PRESENTED BY PERRY J TIBERIO, MD, PHD

NOVEMBER 1, 2024

Critical Care Compass: Navigating the Year's Most Interesting Studies

AHN ANNUAL PCCM SYMPOSIUM 2024

AHN

No Disclosures

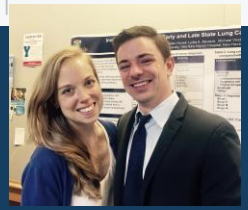
University of Pittsburgh

COLUMBIA | COLUMBIA UNIVERSITY DEPARTMENT OF MEDICINE
DIVISION OF GENERAL MEDICINE

PITT | SWANSON ENGINEERING
BIOENGINEERING

Yale SCHOOL OF MEDICINE | YaleNewHavenHealth

DOWNSTATE
HEALTH SCIENCES UNIVERSITY



AHN

Goal:
Briefly review 3-4 published studies that may influence the practice of critical care.

Outline

1. **Introduction:**
    - A selective list of publications from the last 12-18 months
    - Selected studies
2. **Study Review (4 studies)**
    - Clinical question
    - PICO
    - Patient Selection/Characteristics
    - Results
    - Limitations
    - Will this be practice changing
3. **Conclusion**
    - Summary Table
    - Notable mentions
4. **Discussion**

