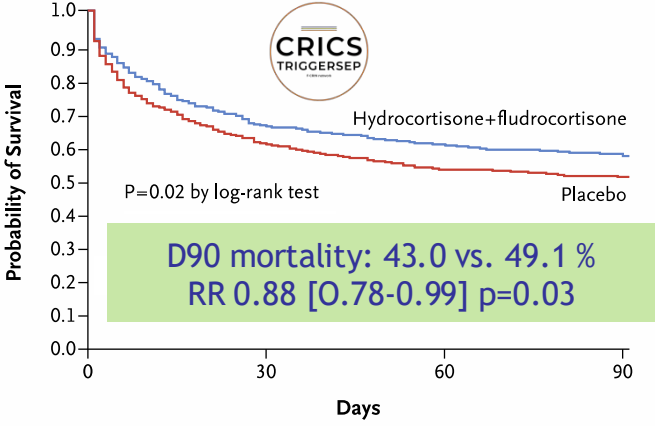
Très peu de résultats probants

Slim MA et al. Crit Care 2024;28:183.

Corticosteroids in septic shock



Septic shock + SOFA ≥ 6,
[Hydrocortisone 50 mg x 4/d
+ fludrocortisone 50 µg x 1/d] x 7 d
n=1241/1280 planned
Median SAPS II : 56
NE at inclusion 1.1 µg/kg/min

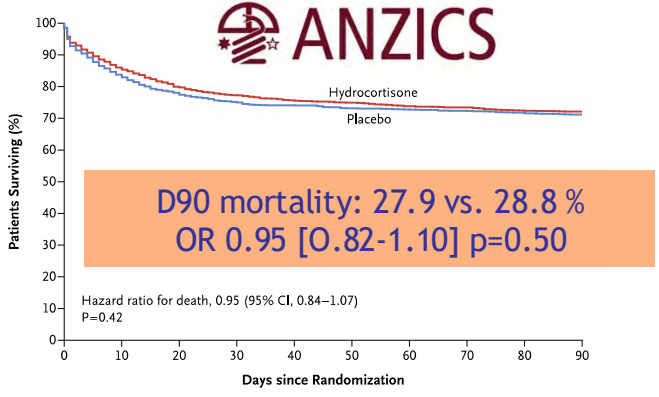


D90 mortality: 43.0 vs. 49.1 %
RR 0.88 [0.78-0.99] p=0.03

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

ADRENAL
Trial Results

SIRS + MV + vasopressors,
Hydrocortisone 50 mg x 4/d x 7 d
n=3658 with primary outcome /3800
Median APACHE II: 24.5
NE at inclusion 0.2 µg/kg/min

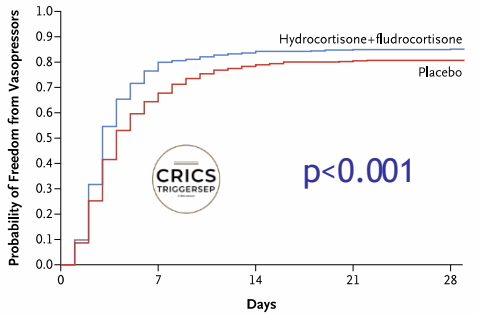


D90 mortality: 27.9 vs. 28.8 %
OR 0.95 [0.82-1.10] p=0.50

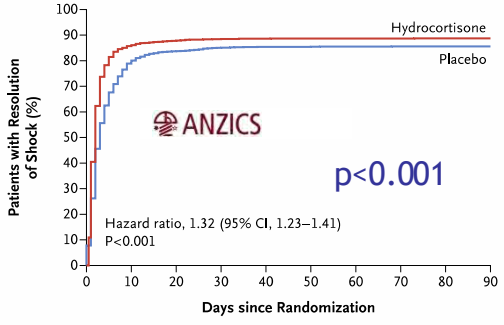
Venkatesh B et al. NEJM 2018;378:797-808.

Corticosteroids in septic shock

Shock resolution time (catecholamine sparing)



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



Venkatesh B et al. NEJM 2018;378:797-808.

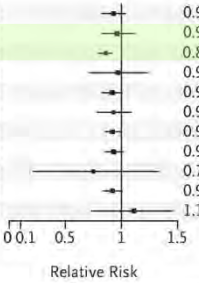
IPDMA: the role of fludrocortisone

Evidence

Patient-Level Meta-Analysis of Low-Dose Hydrocortisone in Adults with Septic Shock

