Respiratory Review of 2026

Advances in Critical Care Medicine

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Key Advances in Critical Care Medicine

A curated overview of landmark trials and guideline updates shaping sepsis management, respiratory failure, mechanical ventilation, and ICU care in 2025.

Sepsis

- **Precision Immunotherapy**
  ImmunoSep Trial
- **Perfusion-Guided Resuscitation**
  ANDROMEDA-SHOCK-2 · TARTARE-2S
- **Choice of Antibiotics duration**
  ADAPT-Sepsis (PCT vs CRP)
- **Adjunctive Vasopressor**
  Terlipressin in Refractory Shock
- **Organ Dysfunction Assessment**
  SOFA-2 Score

Respiratory Failure & MV

- **Oxygen Therapy**
  UK-ROX Trial
- **Ventilation Strategy**
  PAV Trial · Closed-Loop Ventilation
- **Sedation Strategy**
  SESAR Trial
- **Tracheal intubation**
  Ketamine vs. Etomidate

ICU Management

- **Delirium Management**
  Dexmedetomidine for Hyperactive Delirium
- **PADIS Guideline Update**
  Pain, Agitation, Delirium, Immobility & Sleep

CHAPTER 1

Sepsis

Landmark trials from 2025 redefine how we stratify immune phenotypes, guide hemodynamic resuscitation, steward antibiotics, and support failing vasomotor tone in septic shock.

Precision Immunotherapy in Sepsis

Research

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Precision Immunotherapy to Improve Sepsis Outcomes
The ImmunoSep Randomized Clinical Trial

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Immune Stratification

MALS (Macrophage activation–like syndrome) Phenotype

Ferritin >4420 ng/mL → Anakinra (IL-1 receptor antagonist)

Immunoparalysis Phenotype

Ferritin ≤4420 ng/mL + low HLA-DR expression → Interferon-γ

Background & Objective

Sepsis manifests as a highly heterogeneous immune syndrome. The optimal strategy for immune phenotype–guided therapy remained unclear. This trial aimed to determine whether precision immunotherapy based on immune phenotype improves organ dysfunction by day 9.

Study Design

Multicenter, randomized, double-blind, double-dummy, placebo-controlled trial conducted across 6 countries (2021–2024). Enrolled sepsis patients with confirmed infection (pneumonia, VAP, bacteremia).

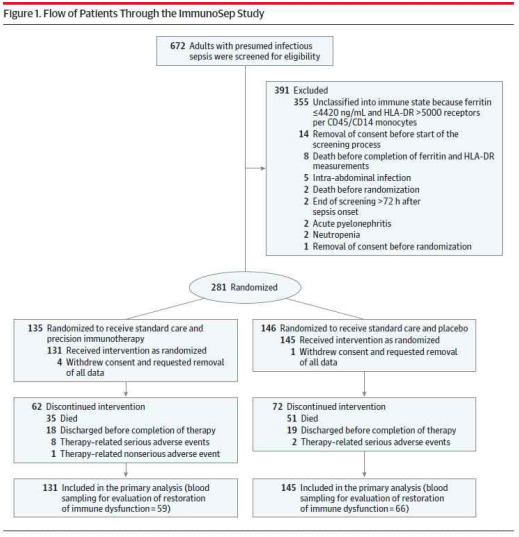
JAMA. 2026 Mar 3;335(9):775-786.

IMMUNOSEP · JAMA 2026

Precision Immunotherapy in Sepsis

Patient Flow & Enrollment

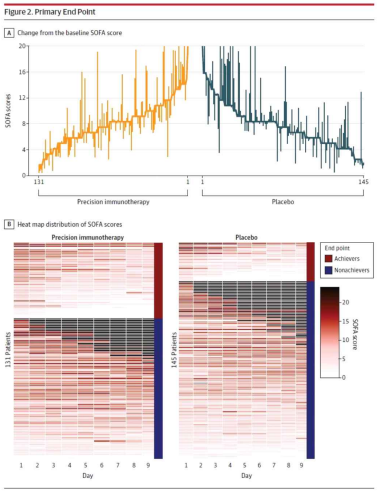
Of 672 adults screened, **281 were randomized**: 135 to precision immunotherapy, 146 to placebo. Among randomized patients, **48 (17.4%) were classified as MALS** (25 anakinra, 23 placebo) and **228 (82.6%) as sepsis-induced immunoparalysis** (106 interferon-γ, 122 placebo). Final primary analysis included 131 precision immunotherapy and 145 placebo patients.



JAMA. 2026 Mar 3;335(9):775-786.

Precision Immunotherapy in Sepsis

Primary Endpoint & Outcomes



A, The parallel line plot represents change for each participant in the trial, from the baseline Sequential Organ Failure Assessment (SOFA) score measured before initiating the study drug to the mean SOFA score for days 2 through 9. Each single line represents this change for each participant and is ordered by baseline SOFA score.

B, The SOFA scores are presented for each treatment group over the 9 days of follow-up. Treatment started on day 1 (baseline). Each group is separated into achievers and nonachievers of the primary end point. Achievers were defined as patients reaching at least a 1.4-point decrease of the mean SOFA score between days 2 and 9 from the baseline SOFA score.

The SOFA score is calculated by assigning 0 to 4 points for the degree of dysfunction in respiratory, cardiovascular, hepatic, coagulation, kidney, and neurological organ systems, based on specific clinical and laboratory criteria. Total score ranges from 0 to 24. Higher scores indicate more severe organ dysfunction and higher mortality risk.

Precision immunotherapy showed greater improvement in SOFA scores compared with placebo over time.
A higher proportion of patients achieved clinically meaningful organ function recovery.

Table 2. Primary and Main Secondary Outcomes of the ImmunoSep Trial

End points	No./total (%) of patients: Precision immunotherapy	Placebo	Difference, % (95% CI)	OR unadjusted (95% CI)	P value
Primary end point					
≥1.4-point decrease of mean SOFA score at 2 to 9[a]	46/131 (35.1)	26/145 (17.9)	17.2 (6.8 to 27.7)	2.48 (1.42 to 4.32)	.002
Main secondary outcomes					
28-d Mortality	57/131 (43.5)	72/145 (49.7)	6.1 (−5.6 to 17.6)	0.78 (0.49 to 1.26)	.14
90-d Mortality	90/131 (68.7)	98/145 (67.6)	1.1 (−9.8 to 11.9)	1.05 (0.63 to 1.75)	.90
≥1.4-Point decrease of mean SOFA score at 3 to 15[a]	52/131 (39.7)	34/145 (23.4)	16.3 (5.3 to 26.8)	2.15 (1.28 to 3.61)	.004
Reversal of sepsis-induced immune dysfunction[b]	46/59 (78.0)	32/66 (48.5)	29.5 (12.5 to 44.0)	3.76 (1.72 to 8.22)	.001
Assessment of infection by d 15[c]					
Resolution	58/131 (44.3)	46/145 (31.7)			
Intermediate	11/131 (8.4)	9/145 (6.2)			
Failure	32/131 (24.4)	44/145 (30.3)	NA	0.59 (0.38 to 0.91)[c]	.02
Superinfection	30/131 (22.9)	46/145 (31.7)			

Abbreviations: OR, odds ratio; NA, not applicable; SOFA, Sequential Organ Failure Assessment.

[a] The SOFA score is calculated by assigning 0 to 4 points for the degree of dysfunction of the respiratory, cardiovascular, hepatic, coagulation, kidney, and neurological organ systems, based on specific clinical and laboratory criteria. Total score ranges from 0 to 24. Higher scores indicate more severe organ dysfunction and higher mortality risk.

[b] Defined as at least a 15% decrease of ferritin for patients with macrophage activation-like syndrome remaining decreased over follow-up time blood draws, and increase of the absolute number of human leukocyte antigen DR receptors to more than 8000 per CD45/CD14 monocyte remaining higher than these values over follow-up time blood draws. Patients not having at least 2 serial blood draws to confirm the permanence of the changes were considered not to have attained reversal of sepsis-induced organ dysfunction.

[c] Using predefined criteria (eTable 3 in Supplement 2) any infection at day 15 was characterized as resolved, intermediate, treatment failure, or superinfection. The OR expresses the risk of worse outcome of the precision immunotherapy group vs the placebo group.

Primary endpoint: ≥1.4-point SOFA decrease (days 2–9) was achieved in **46/131 (35.1%) precision immunotherapy vs. 26/145 (17.9%) placebo** (OR 2.48, 95% CI 1.42–4.32; p=.002). Reversal of sepsis-induced immune dysfunction: 46/59 (78.0%) vs. 32/66 (48.5%) (OR 3.76; p<.001).

JAMA. 2026 Mar 3;335(9):775-786.

Meaning A precision immunotherapy strategy **showed improvement** in organ dysfunction at day 9.

Precision Immunotherapy in Sepsis

Subgroup Analysis

Interaction analysis identified potential benefit among patients with **Charlson Comorbidity Index ≥ 5** and **SOFA score ≥10**, who showed higher likelihood of achieving the primary endpoint and possible reduction in 28-day mortality. No significant interaction was observed for 90-day mortality.

	OR	95% CIs	P-value
APACHE II ≥25	0.47	0.30-1.62	.70
APACHE II ≥25 x Precision Immunotherapy	1.85	0.66-5.19	.24
CCI ≥5	0.22	0.09-0.53	.001
CCI ≥5 x Precision Immunotherapy	5.79	2.34-15.05	<.0001
SOFA ≥10	0.56	0.27-1.19	.13
SOFA ≥10 x Precision Immunotherapy	3.08	1.37-6.96	.007

Safety Profile

Serious AEs

88.8% overall — consistent with critically ill population

Drug-Related SAEs

2 anakinra · 7 interferon-γ · 4 placebo

Notable Signals

Anemia more frequent with anakinra; hemorrhage more frequent with interferon-γ

Overall Assessment

No major safety concerns identified

JAMA. 2026 Mar 3;335(9):775-786.

Personalized Hemodynamic Resuscitation

Research

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Personalized Hemodynamic Resuscitation Targeting Capillary Refill Time in Early Septic Shock

The ANDROMEDA-SHOCK-2 Randomized Clinical Trial

The ANDROMEDA-SHOCK-2 Investigators for the ANDROMEDA Research Network, Spanish Society of Anesthesiology, Reanimation and Pain Therapy (SEDAR), and Latin American Intensive Care Network (LIVEN)

Background & Objective

Optimal hemodynamic resuscitation strategy in early septic shock remains uncertain. This trial evaluated whether capillary refill time (CRT)–guided personalized hemodynamic resuscitation (CRT-PHR) improves clinical outcomes compared to usual care.

JAMA. 2025 Dec 9;334(22):1988-1999.

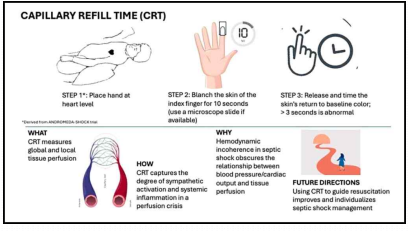
Study Design

Scale

86 centers · 19 countries · 2022–2025

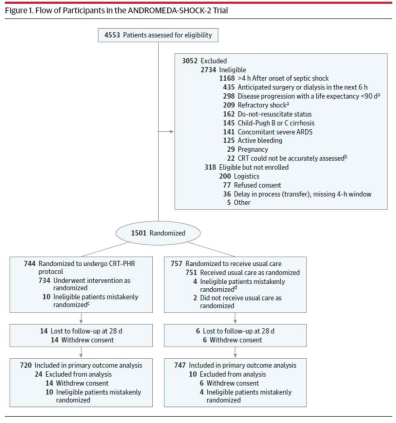
Intervention

CRT-PHR (n=720): fluids, vasopressors & inotropes guided by physiologic assessment vs. usual care (n=747)



Personalized Hemodynamic Resuscitation

Trial Flow & CRT-PHR Algorithm



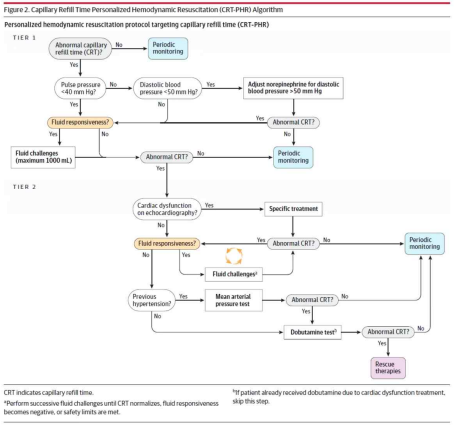


Figure 2. Capillary Refill Time Personalized Hemodynamic Resuscitation (CRT-PHR) Algorithm

CRT indicates capillary refill time.

[a]Perform successive fluid challenges until CRT normalizes, fluid responsiveness becomes negative, or safety limits are met.

[b]If patient already received dobutamine due to cardiac dysfunction treatment, skip this step.

CRT-Guided Hemodynamic Algorithm

- Step 1: Assess capillary refill time (CRT)
- If abnormal → evaluate perfusion (pulse pressure, diastolic pressure, fluid responsiveness)
- Step 2: Intervene stepwise
  - Fluids (if responsive)
  - Vasopressors (for low diastolic pressure)
  - Inotropes (if cardiac dysfunction)
- Goal: Normalize CRT with individualized treatment

The two-tier CRT-PHR algorithm integrates CRT normalization with hemodynamic assessments (pulse pressure, diastolic BP, fluid responsiveness, echocardiography) to guide escalation of vasopressors, fluids, and dobutamine in a protocolized, individualized manner.

JAMA. 2025 Dec 9;334(22):1988-1999.

Personalized Hemodynamic Resuscitation

Hemodynamic Therapies & Outcomes at Hour 6

Table 2. Hemodynamic Therapies and Resuscitation-Related Variables at Hour 6

	CRT-PHR group	Usual care group	Absolute difference (95% CI)
Therapy			
Norepinephrine, No./total No. (%)	648/684 (94.7)	634/694 (91.4)	3.4 (0.7 to 6.1)
Norepinephrine dose, mean (SD), μgr/kg/min	0.28 (0.34) [n = 655]	0.27 (0.41) [n = 634]	−0.01 (−0.05 to 0.03)
Vasopressin, No./total No. (%)	251/684 (36.7)	229/694 (33.0)	3.7 (−1.3 to 8.7)
Dobutamine, No./total No. (%)	84/684 (12.3)	37/694 (5.3)	7.0 (4.0 to 9.9)
Volume of resuscitation fluids, mean (SD), mL	595 (679) [n = 672]	847 (832) [n = 676]	−251 (−316 to −187)
Net fluid balance, mean (SD), mL	990 (1016) [n = 629]	1227 (1225) [n = 622]	−242 (−385 to −99)
Hemodynamic and perfusion-related variable			
Central venous pressure, mean (SD), mm Hg	9.1 (4.1) [n = 541]	9.8 (4.8) [n = 544]	−0.6 (−1.1 to −0.1)
Mean arterial pressure, mean (SD), mm Hg	74.1 (9.4) [n = 682]	73.6 (9.0) [n = 690]	0.6 (−0.5 to 1.7)
Capillary refill time, mean (SD), s	2.8 (1.4) [n = 679]	3.4 (1.9) [n = 684]	−0.6 (−0.7 to −0.4)
Lactate level, mean (SD), mmol/L	3.2 (2.4) [n = 659]	3.5 (3.0) [n = 664]	−0.3 (−0.5 to −0.1)
Central venous oxygen saturation, mean (SD), %	74.4 (8.9) [n = 588]	72.4 (9.9) [n = 596]	1.9 (0.8 to 3.0)

Table 3. Primary and Secondary Outcomes

Outcome	CRT-PHR group (n = 720)	Usual care group (n = 747)	Effect estimate (95% CI)	P value
Primary outcome through 28 d, win/# No. of wins (%)				
Hierarchical composite of death, duration of vital support, and length of hospital stay[a]	331 (33.08.9)	312 767 (42.1)	SWR, 1.16 (1.02 to 1.33)	.04
Secondary outcomes				
All-cause mortality within 28 d, No. (%)[b]	191 (26.5)	199 (26.6)	HR, 0.99 (0.81 to 1.21)	.91
Vital support–free days within 28 d[c]				
Mean (SD)	16.5 (11.3)	15.4 (11.8)	pOR, 1.28 (1.06 to 1.54)	NA
Median (IQR)	23.0 (0 to 25.0)	22.0 (0 to 25.0)		
Length of hospital stay up to day 28, d[d]				
Mean (SD)	15.3 (9.0)	16.2 (9.4)	MD, −0.85 (−1.80 to 0.10)	NA
Median (IQR)	13.0 (8.0 to 25.0)	15.0 (8.0 to 28.0)		

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; CRT-PHR, capillary refill time personalized hemodynamic resuscitation; HR, hazard ratio; MD, mean difference; NA, not applicable; pOR, proportional odds ratio; SWR, stratified win ratio.

