2025년도 춘계학술대회 제25차 Workshop

호흡기내과 의사를 위한 Respiratory Review of 2025

Critical Care Medicine

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호흡기내과
장유진

Content

- Sepsis management
- Antibiotic therapy in CAP and VAP
- Cognition-motor dissociation

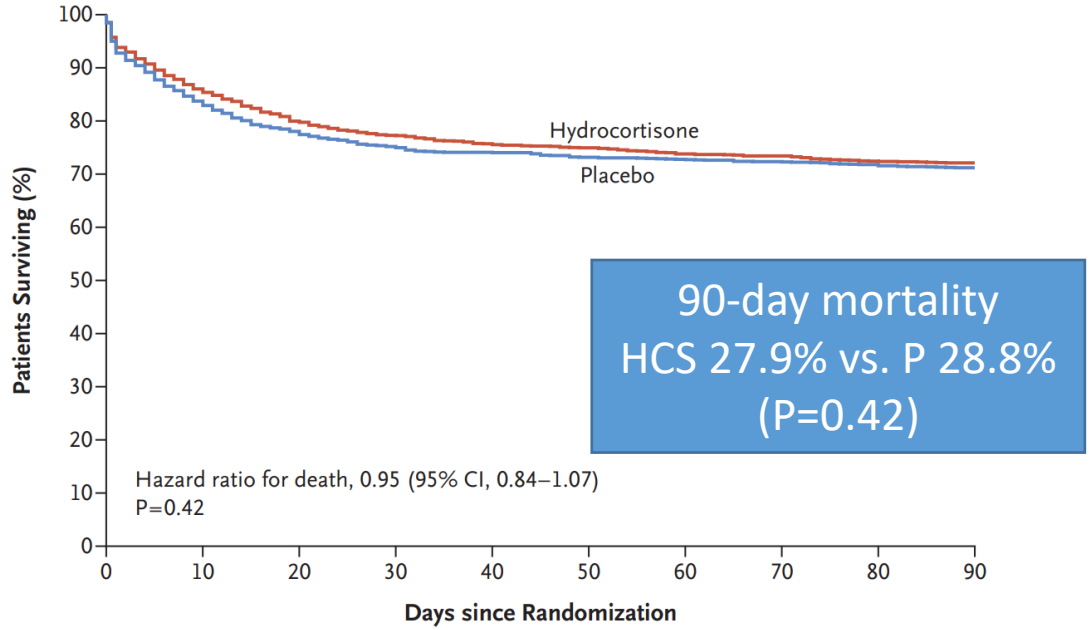
Steroids in sepsis

ADRENAL trial

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 1, 2018 VOL. 378 NO. 9

Adjunctive Glucocorticoid Therapy in Patients with Septic Shock



90-day mortality
HCS 27.9% vs. P 28.8%
(P=0.42)

No. at Risk										
Hydrocortisone	1832	1591	1481	1418	1388	1374	1356	1348	1328	1321
Placebo	1826	1546	1433	1376	1354	1337	1330	1322	1312	1300

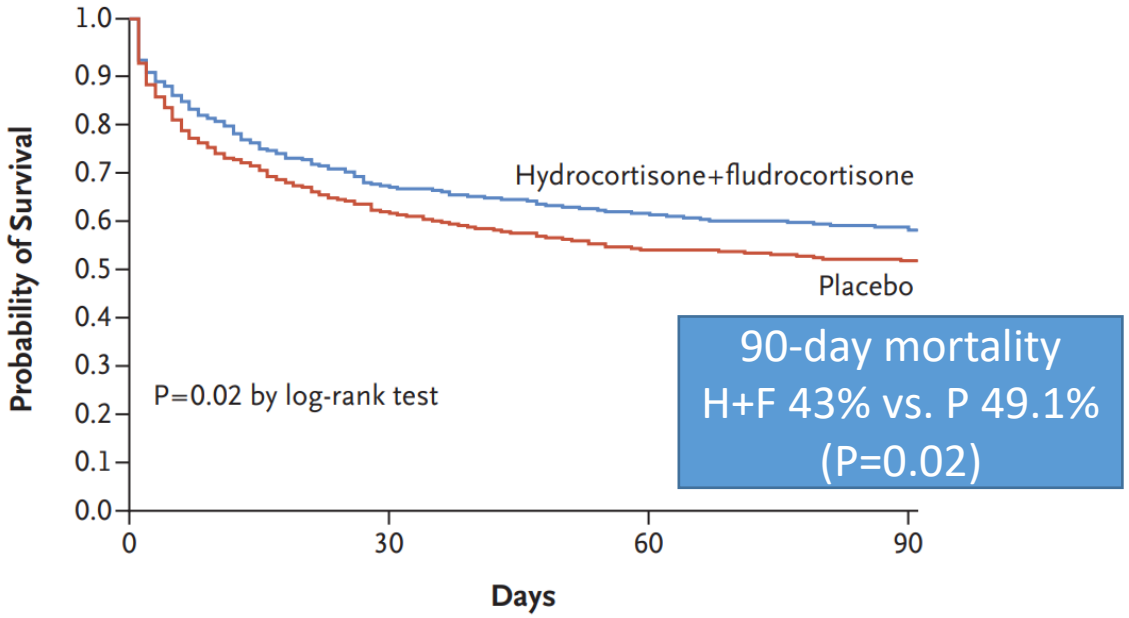
B. Venkatesh et al., N Engl J Med 2018;378:797-808

APROCCHSS trial

ORIGINAL ARTICLE

Hydrocortisone plus Fludrocortisone for Adults with Septic Shock

D. Annane, A. Renault, C. Brun-Buisson, B. Megarbane, J.-P. Quenot, S. Siami, A. Cariou, X. Forceville, C. Schwebel, C. Martin, J.-F. Timsit, B. Misset,



90-day mortality
H+F 43% vs. P 49.1%
(P=0.02)

No. at Risk				
Hydrocortisone+ fludrocortisone	614	405	372	353
Placebo	627	381	333	319

D. Annane et al., N Engl J Med 2018;378:809-18

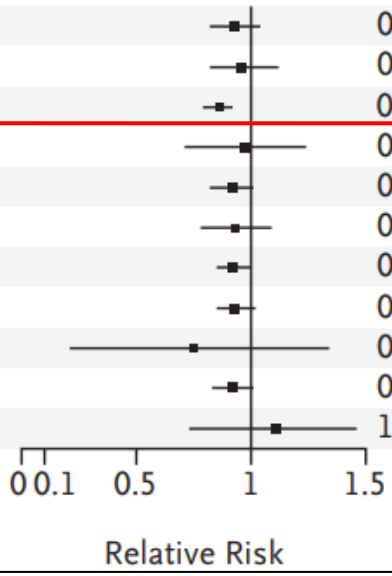
ORIGINAL ARTICLE

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

- Individual patient-level data meta-analysis (IPMDA)
- 90-day all-cause mortality in HCS (n=4,258) vs. Placebo (n=3,624)

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)



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

ONLINE REVIEW ARTICLE

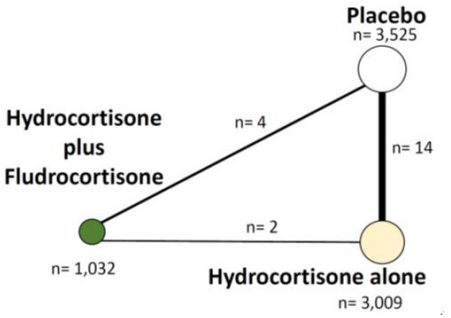
OPEN

Do We Need to Administer Fludrocortisone in Addition to Hydrocortisone in Adult Patients With Septic Shock? An Updated Systematic Review With Bayesian Network Meta-Analysis of Randomized Controlled Trials and an Observational Study With Target Trial Emulation*

Pei-Chun Lai. MD. PhD[1,2]

Septic shock

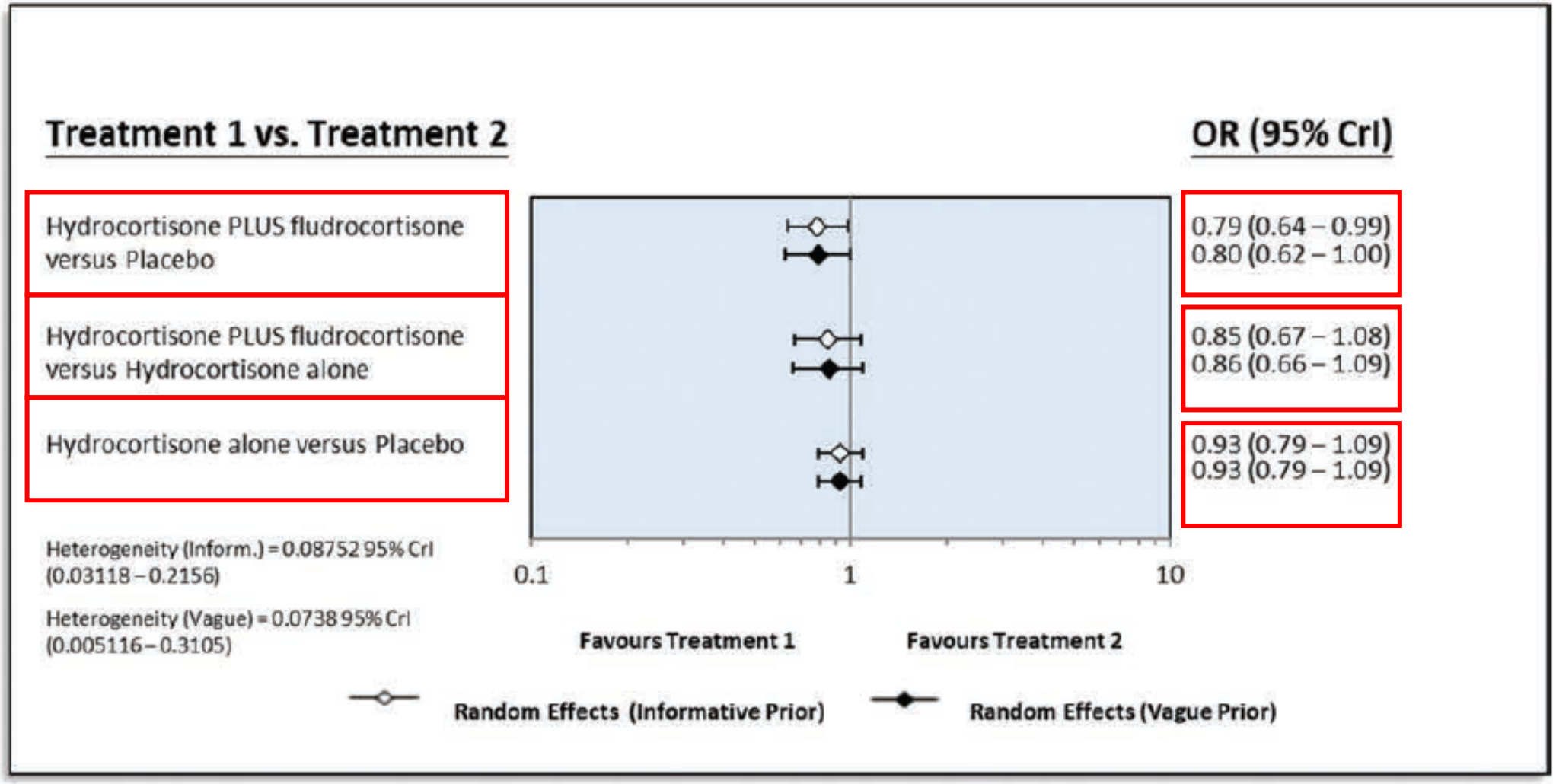
Hydrocortisone + Fludrocortisone
vs. Hydrocortisone alone
vs. Placebo



- Bayesian network meta-analysis of 19 studies involving 95,841 patients
- Hydrocortisone plus fludrocortisone vs. Placebo
- Primary outcome : short-term mortality (28 or 30-day)
- Gastroduodenal bleeding, superinfection and hyperglycemia

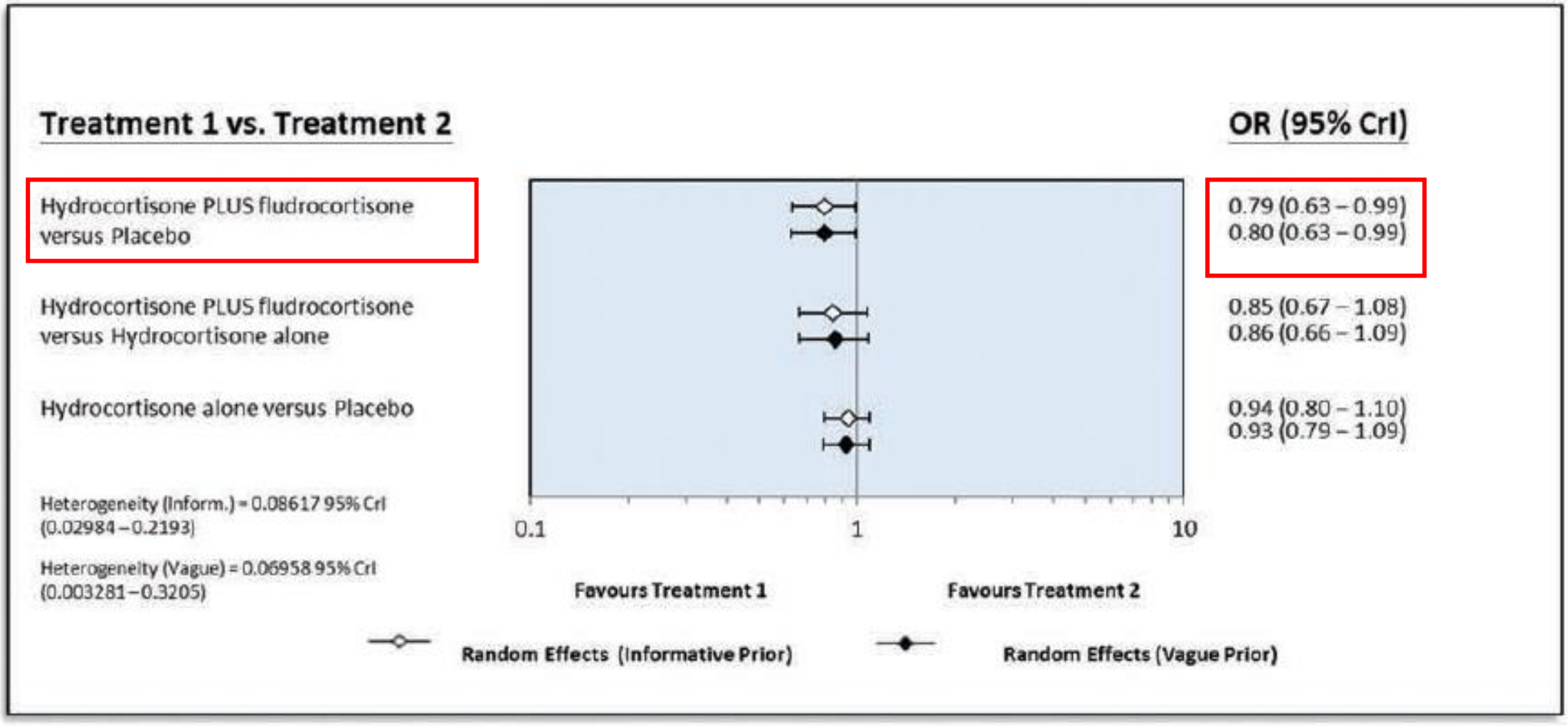
PC Lai et al.,Crit Care Med 2024; 52:e193–e202

All patients



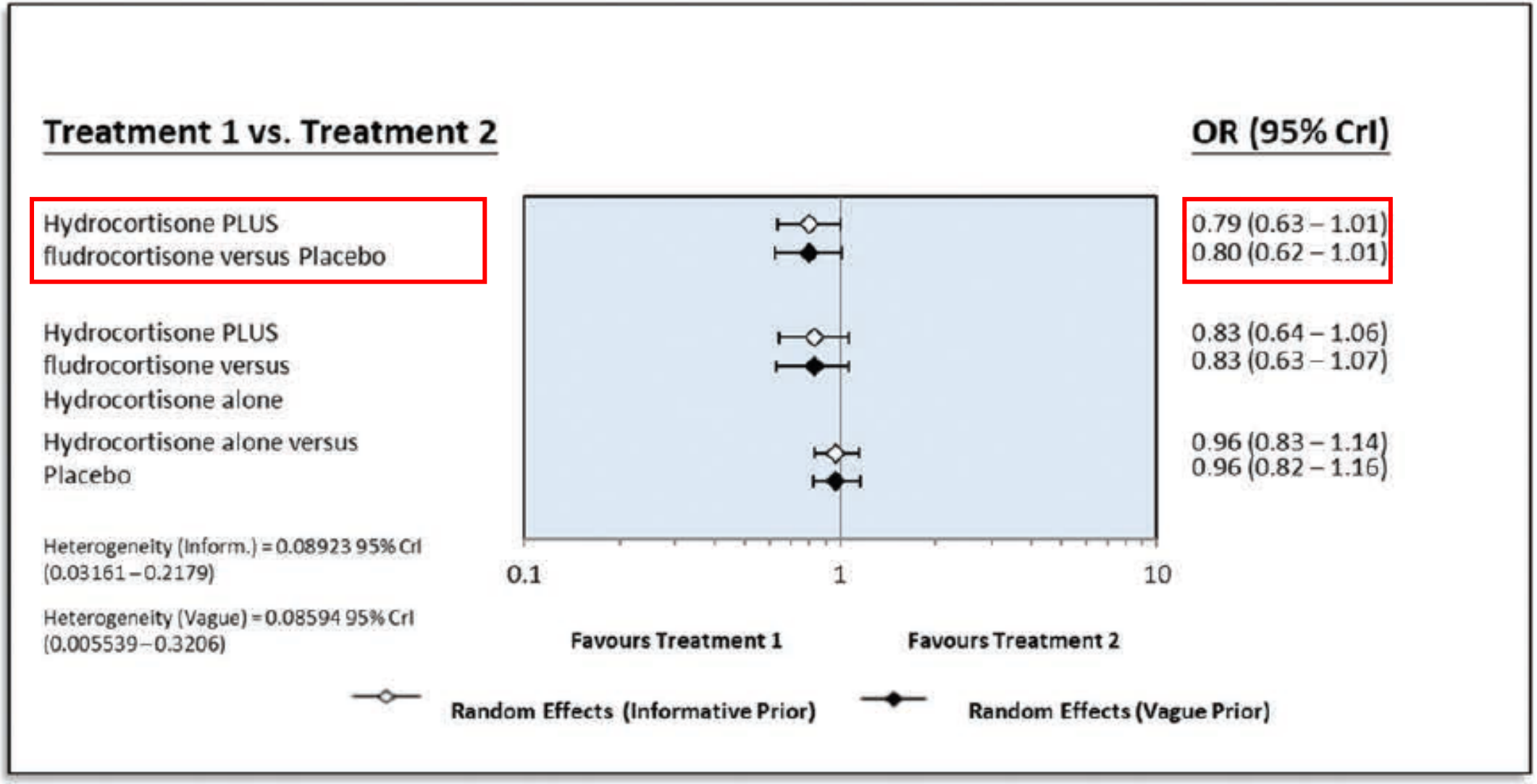
PC Lai et al.,Crit Care Med 2024; 52:e193–e202