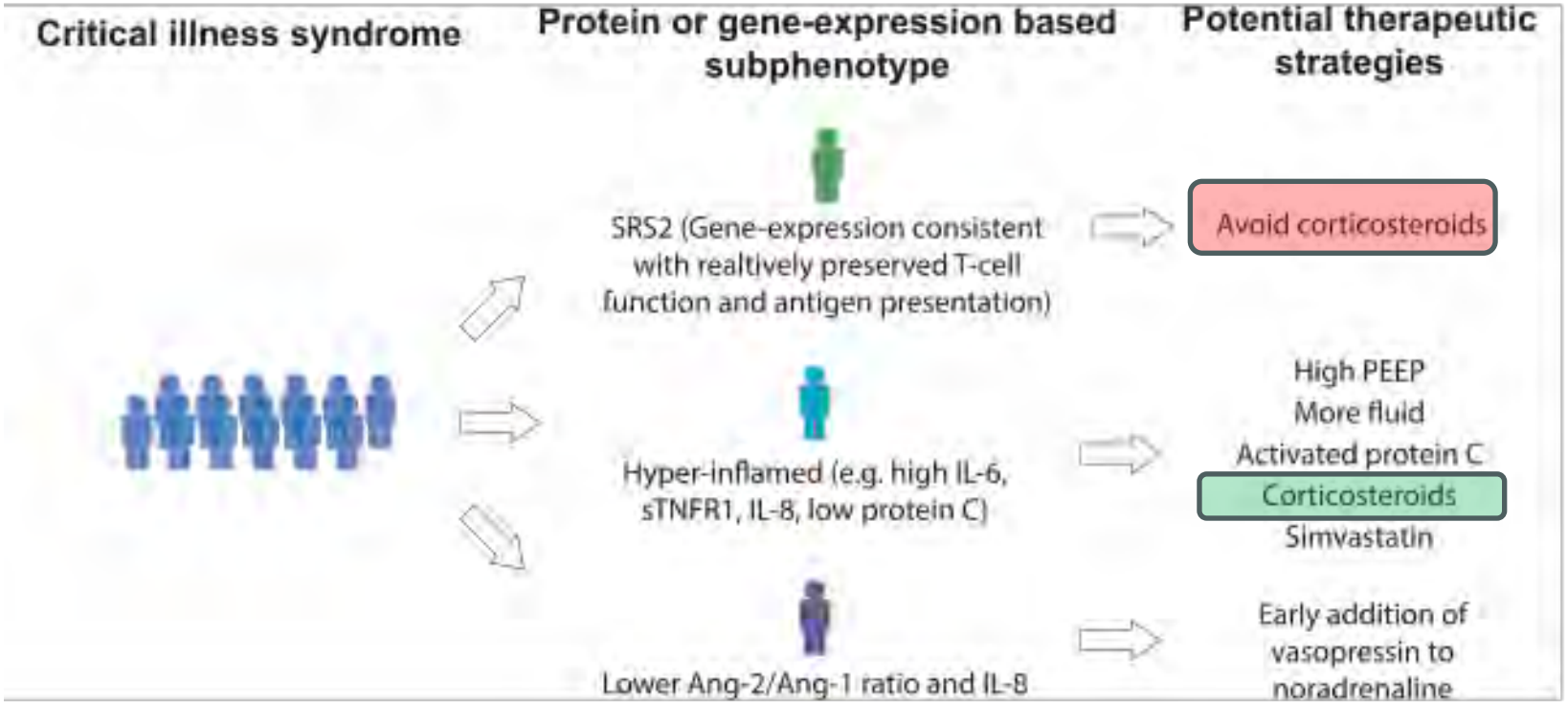
A

Treatment	Subgroup	Total No. of Patients (treatment+ control) (%)	No. Treated (%)	No. of Deaths in Treated (%)	No. Placebo (%)	No. of Deaths in Placebo (%)	Relative Risk (CI)
Overall		5929 (100)*	2966 (100)	1026 (36)	2963 (100)	1069 (37)	0.93 (0.82–1.04)
Hydrocortisone	Without fludrocortisone	4389 (74)	2202 (74)	665 (31)	2187 (74)	656 (31)	0.96 (0.82–1.12)
	With fludrocortisone	1540 (26)	764 (26)	361 (47)	776 (26)	413 (53)	0.86 (0.79–0.92)
Taper	Taper	657 (11)	329 (11)	135 (51)	328 (11)	127 (49)	0.97 (0.71–1.24)
	No taper	5272 (89)	2637 (89)	891 (34)	2635 (89)	942 (36)	0.92 (0.82–1.01)
Continuous	Continous	3844 (65)	1922 (65)	538 (29)	1922 (65)	552 (30)	0.93 (0.78–1.09)
	Bolus	2085 (35)	1044 (35)	488 (48)	1041 (35)	517 (51)	0.92 (0.85–1.00)
Steroid duration	Fixed	5771 (97)	2888 (97)	999 (35)	2883 (97)	1043 (37)	0.93 (0.85–1.02)
	Shock reversal	158 (3)	78 (3)	27 (60)	80 (3)	26 (63)	0.75 (0.21–1.34)
Steroid initiation	<24 h	5723 (97)	2865 (97)	982 (35)	2858 (97)	10,255 (37)	0.92 (0.83–1.01)
	>24 h	176 (3)	85 (3)	40 (56)	91 (3)	39 (50)	1.11 (0.73–1.46)



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

Subphénotypes fondés sur l'expression génique et les protéines



Antcliffe DB et al. Intensive Care Med 2025;51:756-68.

CAP-related septic-shock

APROCCHSS trial, post-hoc

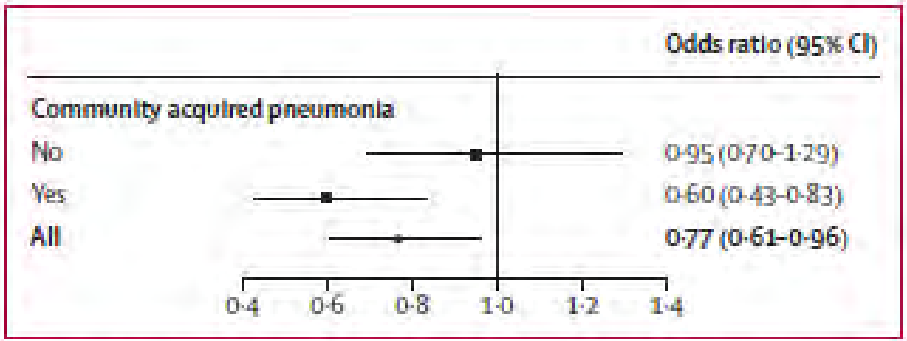


Figure 1: Forest plot of corticosteroid effects across subgroups with or without community acquired pneumonia