A List of Studies Published Over the Last 18 Months

Acetaminophen for Prevention and Treatment of Organ Dysfunction in Critically Ill Patients With Sepsis: The ASTER Randomized, Clinical Trial
Defining the Time-Limited Trial for Patients with Critical Illness: An Official American Thoracic Society Workshop Report - PMC
2024 Focused Update: Guidelines on Use of Corticosteroids in Sepsis, Acute Respiratory Distress Syndrome, and Community-Acquired Pneumonia
Ghrelin for Neuroprotection in Post–Cardiac Arrest Coma: A Randomized Clinical Trial | Neurology
Microaxial Flow Pump or Standard Care in Infarct-Related Cardiogenic Shock | New England Journal of Medicine
Noninvasive Ventilation for Preoxygenation during Emergency Intubation
Survival, Function, and Cognition After Hospitalization in Long-Term Acute Care Hospitals | Critical Care Medicine | JAMA Network Open
Stress Ulcer Prophylaxis during Invasive Mechanical Ventilation | New England Journal of Medicine
Electroencephalography-Guided Anesthesia and Delirium in Older Adults After Cardiac Surgery: The ENGAGES-Canada Randomized Clinical Trial | Neurology | JAMA
Landiolol and Organ Failure in Patients With Septic Shock: The STRESS-L Randomized Clinical Trial | Resuscitation | JAMA
Ceftriaxone to prevent early ventilator-associated pneumonia in patients with acute brain injury: a multicentre, randomised, double-blind, placebo-controlled, assessor-masked superiority trial - The Lancet Respiratory Medicine
Default Palliative Care Consultation for Seriously Ill Hospitalized Patients: A Pragmatic Cluster Randomized Trial
Small-Volume Blood Collection Tubes to Reduce Transfusions in Intensive Care: The STRATUS Randomized Clinical Trial | Pathology and Laboratory Medicine | JAMA
Efficacy of haloperidol to decrease the burden of delirium in adult critically ill patients: the EuRDICE randomized clinical trial
Sodium Bicarbonate for Metabolic Acidosis in the ICU: Results of a Pilot Randomized, Double-Blind Clinical Trial
Liberal or Restrictive Transfusion Strategy in Patients with Traumatic Brain Injury | New England Journal of Medicine
Video Laryngoscopy vs Direct Laryngoscopy for Endotracheal Intubation in the Operating Room: A Cluster Randomized Clinical Trial | Surgery | JAMA | JAMA Network
Video versus Direct Laryngoscopy for Tracheal Intubation of Critically Ill Adults | New England Journal of Medicine
Simvastatin in Critically Ill Patients with Covid-19 | New England Journal of Medicine
High-Dose Inhaled Nitric Oxide in Acute Hypoxemic Respiratory Failure Due to COVID-19: A Multicenter Phase II Trial
The impact of higher protein dosing on outcomes in critically ill patients with acute kidney injury: a post hoc analysis of the EFFORT protein trial | Critical Care
Antibiotics With or Without Rifaximin for Acute Hepatic Encephalopathy in Critically Ill Patients With Cirrhosis: A Double-Blind, Randomized Controlled (ABIE) Trial
Continuous positive airway pressure versus high-flow nasal cannula oxygen therapy for acute hypoxemic respiratory failure: A randomized controlled trial - Nagata - 2024 - Respirology - Wiley Online Library
Remimazolam besylate versus propofol for deep sedation in critically ill patients: a randomized pilot study
Extracorporeal Carbon Dioxide Removal to Avoid Invasive Ventilation During Exacerbations of Chronic Obstructive Pulmonary Disease: VENT-AVOID Trial—A Randomized Clinical Trial | American Journal of Respiratory and Critical Care Medicine
Racial Differences in Shared Decision-Making About Critical Illness
Alveolar Hemorrhage in Antineutrophil Cytoplasmic Antibody–Associated Vasculitis: Results of an International Randomized, Controlled Trial (PEXIVAS) | American Journal of Respiratory and Critical Care Medicine