RCTs



PC Lai et al.,Crit Care Med 2024; 52:e193–e202

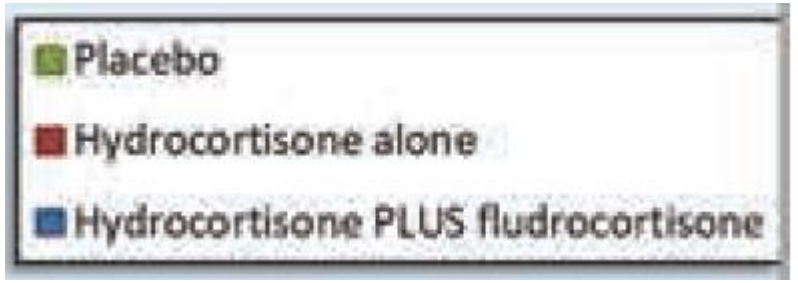
RCTs administering an initial daily HCS 200mg



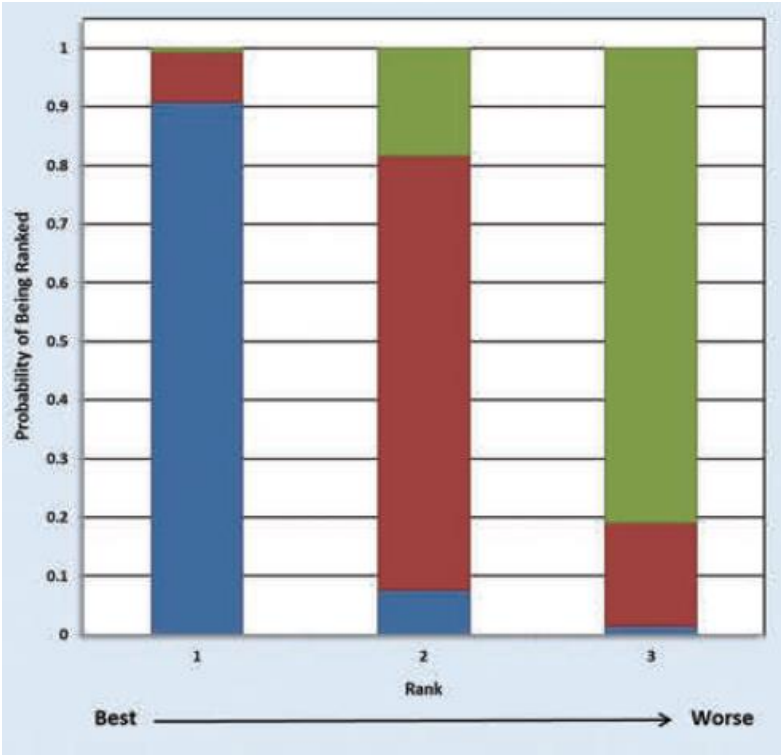
PC Lai et al.,Crit Care Med 2024; 52:e193–e202

Random effects (informative) rankogram

The Surface Under the Cumulative Ranking curve Analysis (SUCRA) for **HCS/FD, HCS alone and Placebo : 0.9469, 0.4542, and 0.0989**

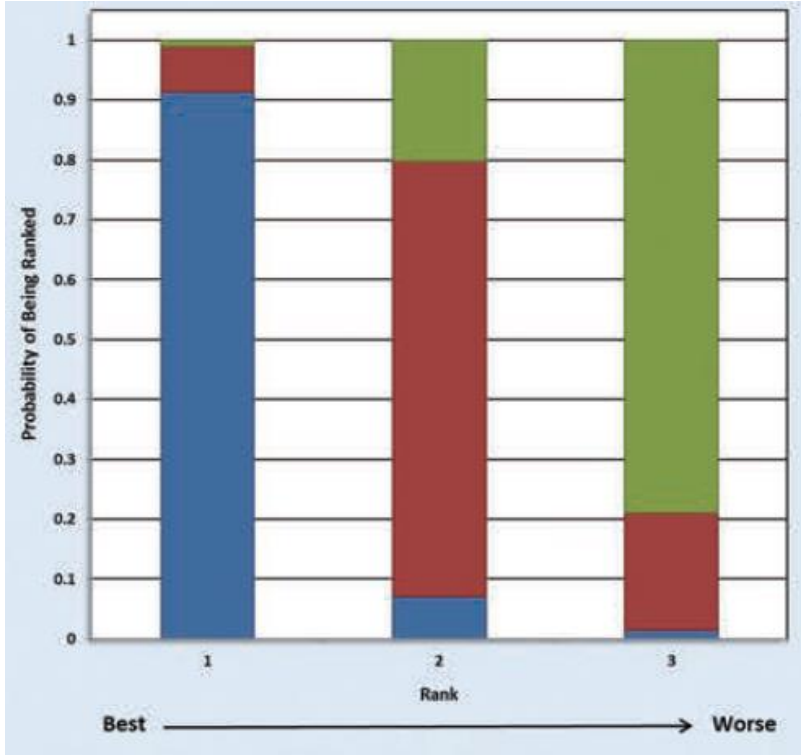


All



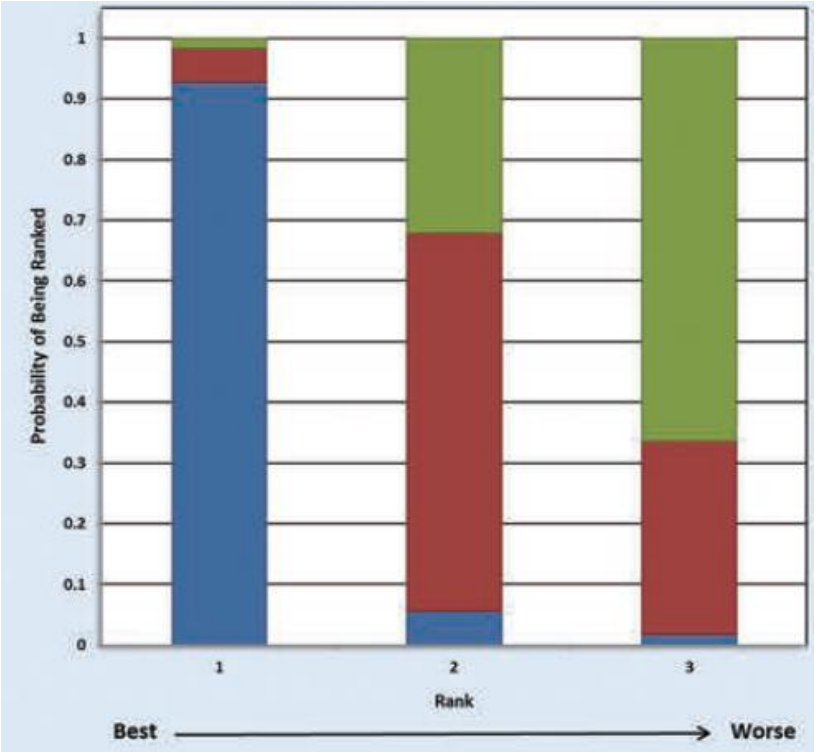
1 2 3

RCTs



1 2 3

RCTs (HCS 200 mg)



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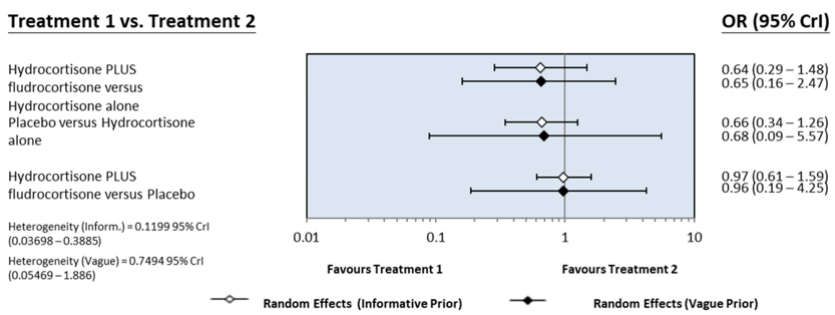
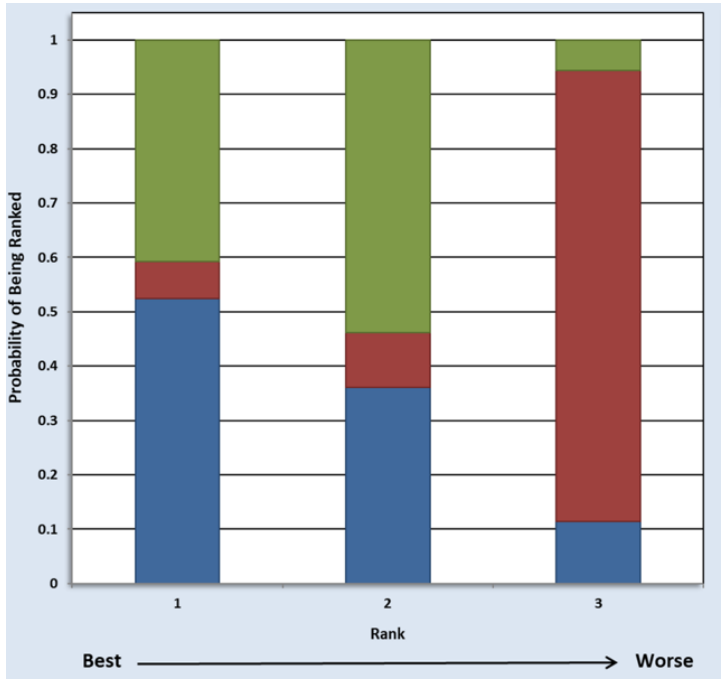
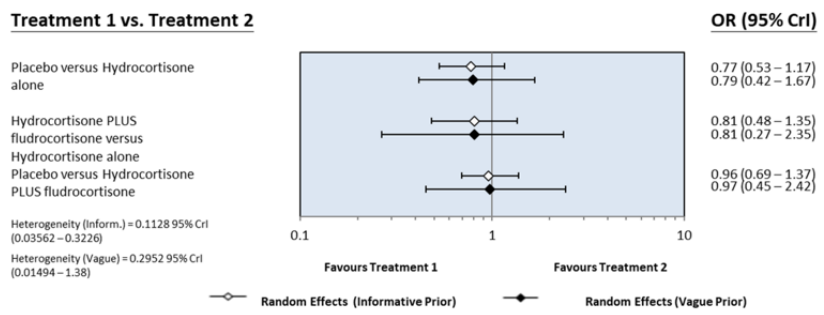
PC Lai et al.,Crit Care Med 2024; 52:e193–e202

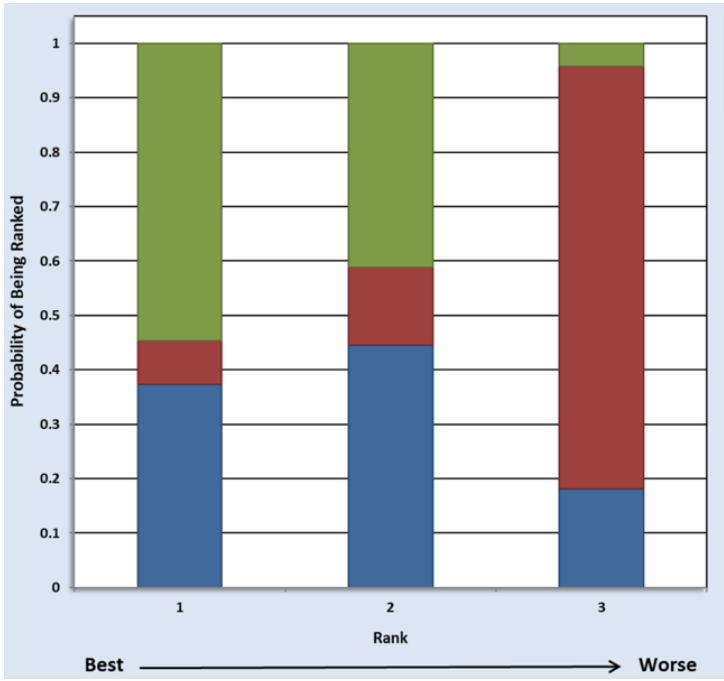
GI bleeding



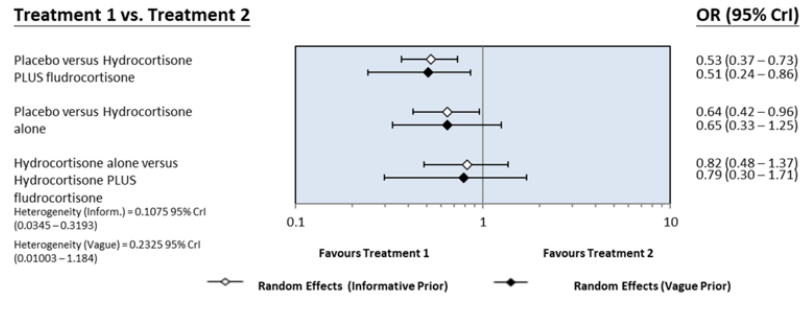


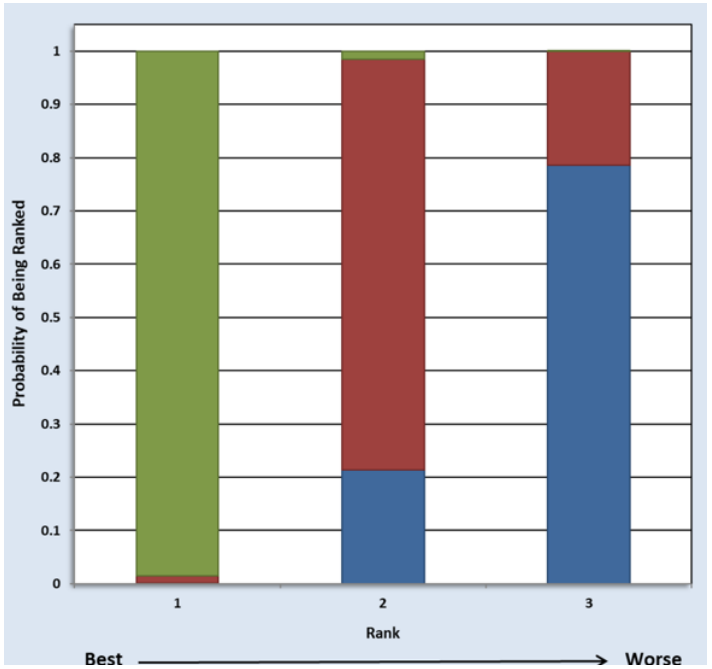
Superinfection

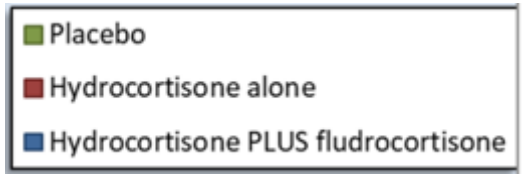




Hyperglycemia







PC Lai et al.,Crit Care Med 2024; 52:e193–e202

Comparative analysis for short-term mortality

Outcome	Odds ratios (95% credible intervals) in the estimation of effects				Comments
	Hydrocortisone plus fludrocortisone		Hydrocortisone alone		
Short-term mortality, including RCTs and observational studies using TTE					
Placebo Comparator 1104/3525[1] (31.3%)	**OR 0.79** (0.63 to 0.99) Network estimate	**48 fewer per 1000** (90 fewer to 2 fewer)	**OR 0.94** (0.80 to 1.10) Network estimate	**13 fewer per 1000** (46 fewer to 21 more)	Among the three groups, hydrocortisone plus fludrocortisone was found to be associated with low short-term mortality.
	⊕⊕◯◯ **Low** confidence in estimate due to imprecision		⊕⊕◯◯ **Low** confidence in estimate due to imprecision		
Rank 3 (SUCRA 0.1102)	Rank 1 (SUCRA 0.9501)		Rank 2 (SUCRA 0.4397)		

PC Lai et al.,Crit Care Med 2024; 52:e193–e202

Conclusion

In adults with septic shock, hydrocortisone plus fludrocortisone improved short-term survival with minimal adverse events compared with hydrocortisone alone or placebo. However, these findings are not definitive due to the limited certainty of evidence and wide NNT range. Additional large-scale, placebo-controlled RCTs are needed to provide conclusive evidence.