[a] The stratified win ratio was calculated using treatment as a fixed effect stratified by the median APACHE II score. Patients in the CRT-PHR group were compared with those in the usual care group within each APACHE II stratum, following a hierarchical order of the primary outcome assessed within 28 days: death, duration of vital support, and length of hospital stay. If 1 patient survived and the other did not, the survivor's group was assigned the win. If both patients died, the comparison was considered an early tie. If both survived, the comparison proceeded to duration of vital support and, if tied (same duration in days), to length of hospital stay. The stratified win ratio reflects the number of wins in the CRT-PHR group vs the usual care group, accounting for outcome hierarchy and stratification. Duration of vital support was defined as the time between randomization and cessation of all vital support. For patients who resumed vital support, the time of final support cessation was the end of the last period.

[b] HR was calculated with Cox proportional hazards, with adjustments for baseline APACHE II score.

[c] Vital support–free days were defined as the number of days between the date of randomization and the maximum end date of vasopressor use, mechanical ventilation, or kidney replacement therapy, within the first 28 days. Any death occurring within 28 days was assigned a value of 0 support-free days. The pOR was calculated with cumulative logistic regression adjusted for baseline APACHE II score.

[d] MD was calculated with a generalized linear model with generalized additive model for location, scale and shape, adjusted for baseline APACHE II score.

CRT-PHR was associated with **significantly fewer resuscitation fluids** (595 vs. 847 mL, p<.05), **lower net fluid balance** (990 vs. 1227 mL), shorter CRT, lower lactate, and higher $ScvO_2$ at hour 6. Primary composite outcome (death, vital support, hospital LOS) favored CRT-PHR (SWR 1.16, 95% CI 1.02–1.33; p=.04).

JAMA. 2025 Dec 9;334(22):1988-1999.

Meaning A CRT-guided resuscitation strategy **showed improvement** in patient-centered outcomes in early septic shock.

Personalized Hemodynamic Resuscitation

Primary Outcome Analysis & Clinical Implications

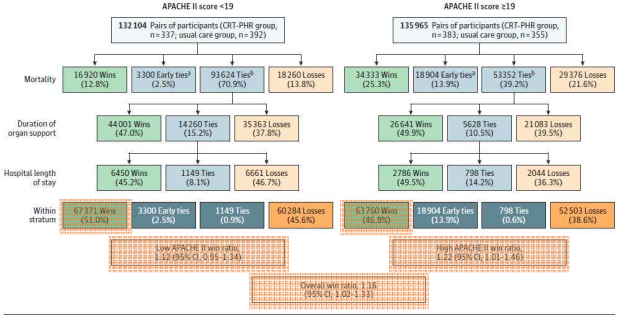
Safety

No significant difference in serious adverse events. No safety signal attributable to the CRT-guided protocol in either APACHE II stratum.

Clinical Implications

CRT is a viable physiologic target for early septic shock resuscitation. The protocol reduces organ support duration and supports individualized hemodynamic management — reinforcing precision medicine principles in the ICU.

Figure 3. Primary Outcome Analysis



Distribution of wins, ties, and losses for the CRT-PHR group among both APACHE II strata at each level of the hierarchical primary composite outcome. Every possible pair of participants between groups was compared in a hierarchical fashion with a win, loss, or tie determined by the outcome evaluated at each level of the hierarchy. Percentages are calculated for each level of the hierarchy.

APACHE indicates Acute Physiology and Chronic Health Evaluation; CRT-PHR, capillary refill time personalized hemodynamic resuscitation.

[a]Early ties were determined when both participants in the pair died before 28 days following randomization. No further pairwise outcome comparisons were made for early ties.

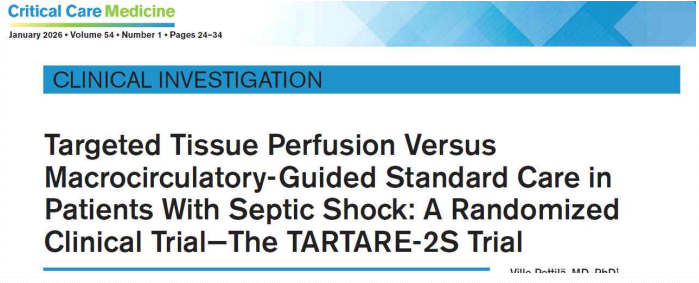
[b]Ties were determined when both participants survived 28 days or more following randomization.

CRT-guided resuscitation improved composite outcomes (win ratio 1.16), particularly in more severe patients.

JAMA. 2025 Dec 9;334(22):1988-1999.

TARTARE-2S · CRIT CARE MED 2026

Targeted Tissue Perfusion Strategy



Background & Objective

To determine whether a targeted tissue perfusion (TTP) strategy improves outcomes compared with MAP-guided standard care (2012 Surviving Sepsis Campaign) in septic shock patients with lactate >3 mmol/L.

Study Design

Design

Randomized, parallel-group, open-label clinical trial · 3 European ICUs (2016–2022)

Population

219 septic shock patients with lactate >3 mmol/L (TTP n=111 vs SC n=108)

Intervention

TTP: CRT + peripheral skin temperature + lactate; permissive MAP 50–65 mmHg

Crit Care Med. 2026 Jan 1;54(1):24-34.

Targeted Tissue Perfusion Strategy

Flowchart and Mean arterial pressure

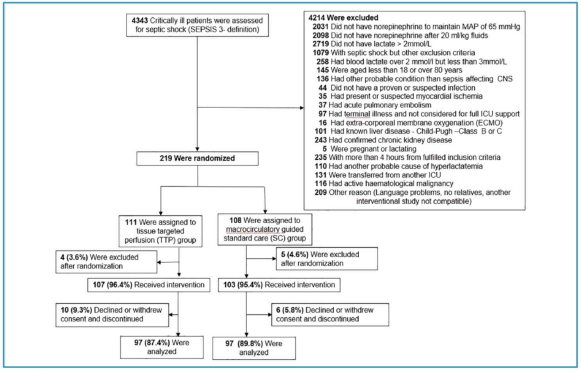


Figure 1. Trial flowchart. ECMO = extracorporeal membrane oxygenation, MAP = mean arterial pressure, SC = standard care, TTP = targeted tissue perfusion.

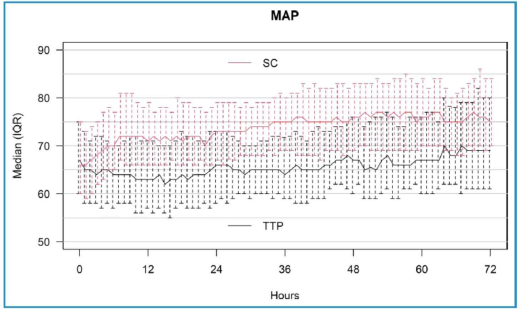


Figure 2. Mean arterial pressure (median [interquartile range (IQR)]) from randomization (0 hr) to 72 hr (targeted tissue perfusion [TTP], standard care [SC]-mean arterial pressure [MAP]-guided; $p < 0.001$ [time]; $p < 0.001$ [group]; and $p = 0.051$ [time-group interaction]).

Mean arterial pressure (MAP) was consistently lower in the TTP group compared with standard care over the first 72 hours.

Crit Care Med. 2026 Jan 1;54(1):24-34.

Meaning A tissue perfusion–guided strategy was feasible and safe, but **did not improve** clinical outcomes.

Targeted Tissue Perfusion Strategy

Outcome Data & Key Findings

TABLE 2.
Primary Composite Outcomes and Secondary Outcomes

Outcomes	Targeted Tissue Perfusion Group ($n = 97$)	Standard Care Group ($n = 97$)	Difference in Medians/Proportions (95% CI)	p
Primary outcome				
Days alive in 30 d with normal lactate and without vasopressor or inotropic agents, d, median (IQR)	23 (10–27)	22 (1–27)	0.59 (–3 to 4)	0.418
Secondary outcomes				
Days alive in 30 d, median (IQR)	30 (30–30)	30 (16–30)	1.12 (0.59–2.12)[b]	0.740[a]
Deaths at day 30, count (%)	24 (24.7)	27 (27.8)	–3.1 (–16.5 to 10.3)	0.745
Time to normal lactate, d, median (IQR)	2 (0–6)	2 (0–5)	0.15 (–2 to 2)	0.917
Days alive with normal lactate in 30 d, median (IQR)	25 (15–29)	25 (8–29)	0.37 (–2 to 4)	0.597
Time to no vasopressor or inotropic agents, d, median (IQR)	3 (1–5)	3 (2–6)	–0.46 (–2 to 0)	0.211
Time to normal lactate and no vasopressor or inotropic agents, median (IQR)	4 (2–9)	5 (2–8)	–0.44 (–2 to 1)	0.553
Days alive in 30 d without vasopressor or inotropic agents, median (IQR)	26 (13–28)	24 (3–27)	1.03 (–2 to 3)	0.239
Days alive without RRT in 30 d, median (IQR)	30 (15–30)	30 (14–30)	–0.23 (–6 to 5)	0.920
Days alive without MV in 30 d, median (IQR)	25 (11–28)	24 (4–28)	0.37 (–3 to 3)	0.626
Days alive without any organ support (RRT, MV) in 30 d, median (IQR)	24 (8–28)	24 (4–28)	0.06 (–4 to 4)	0.959
AKI, *n* (%)	78 (80)	69 (71)	9.3 (–3.7 to 22.2)[c]	0.180
AKI with RRT, *n* (%)	35 (36)	31 (32)	4.1 (–10.2 to 18.5)[c]	0.650
Total amount of norepinephrine given in 96 hr, μg/kg, *n* (%)	766 (819)	947 (1061)	12.2 (–293 to 295)	0.340

AKI = acute kidney injury, IQR = interquartile range, MV = mechanical ventilation, RRT = renal replacement therapy.
[a]Adjusted by site and hypertension.
[b]Competing risk analysis, difference as hazard ratio adjusted by site and hypertension.
[c]Difference in risk (95% CI).

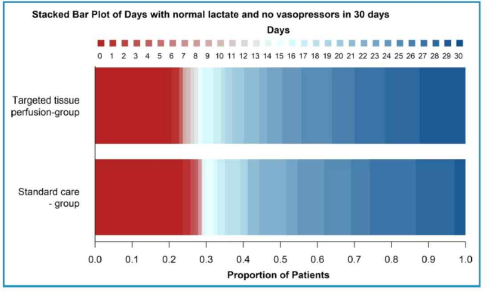


Figure 3. *Stacked bar plots* of the primary outcome, number of days with normal lactate, and no vasopressors in 30 d as *horizontally stacked proportions* in each treatment group; *red* represents worse outcome, *blue* represents better outcome (interpretation, e.g., in the standard care group 60% of the patients had at least 20 d alive without vasopressors and with normal lactate).

The TTP strategy was feasible without additional safety concerns compared with standard care, supporting peripheral perfusion markers as clinically actionable targets in high-lactate septic shock.

Crit Care Med. 2026 Jan 1;54(1):24-34.

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Biomarker-Guided Antibiotic Duration

Research

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Biomarker-Guided Antibiotic Duration for Hospitalized Patients With Suspected Sepsis

The ADAPT-Sepsis Randomized Clinical Trial

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Background & Objective

Biomarker-guided antibiotic stewardship using procalcitonin (PCT) and C-reactive protein (CRP) has been proposed to safely reduce antibiotic exposure in sepsis, but the evidence base remained uncertain prior to this trial. This RCT evaluated whether PCT- or CRP-guided strategies reduce antibiotic duration without compromising safety.

Study Design

Scale

Multicenter RCT · 41 UK ICUs · n=2,760 · 2018–2024

Arms

Daily PCT-guided (n=918) vs. CRP-guided (n=924) vs. standard care (n=918)

JAMA. 2025 Feb 25;333(8):682-693.

ADAPT-SEPSIS · JAMA 2025

Biomarker-Guided Antibiotic Duration

Patient Flow & Outcome Data

Figure 1. Recruitment, Randomization and Follow-Up in the ADAPT-Sepsis Trial

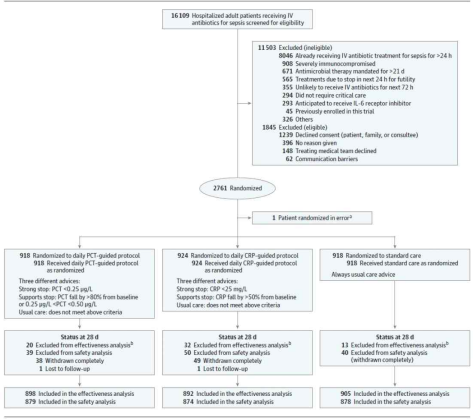
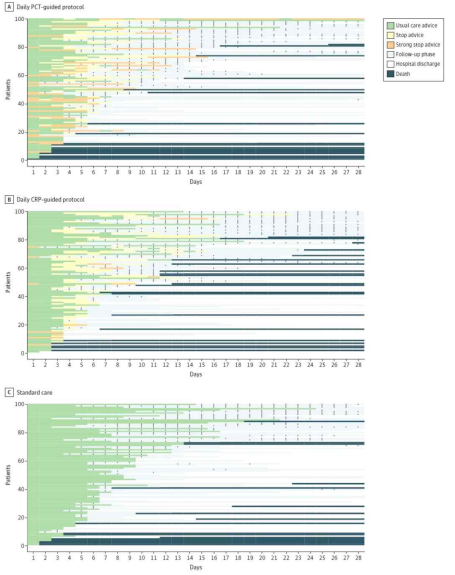


Figure 2. Indicative Maps of Patient Care Pathways



Trial patients were drawn at random (100 per group) and shown to indicate their care pathways from randomization to day 28 in each group. When antibiotics were stopped and protocol advice ended, the patient entered the follow-up phase or was discharged from the hospital. Any antibiotics administered during the follow-up phase are shown by black X's. Patients in each panel are ordered by length of total antibiotics from randomization to day 28.

JAMA. 2025 Feb 25;333(8):682-693.

Meaning Daily PCT-guided therapy **reduced antibiotic duration** without compromising safety, whereas CRP **showed no benefit**.