Propafenone versus amiodarone for supraventricular arrhythmias in septic shock: a randomised controlled trial | Intensive Care Medicine
Hydrocortisone plus fludrocortisone for community-acquired pneumonia-related septic shock: a subgroup analysis of the APROCCHSS phase 3 randomised trial - The Lancet Respiratory Medicine
Thiamine administration in septic shock: a post hoc analysis of two randomized trials | Critical Care
Inhaled Amikacin to Prevent Ventilator-Associated Pneumonia | New England Journal of Medicine
Ambulatory Intensive Care for Medically Complex Patients at a Health Care Clinic for Individuals Experiencing Homelessness: The SUMMIT Randomized Clinical Trial | Health Policy | JAMA Network Open
Lower vs Higher Oxygenation Target and Days Alive Without Life Support in COVID-19: The HOT-COVID Randomized Clinical Trial
Tranexamic acid in upper gastrointestinal bleed in patients with cirrhosis: A randomized controlled trial.
A Randomized Trial of Intravenous Amino Acids for Kidney Protection
Phase-3 trial of recombinant human alkaline phosphatase for patients with sepsis-associated acute kidney injury (REVIVAL) | Intensive Care Medicine
Continuous vs Intermittent β-Lactam Antibiotic Infusions in Critically Ill Patients With Sepsis: The BLING III Randomized Clinical Trial
Efficacy and safety of a structured de-escalation from antipseudomonal β-lactams in bloodstream infections due to Enterobacterales (SIMPLIFY): an open-label, multicentre, randomised trial - The Lancet Infectious Diseases
Dapagliflozin for Critically Ill Patients With Acute Organ Dysfunction: The DEFINE-ED Randomized, Clinical Trial | Nephrology | JAMA
Effect of Noninvasive Airway Management of Comatose Patients With Acute Poisoning: A Randomized, Clinical Trial | Emergency Medicine | JAMA
Cefepime vs Piperacillin-Tazobactam in Adults Hospitalized With Acute Infection: The ACORN Randomized Clinical Trial | Critical Care Medicine | JAMA
Conservative versus Liberal Oxygenation Targets in Intensive Care Unit Patients (ICONIC): A Randomized Clinical Trial | American Journal of Respiratory and Critical Care Medicine
Propofol and survival: an updated meta-analysis of randomized clinical trials | Critical Care | Full Text
Individualised, short-course antibiotic treatment versus usual long-course treatment for ventilator-associated pneumonia (REGARD-VAP): a multicentre, individually randomised, open-label, non-inferiority trial - The Lancet Respiratory Medicine
Long-term outcomes with haloperidol versus placebo in acutely admitted adult ICU patients with delirium | Intensive Care Medicine
Convalescent Plasma for Covid-19–Induced ARDS in Mechanically Ventilated Patients | New England Journal of Medicine
Extracorporeal Life Support in Infarct-Related Cardiogenic Shock | New England Journal of Medicine
Individualised, perioperative open-lung ventilation strategy during one-lung ventilation (iPROVE-OLV): a multicentre, randomised, controlled clinical trial - The Lancet Respiratory Medicine
Early In-Bed Cycle Ergometry in Mechanically Ventilated Patients | NEJM Evidence
A Patient-Level Meta-Analysis of Intensive Glucose Control in Critically Ill Adults | NEJM Evidence
Ceftriaxone to prevent early ventilator-associated pneumonia in patients with acute brain injury: a multicentre, randomised, double-blind, placebo-controlled, assessor-masked superiority trial - The Lancet Respiratory Medicine
Andexanet for Factor Xa Inhibitor–Associated Acute Intracerebral Hemorrhage | New England Journal of Medicine
Effect of High-Intensity vs Low-Intensity Noninvasive Positive Pressure Ventilation on the Need for Endotracheal Intubation in Patients With an Acute Exacerbation of Chronic Obstructive Pulmonary Disease: The HAPPEN Randomized Clinical Trial