Hydrocortisone + fludrocortisone vs. placebo

(OR 0.79, 95% CrI 0.64-0.99, number needed to treat (NNT): 21 [12-500])

Limitation

- High-income countries
- Mechanical ventilation in over 90% of participants
  : potential benefits for acute respiratory failure

Hydrocortisone plus fludrocortisone for CAP-related septic shock

Hydrocortisone plus fludrocortisone for community acquired pneumonia-related septic shock: a subgroup analysis of the APROCCHSS phase 3 randomised trial

*Nicholas Heming, Alain Renault, Emmanuelle Kuperminc, Christian Brun-Buisson, Bruno Megarbane, Jean-Pierre Quenot, Shidasp Siami, Alain Cariou, Xavier Forceville, Carole Schwebel, Marc Leone, Jean-Francois Timsit, Benoît Misset, Mohamed Ali Benali, Gwenhael Colin, Bertrand Souweine, Karim Asehnoune, Emmanuelle Mercier, Loïc Chimot, Claire Charpentier, Bruno François, Thierry Boulain, Frank Petitpas, Jean Michel Constantin, Gilles Dhonneur, François Baudin, Alain Combes, Julien Bohé, Jean-François Loriferne, Fabrice Cook, Michel Slama, Olivier Leroy, Gilles Capellier, Auguste Dargent, Tarik Hissem, Rania Bounab, Virginie Maxime, Pierre Moine, Eric Bellissant, Djillali Annane for the APROCCHSS investigators and CRICS-TRIGGERSEP network**

CAP vs. non-CAP Septic shock

- CAP vs. non-CAP related septic shock
- Subgroup analysis of phase 3 RCT from Activated Protein C and Corticosteroids for Human Septic Shock **(APROCCHSS)** trial from 34 centres in France
- 7-day treatment with daily administration of IV hydrocortisone 50mg bolus q6h + a tablet of 50 µg of fludrocortisone via NG tube vs. Placebo

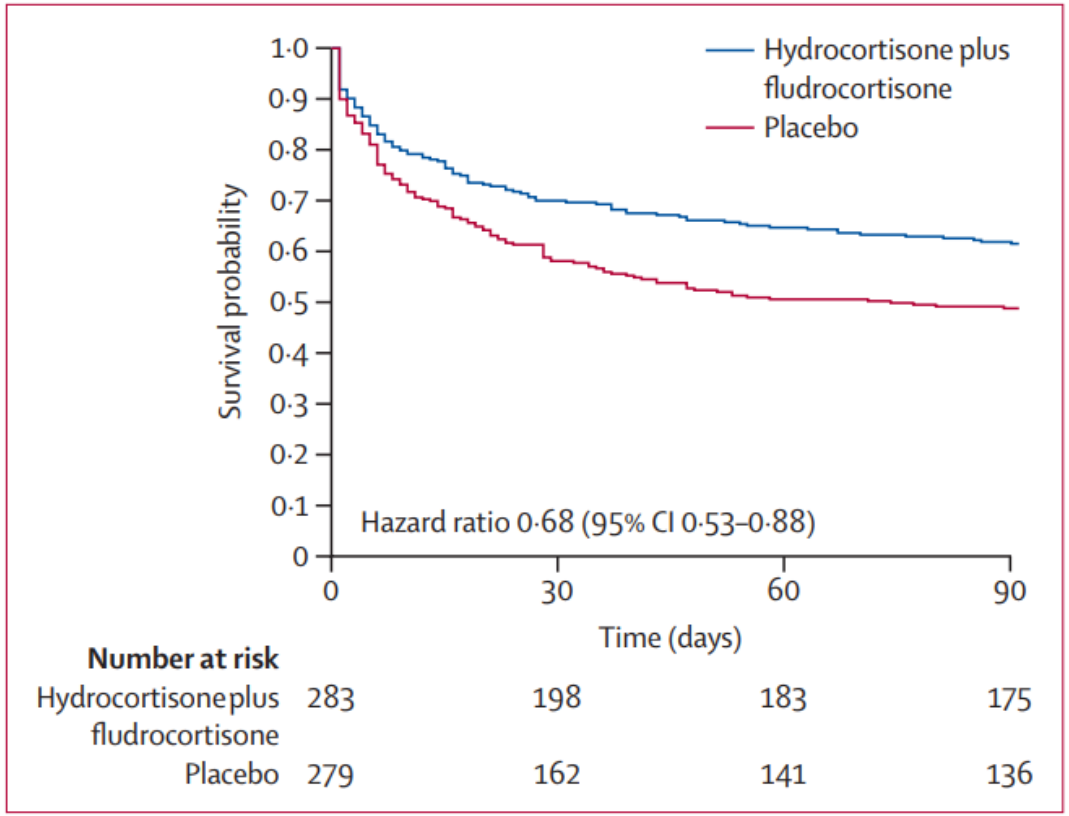
Heming N, et al., Lancet Respir Med. 2024;12:366-374

	Patients with community acquired pneumonia			Patients without community acquired pneumonia			p value for multiplicative interaction	p value for additive interaction
	Placebo (n=279)	Hydrocortisone plus fludrocortisone (n=283)	Odds ratio (95% CI)	Placebo (n=329)	Hydrocortisone plus fludrocortisone (n=319)	Odds ratio (95% CI)		
Primary outcome: deaths from any cause at day 90								
Primary analysis	143 (51%)	109 (39%)	0·60 (0·43–0·83)	157 (48%)	148 (46%)	0·95 (0·70–1·29)	0·046	0·046
Adjusted analysis on covariates imbalances	..	..	..	..	..	..	0·042	0·041
Sensitivity analysis, excluding ARDS	43/106 (41%)	31/109 (28%)	0·58 (0·33–1·03)	68/174 (39%)	68/172 (40%)	1·02 (0·66–1·57)	0·124	0·130
Vasopressor-free days to day 90,† n=; mean (SD); median (IQR)	n=272 (7);* 45 (40); 42 (1–87)	n=276 (7);* 56 (39); 84 (7–88)	..	n=326 (3);* 49 (40); 73 (1–88)	n=315 (4);* 52 (40); 81 (5–88)	..	..	0·088
Ventilator-free days to day 90,† n=; mean (SD); median (IQR)	n=274 (5);* 38 (38); 23 (0–80)	n=278 (5);* 46 (38); 67 (0–83)	..	n=327 (2);* 43 (40); 49 (0–84)	n=317 (2);* 45 (39); 53 (0–84)	..	..	0·108
Organ failure-free days to day 90,† n=; mean (SD); median (IQR)	n=272 (7);* 42 (39); 27 (0–84)	n=278 (5);* 53 (39); 77 (1–87)	..	n=325 (4);* 47 (40); 64 (0–86)	n=317 (2);* 49 (40); 77 (0–86)	..	..	0·057
Intensive care unit-free days to day 90,† n=; mean (SD); median (IQR)	n=278 (1);* 35 (37); 17 (0–76)	n=283 (0);* 44 (37); 61 (0–79)	..	n=329 (0);* 41 (38); 45 (0–81)	n=318 (1);* 41 (38); 52 (0–80)	..	..	0·073
Hospital-free days to day 90,† n=; mean (SD); median (IQR)	n=278 (1);* 27 (32); 0 (0–61)	n=283 (0);* 34 (33); 32 (0–68)	..	n=329 (0);* 31 (34); 10 (0–68)	n=318 (1);* 29 (32); 5 (0–63)	..	..	0·010

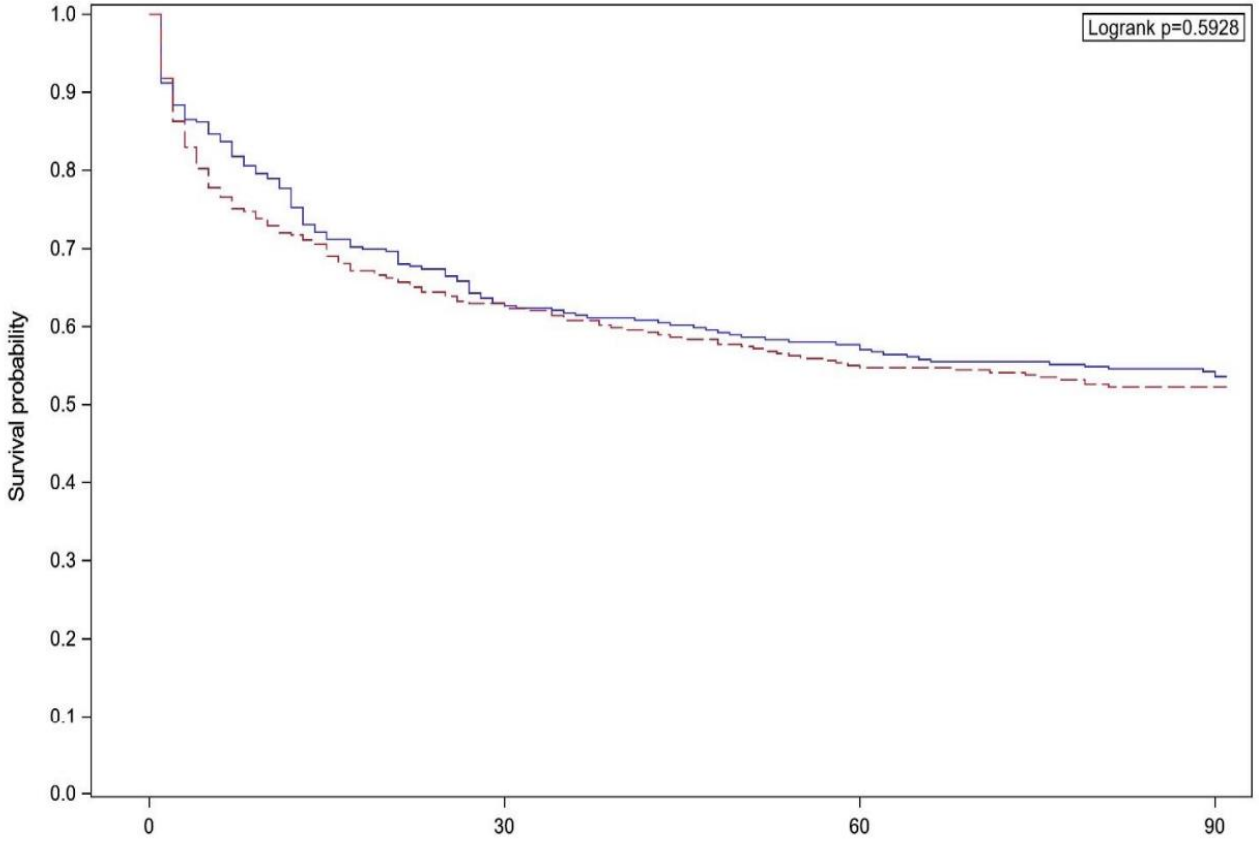
Data are n (%) or n/N (%) unless otherwise stated. *Values in brackets indicate missing values. †Patients who died before day-90 were assigned zero free days.

Table 2: **Primary and secondary outcomes in patients with and without community acquired pneumonia-related sepsis**

90-day survival



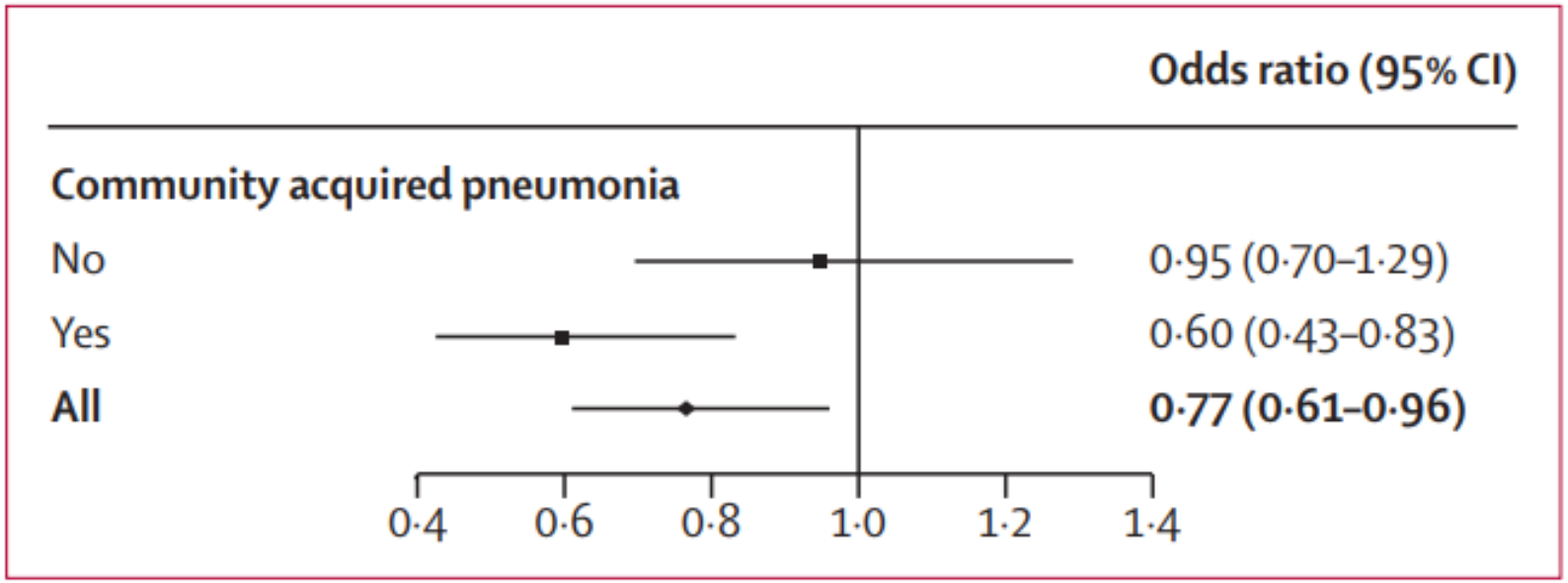
CAP-related septic shock



Non-CAP-related septic shock

Heming N, et al., Lancet Respir Med. 2024;12:366-374

Corticosteroid effects across subgroups with or without CAP



A significant statistical heterogeneity in 90-day mortality (multiplicative interaction p=0.046)

Heming N, et al., Lancet Respir Med. 2024;12:366-374

90-day all cause mortality with/without ARDS

Deaths from any cause at day-90 no./total no. (%)	All [µ]		All [µ]
	Placebo	Hydrocortisone plus Fludrocortisone	All
Male	225/424 (53.1 %)	173/402 (43.0 %)	398/826 (48.2 %)
Female	83/202 (41.1 %)	91/212 (42.9 %)	174/414 (42.0 %)
Age [18 ; 64] years	93/261 (35.6 %)	91/267 (34.1 %)	184/528 (34.8 %)
Age [65 ; 84] years	177/308 (57.5 %)	145/307 (47.2 %)	322/615 (52.4 %)
Age ≥ 85 years	38/57 (66.7 %)	28/40 (70.0 %)	66/97 (68.0 %)
With ARDS	186/328 (56.7 %)	155/320 (48.4 %)	341/648 (52.6 %)
Without ARDS	115/288 (39.9 %)	105/290 (36.2 %)	220/578 (38.1 %)

With ARDS : OR 0.72 (95% CI: 0.53-0.98)

Without ARDS : OR 0.85 (95% CI: 0.61-1.20)

(p=0.45, multiplicative interaction, p=0.42 additive interaction)

	Patients with community acquired pneumonia			Patients without community acquired pneumonia			p value for multiplicative interaction	p value for additive interaction
	Placebo (n=279)	Hydrocortisone plus fludrocortisone (n=283)	Odds ratio (95% CI)	Placebo (n=329)	Hydrocortisone plus fludrocortisone (n=319)	Odds ratio (95% CI)		
Primary outcome: deaths from any cause at day 90								
Primary analysis	143 (51%)	109 (39%)	0·60 (0·43–0·83)	157 (48%)	148 (46%)	0·95 (0·70–1·29)	0·046	0·046
Adjusted analysis on covariates imbalances	..	..	..	..	..	..	0·042	0·041
Sensitivity analysis, excluding ARDS	43/106 (41%)	31/109 (28%)	0·58 (0·33–1·03)	68/174 (39%)	68/172 (40%)	1·02 (0·66–1·57)	0·124	0·130

Adverse events

	Patients with community acquired pneumonia			Patients without community acquired pneumonia			p for multiplicative interaction	p for additive interaction
	Placebo (n=279)	Hydrocortisone plus fludrocortisone (n=283)	Odds ratio (95% CI)	Placebo (n=329)	Hydrocortisone plus fludrocortisone (n=319)	Odds ratio (95% CI)		
≥1 serious adverse event by day 180	167 (60%)	138 (49%)	0·64 (0·46–0·89)	185 (56%)	181 (57%)	1·02 (0·75–1·39)	0·044	0·042
≥1 serious bleeding event by day 28	54 (19%)	54 (19%)	0·98 (0·65–1·50)	58 (18%)	71 (22%)	1·34 (0·91–1·97)	0·290	0·284
Gastroduodenal bleeding	20 (7%)	12 (4%)	0·57 (0·28–1·20)	21 (6%)	25 (8%)	1·25 (0·68–2·28)	0·109	0·119
≥1 episode of superinfection by day 180	94 (34%)	101 (36%)	1·09 (0·77–1·55)	77 (23%)	88 (28%)	1·25 (0·88–1·78)	0·602	0·679
Site of superinfection								
Lung	68 (24%)	69 (24%)	1·00 (0·68–1·47)	44 (13%)	57 (18%)	1·41 (0·92–2·16)	0·243	0·330
Blood	28 (10%)	24 (8%)	0·83 (0·47–1·47)	18 (5%)	25 (8%)	1·47 (0·79–2·75)	0·188	0·211
Catheter-related	18 (6%)	23 (8%)	1·28 (0·68–2·43)	17 (5%)	17 (5%)	1·03 (0·52–2·06)	0·653	0·590
Urinary tract	15 (5%)	21 (7%)	1·41 (0·71–2·80)	16 (5%)	19 (6%)	1·24 (0·63–2·45)	0·793	0·727
Other	24 (9%)	42 (15%)	1·85 (1·09–3·15)	29 (9%)	27 (8%)	0·96 (0·55–1·66)	0·090	0·059
New sepsis	64 (23%)	71 (25%)	1·13 (0·76–1·66)	52 (16%)	61 (19%)	1·26 (0·84–1·89)	0·695	0·803
New septic shock	55 (20%)	55 (19%)	0·98 (0·65–1·49)	44 (13%)	53 (17%)	1·29 (0·84–1·99)	0·374	0·420
Hyperglycaemia								
≥1 episode of blood glucose levels of ≥150 mg/dl by day 7	234 (84%)	260 (92%)	2·17 (1·28–3·70)	272 (83%)	280 (88%)	1·51 (0·97–2·34)	0·296	0·457
Number of days with ≥1 episode of blood glucose levels of ≥150 mg/dl by day 7, mean (SD); median (IQR)	3·6 (2·5); 4 (1–6)	4·6 (2·4); 6 (3–7)	..	3·2 (2·5); 3 (1–6)	4·1 (2·5); 4 (2–6)	..	..	0·529
Neurologic sequelae by day 28*								
Last Muscular Disability Rating Scale score of >1	58 (21%)	78 (28%)	1·45 (0·98–2·14)	70 (21%)	75 (24%)	1·14 (0·79–1·65)	0·375	0·351
Last Muscular Disability Rating Scale score of >3	43 (15%)	58 (20%)	1·42 (0·92–2·19)	49 (15%)	50 (16%)	1·06 (0·69–1·63)	0·357	0·316
Last Muscular Disability Rating Scale score of 5	35 (13%)	38 (13%)	1·08 (0·66–1·77)	30 (9%)	35 (11%)	1·23 (0·74–2·05)	0·726	0·793

Data are n (%) unless otherwise stated. *Neurologic sequelae were assessed according to the score on the Muscular Disability Rating Scale (MDRS), with a score of 1 indicating no deficit, 2 minor deficits with no functional disability, 3 distal motor deficit, 4 mild-to-moderate proximal motor deficit, and 5 severe proximal motor deficits.

Table 3: **Adverse events**

Heming N, et al., Lancet Respir Med. 2024;12:366-374

Conclusion

Interpretation In a pre-specified subgroup analysis of the APROCCHSS trial of patients with CAP and septic shock, hydrocortisone plus fludrocortisone reduced mortality as compared with placebo. Although a large proportion of patients with CAP also met criteria for ARDS, the subgroup analysis was underpowered to fully discriminate between ARDS and CAP modifying effects on mortality reduction with corticosteroids. There was no evidence of a significant treatment effect of corticosteroids in the non-CAP subgroup.

Heming N, et al., Lancet Respir Med. 2024;12:366-374

Limitations

- Limited statistical power of the subgroup analysis
- Lack of stratified randomization by CAP status (baseline imbalances in treatment group)
- Overlap between ARDS and CAP

Fludrocortisone in septic shock

- Mineralocorticoid effect = Na+ retaining properties ?