Biomarker-Guided Antibiotic Duration

Key Findings & Clinical Implications

Table 2. Primary and Secondary Outcomes

Outcomes	Daily PCT-guided protocol (n = 918)	Daily CRP-guided protocol (n = 924)	Standard care (n = 918)	Unadjusted treatment effect (95% CI)	
				Standard care vs daily PCT-guided protocol	*P* value[a]
Primary outcomes					
Effectiveness: 1 - (1 - total antibiotic treatment duration to 28 d after randomization, mean (SD), 0 [No.])	9.8 (7.2) [880]	10.6 (7.7) [874]	10.7 (7.6) [891]	MD: 0.86 (0.16 to 1.56), .02	MD: 0.05 (−0.65 to 0.75) .88
Safety: 28-d all-cause mortality, No./total (%)[b]	184/879 (20.9)	184/874 (21.1)	170/878 (19.4)	AD: 1.57 (−2.18 to 5.32) .02[c]	AD: 1.69 (−2.07 to 5.45) .03[c]
Sensitivity analysis					
Per-protocol analysis for both effectiveness and safety outcomes					
Effectiveness: total antibiotic treatment duration to 28 d after randomization, mean (SD), days [No.]	9.8 (7.2) [880]	10.6 (7.7) [874]	10.7 (7.6) [891]	MD: 0.86 (0.16 to 1.56), .02	MD: 0.05 (−0.65 to 0.75) .88
Safety: 28-d all-cause mortality, No./total (%)	176/860 (20.5)	182/854 (21.3)	166/864 (19.2)	AD: 1.25 (−2.51 to 5.02) .02[c]	AD: 2.10 (−1.70 to 5.90) .04[c]
CACE analysis for the effectiveness outcome				MD: 1.00 (0.22 to 1.77) .01	0.10 (−0.70 to 0.91) .81
Imputation analysis, mean (SD) [No.]	9.8 (7.3) [915]	10.6 (7.9) [918]	10.8 (7.7) [916]	MD: 0.99 (0.29 to 1.69) .005	MD: 0.15 (−0.55 to 0.85) .67
Pocock win ratio[d]				Odds: 1.12 (1.00 to 1.25) .04	Odds: 0.98 (0.88 to 1.10) .77
Secondary outcomes					
Antibiotic treatment duration for initial sepsis period, mean (SD), days [No.]	7.0 (5.7) [893]	7.4 (6.0) [889]	8.1 (6.1) [902]	MD: 1.13 (0.58 to 1.68)	MD: 0.71 (0.16 to1.26)
Antibiotic dose from randomization until 28-d, median (IQR), DDD	11.5 (6.0 to 19.1) [797]	12.0 (6.0 to 20.1) [773]	11.0 (5.8 to 19.8) [760]		
Antibiotic dose for sepsis period, median (IQR), DDD [No.]	8.0 (4.0 to 14.0) [851]	8.0 (4.2 to 15.0) [830]	9.0 (4.8 to 17.0) [825]		
Unscheduled care escalation or readmission					
No. of events	314	349	365		
No. of patients≥1 event, No./total (%)	208/888 (23.4)	234/894 (26.2)	236/900 (26.2)	AD: 2.80 (−1.16 to 6.76) OR: 1.16 (0.94 to 1.44)	AD: 0.05 (−3.91 to 4.03) OR: 1.00 (0.81 to 1.24)
Time to first deemed fit for hospital discharge, mean (SD), d [No.]	12.5 (7.9) [190]	13.0 (6.9) [215]	12.4 (7.2) [194]	MD: −0.09 (−1.56 to 1.38)	MD: −0.59 (−2.02 to 0.83)
Time to hospital discharge (survivors), mean (SD), d [No.]	12.6 (6.8) [439]	12.6 (6.9) [441]	12.7 (6.8) [436]	MD: 0.10 (−0.81 to 1.01)	MD: 0.11 (−0.80 to 1.02)
Length of ICU stay, median (IQR), [No.]	6.2 (3.1 to 12.3) [763]	6.0 (3.1 to 11.9) [771]	5.8 (3.0 to 12.4) [762]		
Infection relapse or recurrence requiring further antibiotic treatment					
Events, No.	15	8	5		
≥1 Event, No./total (%)	11/908 (1.2)	5/908 (0.6)	5/913 (0.5)	AD: −0.66 (−1.51 to 0.01) OR: 0.45 (0.16 to 1.30)	AD: −0.003 (−0.85 to 0.67) OR: 0.99 (0.29 to 3.44)

- PCT-guided therapy reduced antibiotic duration.
- There was no difference in mortality.
- CRP-guided therapy showed no clinical benefit.

=> PCT-guided therapy safely reduces antibiotic exposure without improving clinical outcomes.

Table 2. Primary and Secondary Outcomes (continued)

Outcomes	Daily PCT-guided protocol (n = 918)	Daily CRP-guided protocol (n = 924)	Standard care (n = 918)	Unadjusted treatment effect (95% CI)	
				Standard care vs daily PCT-guided protocol	*P* value[a]
New infection or superinfection at a different anatomical site					
No. of events	41	39	32		
≥1 Event, No./total (%)	29/908 (3.2)	27/908 (3.0)	24/913 (2.6)	AD: −0.57 (−2.13 to 0.93) OR: 0.82 (0.47 to 1.42)	AD: −0.34 (−1.90 to 1.15) OR: 0.88 (0.50 to 1.54)
Suspected clinically relevant antibiotic-related events					
No. of events	118	137	118		
≥1 Event, No./ (%)	71/888 (8.0)	77/894 (8.6)	70/900 (7.8)	AD: −0.21 (−2.81 to 2.30) RD: −2.80 (−18.18 to 32.80) OR: 0.97 (0.69 to 1.37)	AD: −0.84 (3.43 to 9.44) RD: −10.74 (−46.12 to 24.36) OR: 0.89 (0.64 to 1.25)
90-d All-cause mortality, No./total (%)	217/847 (25.6)	223/846 (26.4)	215/842 (25.5)	AD: −0.09 (−4.29 to 4.08) OR: 1.00 (0.80 to 1.24)	AD: −0.82 (−5.03 to 3.34) OR: 0.96 (0.77 to 1.19)

Abbreviations: AD, absolute difference; CACE, complier average causal effect; DDD, defined daily dose; ICU, intensive care unit; MD, mean difference; OR, odds ratio; RD, relative difference.

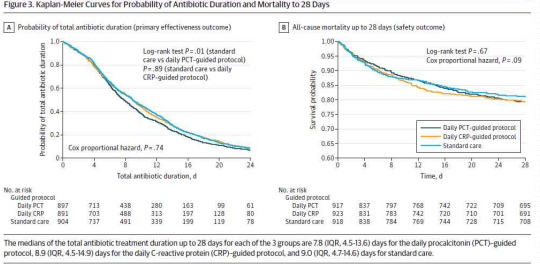
[a] *P* values for primary outcomes analyses only.

[b] For 28-day all-cause mortality, the comparisons are made as daily PCT-guided protocol vs standard care, and daily CRP-guided protocol vs standard care.

[c] *P* values of the test if the RD is less than or equal to the prespecified margin 5.4% (significance level = .025).

[d] Using 28-day all-cause mortality status and total antibiotic duration to 28 days after randomization. The win-ratio is the odds that the intervention treatment wins for any randomly chosen patients' pair (intervention vs control).

Figure 3. Kaplan-Meier Curves for Probability of Antibiotic Duration and Mortality to 28 Days



The medians of the total antibiotic treatment duration up to 28 days for each of the 3 groups are 7.8 (IQR, 4.5-13.6) days for the daily procalcitonin (PCT)-guided protocol, 8.9 (IQR, 4.5-14.9) days for the daily C-reactive protein (CRP)-guided protocol, and 9.0 (IQR, 4.7-14.6) days for standard care.

TERLIPRESSIN · CRIT CARE 2025

Adjunctive Vasopressor Therapy

Tongyoo *et al. Critical Care* (2025) 29:443
https://doi.org/10.1186/s13054-025-05669-0

Critical Care

RESEARCH Open Access

Adjunctive terlipressin versus placebo in the treatment of refractory septic shock: a randomized, placebo-controlled trial

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Background & Objective

The role of terlipressin as an adjunct vasopressor in refractory septic shock remains controversial. This trial evaluated its efficacy vs. placebo in patients requiring high-dose catecholamines, aiming to achieve MAP ≥65 mmHg with reduced catecholamine exposure at 6 hours.

- Terlipressin: V1 receptor stimulation → vasoconstriction → MAP↑

Study Design & Population

Design

Single-center, prospective, double-blind RCT

Eligibility

Septic shock requiring high-dose vasopressors (NE >0.2 μg/kg/min or epinephrine)

Primary Outcome

MAP ≥65 mmHg with reduced catecholamine dose at 6 hours

Crit Care. 2025 Oct 21;29(1):443.

Adjunctive Vasopressor Therapy

Efficacy Data

Table 2 Primary and secondary outcomes

Outcomes	Terlipressin (*n* = 66)	Placebo (*n* = 64)	Relative risk (95%CI)	*P*
Primary outcomes				
Achieve target MAP ≥ 65 mmHg with norepinephrine and/or epinephrine dose ≤ 0.2 mcg/kg/min at 6th h, *n* (%)	15 (22.7)	6 (9.4)	1.51 (1.06–2.14)	0.039
Secondary outcomes				
Hospital mortality, *n* (%)	45 (68.2)	48 (75.0)	0.85 (0.60–1.21)	0.389
28-d mortality, *n* (%)	40 (60.6)	41 (64.1)	0.93 (0.66–1.31)	0.684
ICU mortality, *n* (%)	39 (59.1)	37 (57.8)	1.03 (0.73–1.45)	0.882
Achieve target MAP ≥ 65 mmHg with norepinephrine and/or epinephrine dose ≤ 0.2 mcg/kg/min at 24th h, *n* (%)	27 (40.9)	19 (29.7)	1.26 (0.91–1.77)	0.181
Achieve target MAP ≥ 65 mmHg with no vasopressor at 72nd h, *n* (%)	32 (48.9)	26 (40.6)	1.17 (0.83–1.64)	0.306
Time to achieve MAP ≥ 65 mmHg, median (IQR), h:min	1 (0:00–1:30)	1 (0:15–2:00)		0.437
Serum lactate decrease at 6 h, %[a]	−11 (−35 to 16)	−5 (−35 to 18)		0.762
Catecholamine duration, median (IQR), h	61 (37–88)	67 (38–111)		0.463
Study drug duration, median (IQR), h	24 (13–46)	28 (9–48)		0.903
Vasoactive dose (include terlipressin) at 24 h, median (IQR), mcg/kg/min[b]	0.16 (0.04–0.42)	0.26 (0.09–0.43)		0.084
Catecholamine dose (do not include terlipressin) at 24 h, median (IQR), mcg/kg/min[c]	0.06 (0.04–0.41)	0.26 (0.09–0.43)		0.037
Maximum terlipressin dose, median (IQR), mcg/kg/min[d]	Catecholamine dose = norepinephrine dose + epinephrine dose + |dopamine/100| + |dobutamine /100|	0.007 (0.005–0.019)	0.008 (0.005–0.026)	0.684

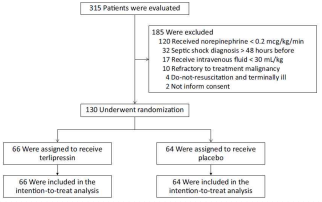

Table 2 (continued)

Outcomes	Terlipressin (*n* = 66)	Placebo (*n* = 64)	Relative risk (95%CI)	*P*
ICU length of stay, median (IQR), d	8 (4–15)	7 (4–18)		0.777
Hospital length of stay, median (IQR), d	15 (5–30)	20 (6–31)		0.526
Adverse events, *n* (%)				
Arrhythmia				
- Atrial fibrillation	9 (13.6)	8 (12.5)	1.05 (0.61–1.80)	0.848
- Supraventricular tachycardia	4 (6.1)	3 (4.7)	1.16 (0.48–2.77)	1.000
-Ventricular fibrillation/tachycardia	3 (4.5)	3 (4.7)	0.98 (0.43–2.23)	1.000
Digital ischemia	19 (28.8)	17 (27.4)	1.04 (0.69–1.55)	0.863
Digital gangrene	2 (3.0)	1 (1.6)	1.48 (0.29–7.44)	1.000
Bowel ischemia	0 (0)	2 (3.1)	0.48 (0.41–0.58)	0.240
Recurrent shock	23 (34.8)	21 (32.8)	1.05 (0.72–1.52)	0.806

- Primary outcome: Higher achievement of MAP ≥65 mmHg at 6 h with terlipressin (22.7% vs 9.4%, p=0.039)
- Secondary outcomes: No difference in mortality (ICU, 28-day, hospital)
- Hemodynamic effects: Lower catecholamine dose at 24 h in terlipressin group
- Safety: No significant difference in adverse events

Crit Care. 2025 Oct 21;29(1):443.

Meaning Terlipressin **reduced catecholamine requirements** without improving mortality or increasing ischemic risk.

Adjunctive Vasopressor Therapy

Outcome Measures & Safety

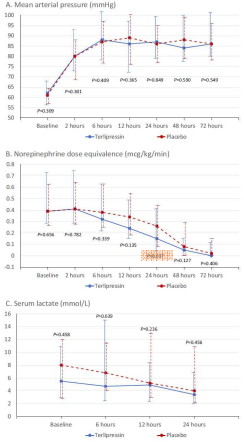

Fig. 2 Temporal trends in hemodynamic and metabolic variables after randomization **a** Mean arterial pressure, **b** cumulative catecholamine dose (expressed as norepinephrine equivalents), and **c** serum lactate concentrationData are median (IQR) over the first 72 h after enrollment. The horizontal dashed line in Panel A marks the target mean arterial pressure of 65 mmHg.

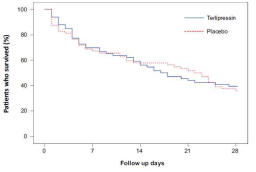

Fig. 3 Kaplan—Meier survival curves through day 28Twenty-eight–day survival did not differ significantly between groups (hazard ratio = 0.956, 95% CI = 0.618–1.478, *P* = 0.838).

- Terlipressin reduced catecholamine requirement.
- No improvement in tissue perfusion (lactate).
- No survival benefit.

Table 3 Univariate and multivariate analysis for independent predictors of terlipressin responders

Clinical parameters	Univariate		Multivariate	
	Odd ratio (95%CI)	P-value	Adjusted Odd ratio (95%CI)	P-value
APACHE II > 25	0.69 (0.51–0.91)	0.008	N/A	
SOFA > 12	2.13 (1.39–3.23)	< 0.001	33.33 (3.45–100.0)	0.003
Coronary artery disease	1.64 (0.87–3.09)	0.040	N/A	
Pneumonia	1.31 (1.02–1.68)	0.046	N/A	
Initial serum lactate < 4 mmol/L	2.17 (1.37–3.45)	< 0.001	33.33 (3.12–100.0)	0.004
Total dose of catecholamine > 0.25 mcg/kg/min before study drug[a]	0.28 (0.11–0.75)		N/A	
Adrenaline	0.68 (0.49–0.96)	< 0.001	N/A	
pH > 7.3	1.55 (1.20–2.02)	0.015	N/A	
HCO_3 > 18 mmol/L	1.36 (0.95–1.95)	0.001	N/A	
Mechanical ventilator	0.53 (0.22–1.25)	0.042	N/A	

- Better response in patients with:
  - Lower SOFA
  - Lower lactate

Crit Care. 2025 Oct 21;29(1):443.

SOFA-2 · JAMA 2025

Updated Organ Dysfunction Score

Research

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Development and Validation of the Sequential Organ Failure Assessment (SOFA)-2 Score

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Study Design

Scale

Large federated analysis · 1,319 ICUs · 9 countries · 2014–2023

Dataset

Development and external validation using >2 million ICU patient records

Background & Objective

Acute organ dysfunction remains the defining feature of critical illness and sepsis. The SOFA score has been the standard since its introduction ~30 years ago but has not been updated to reflect modern ICU practices, therapies, or data infrastructure. This initiative aimed to develop a data-driven, updated organ dysfunction score — SOFA-2.

JAMA. 2025 Dec 16;334(23):2090-2103.