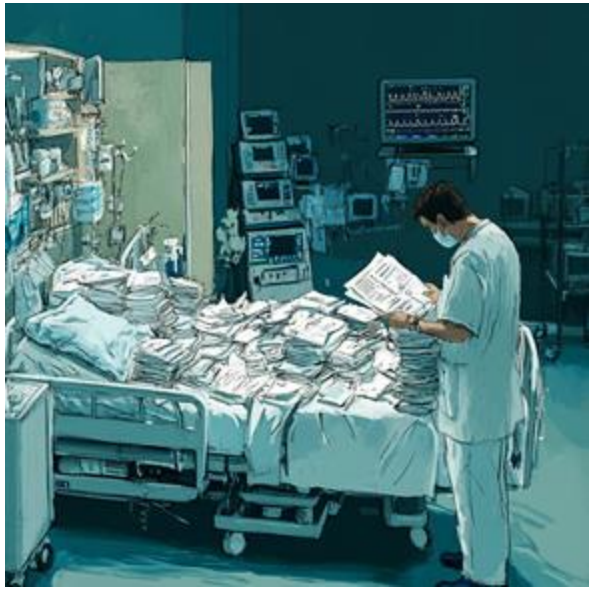


Image created using MidJourney

Selected Studies

1. Pre-oxygenation/Intubation:
    a. Noninvasive Ventilation for Preoxygenation during Emergency Intubation | New England Journal of Medicine

2. Steroids/Pneumonia:
    a. Hydrocortisone in Severe Community-Acquired Pneumonia

3. ID/Antibiotics:
    a. Cefepime vs Piperacillin-Tazobactam in Adults Hospitalized With Acute Infection: The ACORN Randomized Clinical Trial | Critical Care Medicine | JAMA

4. COPD/Respiratory failure/intubation:
    a. Effect of High-Intensity vs Low-Intensity Noninvasive Positive Pressure Ventilation on the Need for Endotracheal Intubation in Patients With an Acute Exacerbation of Chronic Obstructive Pulmonary Disease: The HAPPEN Randomized Clinical Trial