  → Hydrocortisone : fludrocortisone = 1:125 → 200mg vs. 6.25mg

Goodman & Gilman's: The Pharmacological Basis of Therapeutics. 14th Edition

- Cortisol-induced Na+ retention not mediated by mineralocorticoid receptor but various receptors

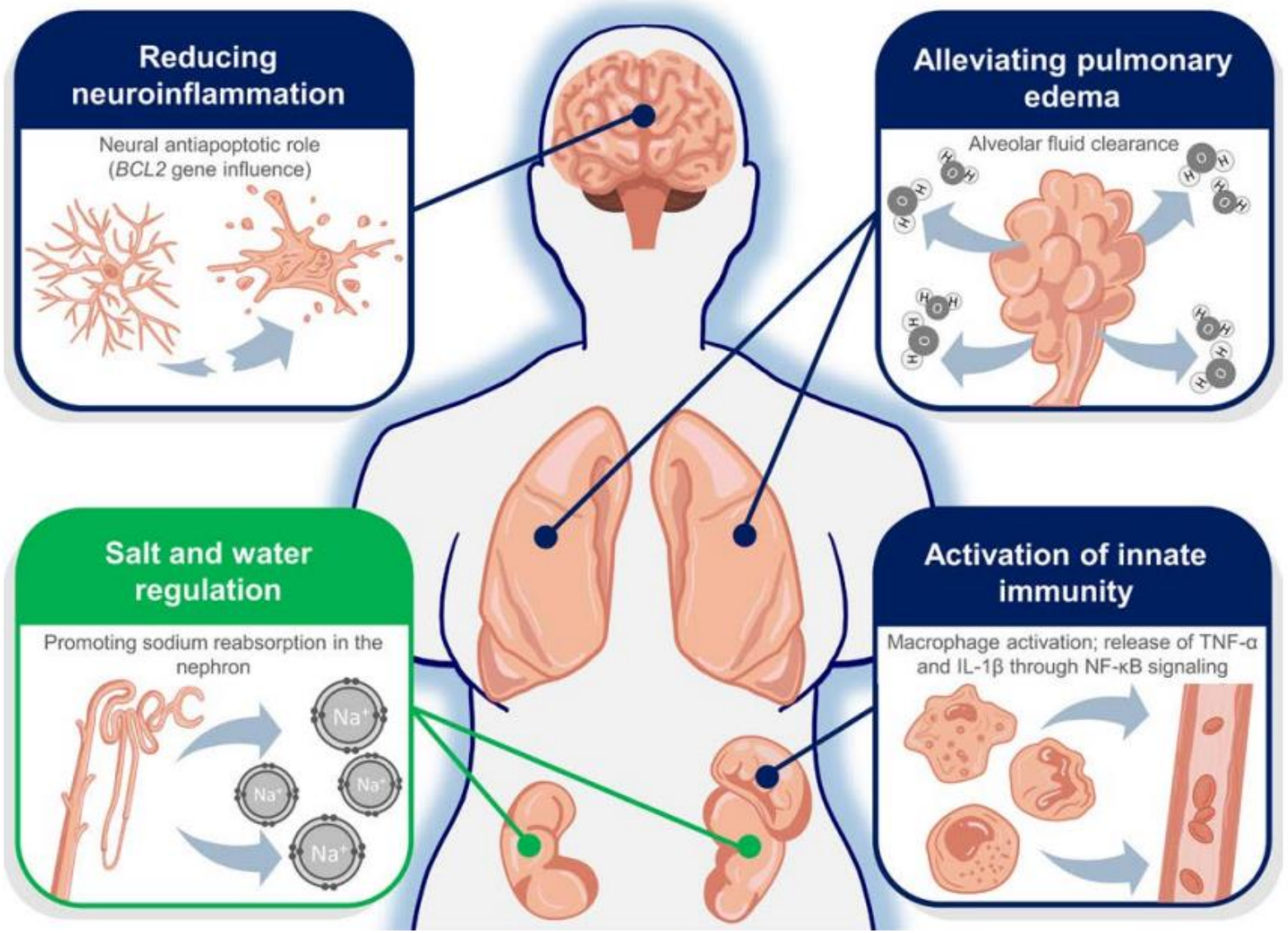
Whitworth JA et al., J Endocrinol Invest 1995; 18:586–591

- Mineralocorticoid synthesis lower in sepsis non-survivors → reduction in endogenous mineralocorticoid responsiveness than glucocorticoid responsiveness in survival of septic shock

Briegel J et al., Crit Care 2022; 26:343

Bosch, Nicholas A, et al., Critical Care Medicine 2024; 52(4):p 678-682

Potential mechanisms of benefit from fludrocortisone in septic shock



Mineralocorticoid receptor (MR)

Bosch, Nicholas A, et al., Critical Care Medicine 2024; 52(4):p 678-682

Issues to be considered

- What is the actual clinical effect of fludrocortisone ?
- Which effect plays a key role in enhancing survival rates?
- Which population is likely to benefit?
- What biomarkers can distinguish between them?
- What is the appropriate dosage and mode of fludrocortisone administration?

ORIGINAL

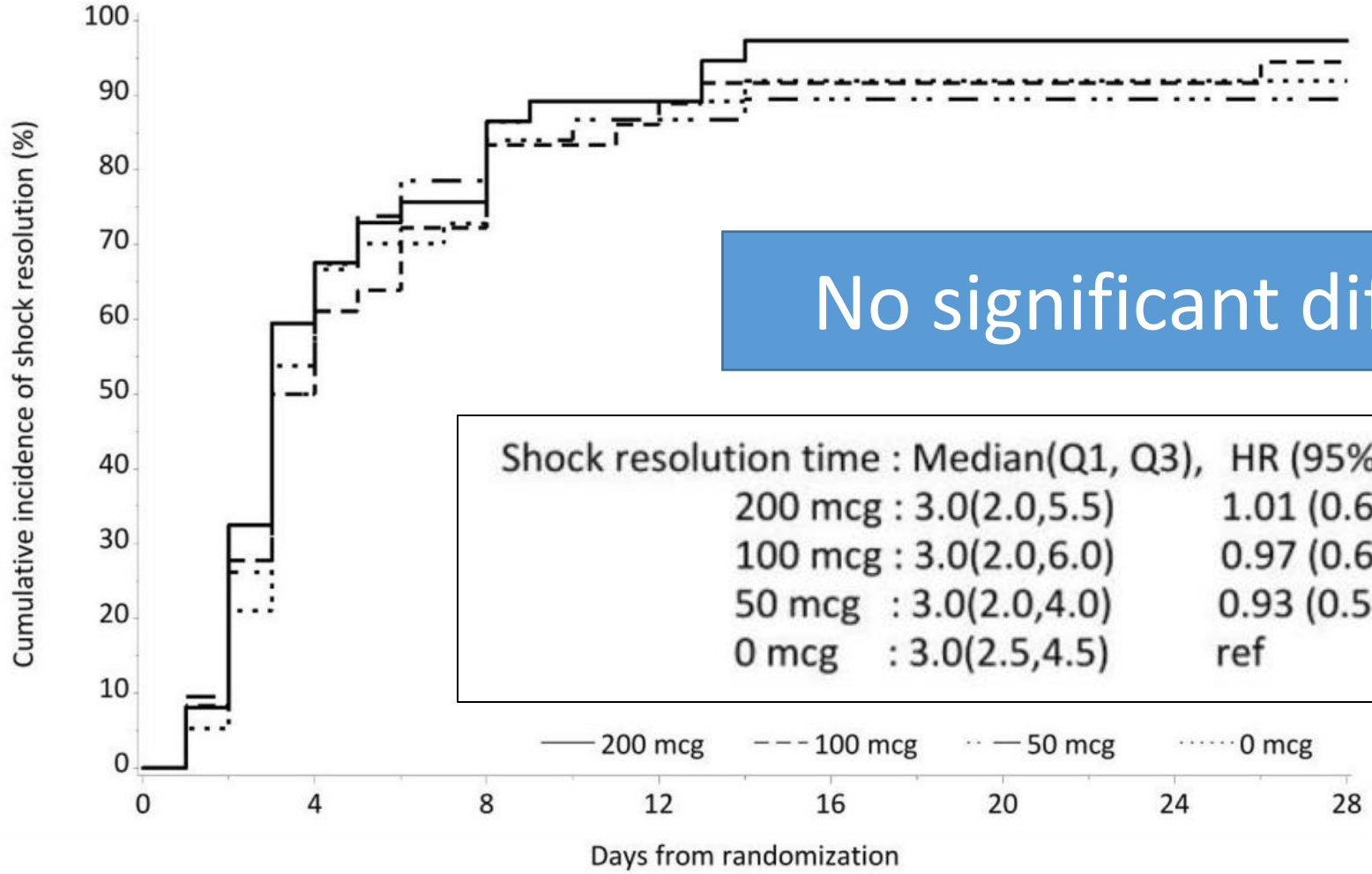
Fludrocortisone dose–response relationship in septic shock: a randomised phase II trial

James Walsham[1,5], Naomi Hammond[2,3,4], Antje Blumenthal[5], Jeremy Cohen[5,6,7], John Myburgh[2,4,8],

- FluDReSS Trial
- Phase II Study of fludrocortisone (153 patients)
- 3 different doses : 50, 100, and 200 µg/day
- Primary endpoint : time to shock resolution
- Safety outcomes
- Pharmacokinetic studies to assess absorption

J Walsham et al., Intensive Care Med (2024) 50:2050–2060

Cumulative incidence plot of shock resolution



No significant difference

Shock resolution time : Median(Q1, Q3),	HR (95%CI)
200 mcg : 3.0(2.0,5.5)	1.01 (0.63 - 1.62)
100 mcg : 3.0(2.0,6.0)	0.97 (0.61 - 1.57)
50 mcg : 3.0(2.0,4.0)	0.93 (0.59 - 1.49)
0 mcg : 3.0(2.5,4.5)	ref

J Walsham et al., Intensive Care Med (2024) 50:2050–2060

Secondary outcomes

	Fludrocortisone				Hazard ratio[A], Absolute risk diff.[Φ], or Mean diff.[r]		
	0 µg (*N* = 38)	50 µg (*N* = 42)	100 µg (*N* = 36)	200 µg (*N* = 37)	50 µg	100 µg	200 µg
Median time to resolution of shock (IQR), days [A]	3 (2.5; 4.5)	3 (2; 4)	3 (2; 6)	3 (2; 5.5)	0.93 (0.59, 1.49)	0.97 (0.61, 1.57)	1.01 (0.63, 1.62) p = 0.96
Time to resolution of shock-adjusted model [A a]					0.93 (0.58, 1.49)	0.93 (0.58, 1.51)	1.07 (0.66, 1.71) p = 0.79
28 day resolution of shock—no./total no. (%) [Φ]	28/38 (73.7)	33/42 (78.6)	32/36 (88.9)	32/37 (86.5)	– 0.02 (– 0.14, 0.11)	0.05 (– 0.05, 0.15)	0.05 (– 0.05, 0.15) p = 0.61
Recurrence of shock—no./total no. (%) [Φ]	9/38 (23.7)	11/42 (26.2)	6/36 (16.7)	10/37 (27)	0.03 (– 0.16, 0.21)	– 0.07 (– 0.25, 0.11)	0.03 (– 0.16, 0.23) p = 0.80
28 day mortality—no./total no. (%) [Φ]	9/38 (23.7)	7/42 (16.7)	4/36 (11.1)	4/37 (10.8)	– 0.07 (– 0.25,0.11)	– 0.13 (– 0.3,0.04)	– 0.13 (– 0.30, 0.04) p = 0.22
Median days to mortality (IQR)—days [A]	11 (8; 12)	9 (7; 18)	7.5 (4.5; 13.5)	14 (10.5; 17)	0.7 (0.26, 1.88)	0.48 (0.15, 1.57)	0.43 (0.13, 1.4) p = 0.16

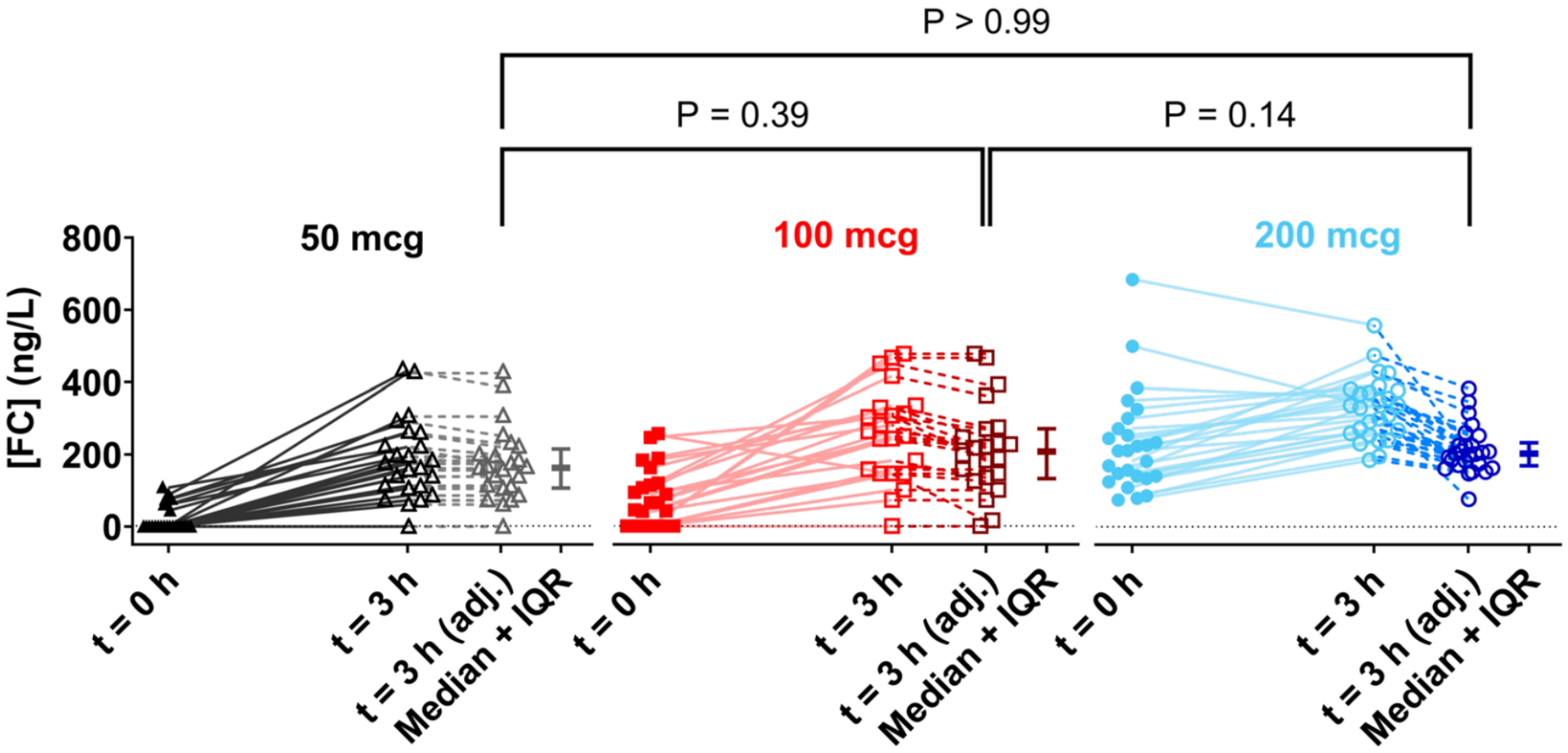
J Walsham et al., Intensive Care Med (2024) 50:2050–2060

Safety outcomes

	Fludrocortisone				*P* value
	0 µg	50 µg	100 µg	200 µg	
Hypernatraemia (> 150 mmol/l) (%)	29	19	22	30	0.64
Hyponatraemia (< 135 mmol/l) (%)	44	59	47	50	0.63
Hyperkalaemia (> 5.0 mmol/l) (%)	18	31	25	30	0.58
Hypokalaemia (< 3.5 mmol/l) (%)	56	66	57	58	0.81
Daily fluid balance Median (IQR) mls	53 (– 1104; 1094)	7 (– 1108; 1007)	368 (– 736; 1279)	102 (– 989; 1040)	0.05
New infection (%)	18	14	19	16	0.94

J Walsham et al., Intensive Care Med (2024) 50:2050–2060

Fludrocortisone plasma levels



J Walsham et al., Intensive Care Med (2024) 50:2050–2060

Conclusion

Enteral fludrocortisone resulted in detectable plasma fludrocortisone concentrations in the majority of critically ill patients with septic shock, although they varied widely indicating differing absorption and bioavailability.

It was not associated with shorter time to shock resolution.

Future studies

- Direct evidences
- Dose and administration of fludrocortisone

→ ***A large-scaled RCT needed***

Vasopressin initiation in septic shock

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Optimal Vasopressin Initiation in Septic Shock
The OVISS Reinforcement Learning Study

Alexandre Kalimouttou, MD; Jason N. Kennedy, MS; Jean Feng, PhD; Harvineet Singh, PhD; Suchi Saria, PhD; Derek C. Angus, MD, MPH; Christopher W. Seymour, MD, MSc; Romain Pirracchio, MD, MPH, PhD

Question Does a reinforcement learning model identify the optimal initiation rule for vasopressin in patients with septic shock who are receiving norepinephrine?