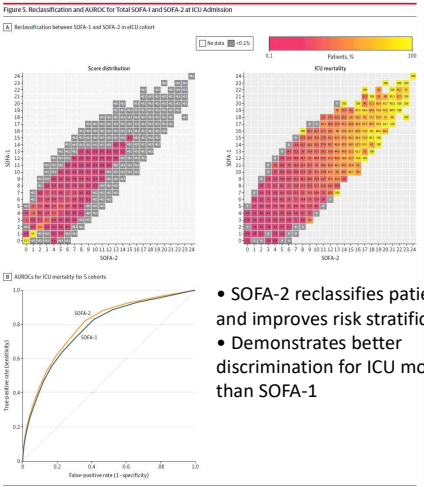
Updated Organ Dysfunction Score

Score Structure & Performance

Table 2. The SOFA-2 Score[a,b]

Organ system	Score 0	1	2	3	4
Brain[c,d]	GCS 15 (or thumbs-up, fist, or peace sign)	GCS 13-14 (or localizing to pain)[d] or need for drugs to treat delirium[e]	GCS 9-12 (or withdrawal to pain)	GCS 6-8 (or flexion to pain)	GCS 3-5 (or extension to pain, no response to pain, generalized myoclonus)
Respiratory[f]	Pao_2:Fio_2 ratio >300 mm Hg (>40 kPa)	Pao_2:Fio_2 ratio ≤300 mm Hg (≤40 kPa)	Pao_2:Fio_2 ratio ≤225 mm Hg (≤30 kPa)	Pao_2:Fio_2 ratio ≤150 mm Hg (≤20 kPa) and advanced ventilatory support[g,h]	Pao_2:Fio_2 ratio ≤75 mm Hg (≤10 kPa) and advanced ventilatory support[g,h] or ECMO[i]
Cardiovascular[j,k,l,m]	MAP ≥70 mm Hg, no vasopressor or inotrope use	MAP <70 mm Hg, no vasopressor or inotrope	Low-dose vasopressor: (sum of norepinephrine and epinephrine ≤0.2 μg/kg/min) or any dose of other vasopressor or inotrope	Medium-dose vasopressor (sum of norepinephrine and epinephrine >0.2 to ≤0.4 μg/kg/min) or low-dose vasopressor (sum norepinephrine and epinephrine ≤0.2 μg/kg/min) with any other vasopressor or inotrope	High-dose vasopressor (sum of norepinephrine and epinephrine >0.4 μg/kg/min) or medium-dose vasopressor (sum of norepinephrine and epinephrine >.02 to ≤0.4 μg/kg/min) with any other vasopressor or inotrope or mechanical support[l,n]
Liver	Total bilirubin ≤1.20 mg/dL (≤20.6 μmol/L)	Total bilirubin ≤3.0 mg/dL (≤51.3 μmol/L)	Total bilirubin ≤6.0 mg/dL (≤102.6 μmol/L)	Total bilirubin ≤12.0 mg/dL (≤205 μmol/L)	Total bilirubin >12 mg/dL (>205 μmol/L)
Kidney	Creatinine ≤1.20 mg/dL (≤110 μmol/L)	Creatinine ≤2.0 mg/dL (≤170 μmol/L) or urine output <0.5 mL/kg/h for 6-12 h	Creatinine ≤3.50 mg/dL (≤300 μmol/L) or urine output <0.5 mL/kg/h for ≥12 h	Creatinine >3.50 mg/dL (>300 μmol/L) or urine output <0.3 mL/kg/h for ≥24 h or anuria (0 mL) for ≥12 h	Receiving or fulfils criteria for RRT (includes chronic use)[o,p,q]
Hemostasis	Platelets >150 × 10^3/μL	Platelets ≤150 × 10^3/μL	Platelets ≤100 × 10^3/μL	Platelets ≤80 × 10^3/μL	Platelets ≤50 × 10^3/μL

- Final score: sum of worst values within 24 hours
- Missing values (Day 1): scored as 0; thereafter carry forward last observation
- Vasopressors counted only if infused ≥1 hour
- Use SpO_2/FiO_2 only when PaO_2/FiO_2 is unavailable
- ECMO: respiratory failure → respiratory; circulatory failure → cardiovascular

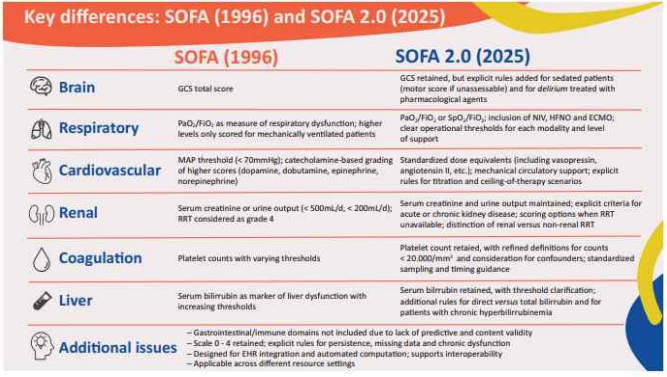


- SOFA-2 reclassifies patients and improves risk stratification
- Demonstrates better discrimination for ICU mortality than SOFA-1

JAMA. 2025 Dec 16;334(23):2090-2103.

Updated Organ Dysfunction Score

Key Changes in SOFA-2



SOFA - Sequential Organ Failure Assessment; GCS - Glasgow Coma Scale; NIV - noninvasive ventilation; HFNO - high-flow nasal oxygen; ECMO - extracorporeal membrane oxygenation; MAP - mean arterial pressure; RRT - renal replacement therapy; EHR - electronic health record.

Figure 1 - Key differences between the original SOFA and SOFA 2.0 scores.

Same 6 Organ Systems

Respiratory, cardiovascular, hepatic, coagulation, renal, and neurological domains retained for continuity

Modern ICU Practice

Updated to reflect current treatment landscape including HFNO, ECMO, and continuous RRT

Expanded Variables

Incorporates high-flow nasal oxygen, ECMO, renal replacement therapy, and additional physiologic parameters

Broader Applicability

Improved performance across diverse ICU settings and geographies — validated in >2M patients

Crit Care Sci. 2025 Nov 13;37:e20250395.

CHAPTER 2

RESPIRATORY FAILURE & MV

Key clinical trials and emerging evidence shaping ventilatory management in the critically ill — 2025 update.

UK-ROX TRIAL · JAMA 2025

Oxygen Strategy in ICU

Research

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Conservative Oxygen Therapy in Mechanically Ventilated Critically Ill Adult Patients

The UK-ROX Randomized Clinical Trial

Daniel S. Martin, PhD; Doug W. Gould, PhD; Tasnin Shahid, BSc; James C. Doidge, PhD; Alex Cowden, MSc; Zia Sadique, PhD; Julie Camsooksai, BSc; Walton N. Charles, MSc; Miriam Davey, PGDip; Amelia Francis-Johnson, MSc; Roger M. Garrett, PhD; Michael P. W. Grocott, MD; Joanne Jones, RN; Lamprini Lampro, MSc; Diane M. Mackle, PhD; B. Ronan O'Driscoll, MD; Alvin Richards-Belle, BSc; Anthony J. Rostron, PhD; Tamás Szakmány, PhD; Alex Warren, MBBS; Paul J. Young, MD, PhD; Kathryn M. Rowan, PhD; David A. Harrison, PhD; Paul R. Mouncey, MSc; for the UK-ROX Investigators

Background

Supplemental oxygen is nearly universal in the ICU, yet optimal SpO_2 targets remain undefined. Both hyperoxia and hypoxia carry potential harms, motivating large-scale pragmatic evaluation.

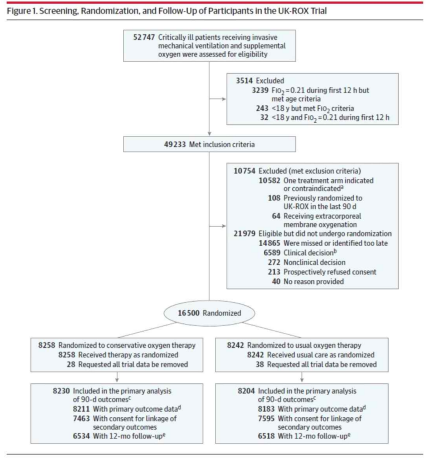
Design & Intervention

- **Design:** Multicenter pragmatic RCT — 97 UK ICUs, n = 16,500 (2021–2024)
- **Conservative arm:** SpO_2 target 88–92% (90%)
- **Usual care arm:** Oxygen at clinician discretion
- **Primary outcome:** 90-day all-cause mortality

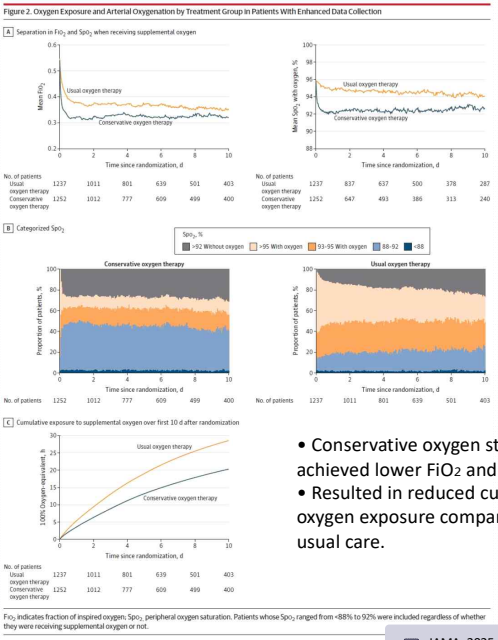
JAMA. 2025 Aug 5;334(5):398–408.

UK-ROX TRIAL · JAMA 2025

Oxygen Strategy in ICU



Screening, randomization, and follow-up flow, alongside oxygen exposure profiles by treatment arm over the study period.



- Conservative oxygen strategy achieved lower FiO_2 and SpO_2 targets.
- Resulted in reduced cumulative oxygen exposure compared with usual care.

JAMA. 2025 Aug 5;334(5):398–408.

Meaning Conservative oxygen therapy **does not improve** mortality in mechanically ventilated ICU patients.

Oxygen Strategy in ICU

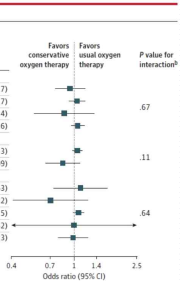
Clinical Outcomes and Subgroup Analysis

Table 2. Primary and Secondary Clinical Outcomes

Outcome	Conservative oxygen therapy group	Usual oxygen therapy group	Adjusted effect (95% CI)		*P* value
			Estimate available case[a]	Multiply imputed[b]	
Primary outcome					
90-d Mortality, No./total (%)	2908/8211 (35.4)	2858/8183 (34.9)	RD, 0.7 (−0.6 to 2.1)	RD, 0.7 (−0.7 to 2.0)	.28
			RR, 1.02 (0.98 to 1.06)	RR, 1.02 (0.98 to 1.06)	
			OR, 1.04 (0.97 to 1.11)	OR, 1.04 (0.97 to 1.11)	
Secondary outcomes					
Duration of ICU stay, median (IQR), d [No.]					
Overall	6.6 (3.1 to 13.3) [7333]	6.8 (3.1 to 13.8) [7448]			
Survivors	7.3 (3.6 to 14.9) [5211]	7.7 (3.8 to 15.3) [5290]	sHR, 1.00 (0.96 to 1.04)	sHR, 1.00 (0.96 to 1.04)	.97
Nonsurvivors	4.9 (1.7 to 10.4) [2122]	4.6 (1.7 to 9.8) [2158]			
Duration of acute hospital stay, median (IQR), d [No.]					
Overall	14 (7 to 30) [7323]	14 (7 to 31) [7434]			
Survivors	20 (11 to 40) [4791]	21 (10 to 42) [4906]	sHR, 0.98 (0.94 to 1.02)	sHR, 0.98 (0.94 to 1.02)	.27
Nonsurvivors	7 (3 to 14) [2532]	7 (3 to 13) [2528]			
Days alive and free from organ support at 30 d, median (IQR), d[c]	16 (−1 to 25) [7327]	16 (−1 to 25) [7444]	POR, 1.00 (0.95 to 1.06)	POR, 1.01 (0.96 to 1.07)	.64
30-d Mortality, No./total (%)	2435/7449 (32.7)	2427/7573 (32.0)			
Survivors free from organ support, d [No.]	23 (16 to 26) [4933]	23 (15 to 26) [5054]			
Mortality at ICU discharge, No./total (%)	2122/7334 (28.9)	2161/7453 (29.0)	RD, 0.2 (−1.2 to 1.6)	RD, −0.1 (−1.3 to 1.1)	.94
Mortality at acute hospital discharge, No./total (%)	2533/7335 (34.5)	2535/7458 (34.0)	RD, 0.9 (−0.6 to 2.3)	RD, 0.5 (−0.8 to 1.9)	.46
60-d Mortality, No./total (%)	2637/7449 (35.4)	2617/7573 (34.6)	RD, 1.1 (−0.2 to 2.5)	RD, 0.8 (−0.6 to 2.2)	.25
1-y Mortality, No./total (%)	2295/5636 (40.7)	2314/5755 (40.2)	RD, 1.0 (−0.7 to 2.6)	RD, 3.3 (−0.7 to 7.3)	.34

Figure 3. Subgroup Analyses of Primary Outcome

Subgroup	90-d Mortality, No./total (%)		Risk difference (95% CI)[a]	Odds ratio (95% CI)[a]	*P* value for interaction[b]
	Conservative oxygen therapy group	Usual oxygen therapy group			
Current or suspected diagnosis					
HIE	437/754 (58.0)	438/748 (58.6)	-1.3 (-6.2 to 3.6)	0.94 (0.76 to 1.17)	
Sepsis	1010/2734 (36.9)	986/2699 (36.5)	0.9 (-1.6 to 3.3)	1.04 (0.93 to 1.17)	.67
Acute brain injury (except HIE)	78/183 (42.6)	83/179 (46.4)	-3.2 (-12.8 to 6.5)	0.86 (0.56 to 1.34)	
None of the prespecified subgroups	1383/4540 (30.5)	1351/4557 (29.6)	1.0 (-0.8 to 2.8)	1.05 (0.96 to 1.16)	
Confirmed or highly suspected COVID-19					
No	2665/7677 (34.7)	2577/7623 (33.8)	1.0 (-0.4 to 2.4)	1.05 (0.98 to 1.13)	.11
Yes	243/534 (45.5)	281/560 (50.2)	-3.7 (-9.3 to 2.0)	0.85 (0.66 to 1.09)	
Ethnic group					
Asian	98/263 (37.3)	90/241 (37.3)	1.9 (-6.1 to 9.9)	1.10 (0.74 to 1.63)	
Black	35/138 (25.4)	50/152 (32.9)	-6.1 (-15.7 to 3.4)	0.71 (0.41 to 1.22)	
White	2236/6070 (36.8)	2215/6201 (35.7)	1.3 (-0.3 to 2.9)	1.07 (0.99 to 1.15)	.64
Mixed	12/52 (23.1)	15/60 (25.0)	-0 (-15.0 to 14.9)	1.00 (0.39 to 2.52)	
Other or not stated	296/808 (36.6)	294/796 (36.9)	-0.3 (-4.6 to 4.1)	0.99 (0.79 to 1.23)	



[a]Adjusted for site, diagnostic subgroup, age, peripheral oxygen saturation (SpO2), partial pressure of arterial oxygen to fraction of inspired oxygen (Pao_2:Fio_2) ratio, confirmed or highly suspected COVID-19, and date of randomization. A negative risk difference indicates an observed lower mortality in the conservative oxygen therapy groups.

[b]*P* value are from tests of interactions in the odds ratio in the adjusted multilevel logistic regression model.

HIE indicates hypoxic-ischemic encephalopathy.

Conservative oxygen targeting SpO_2 90% did not reduce 90-day mortality compared to usual care (RD 0.7, 95% CI −0.6 to 2.1; RR 1.02). These findings do not support routine use of a conservative SpO_2 target in mechanically ventilated ICU patients.

JAMA. 2025 Aug 5;334(5):398–408.

Assisted Ventilation Strategy

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Proportional-Assist Ventilation for Minimizing the Duration of Mechanical Ventilation

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ABSTRACT

PAV+ is a mode that adjusts ventilatory support in proportion to the patient's inspiratory effort.

Background

Early liberation from MV reduces complications and improves long-term outcomes. Optimal weaning mode remains uncertain.