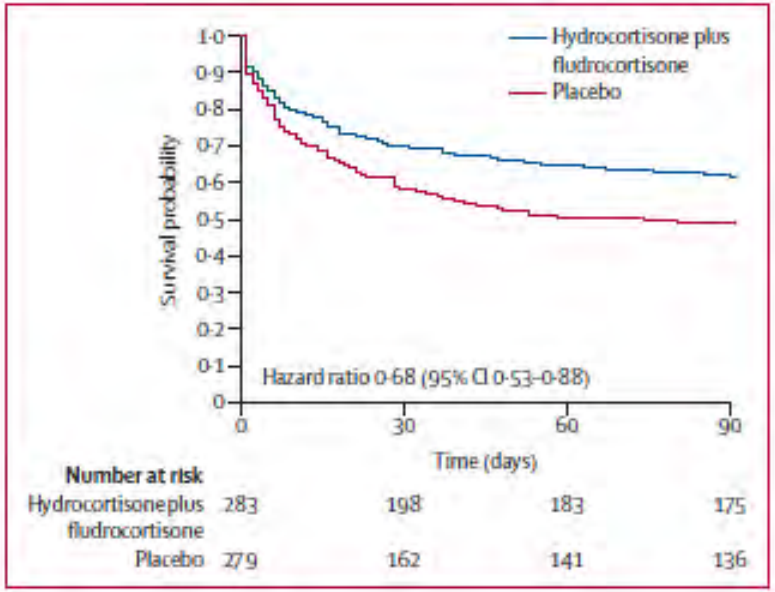
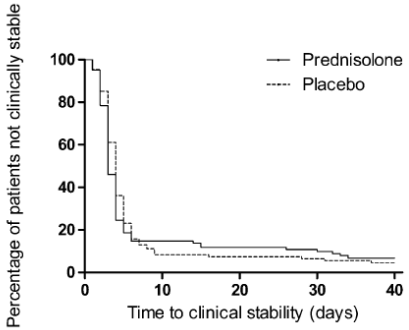


Figure 2: 90-day survival distributions

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

CAP: Outside the ICU

Snijders, AJRCCM 2010



Blum, Lancet 2015

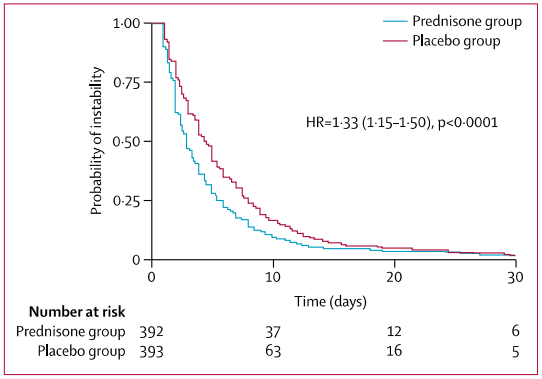
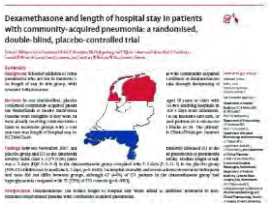


Figure 2: Kaplan-Meier-curve of time to clinical stability



Meijvis, Lancet 2011

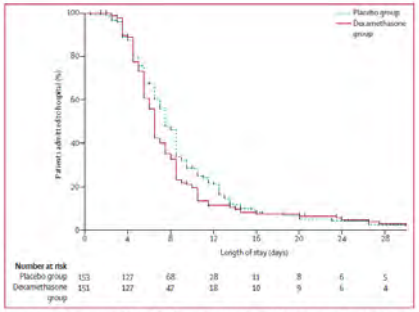
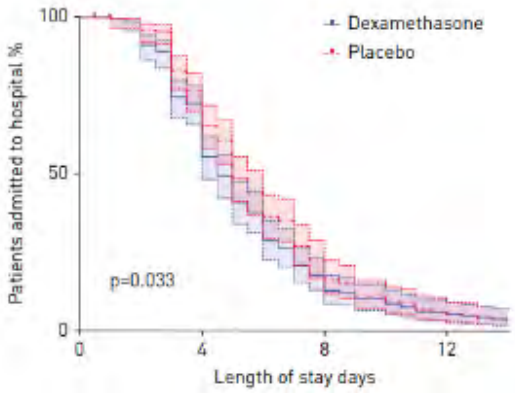
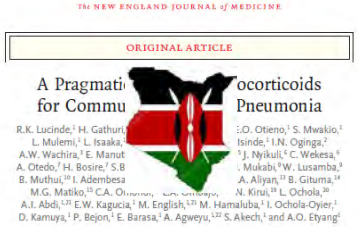