- Among 14,453 critically ill patients with septic shock
- From 232 hospitals in 4 independent datasets
- Clinical, laboratory, and treatment variables grouped hourly for 120 h in the EHR

A. Kalimouttou, et al., JAMA. doi:10.1001/jama.2025.3046

Reward function of a reinforcement learning model

- In-hospital mortality
- Mean arterial blood pressure
- SOFA score
- Norepinephrine dose
- Serum lactate

Table 1. Patient Characteristics[a]

Characteristic	Derivation cohort, No. (%)[b]	Internal and external validation cohorts (validation set), No. (%)[b]			
	UCSF training and test sets (n = 3608)	UCSF internal (n = 628)	MIMIC-IV (n = 3056)	eICU-CRD (n = 910)	UPMC (n = 6251)
Summary of datasets					
Enrollment period	2012-2023	2012-2023	2008-2019	2014-2015	2019-2020
No. of hospitals	5	5	1	208	18
Total No. of admissions	119 730	119 730	76 540	200 859	102 467
Setting	Integrated health system			Health systems across US	Integrated health system in Pennsylvania
	California	California	Boston		
Patient characteristics					
Organ support					
Norepinephrine dose, median (IQR), µg/kg/min	0.05 (0.03-0.10)	0.06 (0.03-0.10)	0.12 (0.06-0.23)	0.26 (0.12-0.46)	0.16 (0.06-0.45)
Vasopressin introduction during shock	908 (25)	151 (24)	1485 (48)	179 (20)	1522 (24)
Mechanical ventilation[g]					
Outcome					
In-hospital mortality	1603 (44)	254 (41)	1186 (38)	256 (28)	2705 (43)

A. Kalimouttou, et al., JAMA. doi:10.1001/jama.2025.3046

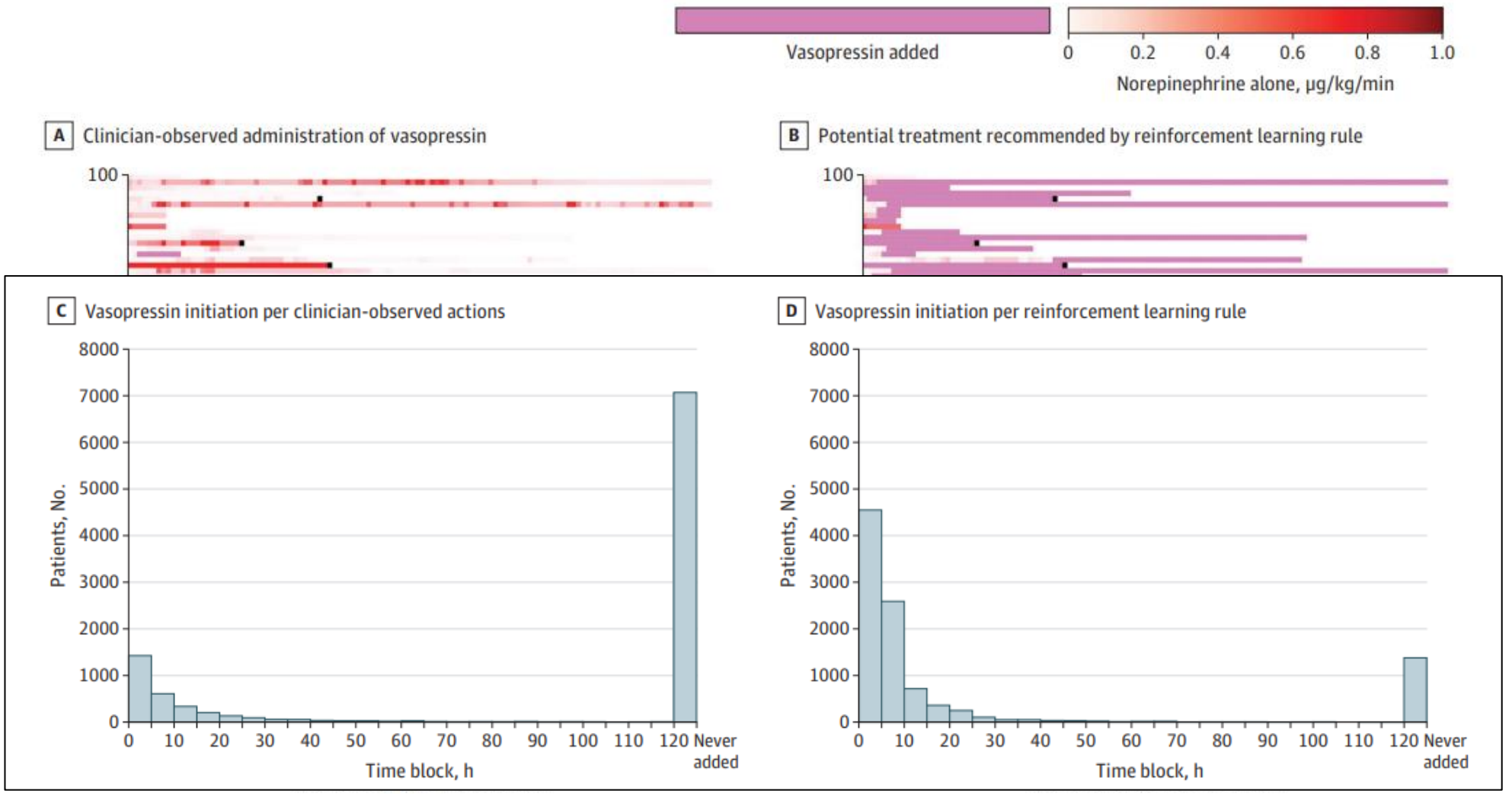
External validation set

Table 2. Patient Data in the Epoch Containing Vasopressin Initiation in External Validation Sets

	Overall			MIMIC-IV			eICU-CRD			UPMC		
	Clinician-observed action	Reinforcement learning rule	*P* value	Clinician-observed action	Reinforcement learning rule	*P* value	Clinician-observed action	Reinforcement learning rule	*P* value	Clinician-observed action	Reinforcement learning rule	*P* value
Patients with vasopressin started, No. (%)	3186 (31)	8884 (87)	<.001	1485 (47)	2649 (87)	<.001	179 (20)	813 (89)	<.001	1522 (24)	5422 (87)	<.001
Norepinephrine dose, median (IQR), µg/kg/min	0.37 (0.17-0.69)	0.2 (0.08-0.45)	<.001	0.28 (0.14-0.40)	0.16 (0.08-0.30)	<.001	0.68 (0.35-1.35)	0.35 (0.13-1.12)	<.001	0.6 (0.20-1.40)	0.2 (0.08-0.51)	<.001
Time since shock onset, median (IQR), h	5 (1-14)	4 (1-8)	<.001	4 (1-12)	5 (2-9)	.01	6 (2-14)	3 (1-7)	<.001	6 (2-17)	4 (1-7)	<.001
SOFA score, median (IQR)[a]	9 (6-12)	7 (5-10)	<.001	10 (8-12)	10 (7-12)	<.001	13 (11-15)	11 (9-13)	<.001	7 (5-10)	6 (3-8)	<.001
Serum lactate, median (IQR), mmol/L	3.6 (1.8-6.8)	2.5 (1.7-4.9)	<.001	2.6 (1.7-5.2)	2.3 (1.7-4.5)	<.001	3.2 (1.7-5.9)	1.7 (1.1-2.9)	<.001	4.7 (2.5-8.8)	2.7 (1.7-5.3)	<.001

A. Kalimouttou, et al., JAMA. doi:10.1001/jama.2025.3046

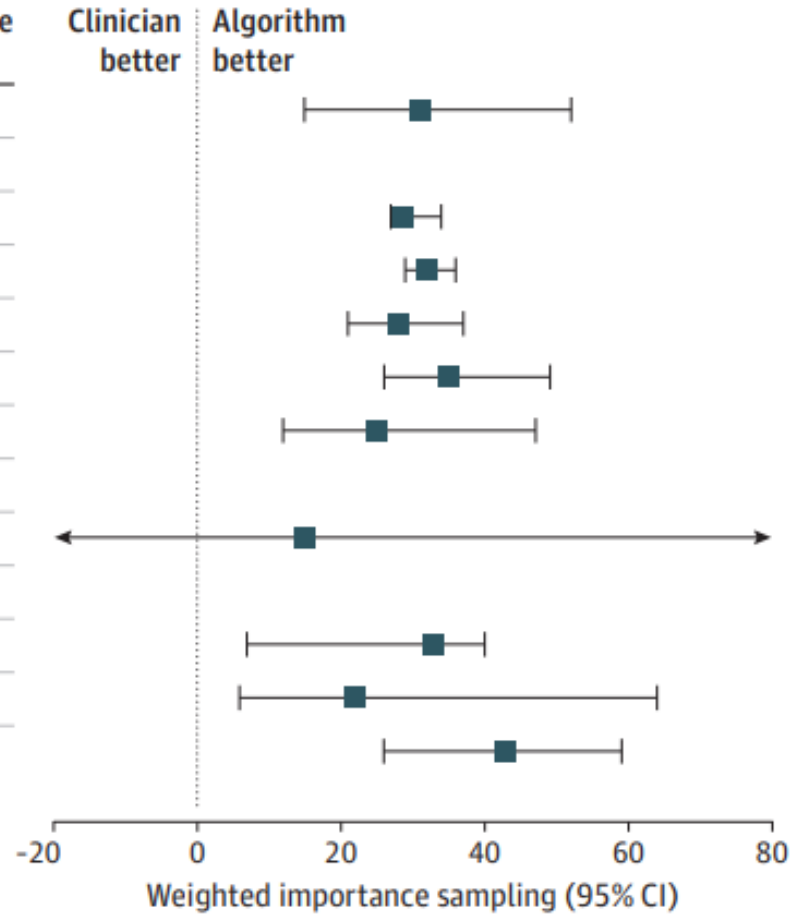
Comparison of Clinician-Observed Administration of Vasopressin With Treatment Recommended by the Reinforcement Learning Rule



A. Kalimouttou, et al., JAMA. doi:10.1001/jama.2025.3046

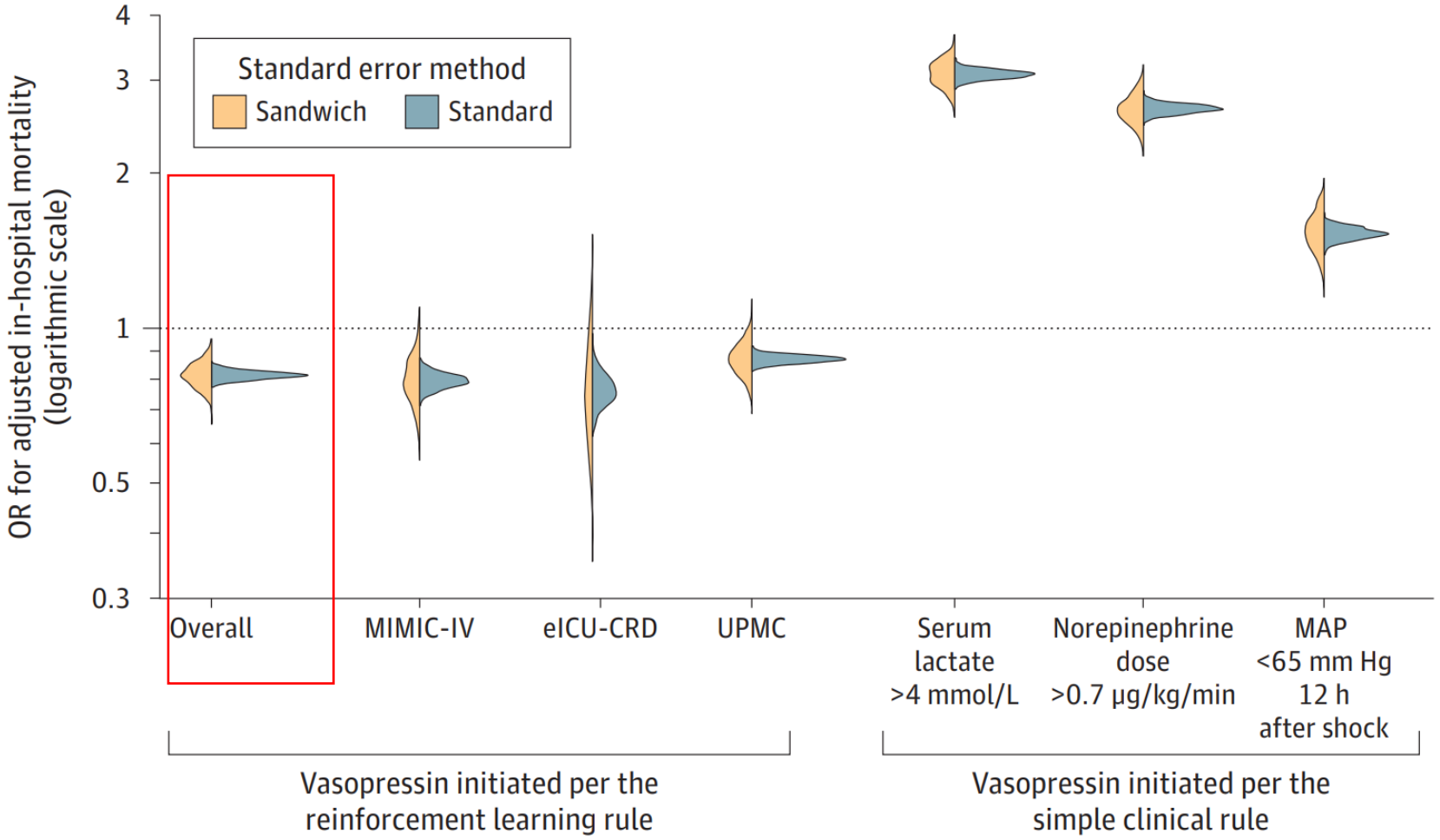
Weighted importance sampling

Category	Weighted importance sampling (95% CI)
Overall reward	31 (15 to 52)
Reward component	
In-hospital mortality	29 (27 to 34)
Mean arterial pressure	32 (29 to 36)
SOFA score	28 (21 to 37)
Norepinephrine dose	35 (26 to 49)
Serum lactate	25 (22 to 27)
Internal validation	
UCSF	15 (-48 to 129)
External validation	
MIMIC-IV	33 (7 to 40)
eICU-CRD	22 (6 to 64)
UPMC	43 (26 to 59)



A. Kalimouttou, et al., JAMA. doi:10.1001/jama.2025.3046

Risk-adjusted odds of in-hospital mortality



Overall in-hospital mortality:
aOR 0.81 [robust 95% CI, 0.73-0.91]

A. Kalimouttou, et al., JAMA. doi:10.1001/jama.2025.3046

Conclusion

In adult patients with septic shock receiving norepinephrine, the use of vasopressin was variable. A reinforcement learning model developed and validated in several observational datasets recommended **more frequent and earlier use of vasopressin** than average care patterns and was **associated with reduced mortality**.

Restrictive fluid therapy in septic shock

ORIGINAL

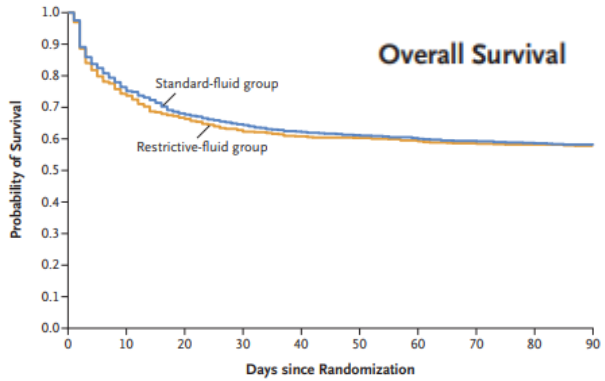
Effects of restrictive fluid therapy on the time to resolution of hyperlactatemia in ICU patients with septic shock. A secondary post hoc analysis of the CLASSIC randomized trial

Christian Ahlstedt[1,2,4*], Praleene Sivapalan[3,4,5], Miroslav Kriz[6], Gustaf Jacobson[1], Tine Sylvest Meyhoff[3,4], Benjamin Skov Kaas-Hansen[3], Manne Holm[1], Jacob Hollenberg[8,9], Marek Nalos[4,6,7], Olav Rooijackers[1,2], Morten Hylander Møller[3,4,5], Maria Cronhjort[10,4,8], Anders Perner[3,4,5] and Jonathan Grip[1,2]

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 30, 2022 VOL. 386 NO. 26

Restriction of Intravenous Fluid in ICU Patients with Septic Shock



- Post hoc analysis of the CLASSIC trial
- Does a restrictive fluid strategy result in slower resolution of hyperlactatemia ?
- Restrictive: IV bolus fluid (250-500 ml of isotonic crystalloid)
  1) Severe hypoperfusion (≥ 4 mmol/L)
  2) MBP < 50 mmHg despite infusion of a vasopressor or an inotropic agent
  3) Mottling beyond the edge of the kneecap (mottling score >2 on a scale of 0 to 5)
  4) Urinary output < 0.1 ml/kg/h during the first 2 h after randomization
- Standard: SCCM guideline
- Primary outcome: the time to resolution of hyperlactatemia

  : first plasma lactate concentration <2 mmol/L within 72 h after randomization, irrespective of subsequent changes

T.S. Meuhoff, et al. N Engl J Med (2022) 386:2459-70
C. Ahlstedt et al., Intensive Care Med (2024) 50:678–686

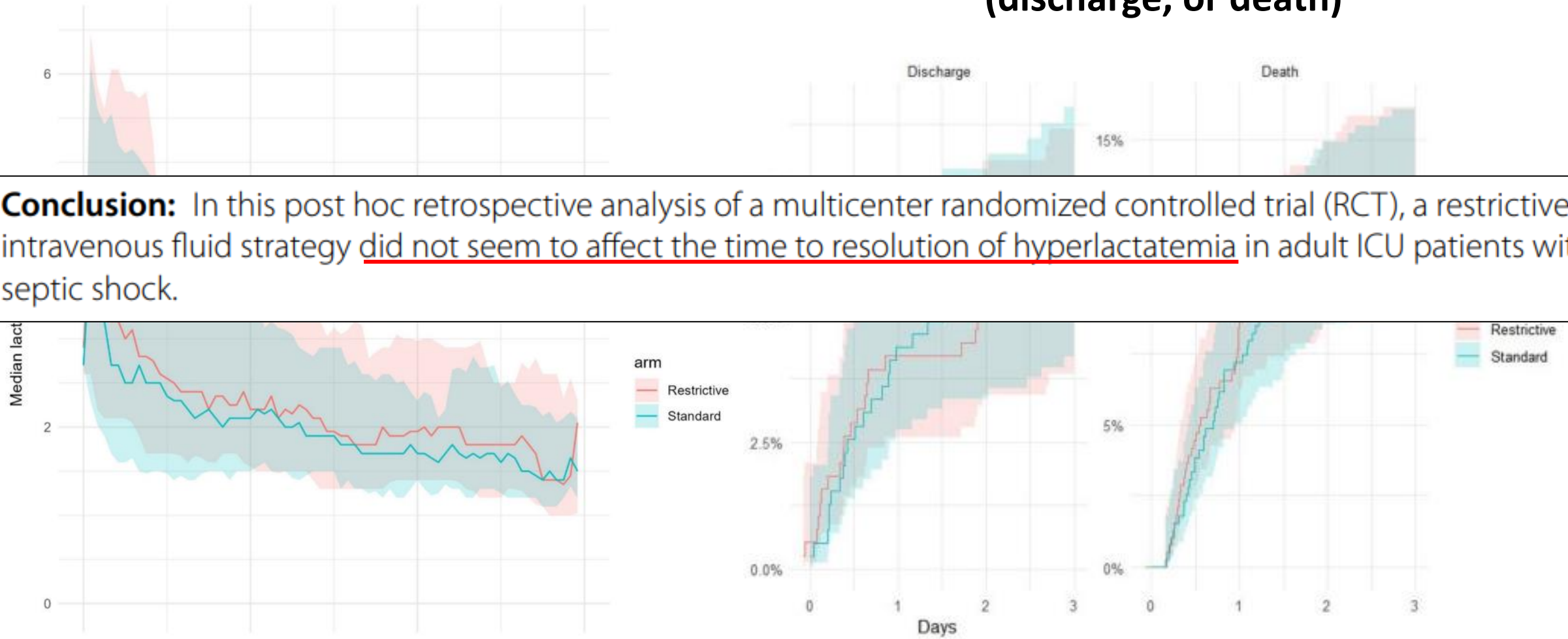
Intravenous and total fluid volumes

Variable	Restrictive group (*N* = 385)	Standard group (*N* = 392)	Difference (restrictive vs. standard)	Unavailable volume[e]
All volumes in milliliters, presented as median and interquartile range [IQR]				
Intravenous fluid volume[a]				
Day 1[b]	500 [0–1200]	1152 [258–2401]	−652	0 (0%)
Day 2	202 [0–883]	788 [100–1573]	−586	49 (6%)
Day 3	0 [0–250]	191 [0–1000]	−191	156 (20%)
Cumulative day 1 to 3	1188 (304–2514)	2696 (1294–4908)	−1508	156 (20%)
Total fluid volume[c]				
Day 1[b]	1476 [758–2667]	2324 [1176–3666]	−848	0 (0%)
Day 2	1949 [1095–2948]	2384 [1305–3435]	−435	49 (6%)
Day 3	1386 [617–2330]	1858 [851–2612]	−472	156 (20%)
Cumulative day 1 to 3	5334 (3476–7578)	6919 (4721–9744)	−1585	156 (20%)
Cumulative fluid balance[d]				
Day 1[b]	712 [−14–1817]	1274 [266–2742]	−562	0 (0%)
Day 2	743 [−138–1607]	942 [120–1984]	−199	49 (6%)
Day 3	249 [−475–844]	260 [−466–1022]	−11	156 (20%)
Cumulative day 1 to 3	1458 (−125–3594)	2521 (906–5257)	−1063	156 (20%)