Study Design

International RCT · Adult patients on MV ≥24h · Partial support phase · Not yet ready for extubation

Interventions

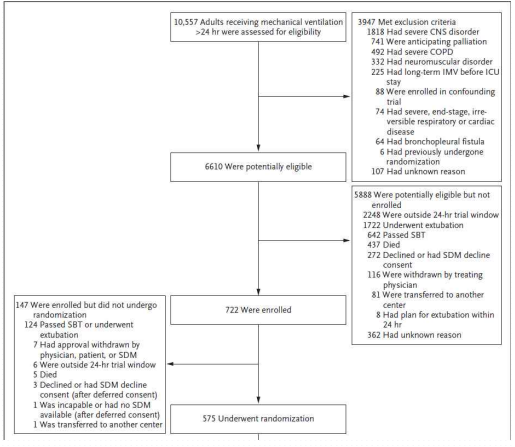
PAV+ (targets normal work of breathing) vs PSV (targets RR and tidal volume)

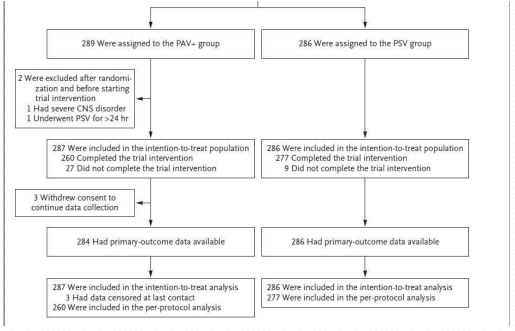
Primary Outcome

Time to successful liberation from mechanical ventilation

N Engl J Med. 2025 Sep 18;393(11):1088–1103.

Assisted Ventilation Strategy





Of 10,557 adults screened, 575 underwent randomization; 289 assigned to PAV+ and 286 to PSV, with high protocol adherence in both arms.

N Engl J Med. 2025 Sep 18;393(11):1088–1103.

Assisted Ventilation Strategy

Table 2. Primary and Secondary Outcomes.

Outcome	PAV+ (N=287)	PSV (N=286)	Hazard Ratio or Relative Risk (95% CI)*	P Value	Absolute Difference (95% CI)†
Median time to event (95% CI) — days‡					
Successful liberation from ventilation: primary outcome	7.3 (6.2 to 9.7)	6.8 (5.4 to 8.8)	0.96 (0.80 to 1.15)	0.58	0.5 (−3.0 to 3.5)
Live ICU discharge	13.0 (10.7 to 15.2)	12.2 (9.9 to 14.1)	0.97 (0.80 to 1.17)	—	0.8 (−2.9 to 4.2)
Live hospital discharge	30.2 (27.0 to 35.5)	29.1 (25.4 to 37.9)	0.91 (0.75 to 1.12)	—	1.1 (−7.3 to 8.0)
Median no. of ventilator-free days (IQR)§					
At day 14	6.7 (0.0 to 10.9)	7.1 (0.0 to 11.3)	—	—	0.4 (−2.9 to 1.5)
At day 21	13.1 (0.0 to 17.9)	13.8 (0.0 to 18.2)	—	—	0.7 (−2.9 to 2.4)
At day 28	19.9 (0.0 to 24.8)	20.5 (0.1 to 25.2)	—	—	0.6 (−3.0 to 2.9)
Death — no./total no. (%)					
In the ICU	55/287 (19.2)	53/286 (18.5)	1.03 (0.74 to 1.46)	—	0.6 (−5.8 to 7.0)
In the hospital	78/287 (27.2)	73/286 (25.5)	1.06 (0.81 to 1.40)	—	1.7 (−5.6 to 8.9)
By day 21	42/287 (14.6)	44/286 (15.4)	0.95 (0.64 to 1.41)	—	−0.8 (−6.6 to 5.1)
By day 28	58/287 (20.2)	54/286 (18.9)	1.07 (0.77 to 1.50)	—	1.3 (−5.2 to 7.8)
By day 90	85/287 (29.6)	76/286 (26.6)	1.13 (0.83 to 1.54)	—	3.0 (−4.3 to 10.4)
Weaning progress: median time to event (95% CI) — days					
First SBT	2.7 (2.1 to 3.3)	2.2 (1.9 to 2.7)	0.91 (0.77 to 1.09)	—	0.5 (−0.4 to 1.2)
First successful SBT	4.1 (3.7 to 5.8)	4.1 (3.2 to 5.4)	0.96 (0.80 to 1.15)	—	0.0 (−1.3 to 1.9)
First extubation or disconnection from ventilator	5.2 (4.2 to 6.4)	4.2 (3.3 to 5.4)	0.88 (0.74 to 1.05)	—	1.0 (−0.7 to 2.3)
Level of weaning difficulty — no./total no. (%)¶					
Short weaning	99/260 (38.1)	95/269 (35.3)	—	—	2.8 (−5.5 to 11.0)
Difficult weaning	77/260 (29.6)	83/269 (30.9)	—	—	−1.2 (−9.1 to 6.6)
Prolonged weaning	49/260 (18.8)	52/269 (19.3)	—	—	−0.5 (−7.2 to 6.2)
Unable to wean and still receiving ventilation at day 90	2/260 (0.8)	4/269 (1.5)	—	—	−0.7 (−2.5 to 1.1)
Died before successful liberation	33/260 (12.7)	35/269 (13.0)	—	—	−0.3 (−6.0 to 5.4)
Weaning complications — no./total no. (%)					
Noninvasive ventilation initiated after extubation	71/231 (30.7)	69/240 (28.8)	1.10 (0.74 to 1.63)	—	2.0 (−6.3 to 10.2)
Tracheostomy performed after randomization‖	58/277 (20.9)	52/271 (19.2)	1.12 (0.73 to 1.70)	—	1.8 (−5.0 to 8.5)
Ventilation continued >7 days after randomization**	146/278 (52.5)	129/275 (46.9)	1.25 (0.90 to 1.75)	—	5.7 (−2.7 to 13.9)
Ventilation continued >21 days after intubation††	80/259 (30.9)	84/256 (32.8)	0.92 (0.63 to 1.33)	—	−1.9 (−10.0 to 6.1)
Reintubation performed <7 days after planned extubation‡‡	53/239 (22.2)	57/245 (23.3)	0.93 (0.61 to 1.44)	—	−1.1 (−8.6 to 6.4)
Ordinal outcome: status of combination of patient disposition and liberation from ventilation at 90 days — no./total no. (%)§§					

Table 2. (Continued.)

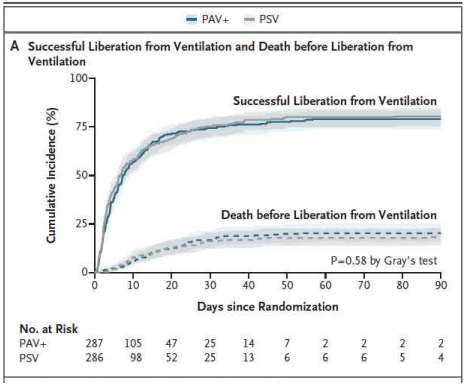
Outcome	PAV+ (N=287)	PSV (N=286)	Hazard Ratio or Relative Risk (95% CI)*	P Value	Absolute Difference (95% CI)†
Died	85/284 (29.9)	76/286 (26.6)	—	—	3.4 (−4.0 to 10.7)
Still receiving ventilation at any location	2/284 (0.7)	4/286 (1.4)	—	—	−0.7 (−2.4 to 1.0)
Not receiving ventilation but in hospital or ICU	21/284 (7.4)	14/286 (4.9)	—	—	2.5 (−1.4 to 6.4)
Discharged from hospital and no longer receiving ventilation	176/284 (62.0)	192/286 (67.1)	—	—	−5.2 (−13.0 to 2.7)
Concurrent-intervention outcome: delirium — no. of trial days/total no. of trial days (%)¶¶					
Too sedated to assess for delirium	872/2266 (38.5)	782/2235 (35.0)	—	—	3.5 (0.7 to 6.3)
Positive test for delirium	324/1394 (23.2)	384/1453 (26.4)	—	—	−3.2 (−6.4 to 0)
Use of assist-control mode					
Use of assist-control mode at least once — no./total no. (%)	169/287 (58.9)	142/286 (49.7)	1.2 (1.0 to 1.4)	—	9.2 (1.1 to 17.4)
Median duration of assist-control use (IQR) — days	0.44 (0.00 to 3.31)	0.00 (0.00 to 1.66)	—	—	0.44 (0.03 to 0.67)
Safety — no./total no. (%)‖‖					
Serious adverse event	31/287 (10.8)	28/286 (9.8)	—	0.79	1.0 (−4.0 to 6.0)
Nonsevere self-extubation	14/287 (4.9)	7/286 (2.4)	—	0.19	2.4 (−0.6 to 5.5)

Median time to liberation was similar (7.3 vs 6.8 days; HR 0.96, 95% CI 0.80–1.15). No differences in ICU or hospital mortality, ventilator-free days, or weaning complications, suggesting equipoise between PAV+ and PSV in this context.

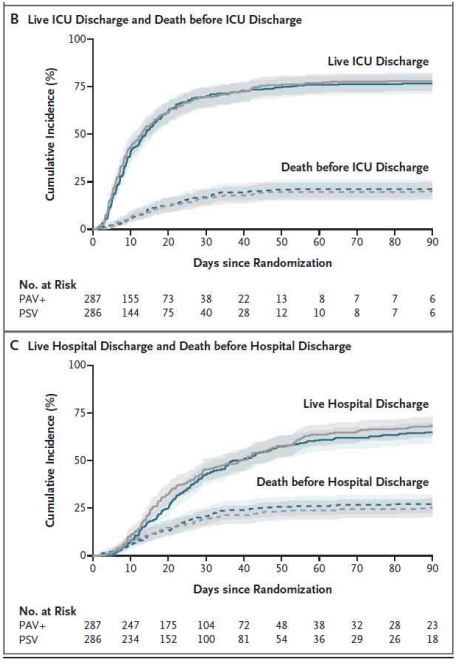
N Engl J Med. 2025 Sep 18;393(11):1088–1103.

Assisted Ventilation Strategy

Survival Curves



- No significant difference between PAV+ and PSV.
- Similar rates of ventilator liberation, discharge, and mortality.

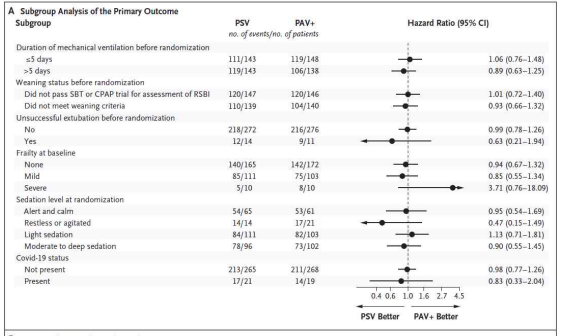


N Engl J Med. 2025 Sep 18;393(11):1088–1103.

Meaning PAV+ **did not improve** clinical outcomes compared with PSV in mechanically ventilated patients.

Assisted Ventilation Strategy

Subgroup analysis



- No subgroup showed benefit of PAV+ over PSV
- Similar weaning patterns between groups
- PAV+ did not reduce time to liberation compared with PSV, suggesting no clear clinical advantage over standard weaning strategies.

N Engl J Med. 2025 Sep 18;393(11):1088–1103.

CLOSED-LOOP VENTILATION · JAMA 2026

Automated Ventilation

Research

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Effect of Automated Closed-Loop Ventilation vs Protocolized Conventional Ventilation on Ventilator-Free Days in Critically Ill Adults

A Randomized Clinical Trial

Jante S. Sinnige, MD; Laura A. Buiteman-Kruizinga, PhD; Janneke Horn, MD, PhD; Frederique Paulus, PhD; Marcus J. Schultz, MD, PhD; Ary Serpa Neto, MD, MSc, PhD; for the ACTiVE Investigators and the Protective Ventilation Network

Background & Objective

Closed-loop ventilation (INTELLiVENT-ASV) continuously adapts settings based on real-time respiratory mechanics and gas exchange, potentially optimizing lung-protective ventilation. This trial asked: does **early automated ventilation increase ventilator-free days at day 28**?

Study Design

International multicenter RCT · 7 ICUs (Netherlands & Switzerland) · 2020–2025 · Adults within 1h of intubation, expected MV ≥ 24h

Intervention

INTELLiVENT-ASV closed-loop (n=602) – ASV system vs Protocolized conventional ventilation (n=599) · Standardized sedation & weaning in both groups

ASV is a closed-loop mode that automatically optimizes ventilation based on real-time patient physiology.

JAMA. 2026 Mar 10;335(10):874–884.

Automated Ventilation

Trial Data

- No difference in ventilator-free days at day 28
- Similar extubation and survival patterns
- No difference in 90-day mortality

Figure 1. Participant Flow Through the ACTIVE Trial

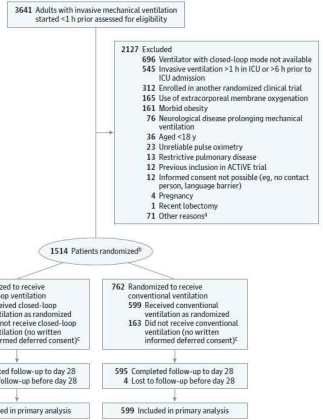
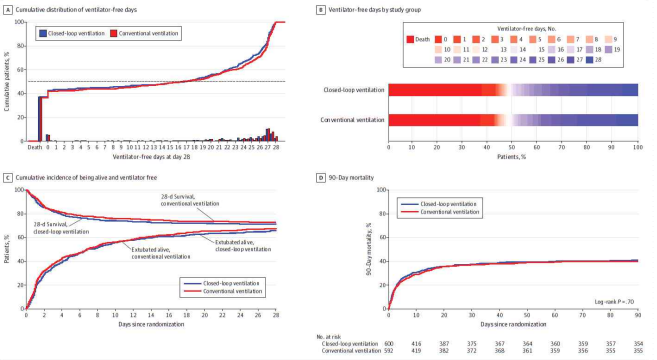


Figure 2. Ventilator-Free Days at Day 28, 28-Day Survival and Extubation Rates, and 90-Day Mortality



Panel A shows distributions of ventilator-free days (primary outcome) for each group, with death shown first. Curves that rise more gradually indicate a more favorable distribution in the number of ventilator-free days at day 28. The height of each curve at death indicates mortality for each group. The height of each curve at any time point indicates the proportion of patients with that number or fewer of ventilator-free days at day 28 (eg, height at day 10 indicates proportion of patients with ≤10 ventilator-free days at day 28). The difference in the height of the curves at any point is the percentile difference in the distribution of ventilator-free days at day 28 associated with that number of days alive and free of ventilation. The bars represent the proportion of patients with each possible value of ventilator-free days. The dashed line represents 50% of patients. Panel B shows ventilator-free days at day 28 as horizontally stacked proportions according to randomization. Red represents worse outcomes; blue, better outcomes. The odds ratio from the primary analysis, which used a cumulative logistic model, was 0.91 (95% CI, 0.77-1.06). There were 601 patients in the closed-loop group and 595 in the conventional group. Panel C shows cumulative incidence functions for being alive and free from invasive ventilation (solid lines) and for being alive (dotted lines) during the 28 days after randomization, with death treated as a competing event. Panel D shows Kaplan-Meier curves for 90-day survival according to randomization. Median observation time in the closed-loop and conventional groups was 4.5 (IQR, 3.5-7.6) days and 6.0 (IQR, 4.0-9.3) days, respectively.

Meaning Early automated closed-loop ventilation did **not improve** ventilator-free days or clinical outcomes compared with conventional ventilation.