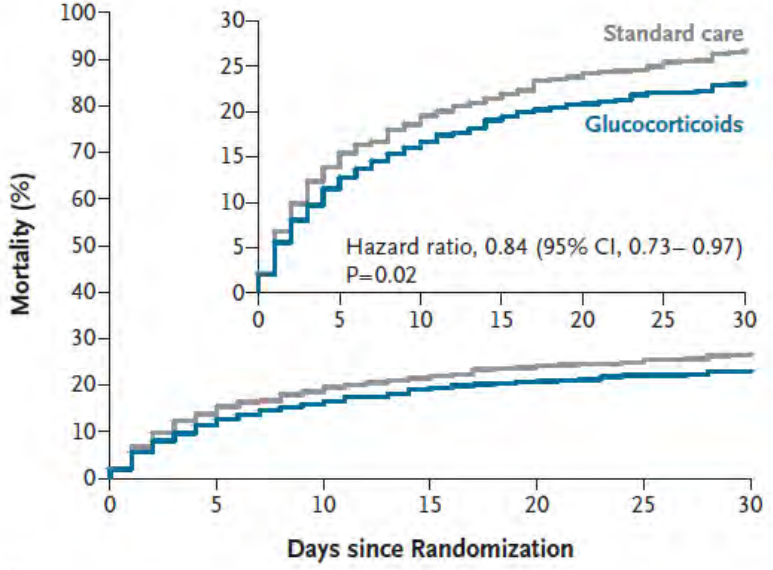
Figure 2: Kaplan-Meier analysis of the effect of dexamethasone on length of hospital stay in all enrolled patients
Patients who died or were admitted to the intensive-care unit were censored on the day of death or the day of admission to the intensive-care unit.

Wittermans, ERJ 2021



In low- or intermediate income countries

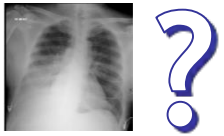


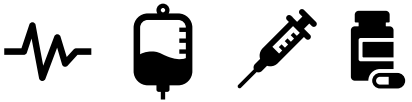


No. at Risk

Standard care	1091	909	848	812	786	774	755
Glucocorticoids	1089	935	877	844	825	811	802

Adjunctive Glucocorticoid	Standard Care	Hazard Ratio for Death (95% CI)
no. of patients with event/total no. (%)		
246/1089 (22.6)	284/1091 (26.0)	0.84 (0.73–0.97)

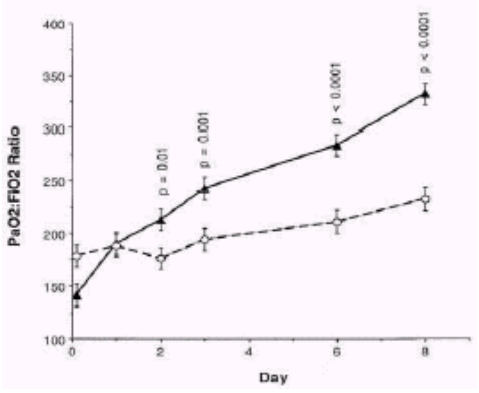




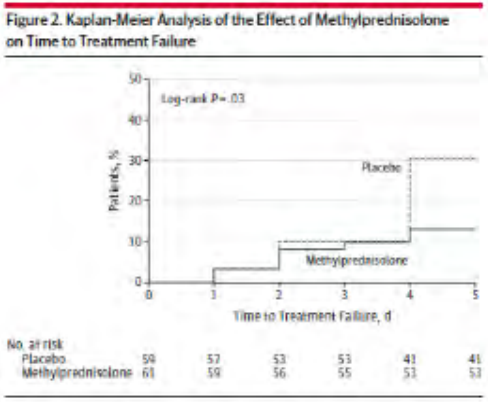
Lucinde RK et al. New Engl J Med 2025;393:2187-97.

sCAP: In the ICU

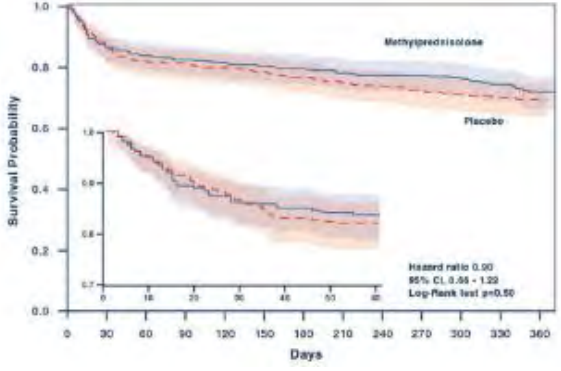
Confalonieri, AJRCCM 2005



Torres, JAMA 2015



Meduri, ICM 2022



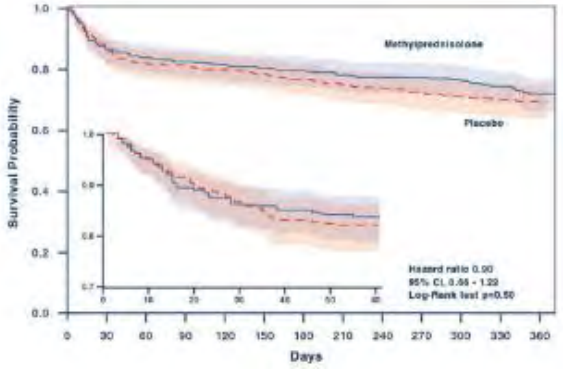
Dequin, NEJM 2023

XXX

sCAP: In the ICU

?

Meduri, ICM 2022



Dequin, NEJM 2023

XXX

Discordant trials ?

	ESCAPe (N=584/1,406)			CAPE COD (N=795/1,200)		
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%

Discordant trials ?