C. Ahlstedt et al., Intensive Care Med (2024) 50:678–686

Plasma lactate concentrations

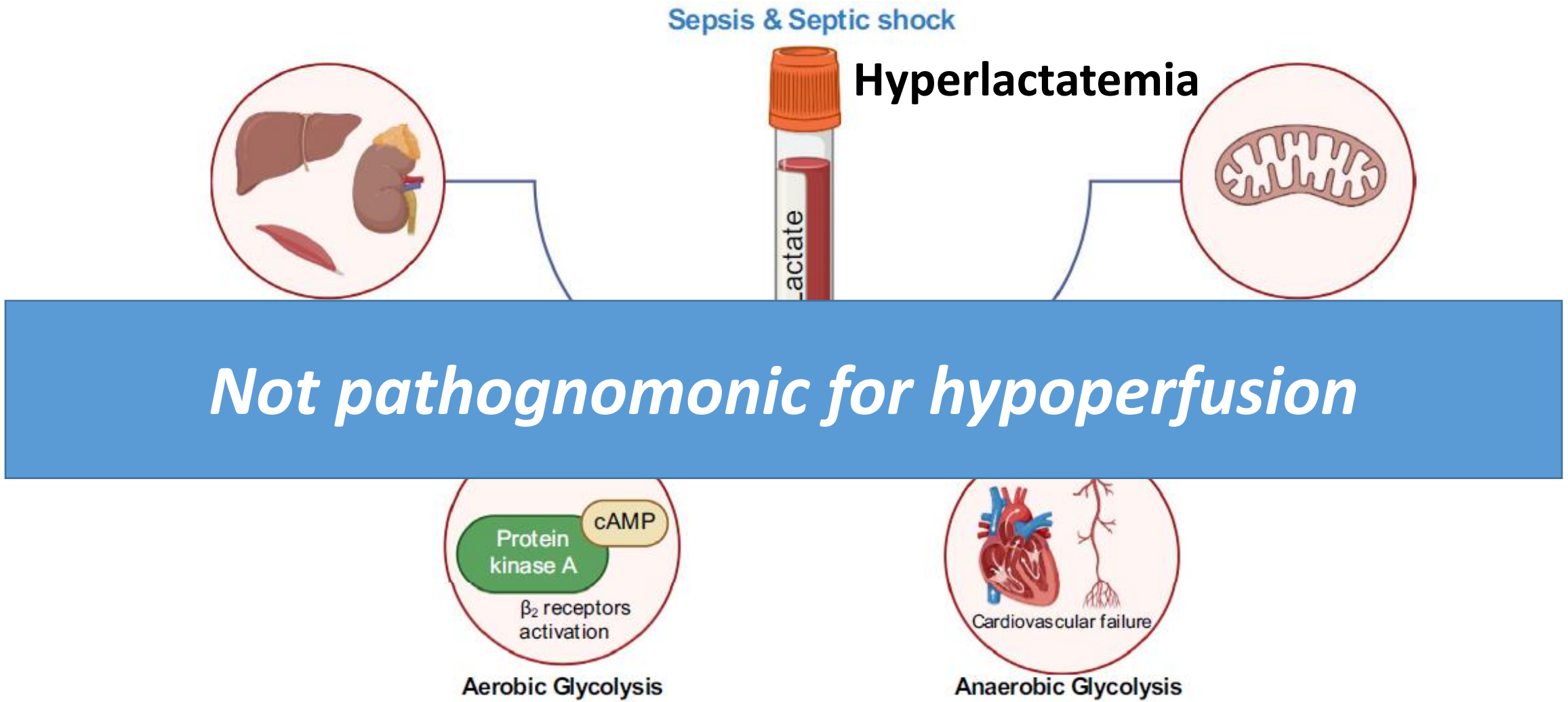
Cumulative probability with 95% CI for the competing risk outcomes (discharge, or death)



Conclusion: In this post hoc retrospective analysis of a multicenter randomized controlled trial (RCT), a restrictive intravenous fluid strategy did not seem to affect the time to resolution of hyperlactatemia in adult ICU patients with septic shock.

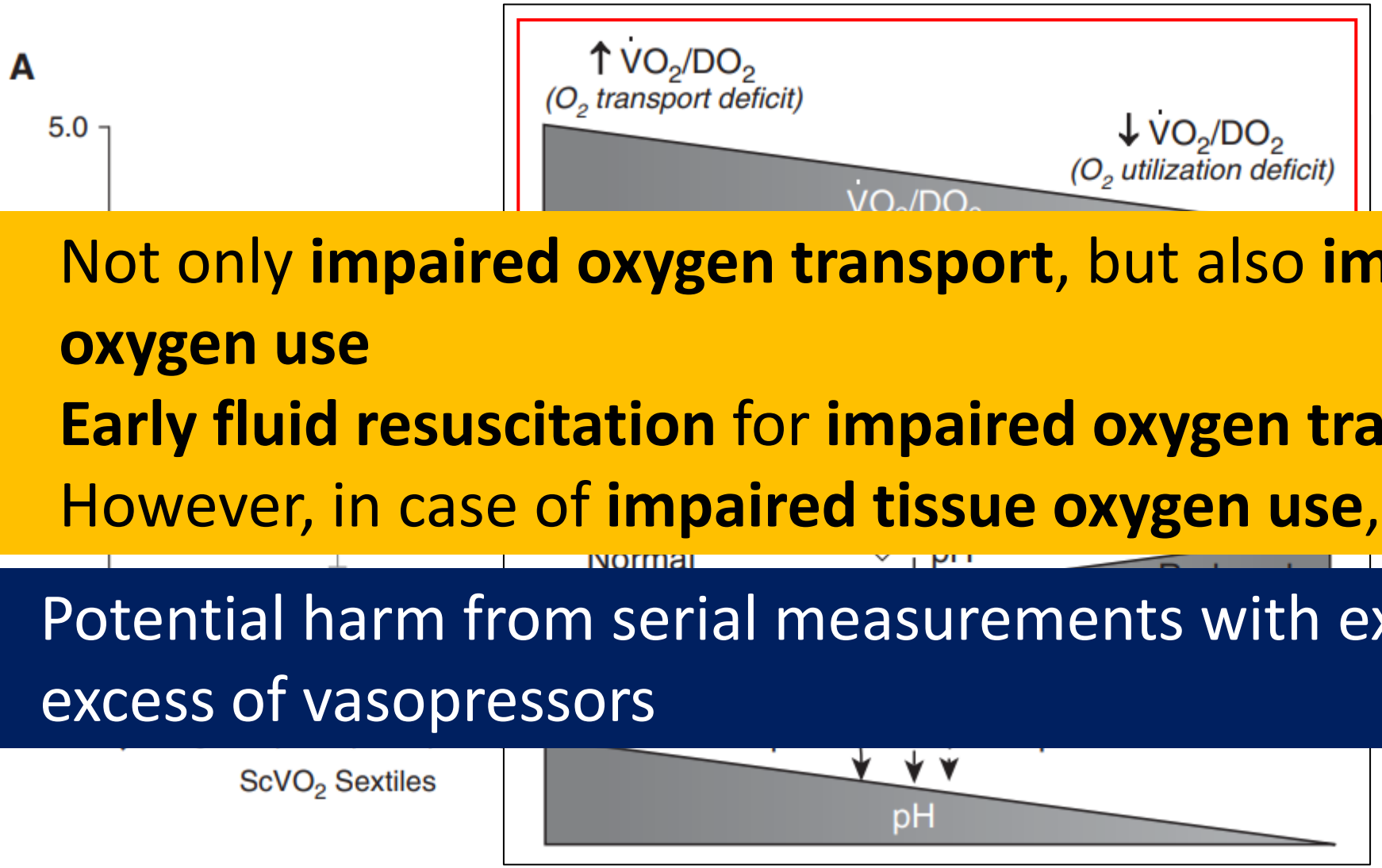
C. Ahlstedt et al., Intensive Care Med (2024) 50:678–686

Why..



M. Legrand, et al., Intensive Care Med (2024) 50:728–730

Lactatemia in human sepsis



- Not only **impaired oxygen transport**, but also **impaired tissue oxygen use**
- **Early fluid resuscitation** for **impaired oxygen transport**
- However, in case of **impaired tissue oxygen use**, may be **ineffective**

- Potential harm from serial measurements with excessive fluids or excess of vasopressors

L. Gattinoni et al., Am J Respir Crit Care Med 200, 5, 582–589

What we should use to guide fluid resuscitation?

- Peripheral perfusion-targeted resuscitation (capillary refill time)

The ANDROMEDA-SHOCK Randomized Clinical Trial
JAMA. 2019;321(7):654-664

- Integration of serum lactate with clinical phenotyping

Simple Intensive Care Studies-I
Intensive Care Med 45:190–200

- CRT-targeted resuscitation based on clinical hemodynamic phenotyping

the ANDROMEDA-SHOCK-2 randomized clinical trial study protocol
Revista Brasileira de terapia intensiva 34:96–106

Antibiotic duration in management of VAP

Individualised short-course vs. usual long-course Tx

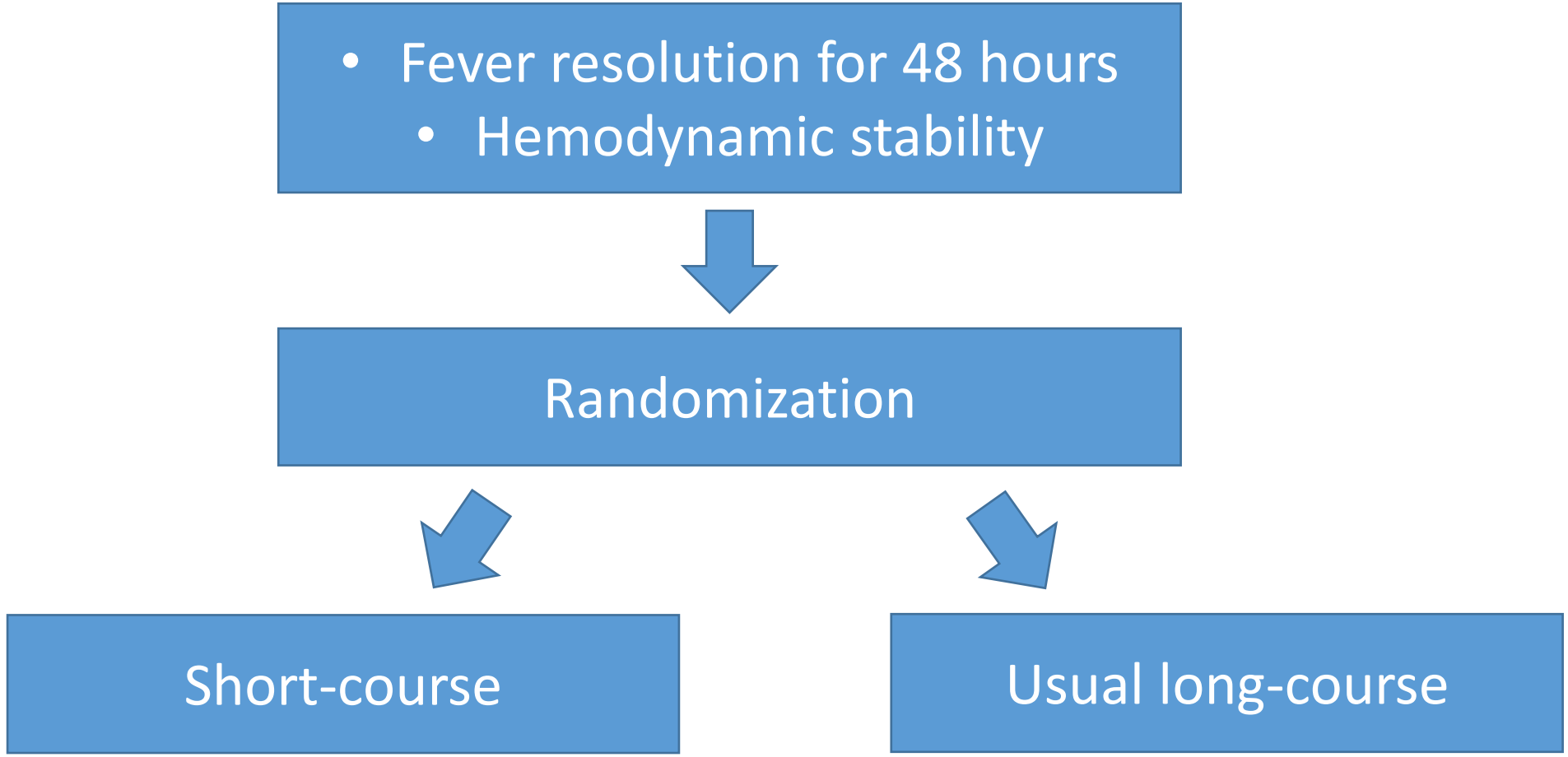
Individualised, short-course antibiotic treatment versus usual long-course treatment for ventilator-associated pneumonia (REGARD-VAP): a multicentre, individually randomised, open-label, non-inferiority trial

Yin Mo, Suchart Booraphun, Andrew Yunkai Li, Pornanan Domthong, Gyan Kayastha, Yie Hui Lau, Ploenchan Chetchotisakd, Direk Limmathurotsakul, Paul Anantharajah Tambyah, Ben S Cooper, on behalf of the REGARD-VAP investigators

- From 2018 to 2022 : 461 patients
- Thirty-nine ICUs from 6 hospitals in Nepal , Singapore & Thailand
- Low-income and middle-income countries
- Short-course : ≤ 7 days and as short as 3-5 days (n=232)
- Long-course : ≥ 8 days (n=229)

Yin Mo et al., Lancet Respir Med 2024; 12:399-408

Study design



Inclusion criteria : Clinically defined pneumonia

Imaging Test Evidence	Signs/Symptoms
Two or more serial chest imaging test results with at least ***one*** of the following (1,2,13): New and persistent **or** Progressive and persistent • Infiltrate • Consolidation • Cavitation • Pneumatoceles, in infants ≤1 year old	For ANY PATIENT, at least ***one*** of the following: • Fever (> 38.0°C or > 100.4°F) • Leukopenia (≤ 4000 WBC/mm^3) or leukocytosis (≥ 12,000 WBC/mm^3) • For adults ≥ 70 years old, altered mental status with no other recognized cause And at least ***two*** of the following (from separate bullets): • New onset of purulent sputum (3) or change in character of sputum (4), or increased respiratory secretions, or increased suctioning requirements • Dyspnea, or tachypnea (5), or new onset or worsening cough • Rales (6) or bronchial breath sounds • Worsening gas exchange (for example, O_2 desaturations [for example, PaO_2/FiO_2 ≤ 240] (7), increased oxygen requirements, or increased ventilator demand)

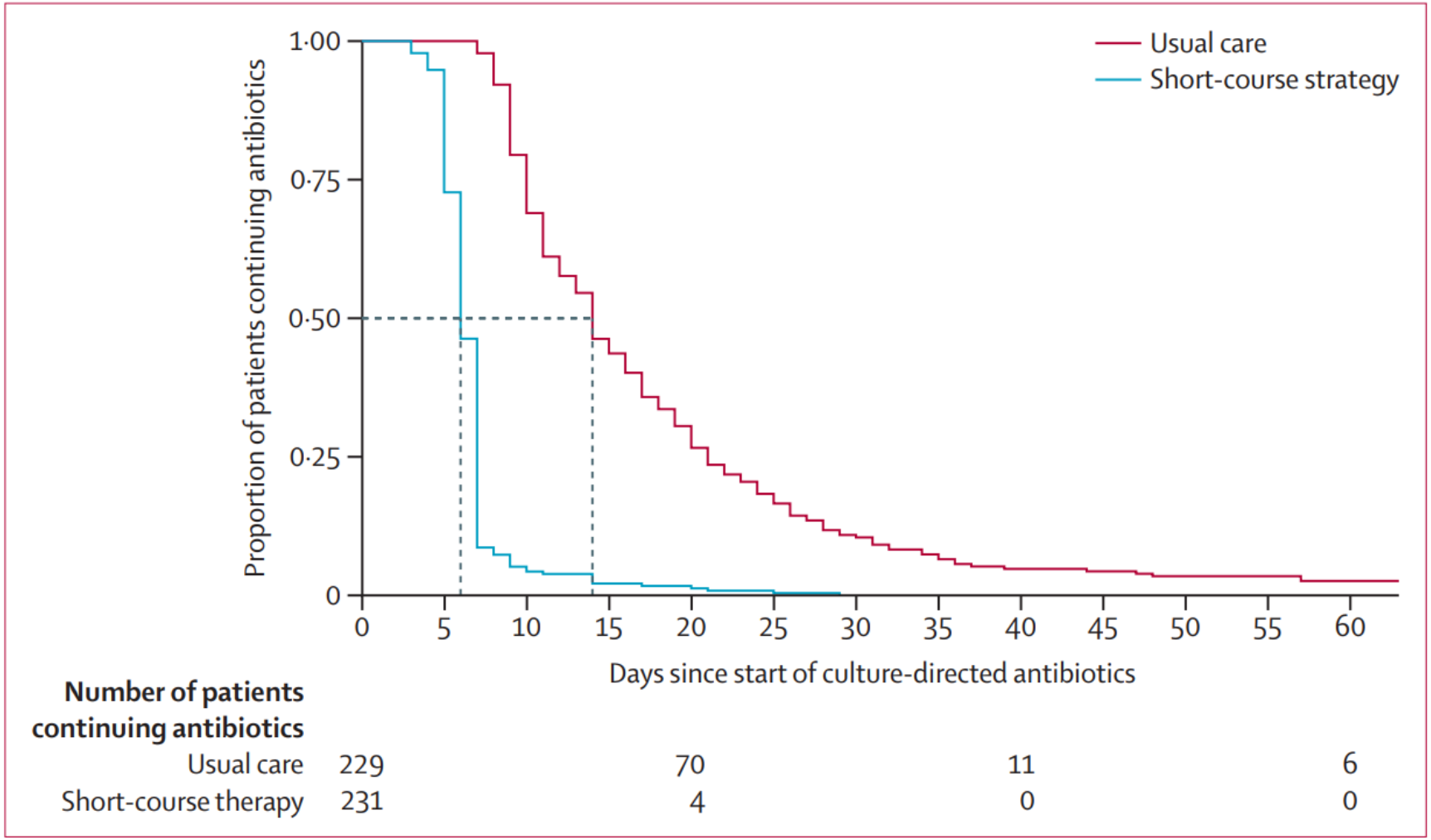
From CDC National Healthcare Safety Network (NHSN)

Exclusion criteria

1. SOFA score of more than 11 points
2. Immunocompromised patients
   - HIV with CD4 <200 cells/mm^3
   - Corticosteroids > 0·5 mg/kg per day for >30 days
   - Chemotherapy in the past 3 months
   - Solid organ or hematopoietic stem-cell transplant
   - Other concurrent infections that required antibiotic treatment for longer than 7 days