PRE-OXYGENATION/ INTUBATION

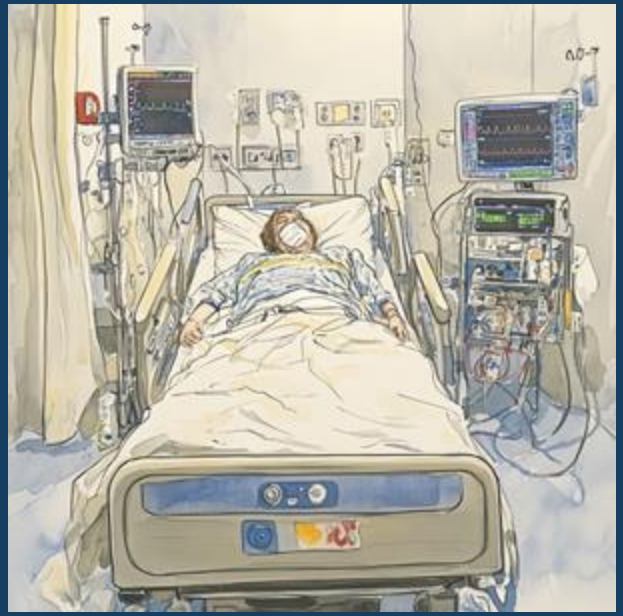


Image created using MidJourney

Does non-invasive ventilation (NIV), specifically bi-level positive pressure (BiPAP), used for pre-oxygenation reduce the incidence of hypoxemia during intubation among critically ill patients?

PREOXI

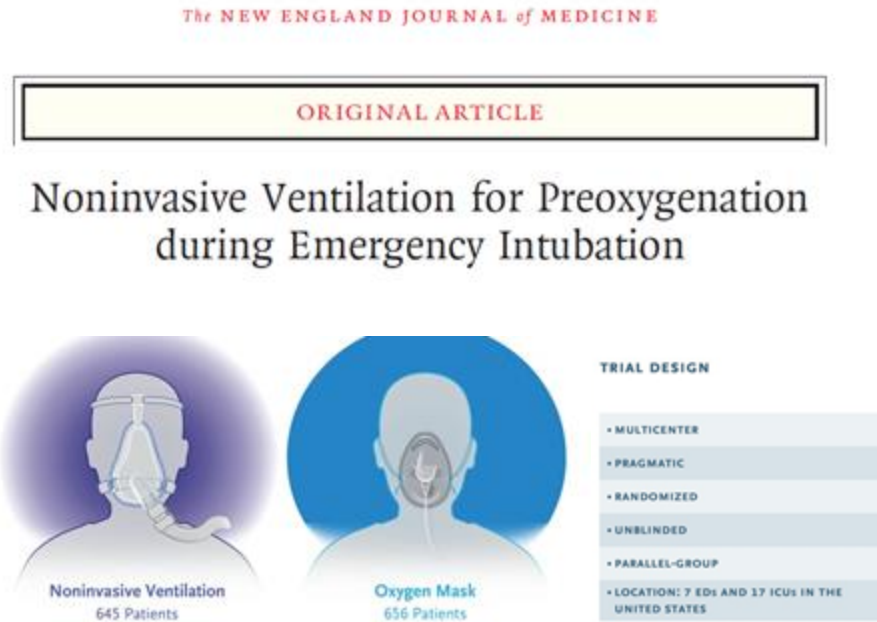
Noninvasive Ventilation for Preoxygenation during Emergency Intubation

Population: Critically ill adults undergoing emergency intubation in emergency departments and intensive care units

Intervention: Preoxygenation with noninvasive ventilation (NIV). This involved using a NIV mask with BIPAP settings of FiO2 100%, EPAP ≥5 cm H2O, IPAP ≥10 cm H2O, and respiratory rate ≥10 breaths per minute

Comparison: Preoxygenation with a standard oxygen mask at ≥15 liters per minute

Outcomes: The primary outcome was the incidence of hypoxemia (oxygen saturation <85%) during or within 2 minutes after intubation. Secondary outcomes included severe hypoxemia (<80%), cardiac arrest, and aspiration.



Gibbs KW, Semler MW, Driver BE, et al. Noninvasive Ventilation for Preoxygenation during Emergency Intubation. N Engl J Med. 2024;390(23):2165-2177.