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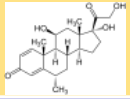
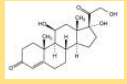
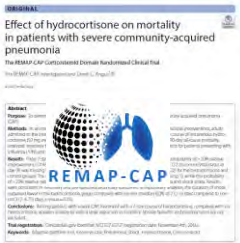
Death on D60	16.0%	P=0.61	18.0%			
Death on D90				9.3%	P=0.02	14.7%
MV	33.0%			44.4%		
Vasopressors	13.0%			11.6%		
PIS class IV or V	82.0%			82.6%		
Age (y)	69			67		

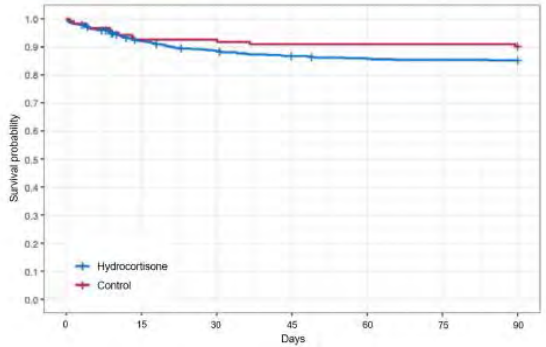
Discordant trials ?




	ESCAPe (N=584/1,406), sCAP & HAP			CAPE COD (N=795/1,200), sCAP		
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%
MV	33.0%			44.4%		
Vasopressors	13.0%			11.6%		
PIS class IV or V	82.0%			82.6%		
Age (y)	69			67		
Sex ratio	26.8			2.27		
Corticosteroid		MPD 40 mg/d x 7d then tapered			HC 200 mg/d x 4-7d then tapered	
Treatment course	20 days for all			8-14 days (median: 5 days)		
Inclusion window	96 hrs post-admission			<24 hrs post 1st severity criterion		

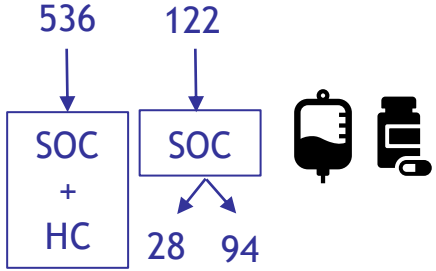
sCAP: Adaptive platform trial





Mortality on D90		1.52 (0.81–2.80)
78/521 (15.0%)	12/122 (9.8%)	
NS		

Probability of harm: 84.3-98.8%
(depending on the sub-groups)

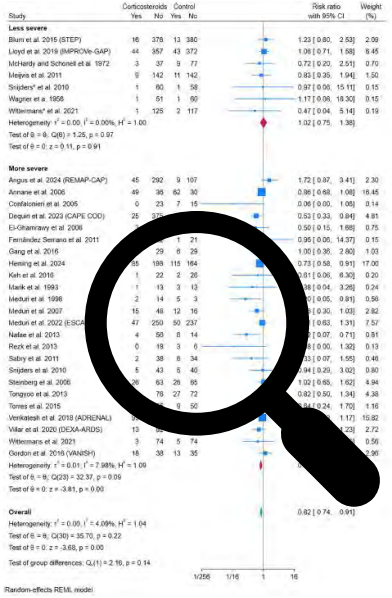


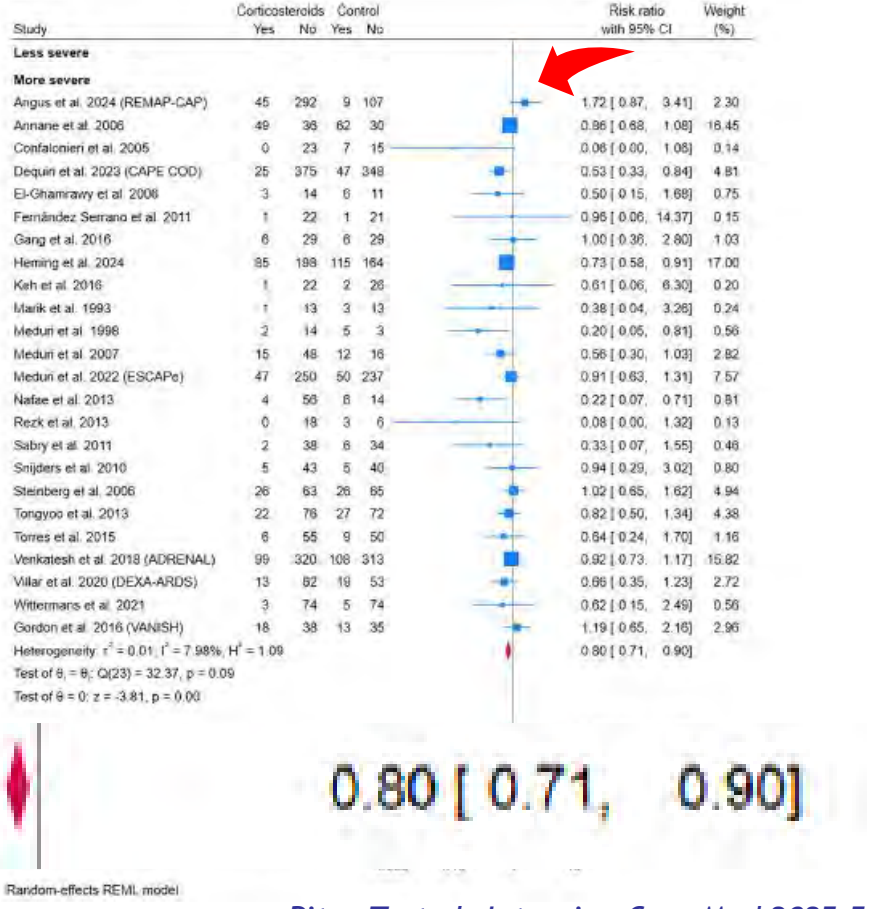
Angus DC & REMAP-CAP investigators, Intensive Care Med 2025;51:665-80.