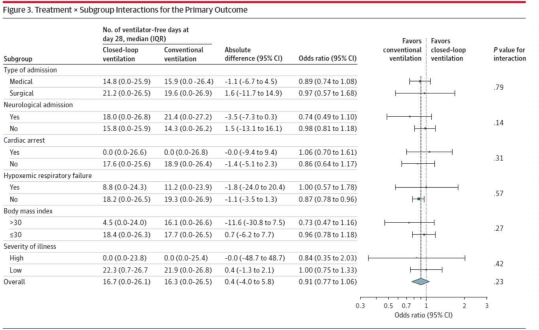
Automated Ventilation

Conclusion and subgroup analysis

Table 2. Primary and Secondary Outcomes*

Outcomes	Closed-loop ventilation (n = 602)	Conventional ventilation (n = 599)	Absolute difference (95% CI)[b]	Effect estimate (95% CI)[b]	*P* value
Primary outcome					
Ventilator-free days at day 28[c]				OR, 0.91 (0.77 to 1.06)	.23
Median (IQR)	16.7 (0.0-26.1) [n = 601]	16.3 (0.0-26.5) [n = 595]	0.4 (−4.0 to 5.8)		
Mean (SD)	13.1 (12.2) [n = 601]	13.4 (12.3) [n = 595]	−0.3 (−1.7 to 1.0)		
Secondary outcomes					
28-Day mortality, No./total (%)	224/602 (37.2)	218/597 (36.5)	0.7 (−4.8 to 6.1)	HR, 1.04 (0.86 to 1.25)	.69
Duration of ventilation in survivors, median (IQR), d	3.3 (1.0-9.4) [n = 377]	2.6 (1.0-8.7) [n = 377]	0.7 (−0.0 to 1.4)	MdD, 0.7 (−0.0 to 1.4)	.05
Time spent in each ventilatory zone, mean (SD), %[d]	n = 78	n = 64			
Optimal	48.4 (40.2)	36.7 (38.4)	12.9 (−0.2 to 25.9)	MD, 12.9 (−0.2 to 25.9)	.05
Acceptable	40.1 (36.6)	27.5 (33.6)	12.5 (1.3 to 23.9)	MD, 12.5 (1.3 to 23.9)	.03
Critical	11.6 (26.9)	35.8 (45.0)	−24.6 (−36.6 to −12.6)	MD, −24.6 (−36.6 to −12.6)	<.001
Acute respiratory distress syndrome, No./total (%)[e]	15/599 (2.5)	12/596 (2.0)	0.5 (−1.2 to 2.2)	AD, 0.5 (−1.2 to 2.2)	.57
Ventilator-associated pneumonia, No./total (%)[f]	13/599 (2.2)	21/596 (3.5)	−1.4 (−3.3 to 0.4)	AD, −1.4 (−3.3 to 0.4)	.13
Severe hypercapnia: $Paco_2$ >55 mm Hg and pH <7.35, No./total (%)	119/599 (19.9)	144/596 (24.2)	−4.1 (−8.7 to 0.5)	AD, −4.1 (−8.7 to 0.5)	.08
Severe atelectasis, No./total (%)[g]	23/599 (3.8)	36/596 (6.0)	−2.2 (−4.7 to 0.3)	AD, −2.2 (−4.7 to 0.3)	.08
Severe hypoxemia: Pao_2 <55 mm Hg, No./total (%)	96/599 (16.0)	126/596 (21.1)	−5.1 (−9.4 to −0.7)	AD, −5.1 (−9.4 to −0.7)	.02
Pneumothorax, No./total (%)[h]	6/599 (1.0)	2/596 (0.3)	0.7 (−0.3 to 1.6)	AD, 0.7 (−0.3 to 1.6)	.16
Need for rescue strategies, No./total (%)[i]	86/599 (14.4)	123/596 (20.3)	−6.0 (−10.2 to −1.7)	AD, −6.0 (−10.2 to −1.7)	.006
Recruitment maneuvers	31/599 (5.2)	30/596 (5.0)	0.1 (−2.4 to 2.5)	AD, 0.1 (−2.4 to 2.5)	.95
Prone positioning	55/599 (9.2)	83/596 (13.9)	−4.8 (−8.4 to −1.2)	AD, −4.8 (−8.4 to −1.2)	.009
Bronchoscopy for atelectasis	33/599 (5.5)	44/596 (7.4)	−1.9 (−4.7 to 0.9)	AD, −1.9 (−4.7 to 0.9)	.19
Extubation failure (reintubation within 24 h of extubation), No./total (%)	32/413 (7.7)	30/412 (7.3)	0.5 (−3.0 to 4.1)	AD, 0.5 (−3.0 to 4.1)	.77
Length of stay, median (IQR), d					
Intensive care unit	4.5 (1.8-11.9) [n = 595]	4.4 (1.8-12.4) [n = 594]	0.1 (−0.9 to 1.1)	MdD, 0.1 (−0.9 to 1.1)	.85
Hospital	12.2 (3.5-27.5) [n = 564]	12.0 (4.0-25.3) [n = 581]	0.3 (−0.8 to 1.4)	MdD, 0.3 (−0.8 to 1.4)	.60
Mortality, No./total (%)					
In intensive care unit	208/558 (37.3)	205/556 (36.9)	0.1 (−5.5 to 5.8)	AD, 0.1 (−5.5 to 5.8)	.97
In hospital	241 (40.0)	233 (38.9)	1.1 (−4.4 to 6.6)	AD, 1.1 (−4.4 to 6.6)	.70
By day 90	246/600 (41.0)	237/592 (40.0)	0.9 (−4.6 to 6.5)	HR, 1.04 (0.87 to 1.24)	.66

Figure 3. Treatment × Subgroup Interactions for the Primary Outcome



Hypoxemic respiratory failure was defined as intubation due to respiratory failure with a ratio of Pao_2 to fraction of inspired oxygen ≤200 mm Hg. The severity of illness subgroup was defined using available severity scores. Patients were classified as having higher severity if their value was above the cohort median for any of the following indexes (in order of preference, depending on data availability): Simplified Acute Physiology Score II, Acute Physiology and Chronic Health Evaluation (APACHE) IV, or APACHE II. If one score was missing, the next available score was used. Body mass index is calculated as calculated as weight in kilograms divided by height in meters squared. The size of the data markers indicates the sample size and the vertical dashed line the overall effect (0.91)

- No difference in ventilator-free days (primary outcome)
- No difference in mortality or length of stay
- Fewer hypoxemia events and rescue interventions

→ No meaningful improvement in patient-centered outcomes

JAMA. 2026 Mar 10;335(10):874–884.

SESAR TRIAL · JAMA 2025

Inhaled Sedation in ARDS

Research

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Inhaled Sedation in Acute Respiratory Distress Syndrome
The SESAR Randomized Clinical Trial

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Background

Optimal sedation for moderate-to-severe ARDS remains uncertain. Inhaled volatile agents (sevoflurane) may offer bronchodilatory and anti-inflammatory effects, but comparative efficacy vs. IV propofol had not been robustly evaluated in a phase 3 trial.

Design & Intervention

Study Design

Phase 3 multicenter RCT · 37 ICUs in France · 2020–2023
Adults with early moderate-to-severe ARDS (PaO_2/FiO_2 <150)

Intervention

Inhaled sevoflurane vs IV propofol (up to 7 days)

Primary outcome

Ventilator-free days at day 28

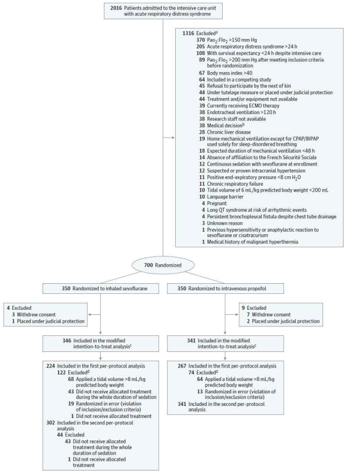
JAMA. 2025 May 13;333(18):1608–1617.

SESAR TRIAL · JAMA 2025

Inhaled Sedation in ARDS

Trial Data

Figure 1. Patient Screening, Enrollment, and Follow-Up in the Sevoflurane for Sedation in ARDS (SESAR) Trial



2016 Patients admitted to the intensive care unit with acute respiratory distress syndrome
1316 Excluded[a]
370 Pao_2:Fio_2 >150 mm Hg
205 Acute respiratory distress syndrome >24 h
108 With survival expectancy <24 h despite intensive care
89 Pao_2:Fio_2 >200 mm Hg after meeting inclusion criteria before randomization
67 Body mass index >40
64 Included in a competing study
45 Refusal to participate by the next of kin
44 Under tutelage measure or placed under judicial protection
44 Treatment and/or equipment not available
39 Currently receiving ECMO therapy
38 Endotracheal ventilation >120 h
38 Research staff not available
38 Medical decision[b]
28 Chronic liver disease
19 Home mechanical ventilation except for CPAP/BIPAP used solely for sleep-disordered breathing
18 Expected duration of mechanical ventilation <48 h
14 Absence of affiliation to the French Sécurité Sociale
12 Continuous sedation with sevoflurane at enrollment
12 Suspected or proven intracranial hypertension
11 Positive end-expiratory pressure <8 cm H_2O
11 Chronic respiratory failure
10 Tidal volume of 6 mL/kg predicted body weight <200 mL
10 Language barrier
4 Pregnant
4 Long QT syndrome at risk of arrhythmic events
4 Persistent bronchopleural fistula despite chest tube drainage
3 Unknown reason
1 Previous hypersensitivity or anaphylactic reaction to sevoflurane or cisatracurium
1 Medical history of malignant hyperthermia
700 Randomized
350 Randomized to inhaled sevoflurane
350 Randomized to intravenous propofol
4 Excluded
3 Withdrew consent
1 Placed under judicial protection
9 Excluded
7 Withdrew consent
2 Placed under judicial protection
346 Included in the modified intention-to-treat analysis[c]
341 Included in the modified intention-to-treat analysis[c]
224 Included in the first per-protocol analysis
122 Excluded[d]
68 Applied a tidal volume >8 mL/kg predicted body weight
43 Did not receive allocated treatment during the whole duration of sedation
19 Randomized in error (violation of inclusion/exclusion criteria)
1 Did not receive allocated treatment
302 Included in the second per-protocol analysis
44 Excluded
43 Did not receive allocated treatment during the whole duration of sedation
1 Did not receive allocated treatment
267 Included in the first per-protocol analysis
74 Excluded[d]
64 Applied a tidal volume >8 mL/kg predicted body weight
13 Randomized in error (violation of inclusion/exclusion criteria)
341 Included in the second per-protocol analysis

Table 2. Primary and Secondary End Points[a]

Variable	Inhaled sevoflurane (n = 346)	Intravenous propofol (n = 341)	Between-group difference (95% CI)[b]	Treatment effect (95% CI)[c]
Primary end point				
Ventilator-free days through day 28, median (IQR)	0.0 (0.0 to 11.9)	0.0 (0.0 to 18.7)	−2.1 (−3.6 to −0.7)	0.76 (0.50 to 0.97)
Key secondary end point				
Death at day 90, No./total (%)	183/346 (52.9)	151/341 (44.3)	8.6 (1.2 to 16.1)	1.31 (1.05 to 1.62)
Secondary end points				
Mortality, No./total (%)[d]				
At 28 d	152/345 (44.1)	132/340 (38.8)	5.2 (-2.1 to 12.6)	1.13 (0.95 to 1.36)
At 14 d	104/345 (30.1)	90/340 (26.5)	3.7 (-3.1 to 10.4)	1.14 (0.90 to 1.45)
At 7 d	67/345 (19.4)	46/340 (13.5)	5.9 (0.4 to 11.4)	1.44 (1.02 to 2.03)
ICU-free days through day 28, median (IQR)	0.0 (0.0 to 6.0)	0.0 (0.0 to 15.0)	−2.5 (−3.7 to −1.4)	0.67 (0.52 to 0.86)
No.	345	341		
Safety secondary end points through day 7				
Mean arterial pressure, median (IQR), mm Hg	80 (75 to 86)	81 (76 to 87)	-1.12 (-2.38 to 0.14)	NR
No. of patients/total patient-days[e]	346/2423	346/2501		
Dose of infused norepinephrine, median (IQR), µg/kg/min	0.31 (0.17 to 0.63)	0.23 (0.12 to 0.49)	0.07 (0.03 to 0.10)	NR
No. of patients/total patient-days[e]	330/1480	308/1398		
Dose of infused epinephrine, median (IQR), µg/kg/min	2.2 (2.2 to 2.2)	0.9 (0.1 to 3.0)	Not estimated[f]	NR
No. of patients/total patient-days[e]	1/1	3/4		
Dose of infused dobutamine, median (IQR), µg/kg/min	3.1 (2.5 to 5.0)	4.2 (2.5 to 5.4)	-1.04 (-2.71 to 0.62)	NR
No. of patients/total patient-days[e]	19/56	28/88		
Serum lactate, median (IQR), mmol/L	1.7 (1.4 to 2.2)	1.6 (1.3 to 2.0)	0.12 (0.02 to 0.23)	NR
No. of patients/total patient-days[e]	344/2137	341/2173		
KDIGO criteria for acute kidney injury, No. (%)[g]				
No acute kidney injury	110 (31.8)	146 (42.8)	-0.11 (-0.18 to -0.04)	1 [Reference]
Stage 1	59 (17.1)	41 (12.0)	0.05 (-0.01 to 0.10)	1.91 (1.62 to 2.25)
Stage 2	61 (17.6)	62 (18.2)	-0.01 (-0.06 to 0.05)	1.31 (1.12 to 1.52)
Stage 3	116 (33.5)	92 (27.0)	0.07 (-0.01 to 0.14)	1.67 (1.47 to 1.91)
Predefined adverse events, No. (%)				
Supraventricular tachycardia or atrial fibrillation	27 (7.8)	23 (6.7)	−0.01 (−0.05 to 0.11)	1.16 (0.68 to 1.98)
Severe hypercapnic acidosis with pH <7.15	11 (3.2)	5 (1.5)	1.7 (−0.5 to 4.0)	2.17 (0.76 to 6.18)
Malignant hyperthermia	2 (0.6)	0	0.6 (−0.2 to 1.4)	Not estimated[f]
Propofol-related infusion syndrome	0	3 (0.9)	−0.9 (−1.9 to 0.1)	Not estimated[f]
Pneumothorax or bronchopleural fistula persistent despite drainage	1 (0.3)	0	0.3 (−0.3 to 0.9)	Not estimated[f]

- Fewer ventilator-free days with sevoflurane
- Higher 90-day mortality
- No meaningful improvement in physiologic parameters

→ Sevoflurane showed worse clinical outcomes than propofol

JAMA. 2025 May 13;333(18):1608–1617.

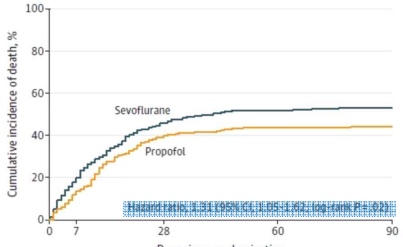
SESAR TRIAL · JAMA 2025

Meaning Inhaled sedation with sevoflurane was associated with **worse outcomes** than propofol in moderate-to-severe ARDS.

Inhaled Sedation in ARDS

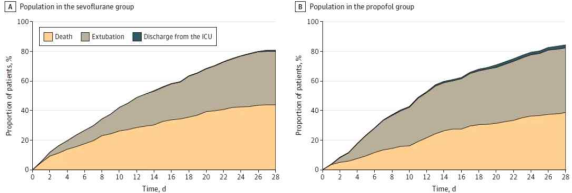
Adverse events & Survival

Figure 2. Kaplan-Meier Estimates of 90-Day Survival in the Modified Intention-to-Treat Population



At 90 days, 183 of 346 patients (52.9%) in the sevoflurane group and 151 of 341 patients (44.3%) in the propofol group had died. The median follow-up times were 40.5 days (IQR, 10.0-90.0) in the sevoflurane group and 90.0 days (IQR, 14.0-90.0) in the propofol group.