PREOXI

Demographics and Characteristics

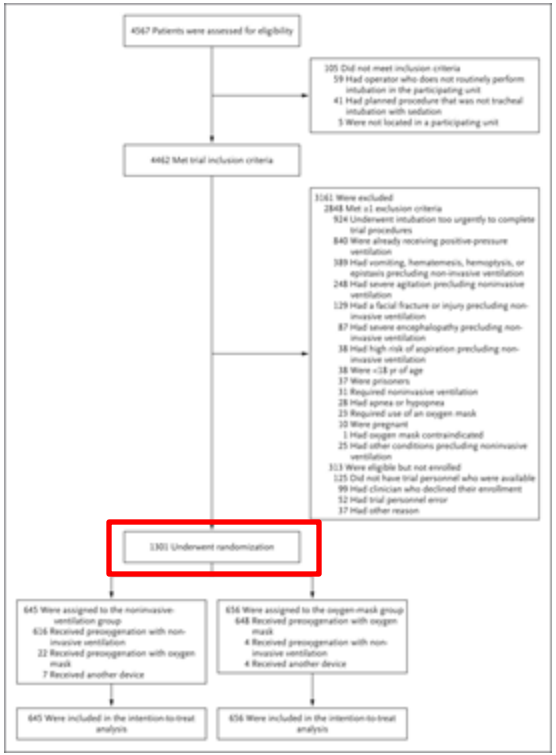


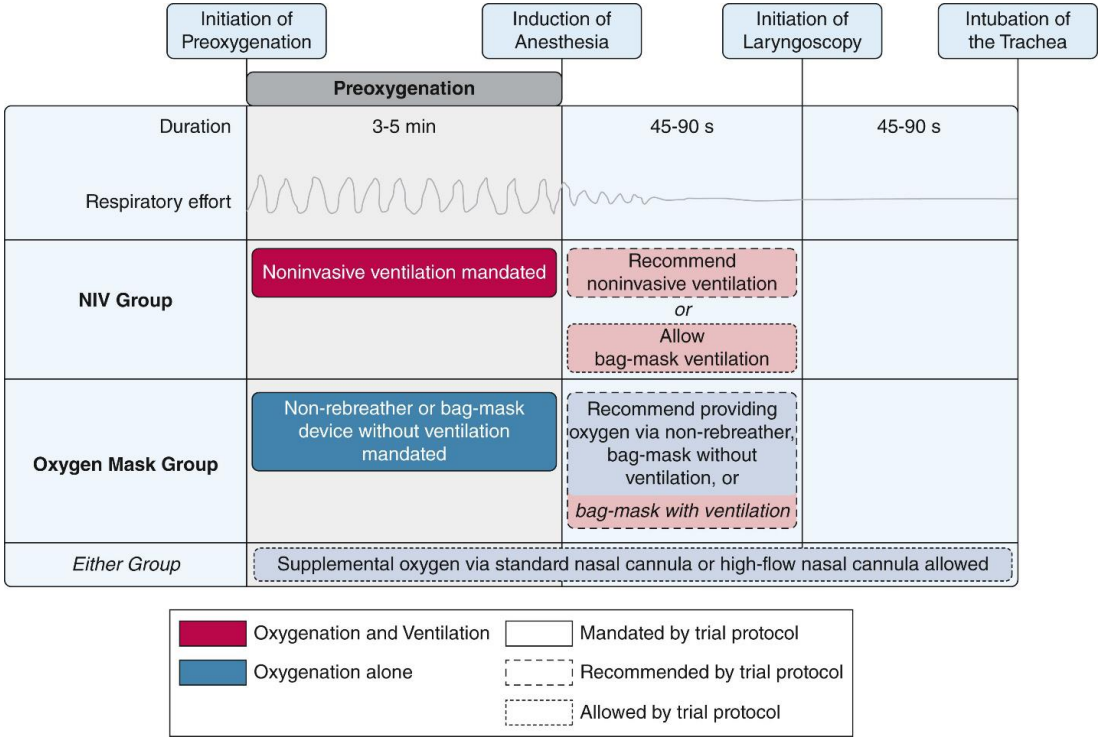
Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Noninvasive Ventilation (N=645)	Oxygen Mask (N=656)
Median age (IQR) — yr	61 (47–71)	61 (47–70)
Female sex — no. (%)	255 (39.5)	260 (39.6)
Race and ethnic group — no. (%)†		
Non-Hispanic White	384 (59.5)	399 (60.8)
Non-Hispanic Black	124 (19.2)	152 (23.2)
Hispanic	80 (12.4)	63 (9.6)
Other	48 (7.4)	36 (5.5)
Not reported	9 (1.4)	6 (0.9)
Median body-mass index (IQR)‡	27.6 (23.3–32.9)	26.6 (22.5–32.4)
Location of intubation — no. (%)		
ICU	476 (73.8)	476 (72.6)
Emergency department	169 (26.2)	180 (27.4)
Chronic conditions — no. (%)§		
Cirrhosis	124 (19.2)	104 (15.9)
Chronic obstructive pulmonary disease	98 (15.2)	81 (12.3)
Congestive heart failure	80 (12.4)	91 (13.9)
Obstructive sleep apnea	45 (7.0)	40 (6.1)
Acute conditions — no. (%)§		
Altered mental status	402 (62.3)	390 (59.5)
Sepsis or septic shock	301 (46.7)	312 (47.6)
Pneumonia	107 (16.6)	102 (15.5)
Gastrointestinal bleeding	107 (16.6)	102 (15.5)
Traumatic injury	40 (6.2)	36 (5.5)
Median APACHE II score (IQR)¶	17 (12–23)	17 (12–23)
Median Glasgow Coma Scale score (IQR)‖	12 (8–15)	12 (8–15)
Treatment or measurement within the hour before enrollment		
Receipt of vasopressors — no. (%)	178 (27.6)	178 (27.1)
Receipt of high-flow nasal cannula — no. (%)**	150 (23.3)	165 (25.2)
Median lowest oxygen saturation (IQR) — %††	95 (92–98)	95 (92–98)
Median highest Fio_2 (IQR)‡‡	0.33 (0.21–0.66)	0.36 (0.21–0.70)
Ratio of oxygen saturation to Fio_2§§		
Median (IQR)	271 (145–426)	268 (124–423)
≤315 — no. (%)	328 (58.9)	331 (59.7)