What about meta-analysises?

Corticosteroids for adult patients hospitalised with non-viral community-acquired pneumonia: a systematic review and meta-analysis

Tyler Pitre[1], Ellen Pauley[2,3], Dipayan Chaudhuri[1], Rohit Saha[4,5], Kristina E. Rudd[6], Jesús Villar[7,8,9,10], Lindsay R. Berry[11], Elizabeth Lorenzi[12], Thomas Hills[13,14], Alistair Nichol[15,16], David A. Harrison[17], Simon Finfer[18,19], Jeremy Cohen[20], John Myburgh[21,22,23], Naomi Hammond[21,22], Domingo Martínez[7], Cristina Fernández[7], David Antcliffe[23], Anthony Gordon[23], André Scherag[24], Holger Bogatsch[25], Frank M. Brunkhorst[26], Balasubramanian Venkatesh[18,27], Djillali Annane[28], Danny McAuley[2,3], Derek C. Angus[6], Bram Rochwerg[29*] and Manu Shankar-Hari[30*]





Pitre T et al. Intensive Care Med 2025;51:917-29.

What about meta-analysises?

Annals of Internal Medicine REVIEW

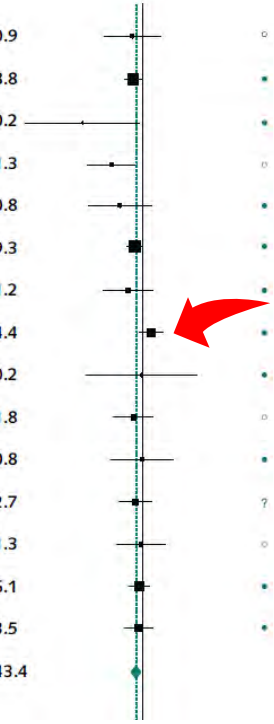
Systemic Corticosteroids, Mortality, and Infections in Pneumonia and Acute Respiratory Distress Syndrome

A Systematic Review and Meta-analysis

Alice Soumare, MD; Thomas Kapfer, MD; Thomas Botrel, MD, MSc; Leslie Adda, PharmD, PhD; Maxime Renaux, MD, MSc; Pierre-Louis Blot, MD, MSc; Jean-Michel Constantin, MD, PhD; Arthur James, MD, PhD; and Rayan Braik, MD, MSc

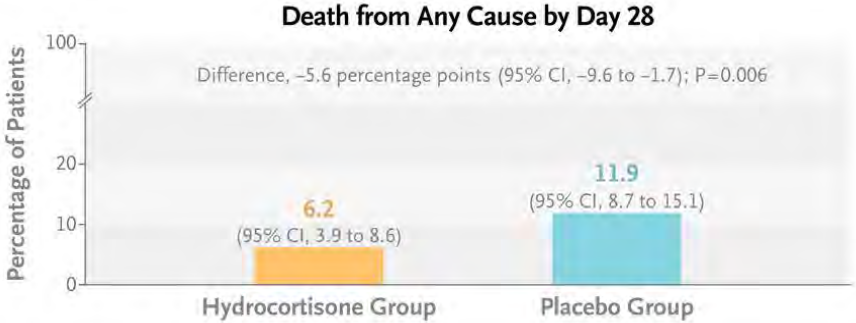
Figure 1. Forest plot of RRs for short-term mortality in patients with severe pneumonia and ARDS.