   (excluding anti-tuberculosis treatment, antifungal medications, and antibiotics meant for chronic suppression of chronic infections or chronic obstructive lung disease)

Duration of antibiotics : 6 days [5-7] vs. 14 days [10-21]



Number of patients continuing antibiotics				
Usual care	229	70	11	6
Short-course therapy	231	4	0	0

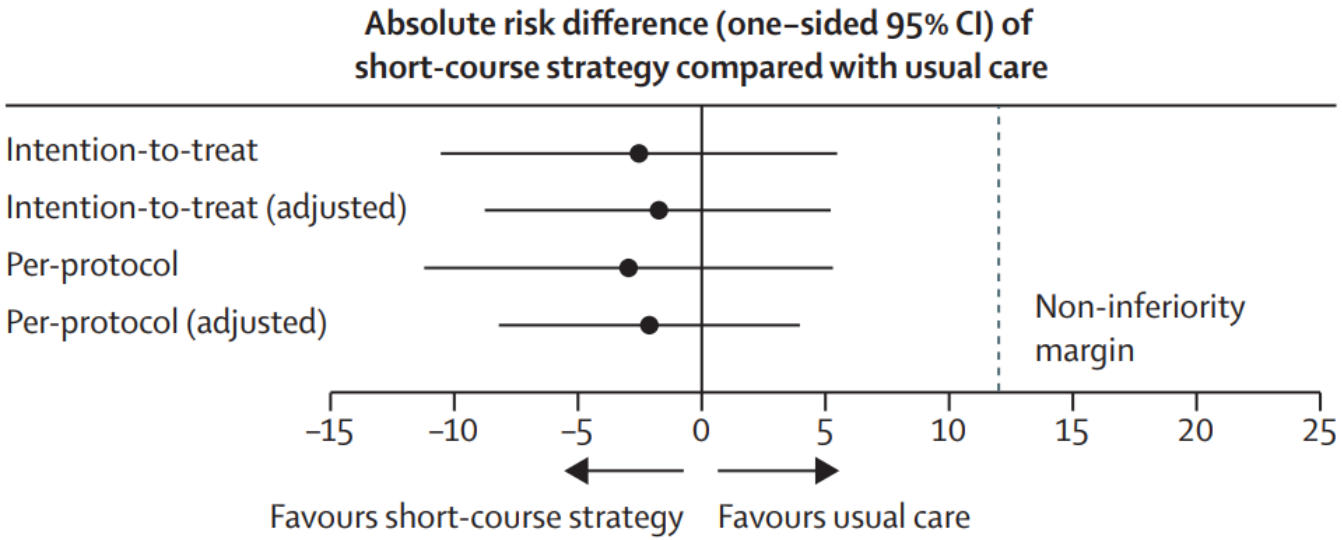
Primary outcome

: 60-day composite endpoint of death or pneumonia recurrence

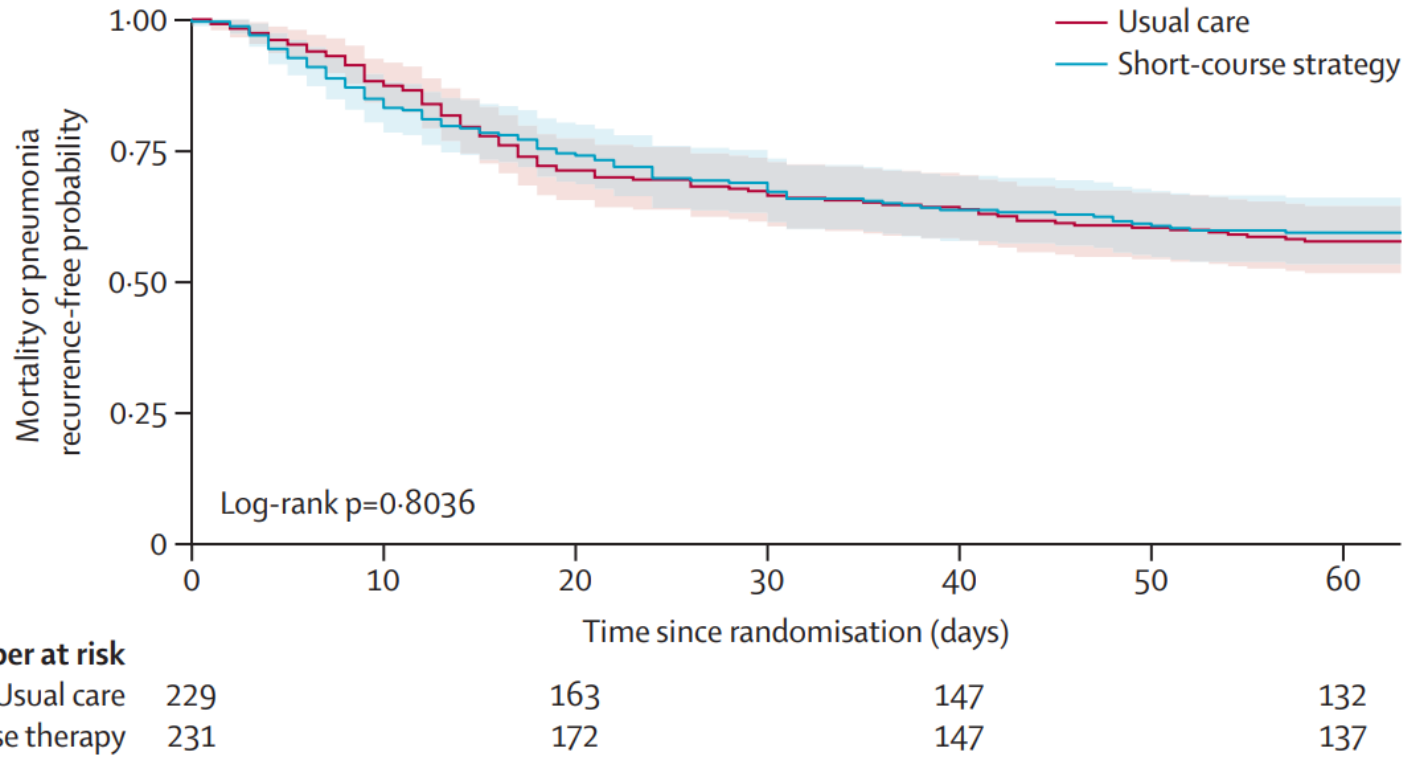
	Mortality (%)	Recurrence of pneumonia (%)	Primary outcome (%)	Unadjusted absolute risk difference (one-sided 95% CI)	Adjusted absolute risk difference (one-sided 95% CI)
Intention-to-treat (n=460)	..	..	..	−3%(−∞ to 5%)	−2%(−∞ to 5%)
Short-course group (n=231)	81 (35%)	33 (14%)	95 (41%)	..	..
Usual care group (n=229)	88 (38%)	30 (13%)	100 (44%)	..	..
Per-protocol (n=435)	..	..	..	−3%(−∞ to 5%)	−2%(−∞ to 4%)
Short-course group (n=211)	76 (36%)	29 (14%)	87 (41%)	..	..
Usual care group (n=224)	87 (39%)	30 (13%)	99 (44%)	..	..

Data are n (%) unless otherwise stated.

Yin Mo et al., Lancet Respir Med 2024; 12:399-408



No difference in primary outcome



Lower duration and lower antibiotic side effects

	Short-course group (n=211)	Usual care group (n=224)	Unadjusted estimates (95% CI; p value)	Adjusted estimates (95% CI; p value)*
Mean (SD) duration of antibiotics during admission, days	20·5 (15·0)	25·7 (15·1)	−5·2 (−8·1 to −2·4; 0·0003)	−5·2 (−7·5 to −2·8; 0·0003)
Mean (SD) duration of mechanical ventilation during admission, days†	29·8 (27·6)	30·0 (27·1)	−0·06 (−5·2 to 5·1; 0·98)	0·14 (−4·2 to 4·5; 0·95)
Mean (SD) duration of ICU admission, days	27·0 (24·2)	28·5 (24·2)	−1·4 (−6·0 to 3·1; 0·54)	−1·3 (−5·2 to 2·5; 0·57)
Mean (SD) duration of stay in hospital, days	35·1 (23·8)	35·0 (23·0)	0·22 (−4·2 to 4·6; 0·92)	−0·15 (−3·8 to 3·5; 0·95)
Readmission to an acute care hospital	40 (19%)	40 (18%)	0·011% (−0·066 to 0·088%; 0·86)	0·014% (−0·047 to 0·074%; 0·71)
Pneumonia recurrence determined by at least one independent assessor	37 (18%)	39 (17%)	0·0013% (−0·071 to 0·074%; 1·00)	0·0010% (−0·057 to 0·059%; 0·98)
Bloodstream infection after enrolment	26 (12%)	30 (13%)	−0·011% (−0·078 to 0·056%; 0·85)	−0·013% (−0·066 to 0·040%; 0·69)
Newly colonised or infected with carbapenem-resistant Gram-negative bacilli after enrolment	37 (18%)	41 (18%)	−0·0077% (−0·084 to 0·069%; 0·93)	−0·0009% (−0·061 to 0·059%; 0·98)
Acute kidney injury‡	11 (5%)	79 (35%)	−30% (−38 to −23%; <0·0001)	−30% (−36 to −24%; <0·0001)
Drug-induced liver injury§	1 (<1%)	2 (1%)	−3% (−6 to 0; 0·093)	−3% (−5 to −1%; 0·033)
Diarrhoea	4 (2%)	5 (2%)	0 (−3 to 3%; 1·00)	−1% (−3 to 2%; 0·69)
Allergy (eg, DRESS, rash, SJS)	1 (<1%)	2 (1%)	0 (−2 to 2%; 1·00)	−1% (−2 to 1%; 0·36)
Any antibiotic side-effects	17 (8%)	86 (38%)	−30% (−38 to −23%; <0·0001)	−31% (−37 to −25%; <0·0001)

Conclusion

Interpretation In this study of adults with VAP, individualised shortened antibiotic duration guided by clinical response was non-inferior to longer treatment durations in terms of 60-day mortality and pneumonia recurrence, and associated with substantially reduced antibiotic use and side-effects. Individualised, short-course antibiotic treatment for VAP could help to reduce the burden of side-effects and the risk of antibiotic resistance in high-resource and resource-limited settings.

Prophylactic antibiotics in VAP

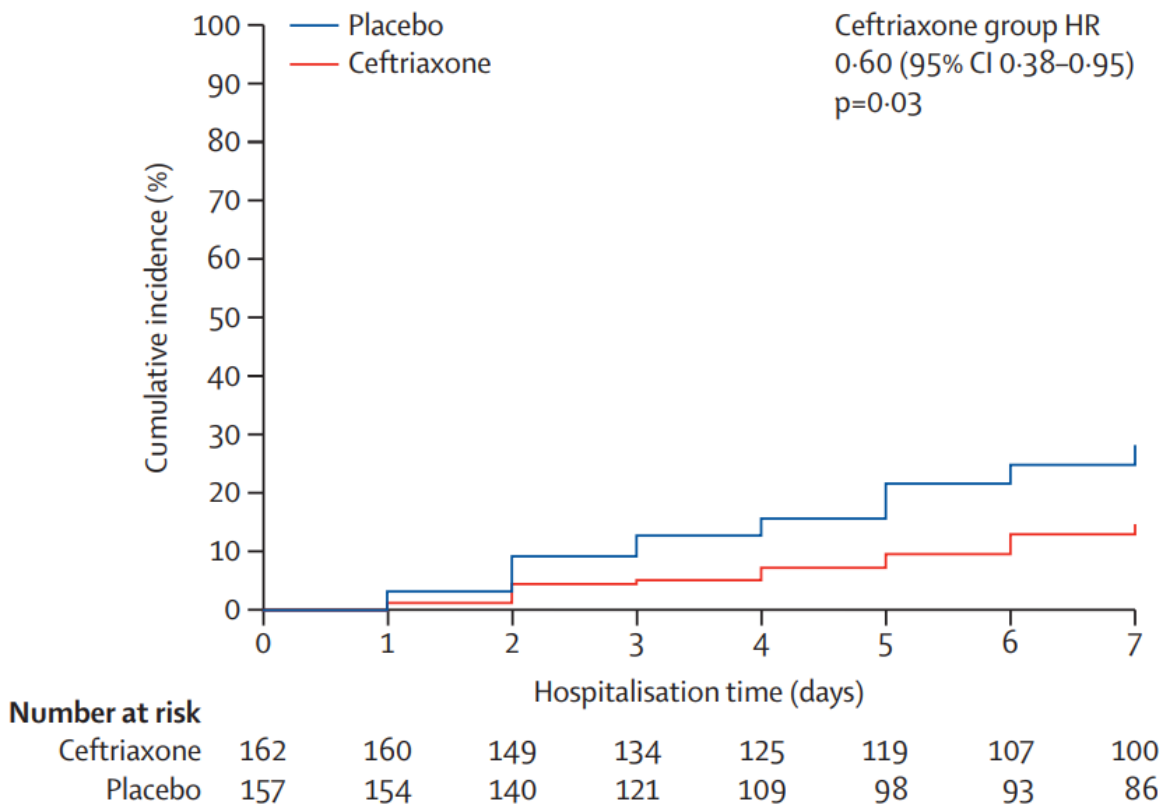
Ceftriaxone to prevent early ventilator-associated pneumonia in patients with acute brain injury: a multicentre, randomised, double-blind, placebo-controlled, assessor-masked superiority trial

*Claire Dahyot-Fizelier, Sigismond Lasocki, Thomas Kerforne, Pierre-Francois Perrigault, Thomas Geeraerts, Karim Asehnoune, Raphaël Cinotti, Yoann Launey, Vincent Cottenceau, Marc Laffon, Thomas Gaillard, Matthieu Boisson, Camille Aleyrat, Denis Frasca, Olivier Mimoz, on behalf of the PROPHY-VAP Study Group and the ATLANREA Study Group**

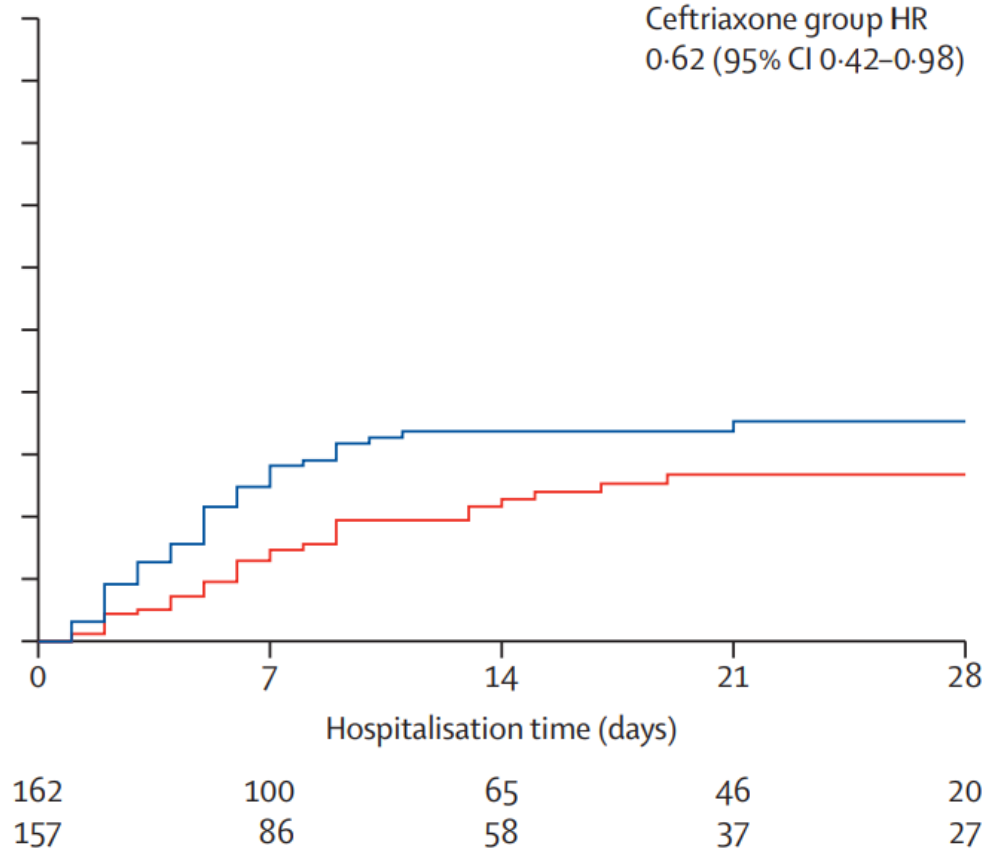
- Comatose adults patients (GCS ≤ 12) stratified to GCS < 8 or ≥ 8 (d/t VAP risk)
- Inclusion: predicted to require MV for more than 48 h after head trauma, stroke and subarachnoid hemorrhage
- Exclusion : coma d/t tumor, infectious disease or cardiac arrest
- Randomization within 12 h after tracheal intubation and within 48 h after hospital admission to start antibiotics promptly enough to prevent early VAP
- Intervention: A single 30-min IV ceftriaxone 2g or saline (placebo)
- Primary outcome : proportion of patients developing early VAP from 2nd to 7th day of MV
- Ceftriaxone (N=162) vs. Placebo (n=157)

C Dahyot-Fizelier et al. Lancet Respir Med (2024) 12:375-85

Cumulative incidence of early and all cased of VAP



Early VAP ↓
Ceftriaxone HR 0.60 (95% CI 0.38-0.95)



VAP during 28 days ↓
Ceftriaxone HR 0.62 (95% CI 0.42-0.98) (p=0.03)

Primary and secondary outcomes

	Ceftriaxone group (n=162)	Placebo group (n=157)	HR	p value
Primary outcome				
Early VAP	23/23 (14%)	51/51 (32%)	0·60 (0·38–0·95)	0·030
Secondary outcomes on day 28				
All VAP	35/33 (20%)	58/57 (36%)	0·62 (0·42–0·98)	..
Late VAP	12/11 (7%)	7/7 (5%)	..	..
Ventilator-free days	9 (0–22)	5 (0–18)	..	0·023
Antibiotic-free days	21 (13–28)	15 (8–21)	..	<0·0001
Time between inclusion and first VAP, days	5 (3–9)	4 (2–6)	..	0·048
Modified Rankin score	..	..	..	0·032
0–1	27/145 (19%)	13/139 (9%)	..	..
2–3	30/145 (21%)	23/139 (17%)	..	..
4–5	63/145 (43%)	64/139 (46%)	..	..
6	25/145 (17%)	39/139 (28%)	..	..
Mortality	25/162 (15%)	39/157 (25%)	0·62 (0·39–0·97)	0·036
Secondary outcomes on day 60	..	..	..	..
ICU-free days	34 (15–49)	26 (0–42)	..	0·0033
Hospital-free days	23 (0–39)	8 (0–33)	..	0·005
Modified Rankin score*	..	..	..	0·17
0–1	44/158 (28%)	31/155 (20%)	..	..
2–3	32/158 (20%)	28/155 (18%)	..	..
4–5	50/158 (32%)	50/155 (32%)	..	..
6	32/158 (20%)	46/155 (30%)	..	..
Mortality	32/161 (20%)	46/157 (30%)	0·66 (0·42–1·04)	0·074

Adverse events during follow-up duration

	Ceftriaxone group (n=95)	Placebo group (n=99)
Cutaneous abscess	1	0
Pulmonary abscess	0	1
Ischaemic stroke	7	5
Delirium	3	0
Anaemia	1	0
Pneumonia	11	13
Cardiac arrest	1	2
Atelectasis	2	0
Bacteraemia	2	2
Tracheobronchitis	3	2
Cutaneous mucosis candidosis	1	1
Cardiac failure	1	2
Anaphylactic shock	1	0
Septic shock	2	1
Hepatic cytolysis	1	0
Refractory cranial hypertension	16	0
Multiorgan failure	0	4
Acute respiratory distress syndrome	4	4
Cerebral rebleeding	4	1
Diabetes insipidus	1	1
Clostridium difficile diarrhoea	1	1
Air embolism	1	2
Pulmonary embolism	2	2
Skin rash	2	2
Erysipelas	1	0
Status epilepticus	2	0
Brain tumour	0	1
Hydrocephalus	1	0
Hyperparathyroidism	1	0
Catheter-related infection	2	2
Urinary infection	0	2
Acute kidney insufficiency	0	1
CNS infection	5	8
Myelofibrosis	1	0
Nausea or emesia	1	2
Pneumothorax	1	1
Pyelonephritis	0	1
Prostatitis	0	1
Sinusitis	1	1
Cerebral salt wasting syndrome	8	4
Thrombopenia	2	0
Thrombophlebitis	1	0
Peritonitis	0	1

Conclusion

- The study finding provide evidence of the efficacy of an early, single dose of ceftriaxone to prevent early VAP in patients with severe brain injury.