Figure 3. Cumulative Numbers of Patients Dead, Extubated (Alive), and Discharged (Alive) From the Intensive Care Unit From Randomization Through Day 28 in the Modified Intention-to-Treat Population

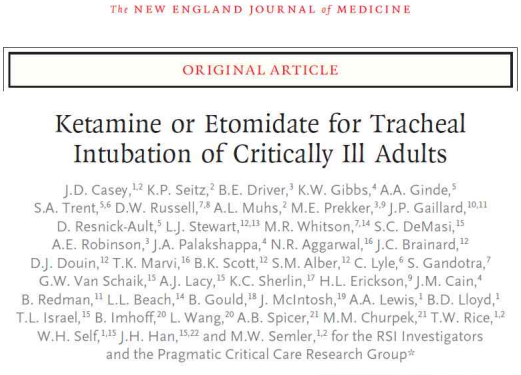


Extubation (alive) was counted as the end of the last period of assisted breathing to day 28. ICU indicates intensive care unit.

- Sevoflurane ↓ ventilator-free days and ↓ 90-day survival.
- Worse patient-centered outcomes vs propofol.
- Propofol remains the preferred sedation in ARDS.
- Inhaled sevoflurane should not be used routinely.

JAMA. 2025 May 13;333(18):1608–1617.

Ketamine or Etomidate for Tracheal Intubation



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Ketamine or Etomidate for Tracheal Intubation of Critically Ill Adults

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ORIGINAL ARTICLE

Evaluation of Etomidate Use and Association with Mortality Compared with Ketamine among Critically Ill Patients

The Clinical problem

Etomidate is widely used for RSI in critically ill patients, but prior studies and meta-analyses have raised concerns about adrenal suppression and a potential increase in mortality. Ketamine offers hemodynamic stability and does not suppress the adrenal axis.

Trial Design

- **Design:** Pragmatic, multicenter, randomized trial
- **Sites:** 14 EDs and ICUs across the United States
- **Population:** Critically ill adults requiring tracheal intubation
- **Primary outcome:** In-hospital death from any cause by day 28
- **Secondary outcome:** Cardiovascular collapse during intubation (SBP <65 mmHg, new/increased vasopressors, or cardiac arrest)
- Patients were randomized to receive intravenous ketamine (1.0–2.0 mg/kg) or etomidate (0.2–0.3 mg/kg) for induction of anesthesia during tracheal intubation.
- A total of 2365 critically ill adults were randomized (ketamine n=1176; etomidate n=1189).
- Median age was 60 years, with 46.7% having sepsis, and intubation was performed in the ED (55.7%) or ICU (44.3%).

Ketamine or Etomidate for Tracheal Intubation

Randomization & mortality

Table 2. Characteristics of the Intubation Procedure.

Characteristic	Ketamine (N=1176)	Etomidate (N=1189)	Difference (95% CI)*
Primary medication for induction of anesthesia — no. (%)†			
Ketamine	1167 (99.2)	3 (0.3)	99.0 (98.4 to 99.6)
Etomidate	6 (0.5)	1184 (99.6)	−99.1 (−99.6 to −98.5)
None	3 (0.3)	2 (0.2)	0.1 (−0.3 to 0.5)
Neuromuscular blocking agent — no. (%)‡			
Rocuronium	810 (69.0)	819 (69.0)	0.0 (−3.7 to 3.7)
Succinylcholine	362 (30.8)	365 (30.7)	0.1 (−3.6 to 3.8)
None	3 (0.3)	3 (0.3)	0.0 (−0.4 to 0.4)
Measurements or treatments at induction of anesthesia			
Median oxygen saturation (IQR) — %§	99 (97–100)	99 (97–100)	0 (−1 to 1)
Preoxygenation — no. (%)	1172 (99.7)	1186 (99.7)	−0.1 (−0.5 to 0.4)
Median systolic blood pressure (IQR) — mm Hg¶	127 (110–147)	127 (110–148)	0 (−3 to 3)
Vasopressor bolus or increased infusion rate — no. (%)	207 (17.6)	234 (19.7)	−2.1 (−5.2 to 1.1)
Laryngoscope used on the first attempt — no. (%)			
Video	1124 (95.6)	1127 (94.8)	0.8 (−0.9 to 2.5)
Direct	49 (4.2)	60 (5.0)	−0.9 (−2.6 to 0.8)
Other‖	3 (0.3)	2 (0.2)	0.1 (−0.3 to 0.5)
Instrument used on the first intubation attempt — no. (%)**			
Endotracheal tube with stylet	672 (57.3)	689 (58.1)	−0.8 (−4.7 to 3.2)
Bougie	455 (38.8)	446 (37.6)	1.2 (−2.7 to 5.1)
Neither endotracheal tube with stylet nor bougie	45 (3.8)	51 (4.3)	−0.5 (−2.1 to 1.1)

Groups were nearly identical at baseline, supporting internal validity of the primary outcome comparison.

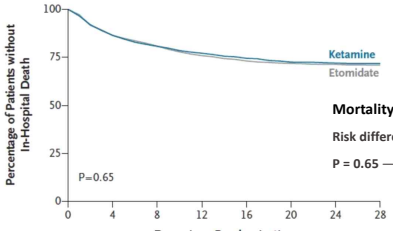

Figure 1. In-Hospital Death, According to Trial Group.

Shown is the percentage of patients without in-hospital death from enrollment through day 28. The incidence of in-hospital death by day 28 (the primary outcome) did not differ significantly between the ketamine group (28.1%) and the etomidate group (29.1%) (risk difference adjusted for trial site, −0.8 percentage points; 95% CI, −4.5 to 2.9; P=0.65 by a generalized linear mixed-effects model with a random effect for trial site).

Mortality at Day 28

Risk difference: −0.8 percentage points (95% CI, −4.5 to 2.9)

P = 0.65 — No statistically significant difference

Meaning **No survival benefit** with ketamine; etomidate remains a stable standard for tracheal intubation.

Ketamine or Etomidate for Tracheal Intubation

Outcomes & Subgroup analysis

Table 3. Outcomes.

Outcome	Ketamine (N = 1176)	Etomidate (N = 1189)	Difference (95% CI)*
Primary outcome: in-hospital death from any cause by day 28 — no. (%)†	330 (28.1)	345 (29.1)	−0.8 (−4.5 to 2.9)‡
Secondary outcome: cardiovascular collapse during the interval between induction of anesthesia and 2 minutes after intubation — no. (%)§	260 (22.1)	202 (17.0)	5.1 (1.9 to 8.3)
Systolic blood pressure <65 mm Hg‖	73 (6.4)	64 (5.5)	0.9 (−1.0 to 2.8)
Receipt of a rescue vasopressor or inotrope‖	250 (21.9)	188 (16.1)	5.8 (2.3 to 9.4)
Cardiac arrest¶	12 (1.0)	10 (0.8)	0.2 (−0.6 to 1.0)
Exploratory procedural outcomes			
Median lowest systolic blood pressure (IQR) — mm Hg§	112 (92–138)	113 (96–141)	−1 (−3 to 1)
Lowest systolic blood pressure <80 mm Hg — no. (%)§	164 (14.4)	123 (10.5)	3.8 (1.1 to 6.5)
Median highest systolic blood pressure (IQR) — mm Hg§	140 (115–164)	141 (118–168)	−2 (−7 to 2)
Highest systolic blood pressure >180 mm Hg — no. (%)§	154 (13.5)	191 (16.5)	−2.9 (−5.9 to 0.0)
Median lowest oxygen saturation (IQR) — %‖	97 (90–100)	97 (89–100)	0 (0 to 2)
Lowest oxygen saturation <80% — no. (%)‖	125 (11.1)	126 (11.1)	0.0 (−2.6 to 2.6)
Successful intubation on the first attempt — no. (%)**	1005 (85.7)	1029 (86.7)	−1.0 (−3.8 to 1.8)
Median time from initiation of anesthesia to intubation (IQR) — sec††	112 (82–155)	103 (80–134)	9.0 (5–13)
Exploratory clinical outcomes†‡‡			
Median ventilator-free days (IQR)	23 (0–26)	23 (0–26)	0 (−1 to 1)
Median vasopressor-free days (IQR)	25 (0–28)	25 (0–28)	0 (−1 to 1)
Median ICU-free days (IQR)	20 (0–24)	19 (0–24)	1 (−1 to 2)
Safety outcomes			
Median systolic blood pressure at 24 hours (IQR) — mm Hg§§	114 (102–130)	114 (103–129)	0 (−2 to 3)
Ongoing receipt of vasopressors at 24 hours — no. (%)¶¶	420 (38.9)	458 (42.3)	−3.4 (−7.5 to 0.7)

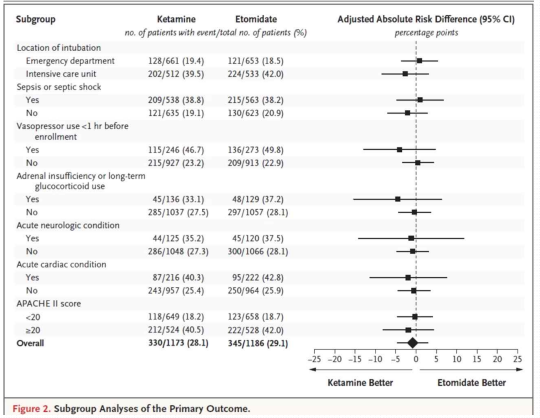

Figure 2. Subgroup Analyses of the Primary Outcome.

- No mortality difference; ketamine associated with more cardiovascular collapse.
- Overall safety was similar, with a small increase in ventricular tachycardia with ketamine.

Forest plot confidence intervals all cross zero. No subgroup demonstrated a statistically significant differential treatment effect — including the sepsis/septic shock population most relevant to the etomidate concern.

CHAPTER 3

ICU Management

Dex & Delirium, PADIS Guideline Update — Five key clinical questions on pain, agitation, delirium, immobility, and sleep in the ICU

DELIRIUM · INTENSIVE CARE MED 2025

Dexmedetomidine for Hyperactive Delirium

Intensive Care Med (2025) 51:2305–2317
https://doi.org/10.1007/s00134-025-08135-1

ORIGINAL

Dexmedetomidine for treatment of hyperactive delirium in non-intubated ICU patients: the 4D randomized clinical trial

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Background

Hyperactive delirium in non-intubated ICU patients is associated with agitation, self-harm, and escalation to intubation. Dexmedetomidine, an α_2-agonist with minimal respiratory depression, is a candidate agent, but evidence from placebo-controlled trials was lacking.

Study Design

Multicenter, placebo-controlled, double-blind RCT · 9 ICUs · Non-intubated patients with hyperactive delirium

Primary Outcome

Composite: agitation duration + delirium duration + need for intubation or deep sedation

Dexmedetomidine for Hyperactive Delirium

Flowchart and outcomes

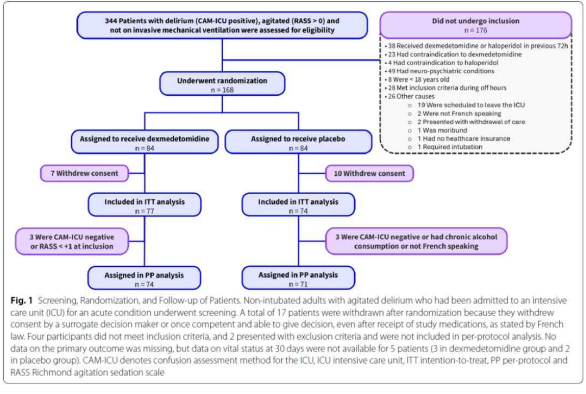

Fig. 1 Screening, Randomization, and Follow-up of Patients. Non-intubated adults with agitated delirium who had been admitted to an intensive care unit (ICU) for an acute condition underwent screening. A total of 17 patients were withdrawn after randomization because they withdrew consent by a surrogate decision maker or once competent and able to give decision, even after receipt of study medications, as stated by French law. Four participants did not meet inclusion criteria, and 2 presented with exclusion criteria and were not included in per-protocol analysis. No data on the primary outcome was missing, but data on vital status at 30 days were not available for 5 patients (3 in dexmedetomidine group and 2 in placebo group). CAM-ICU denotes confusion assessment method for the ICU, ICU intensive care unit, ITT intention-to-treat, PP per-protocol and RASS Richmond agitation sedation scale

Table 2 Use of dexmedetomidine or placebo, and open-label rescue medication on inclusion day in the ICU after randomization

	Placebo (*N* = 74)	Dexmedetomidine (*N* = 77)	Absolute Difference or Median Difference (95% CI)	*P*
Median duration of trial intervention (IQR)—days	4 (3–5)	4 (2–5)	0 (-1 to 1)	0.31
Median daily dose (IQR)—µg.kg^{-1}.h^{-1} †	0.46 (0.30–0.60)	0.32 (0.20–0.42)	-0.13 (-0.21 to -0.03)	**0.03**
Median cumulative dose (IQR)—µg.kg^{-1} †	2.0 (1.2–2.6)	1.1 (0.6–1.6)	-0.9 (-1.5 to -0.3)	**0.02**
Use of open-label rescue medication on inclusion day ‡				
Number of patients requiring the agent(s)	30 (40.5)	16 (21.6)	18.9 (5.2 to 32.6)	**0.03**
Median haloperidol dose (IQR)—milligrams (30/18) §	5 (3–5)	5 (3 to 5)	0 (0 to 0)	0.38
Number of patients requiring other open-label rescue medication	10 (13.5)	1 (1.3)	12.2 (3.7 to 20.7)	**0.03**

‡ Data are presented as median and 25th–75th percentiles (interquartile range) or number (percentage). Results are expressed for the dexmedetomidine group as compared with the placebo group using relative risks (95% CI) for binary and categorical outcomes and with median differences (95% CI) for continuous outcomes

† The median daily infusion rate (in micrograms per kilogram per hour) and the median cumulative dose (in milligrams during trial drug administration) were calculated as the cumulative infusion rate received divided by the total number of days that the patient received dexmedetomidine or placebo; and the cumulative dose received during the total number of days that the patient received dexmedetomidine or placebo, respectively. Doses for placebo are presented as dexmedetomidine-equivalents

§ Patients could receive more than one rescue medication on the same day. Rescue medication was defined as the use of any psychotropic agent to treat uncontrollable agitation, insomnia or delirium (e.g. haloperidol or other psychotropic drugs such as propofol, benzodiazepines or any antipsychotic drug)

‡ Figures depict the number of patients that received haloperidol on inclusion day according to randomization group

CI denotes confidence interval, ICU intensive care unit and IQR interquartile range

P-values < 0.05 are provided in bold

- Lower dexmedetomidine dose vs placebo
- Reduced need for rescue medications
- Fewer patients required haloperidol

→ Improved control of agitation/delirium

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Dexmedetomidine for Hyperactive Delirium