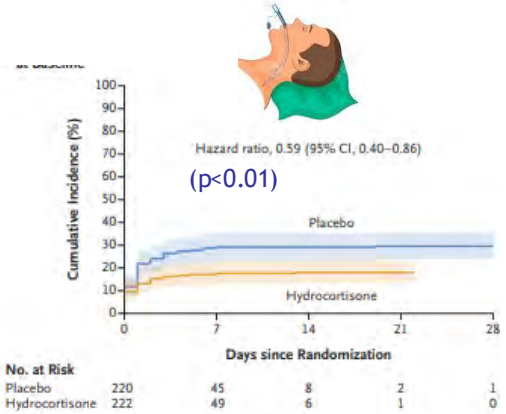
Study, Year (Reference)	Steroids, *n*/*total n*	Control, *n*/ total *n*	RR (95% CI)	Weight, %	Oxygen	ICU	Steroid	Daily Dose, *mg*	Duration, *d*	Risk of Bias ABCDEF
Severe pneumonia										
Wittermans et al, 2021 (33) (PSI IV-V)	3/77	5/79	0.62 (0.15–2.49)	0.9	○	○	DXM	40	4	• • • • –
Dequin et al, 2023 (24)	36/388	57/389	0.63 (0.43–0.94)	8.8	•	•	HC	50	14	• • • • • •
Confalonieri et al, 2005 (20)	0/23	8/21	0.05 (0.00–0.88)	0.2	•	•	HC	67	7	– • • • • –
Nafae et al, 2013 (23)	4/60	6/20	0.22 (0.07–0.71)	1.3	○	•	HC	57	7	– • • • • •
Sabry et al, 2011 (22)	2/40	6/40	0.33 (0.07–1.55)	0.8	•	•	HC	82	7	– • • • • •
Heming et al, 2024 (25) (without ARDS)	31/109	43/106	0.70 (0.48–1.02)	9.3	•	•	HC	50	7	• • • • • •
El-Ghamraway et al, 2006 (21)	3/17	6/17	0.50 (0.15–1.68)	1.2	•	•	HC	67	7	– – – – – –
Angus et al, 2025 (5)	72/480	11/113	1.54 (0.85–2.81)	4.4	•	•	HC	50	7	• – • • • –
Fernández-Serrano et al, 2011 (26)	1/23	1/22	0.96 (0.06–14.37)	0.2	•	○	MP	86	9	• – – • • –
Torres et al, 2015 (27)	6/61	9/59	0.64 (0.24–1.70)	1.8	○	▫	MP	88	5	• • • • • •
Li et al, 2016 (28)	3/29	3/29	1.00 (0.22–4.55)	0.8	•	•	MP	100	7	– • • – • •
Dahra et al, 2024 (29)	7/25	10/25	0.70 (0.32–1.54)	2.7	?	▫	MP	88	5	• • • • • •
Snijders et al, 2010 (32) (PSI IV-V)	5/48	5/45	0.94 (0.29–3.02)	1.3	○	▫	PN	40	7	– • • • • –
Wafy et al, 2021 (31)	13/25	15/25	0.87 (0.53–1.42)	6.1	•	•	PN	40	7	– • • – • •
Wafy et al, 2025 (30)	9/25	11/25	0.82 (0.41–1.62)	3.5	•	•	PN	40	7	– – • • • –
Random-effects model			0.73 (0.57–0.93)	43.4						
Heterogeneity: I^2 = 14%, τ^2 = 0.030, P = 0.29										



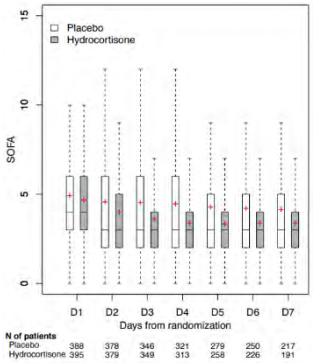
Soumare A et al. Ann Intern Med 2026;179:67-80.

Internal consistency



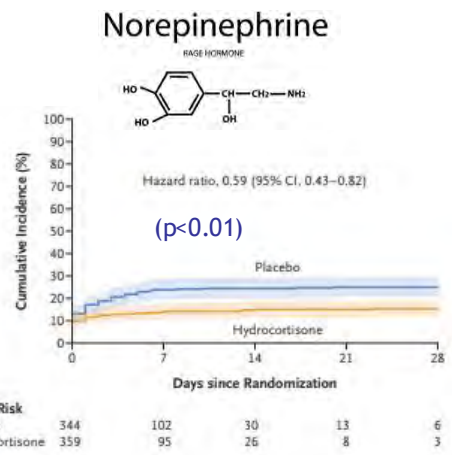


SOFA score



(p=0.003)

Norepinephrine



Dequin PF et al. New Engl J Med 2023;388:1931-41.

Suggested guidelines

Hospitalized patient with community-acquired pneumonia (CAP) in the ICU[a]

Patient with CAP due to influenza or fungi or tuberculosis
- Yes → **Corticosteroids not recommended**
- No ↓

Patient with CAP who is immunocompromized
- Yes → **Corticosteroids not recommended[b]**
- No ↓

Patient with CAP and septic shock
- Yes → **Corticosteroids recommended as for septic shock[c]**
- No ↓

Patient with CAP fulfilling any of the following severity criteria:
1. Initiation of mechanical ventilation (invasive or non-invasive) with a positive end-expiratory pressure level of at least 5 cmH_2O
2. Initiation of oxygen through a high-flow nasal cannula with a PaO_2/FiO_2 ratio <300[d], with a FiO_2 of 50% or more
3. Patient wearing a nonrebreathing mask with estimated PaO_2/FiO_2 ratio <300[d]

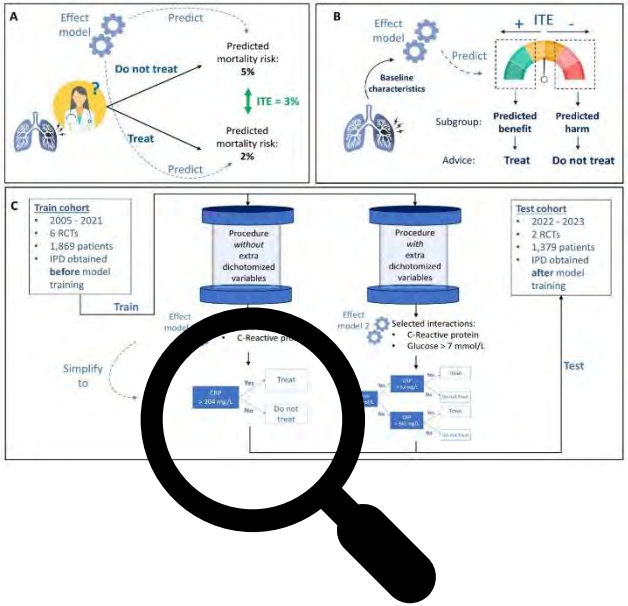
- No → **Corticosteroids not recommended**
- Yes ↓