- The simple measurement was also associated with decreased antibiotics and ventilation exposure and mortality at day 28 as well as decreased ICU and hospital exposure at day 60 without safety concerns.

Cognitive Motor Dissociation

: convert consciousness in critical care

ORIGINAL ARTICLE

Cognitive Motor Dissociation in Disorders of Consciousness

Y.G. Bodien, J. Allanson, P. Cardone, A. Bonhomme, J. Carmona, C. Chatelle, S. Chennu, M. Conte, S. Dehaene, P. Finoia, G. Heinonen, J.E. Hersh, E. Kamau, P.K. Lawrence, V.C. Lupson, A. Meydan, B. Rohaut, W.R. Sanders, J.D. Sitt, A. Soddu, M. Valente, A. Velazquez, H.U. Voss, A. Vrosgou, J. Claassen, B.L. Edlow, J.J. Fins, O. Gosseries, S. Laureys, D. Menon, L. Naccache, A.M. Owen, J. Pickard, E.A. Stamatakis, A. Thibaut, J.D. Victor, J.T. Giacino, E. Bagiella, and N.D. Schiff

- Prospective multi-center cohort study
- Clinical, behavioral, and task-based fMRI and EEG data
- Assessing response to commands on task-based fMRI or EEG in participants without/with an observable response to verbal commands

Table 1. Demographic and Clinical Characteristics of the Participants.*

Variable	All Participants (N = 353)
Median age at injury (IQR) — yr	37.9 (23.8–55.8)
Sex — no. (%)	
Male	226 (64)
Female	125 (35)
Missing	2 (1)
Median time between injury and CRS-R assessment (IQR) — mo†	7.9 (1.0–22.1)
Underwent CRS-R assessment <28 days after injury — no. (%)	90 (25)
Etiologic factor — no. (%)	
Brain trauma	176 (50)
Cardiac arrest or hypoxia	57 (16)
SAH, IVH, ICH, or stroke	65 (18)
Other	55 (16)
Diagnosis — no. (%)‡	
Coma or vegetative state	140 (40)
Minimally conscious state–minus	101 (29)
Minimally conscious state–plus	77 (22)
Emerged from the minimally conscious state	35 (10)

Y.G. Bodien et al., N Engl J Med 2024;391:598-608

Clinical characterisitcs

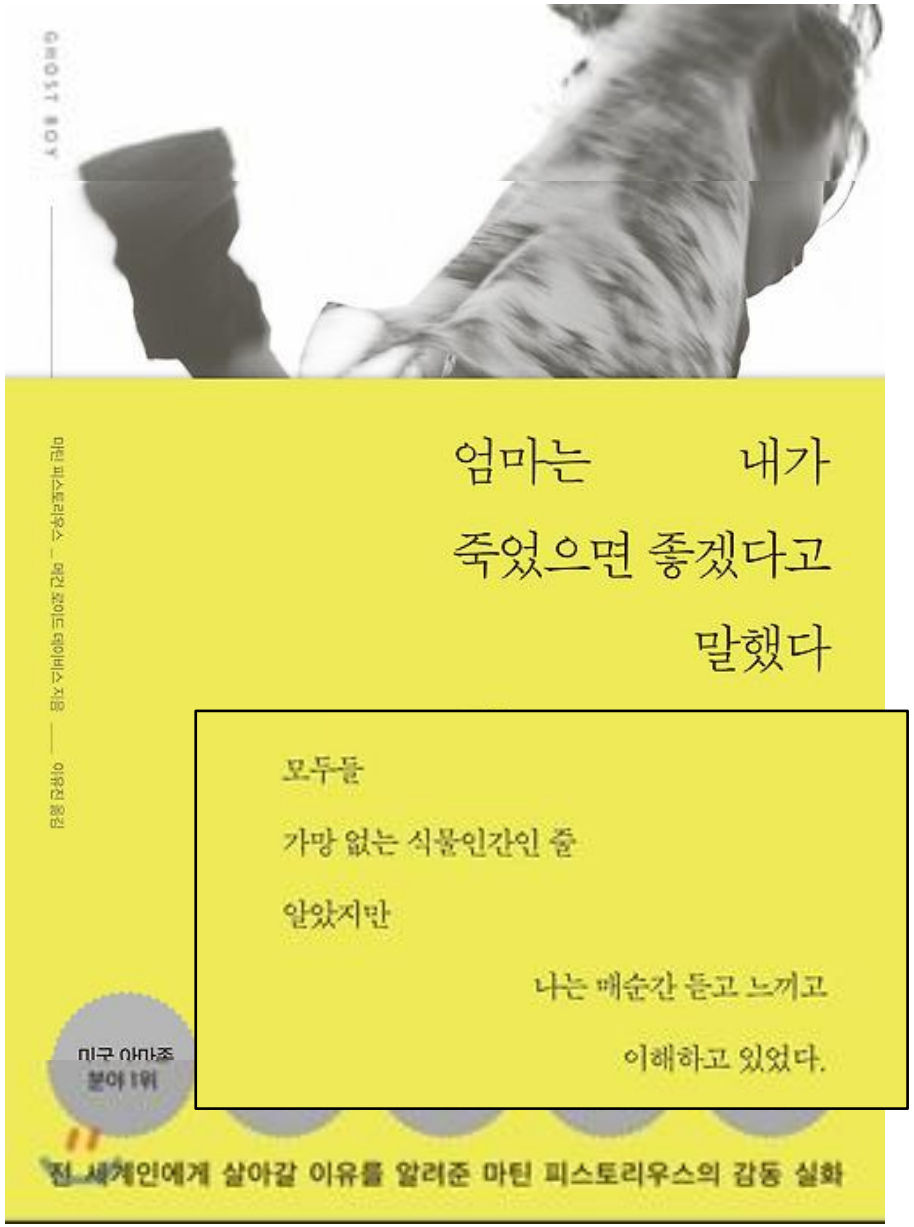
Without observable response to commands

With observable response to commands

Characteristic	No Observable Response to Commands (N=241)	Response to Commands on Imaging† (N=60)	No Response to Commands on Imaging‡ (N=181)	Observable Response to Commands (N=112)	Response to Commands on Imaging* (N=43)	No Response to Commands on Imaging† (N=69)
Diagnosis — no. (%)§						
Coma or vegetative state				9)	26 (60)	51 (74)
Minimally conscious state–minus				1)	17 (40)	18 (26)
Imaging technique — no. (%)						
fMRI only						
EEG only						
fMRI and EEG						
Median age at the time of injury (IQR) — yr				8 (54.5)	29.4 (21.9–46.6)	38.6 (22.3–55.3)
Sex — no. (%)						
Male				1)	30 (70)	50 (72)
Female				9)	13 (30)	19 (28)
Missing						
Median time between injury and CRS-R assessment				9 (8.8)	12.6 (5.5–57.4)	12.9 (3.1–43.8)
Underwent CRS-R assessment <28 days after injur				6)	10 (23)	8 (12)
Underwent CRS-R assessment ≥28 days after injur				4)	33 (77)	61 (88)
Etiologic factor — no. (%)						
Brain trauma				1)	30 (70)	38 (55)
Cardiac arrest or hypoxia				1)	1 (2)	11 (16)
SAH, IVH, ICH, or stroke				5)	9 (21)	8 (12)
Other				3)	3 (7)	12 (17)

The results of our study, which used neuroimaging and electrophysiological techniques, indicate that cognitive motor dissociation is more common than previously realized. Although task-based fMRI and EEG are not yet widely available for the clinical assessment of disorders of consciousness, the knowledge that cognitive motor dissociation is not rare should prompt further study to explore whether its detection can lead to improved outcomes. In addition, the standardization, validation, and simplification of task-based fMRI and EEG methods that are used to detect cognitive motor dissociation are needed to prompt widespread clinical integration of these techniques and investigation of the bioethical implications of the findings.[37]

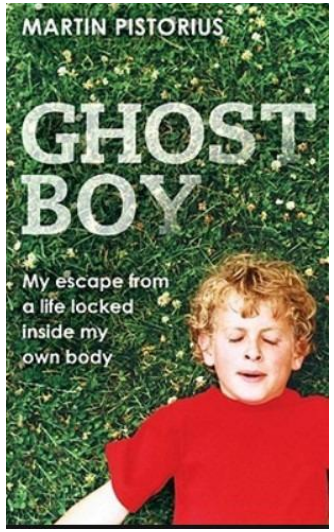
Y.G. Bodien et al., N Engl J Med 2024;391:598-608

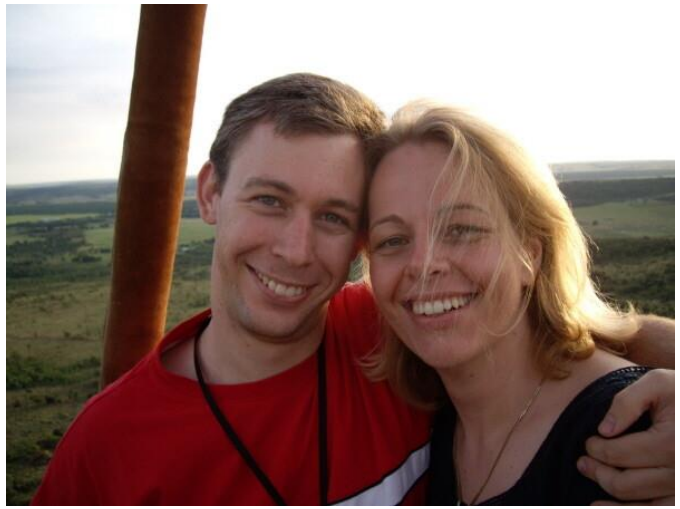


나는 스물다섯 살이다. 하지만 내가 기억하는 과거는 의식 불명 상태에서 깨어난 순간부터 시작된다. 마치 암흑 속에서 번쩍이는 빛을 보는 듯하다. 사람들이 열여섯 살 생일을 맞은 나를 보면서, 턱에 까칠하게 자라난 수염을 밀어주어야 할지를 두고 고민하는 소리가 들려왔다. 나는 이내 두려움에 휩싸였다. 비록 지난 일을 기억하지도 느끼지도 못하지만 내가 어린아이라는 사실을 분명히 알고 있는데, 그들은 나를 성인이 다 된 사람 취급을 하고 있었기 때문이다. 나는 사람들이 이야기하는 대상이 다름 아닌 나란 사실을 점차 깨닫게 되었다. 매일 내 얼굴을 보던 엄마와 아빠, 동생들이 있음을 새삼 인지하게 되면서 말이다.

혹시 어떤 사람이 깨어나 보니 유령이 되어 있는데 자기가 죽었는지도 모른다는 영화를 본 적 있는가? 내 상황이 바로 그랬다. 사람들이 주위에 모여 나를 들여다보고 있음을 알았지만 왜 그러는지는 이해할 수가 없었다. 아무리 애원하고 외치고 소리를 질러도 내 존재를 알릴 수가 없었다. 정신은 쓸모없는 몸 안에 갇힌 채 팔다리를 마음대로 움직일 수도 목소리를 낼 수도 없었다. 사람들에게 내가 다시 깨어났다고 알리고 싶었지만 신호를 보내거나 소리를 낼 수가 없었다. 나는 누구의 눈에도 보이지 않는 유령 소년이었다.

삶이 똑같은 나날로 엮여감에 따라 나는 혼자만의 비밀을 간직한 채 나를 둘러싼 세상을 바라보는 소리 없는 목격자가 되는 데 익숙해졌다. 의식이 돌아온 지 어언 9년이라는 세월이 흘렀다. 그동안 나는 유일한 소유물인 내 정신을 이용해 캄캄한 절망의 심연부터 환상 속 환각에 이르기까지 온갖 것을 탐험하고 다녔다.





Testing for covert consciousness in the ICU using EEG at the bedside.

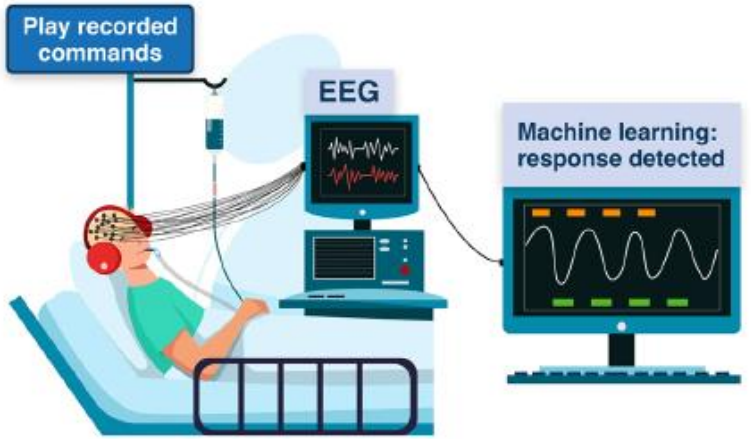
WHAT'S NEW IN INTENSIVE CARE

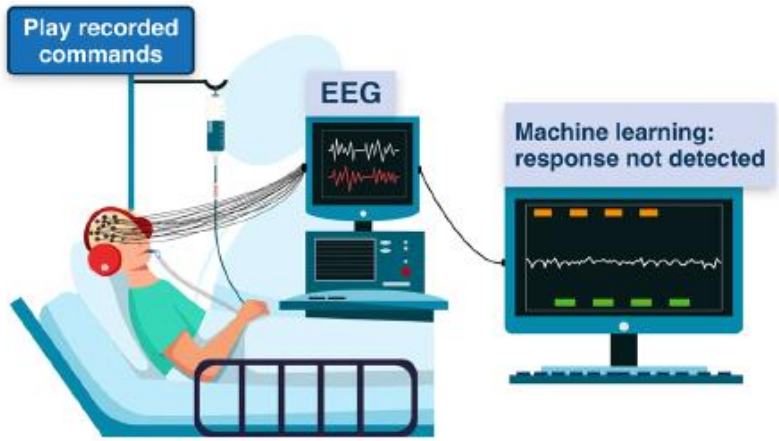
Covert consciousness in critical care

Jan Claassen[1*], Daniel Kondziella[2] and Michael J. Young[3]

CHECKLIST PRIOR TO TESTING FOR COVERT CONSCIOUSNESS :

- **Hearing:** history of deafness, check ear canal → If in doubt perform brainstem auditory potentials
- **Motor weakness:** i.e., spinal cord injury, critical illness neuropathy/myopathy → Test with tactile stimulus
- **Confounders:** sedation, metabolic abnormalities, sepsis, environmental noise → Minimize confounders
- **EEG Signal:** check for artifact, seizures, periodic discharges
- **Neurobehavioral Assessment:** no evidence of motor response to behavioral commands on bedside exam





CMD

- 44% Glasgow Outcome Score- Extended (GOS-E) ≥ 4 at 12 months
- Predictor of time to GOS-E≥4, independent of age, admission neurological status and etiology
- Those that recover, do so earlier than non-CMD patients

NON CMD

- 14% GOS-E≥4 at 12 months
- Consider false negatives (e.g., aphasia, language barrier, inattention)

J Claassen et al., Intensive Care Med (2023) 51:173–176

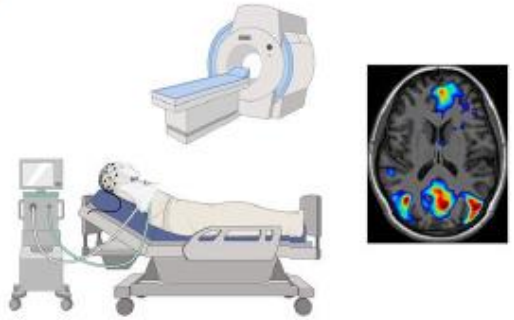
Precision medicine for assessment of disorder of consciousness

Advanced Behavioral Techniques

- Structured neurobehavioral assessments (e.g., CRS-R; MBTr; eye tracking and olfactory response detection technologies) may detect **subtle behavioral signs** of consciousness that may otherwise evade bedside detection.

Resting-State Techniques

- Resting-state techniques (e.g., rsfMRI/EEG) measure synchronous brain activity while an individual is at rest, without exposure to specific stimuli or commands.



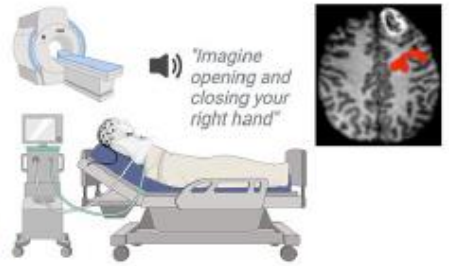
Emerging Paradigms for Precision DoC Assessment

Passive, Stimulus-Based Techniques

- Passive, stimulus-based techniques (e.g., stimulus-based fMRI/EEG) may be used to detect **covert cortical processing** or covert brain complexity, and measure brain responses to passively presented stimuli (e.g., Wernicke's area activation to language).

Active, Task-Based Techniques

- Active, task-based techniques (e.g., task-based fMRI/EEG) may be used to detect **covert consciousness**, and measure brain responses to explicit commands, such as motor imagery, motor action or spatial navigation.



MJ Young et al., Neurocrit Care (2024) 40:865–878

Summary

- Hydrocortisone and fludrocortisone in septic shock
- Effect difference according to CAP vs. non-CAP
- Vasopressin initiation timing
- Restrictive fluid strategy and lactate clearance
- Short-term antibiotic duration in VAP
- Prophylactic antibiotics in VAP
- Concern about convert consciousness in ICU patients

Thank you for your attention.