Outcomes & Adverse Events

Table 3 Clinical outcomes and adverse events

Outcome	Placebo (N = 74)	Dexmedetomidine (N = 77)	Absolute Difference or Median Difference (95% CI)	P
Primary outcome £	15.0 (− 23.9 to 53.9)	− 26.8 (− 45.4 to 10.7)	Z-score: − 30.9 (− 49.4 to − 12.4) Effect-size: − 0.46 [− 0.78 to − 0.13]	**0.001**
Separate items				
Median delay to RASS < 1 (IQR)—hours	2.0 (0.0 to 7.0)	1.0 (1.0 to 2.0)	− 1.0 (− 2.0 to − 0.1) Z-score: − 54.5 (− 58.2 to − 50.7) Effect-size: − 0.66 [− 0.92 to − 0.27]	**0.001**
Median delay to negative CAM-ICU (IQR)—days	1.0 (0.5 to 1.7)	0.8 (0.5 to 1.5)	− 0.1 (− 0.5 to 0.1) Z-score: − 25.1 (− 69.5 to 19.4) Effect-size: − 0.09 [− 0.41 to 0.23]	0.38
Intubation—no. (%)	3 (4.1)	2 (2.6)	− 1.5 (− 7.2 to 4.3) Z-score: − 8.1 (− 40.5 to 24.3) Effect-size: − 0.08 [− 0.40 to 0.24]	0.62
Secondary outcomes £				
Median days alive without delirium or mechanical ventilation (IQR)	4 (2–6)	4 (2–6)	0 (− 1 to 1)	0.61
Median days alive without delirium (IQR)	6 (4–9)	6 (3–9)	0 (− 1 to 1)	0.75
Median days alive without mechanical ventilation (IQR)	6 (3–7)	7 (2–13)	1 (− 1 to 6)	0.38
Median length of ICU stay (IQR)—days	12 (8–19)	13 (7–21)	1 (− 3 to 5)	0.77
Median length of ICU stay post-randomization (IQR)—days	6 (4 to 10)	6 (3–12)	0 (− 2 to 2)	0.90
All− cause mortality at day 7—no. / total no. (%)	5 (6.8)	6 (7.8)	1 (− 7 to 9)	0.81
All− cause mortality at day 30—no. / total no. (%) §	13/72 (18.1)	10/74 (13.5)	− 5 (− 16 to 7)	0.46
Septicemia—no. (%)	4 (5.4)	6 (7.8)	2 (− 5 to 10)	0.56
Pneumonia—no. (%)	14 (18.9)	10 (13.0)	− 6 (− 18 to 6)	0.33
Delirium recurrence—no. (%) €	7 (9.5)	13 (16.9)	7 (− 3 to 18)	0.19
Median number of delirium recurrence (IQR)	1 (1 to 2) (/7)	1 (1 to 2) (/13)	0 (− 2 to 2)	0.73
Open-label dexmedetomidine use during recurrence—no. (%)	4/7 (57.1)	7/13 (53.9)	− 3 (− 49 to 42)	0.89
Median duration of open label dexmedetomidine use in case of delirium recurrence (IQR)—days	9 (3–15) (/4)	3 (2 to 5) (/7)	− 5 (− 15 to 3)	0.34
Safety &				
Median number of days with use of open-label rescue medication (60/45) (IQR)	2 (1–5)	2 (1 to 6)	0 (− 1 to 1)	0.79
Use of open-label rescue medication during first 20 days—no. (%)	60 (81.1)	45 (58.4)	− 22 (− 37.6 to − 6)	**0.003**
Benzodiazepines—no. (%)	23 (53.0)	23 (67.7)	18 (− 4 to 39)	0.11
Hydroxyzine—no. (%)	25 (54.4)	15 (44.1)	− 10 (− 32 to 12)	0.38
Haloperidol—no. (%)	41 (55.4)	33 (42.9)	− 13 (− 28 to 3)	0.13
Neuroleptics—no. (%)	46 (62.2)	34 (44.2)	− 18 (− 34 to − 2)	**0.03**
Adverse Events ‡				
Serious adverse event in ICU related to treatment—no. (%)	0 (0.0)	0 (0.0)	NE	NE
Serious adverse event in ICU non-related to treatment—no. (%)	27 (36.5)	26 (33.8)	− 3 (− 18 to 13)	0.73
Hypotension				
Number of patients with at least 1 episode—no. (%)	41 (55.4)	52 (67.5)	12 (− 3 to 28)	0.13
Number of patients requiring treatment—no./total no. (%)	25/74 (33.8)	34/77 (44.2)	10 (− 5 to 26)	0.20
Days with at least one event requiring treatment during study drug administration—no/total no. (%)	39/71 (54.9)	69/103 (67.0)	12 (− 3 to 27)	0.30
Bradycardia				
Number of patients with at least 1 episode—no. (%)	36 (48.7)	37 (48.1)	0 (− 17 to 15)	0.94
Number of patients requiring treatment—no./total no. (%)	2/74 (2.7)	3/77 (3.9)	1 (− 4 to 7)	0.69

- Improved primary outcome (agitation duration, delirium duration, intubation with deep sedation) and faster sedation control
- No difference in mortality or length of stay
- Reduced need for rescue medications
- No increase in adverse events

→ Effective and safe for delirium control

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Meaning Dexmedetomidine **improves agitation control** without improving major outcomes.

Dexmedetomidine for Hyperactive Delirium

Outcomes & Adverse Events

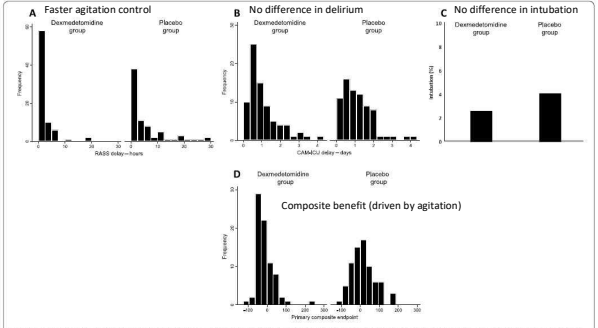

Fig. 2 Frequency Distribution of Primary Outcome and Items of the Primary Outcome. The bars represent the frequency distribution of z-scores of each item of primary outcome and of primary outcome. The higher the frequency at low values, the lower the delay to normalize RASS (in hours) and CAM-ICU (in days) (panel A and B, respectively), and the more favorable primary composite endpoint in each group (panel D). Panel C represents percentages of intubation during study (2 (2.6%) and 3 (4.1%), in dexmedetomidine and placebo groups, respectively). The primary endpoint was defined as a composite score of duration of agitation (in hours), defined by a RASS $\geq +1$, duration of delirium (in days), defined by the time to reach a negative score on the CAM-ICU), or the use of intubation with deep sedation and mechanical ventilation. As aforementioned, the primary endpoint was calculated as suggested by O'Brien: weighted summation of single endpoints with standard procedures leads to asymptotically normal statistics. Continuous (RASS delay and CAM-ICU delay) and dichotomous (intubation) variables were converted to z-scores by subtracting an individual's value from the overall mean and dividing by the standard-deviation of the pooled group. The z-scores were then aligned to the same direction so that worse outcomes have smaller scores. The z-scores were then averaged across endpoints for each patient. Treatment groups were compared with respect to this average z-score. The higher the value of the primary endpoint, the more unfavorable it was. CAM-ICU denotes confusion assessment method for the ICU, ICU intensive care unit and RASS Richmond agitation sedation scale

- Faster control of agitation and delirium (RASS, CAM-ICU)
- Lower need for intubation

→ Dexmedetomidine may be a respiratory-sparing option in hyperactive delirium

- Further validation is needed

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PADIS guideline 2025

PADIS guideline 2025

Why It Matters

Critically ill patients frequently experience pain, agitation, delirium, immobility, and sleep disruption — all of which directly impact clinical outcomes, ICU length of stay, and long-term recovery.

What's New in 2025

- Expands the 2018 SCCM PADIS guidelines with updated evidence
- Adds new domains including **anxiety**
- Developed by a multidisciplinary task force using the **GRADE approach**
- Grounded in systematic reviews and an evidence-to-decision framework

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SPECIAL ARTICLE

A Focused Update to the Clinical Practice Guidelines for the Prevention and Management of Pain, Anxiety, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU

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RATIONALE: Critically ill adults are at risk for a variety of distressing and consequential symptoms both during and after an ICU stay. Management of these symptoms can directly influence outcomes.

OBJECTIVES: The objective was to update and expand the Society of Critical Care Medicine's 2018 Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU.

PANEL DESIGN: The interprofessional inclusive guidelines task force was composed of 24 individuals including nurses, physicians, pharmacists, physiotherapists, psychologists, and ICU survivors. The task force developed evidence-based recommendations using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach. Conflict-of-interest policies were strictly followed in all phases of the guidelines, including task force selection and voting.

METHODS: The task force focused on five main content areas as they pertain to adult ICU patients: anxiety (new topic), agitation/sedation, delirium, immobility, and sleep disruption. Using the GRADE approach, we conducted a rigorous systematic review for each population, intervention, control, and outcome question to identify the best available evidence, statistically summarized the evidence, assessed the quality of evidence, and then performed the evidence-to-decision framework to formulate recommendations.

RESULTS: The task force issued five statements related to the management of anxiety, agitation/sedation, delirium, immobility, and sleep disruption in adults admitted to the ICU. In adult patients admitted to the ICU, the task force issued conditional recommendations to use dexmedetomidine over propofol for sedation, provide enhanced mobilization/rehabilitation over usual mobilization/rehabilitation, and administer melatonin. The task force was unable to issue recommendations on the administration of benzodiazepines to treat anxiety, and the use of antipsychotics to treat delirium.

CONCLUSIONS: The guidelines task force provided recommendations for pharmacologic management of agitation/sedation and sleep, and nonpharmacologic management of immobility in critically ill adults. These recommendations are intended for consideration along with the patient's clinical status.

KEYWORDS: anxiety; antipsychotics; delirium; dexmedetomidine; melatonin; mobility

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Five Key Clinical Questions

The 2025 ICU Management Guidelines address five priority clinical domains, reflecting the most clinically impactful gaps in practice and evidence for critically ill adults.

1. **Anxiety Management**
   Do benzodiazepines for anxiety, vs. no benzodiazepines, impact patient outcomes?

2. **Sedation Strategy**
   Should dexmedetomidine vs. propofol be used for sedation in mechanically ventilated adults?

3. **Delirium Treatment**
   Do antipsychotics for delirium vs. no antipsychotics impact patient outcomes?

4. **Mobilization**
   Does enhanced mobilization/rehabilitation vs. usual care impact outcomes?

5. **Sleep Quality**
   Does melatonin vs. placebo impact patient outcomes in ICU adults?

RECOMMENDATION 1

Benzodiazepines for Anxiety

Guideline Statement

There is **insufficient evidence** to make a recommendation on the use of benzodiazepines to treat anxiety in adult patients admitted to the ICU.

Clinical Implications

- Anxiety in the ICU is common yet underrecognized and poorly standardized in measurement
- The **Faces Anxiety Scale**, Visual Analogue Scale, and Numeric Rating Scale are viable tools for both intubated and non-intubated patients
- Both pharmacologic and **non-pharmacologic strategies** (music therapy, communication aids, family presence) require prospective evaluation
- Standardization of anxiety assessment across trials is an **urgent research priority**

RECOMMENDATION 2

Dexmedetomidine for Sedation

> We **suggest using dexmedetomidine over propofol** for sedation in mechanically ventilated adult ICU patients where light sedation and/or reduction in delirium are of highest priority. *(Conditional recommendation; for intervention; moderate certainty of evidence)*

Rationale

Dexmedetomidine facilitates lighter sedation planes, reduces delirium incidence, and preserves patient cooperation without respiratory depression.

Key Caution

Conditional recommendation reflects clinical context dependency — propofol may still be appropriate when deep sedation or rapid titration is required.

Change from 2018

Previously: dexmedetomidine or propofol both preferred over benzodiazepines.
Now: dexmedetomidine directly preferred over propofol in specific contexts.

RECOMMENDATION 3

Antipsychotics for Delirium

> We are **unable to issue a recommendation for or against** the use of antipsychotics over usual care for the treatment of delirium in adult ICU patients. *(Conditional recommendation; for intervention or comparison; low certainty of evidence)*

Why Neutral?

Low-certainty evidence from heterogeneous trials yields no consistent benefit signal for haloperidol or atypical antipsychotics on delirium duration, days alive without delirium, or mortality in the ICU.

Change from 2018

The 2018 guideline stated antipsychotics were **routinely not recommended**. The 2025 update reflects a more neutral stance driven by accumulating but inconclusive trial evidence, neither ruling them in nor out.

RECOMMENDATION 4

Enhanced Mobilization for ICU Immobility

> We **suggest providing enhanced mobilization/rehabilitation** over usual care to adult patients admitted to the ICU.
>
> *(Conditional recommendation; for intervention; moderate certainty of evidence)*

Evidence Base

Supported by **58 RCTs involving 8,038 patients** — the most evidence-rich recommendation in the 2025 guidelines, substantially strengthened from 2018.

Clinical Benefit

Enhanced mobilization reduces ICU-acquired weakness, shortens duration of delirium, and improves functional recovery and patient-reported outcomes post-discharge.

Implementation

Structured protocols with physiotherapy integration, even during early phases of critical illness, are feasible and associated with improved outcomes.

RECOMMENDATION 5

Melatonin for Patient Outcomes

> We **suggest administering melatonin** over no melatonin in adult patients admitted to the ICU.
>
> *(Conditional recommendation; for intervention; low certainty of evidence)*

Clinical Context

Sleep disruption is nearly universal in ICU patients, associated with delirium, prolonged ventilation, immune dysregulation, and impaired recovery. Melatonin addresses circadian rhythm disruption with a favorable safety profile.

Key Points

- Melatonin was only briefly mentioned in the 2018 guidelines — this is a **new dedicated recommendation**
- Low certainty of evidence reflects limited high-quality RCT data, but risk-benefit profile supports use
- Non-pharmacologic sleep hygiene measures should accompany pharmacologic interventions

2025 ICU Management Guidelines — Summary of Recommendations

Five clinical domains reviewed; key updates vs. the 2018 PADIS guidelines are highlighted below.

영역	권고	권고 강도/근거 수준	2018 대비 변화
1. Anxiety	Insufficient evidence — no recommendation on benzodiazepine use	✕ (No recommendation)	New domain; not previously addressed
2. Sedation	Dexmedetomidine preferred over propofol when light sedation or delirium reduction is priority	Conditional for intervention, moderate certainty	Previously: Dex or Prop over Benzo → Now: Dex over Prop directly
3. Delirium	Unable to recommend for or against antipsychotics over usual care	Conditional for/against	Previously "routinely not recommended" → Now neutral due to insufficient evidence
4. Immobility	Enhanced mobilization/rehab > usual care	Conditional for intervention, moderate certainty	Substantially strengthened (58 RCTs, 8,038 patients)
5. Sleep	Melatonin > no melatonin	Conditional for intervention, low certainty	New recommendation; only mentioned in 2018

KEY TAKEAWAYS

Take Home Message

Critical care is evolving — but not all innovation translates into survival benefit. Here is what the evidence tells us.

Promising Directions

Personalized and physiology-guided strategies are reshaping resuscitation and monitoring in the ICU.

- **Immune phenotyping** — tailoring immunomodulation to individual host response
- **CRT-guided resuscitation** — microcirculatory endpoints offer actionable targets
- **Terlipressin** – Reduced catecholamine requirement without survival benefit
- **ADAPT-sepsis** – PCT-guided therapy — reduced antibiotic use without harm
- **SOFA-2** — updated severity scoring with improved discriminatory power
- **Dexmedetomidine** – Improved agitation, no impact on major outcomes

Principle of Caution

Adoption of novel interventions must be **evidence-based**, prioritizing clinically meaningful endpoints — mortality, ventilator-free days, functional recovery — over physiologic surrogates alone.

Where Evidence Falls Short

Several technology-driven interventions failed to demonstrate benefit in large, well-powered RCTs.

- **Conservative oxygen strategy** — physiologic rationale did not translate to survival benefit
- **PAV+** — proportional assist ventilation showed no superiority over PSV
- **Closed-loop ventilation** — no improvement in patient-centered outcomes
- **Inhaled sedation** — Worse outcomes than propofol
- **Ketamine** — No survival benefit vs etomidate

Current Best Practice

Standard, well-established strategies remain the backbone of ICU care. **Protocolized care and evidence-based sedation** retain strong evidentiary support. New technologies should be applied **selectively and individually**, not universally adopted.

Thank You for Your Attention

Questions are welcome; I will do my best to answer, though I may need your guidance for more complex ones.

Evidence First

Prioritize RCT-level evidence and clinically meaningful outcomes before adopting novel ICU interventions at scale.

Individualize Care

Apply new technologies selectively — patient phenotype, physiology, and clinical context must guide implementation.

Stay Critical

Physiologic plausibility does not equal clinical benefit. Rigorous appraisal of trial design and endpoints remains essential.