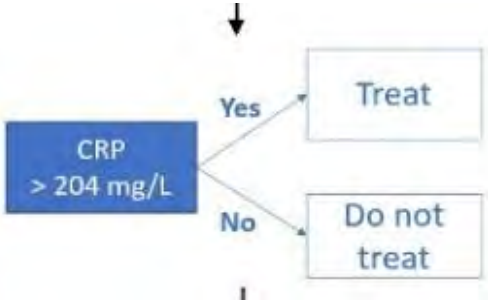
Within 24 hours after the onset of any severity criterion start continuous infusion of hydrocortisone 200 mg per day for a minimum of 4 days[e]

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

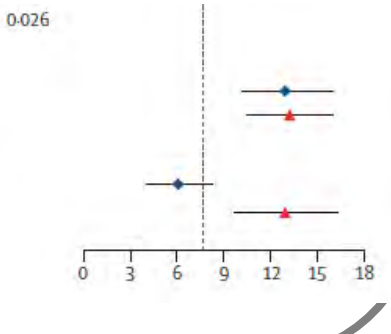
CRP treshold ?

IPDMA
CAP and sCAP





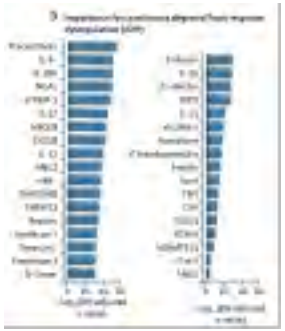
Test cohort subgroups by corticosteroid-effect model					
Predicted no benefit (CRP ≤204 mg/L, n=725)	49/370 (13·2%)	46/355 (13·0%)	0·98 (0·63 to 1·5)	0·3% (−4·2 to 4·1)	350
Predicted benefit (CRP >204 mg/L, n=630)	39/301 (13·0%)	20/329 (6·1%)	0·43 (0·25 to 0·76)	6·9% (2·8 to 10·4)	14

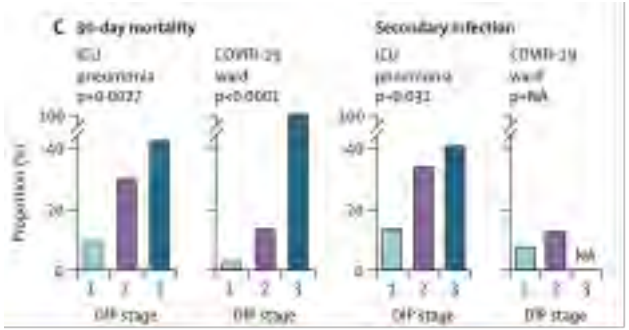


Smit JM et al. Lancet Respir Med 2025;13:221-33.

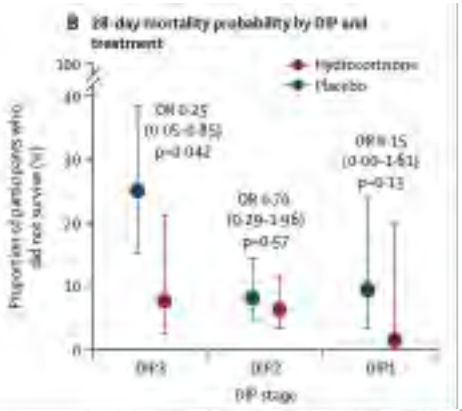
Dysregulated Immune Profile

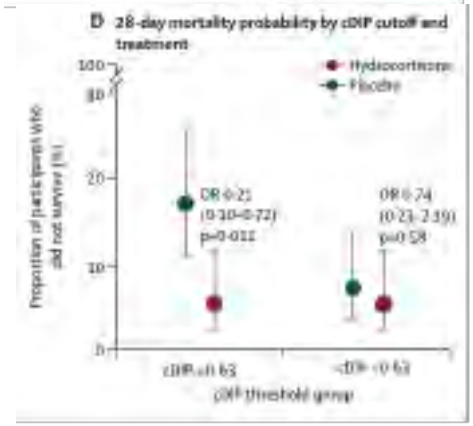
Quantifying immune dysregulation in pneumonia and sepsis with a parsimonious machine-learning model: a multicohort analysis across care settings and reanalysis of a hydrocortisone randomised controlled trial





PCT, IL-6, sTREM-1





Michels EHA et al. Lancet Respir Med 2026;14:327-40.

Essai de conclusion

🎯 **1. Cibler l'hôte** dans le sepsis est une **nécessité biologique** — la définition même de la maladie l'impose !

⚠️ **2.** 30 ans d'**échecs des essais** cliniques parce qu'on n'a **pas tenu compte de l'hétérogénéité** — le "*one-size-fits-all*" est condamné !

🧬 **3.** Les **endotypes** donnent enfin les outils pour **stratifier & cibler** (ImmunoSep montre que c'est faisable)

🛡️**4.** La « ***disease tolerance*** » est un cadre opérationnel pertinent, pour endotyper puis cibler, en promouvant le « ***tissue damage control*** »

🌀 **5.** Mais le **sepsis** est un **système complexe** (non-linéaire, dynamique, émergent), et il reste des **défis majeurs scientifiques** (compréhension), **technologiques** et **pratiques** (faisabilité des endotypes en routine)

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