Gibbs KW, Semler MW, Driver BE, et al. Noninvasive Ventilation for Preoxygenation during Emergency Intubation. N Engl J Med. 2024;390(23):2165-2177.

PREOXI

Study Design



Gibbs KW, Semler MW, Driver BE, et al. Noninvasive Ventilation for Preoxygenation during Emergency Intubation. N Engl J Med. 2024;390(23):2165-2177.

PREOXI

Results: Primary Outcome

The NIV group experienced about half as much hypoxemia (SpO2 < 85%) as those in the oxygen mask group (9.1% vs 18.5%).

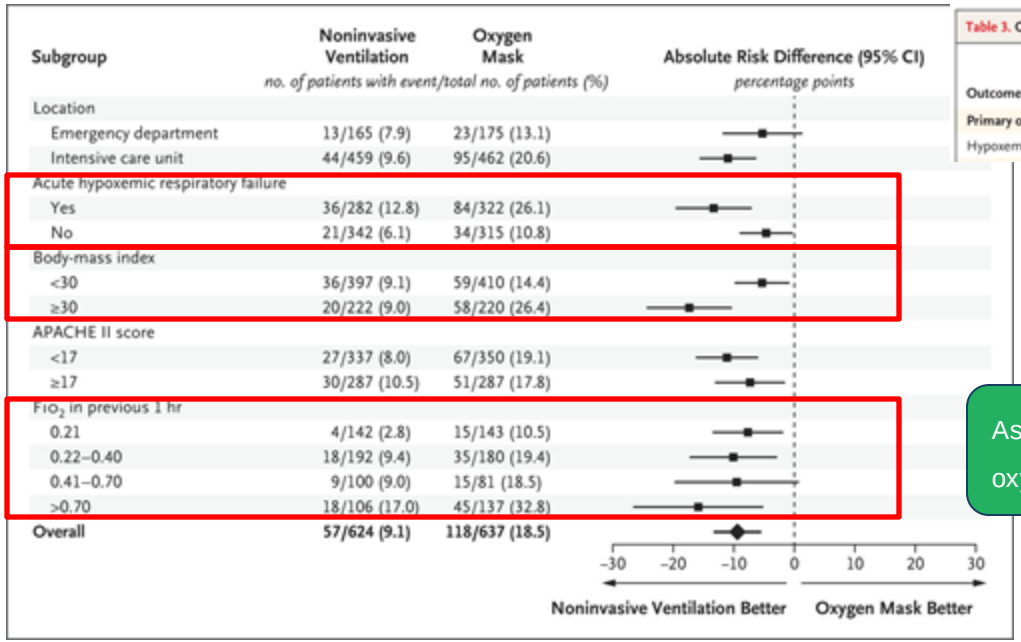


Table 3. Outcomes of Tracheal Intubation.

Outcome	Noninvasive Ventilation (N=645)	Oxygen Mask (N=656)	Difference (95% CI)*
Primary outcome			
Hypoxemia during intubation — no./total no. (%)†‡	57/624 (9.1)	118/637 (18.5)	−9.4 (−13.2 to −5.6)§

As shown to the left, obese patients and those with more severe oxygen needs had the greatest benefit from NIV.

Gibbs KW, Semler MW, Driver BE, et al. Noninvasive Ventilation for Preoxygenation during Emergency Intubation. N Engl J Med. 2024;390(23):2165-2177.

PREOXI

Results: Secondary Outcomes

Fewer patients in the NIV group compared to oxygen only group experienced lowest reported O2 saturations

- < 80% (6.2% vs 13.2%)
- <70% (2.4% vs 5.7%).

There was one peri-intubation cardiac arrest in the NIV group and 7 cardiac arrests in the oxygen only group.

No increase in aspiration events for patients in the NIV compared to the O2 group (0.9% vs 1.4%).

Table 3. Outcomes of Tracheal Intubation.

Outcome	Noninvasive Ventilation (N=645)	Oxygen Mask (N=656)	Difference (95% CI)*
Primary outcome			
Hypoxemia during intubation — no./total no. (%)†‡	57/624 (9.1)	118/637 (18.5)	−9.4 (−13.2 to −5.6)§
Secondary outcome			
Median lowest oxygen saturation (IQR) — %‡	99 (95 to 100)	97 (89 to 100)	2 (1 to 3)
Exploratory procedural outcomes			
Lowest oxygen saturation <80% — no./total no. (%)‡	39/624 (6.2)	84/637 (13.2)	−6.9 (−10.2 to −3.7)
Lowest oxygen saturation <70% — no./total no. (%)‡	15/624 (2.4)	36/637 (5.7)	−3.2 (−5.4 to −1.1)
Cardiovascular collapse — no./total no. (%)¶	113/645 (17.5)	127/656 (19.4)	−1.8 (−6.1 to 2.4)
Systolic blood pressure <65 mm Hg — no./total no. (%)	18/621 (2.9)	28/633 (4.4)	−1.5 (−3.6 to 0.6)
New or increased use of vasopressors — no./total no. (%)	111/645 (17.2)	117/656 (17.8)	−0.6 (−4.8 to 3.5)
Cardiac arrest — no./total no. (%)‖	1/645 (0.2)	7/656 (1.1)	−0.9 (−1.8 to −0.1)
Successful intubation on the first attempt — no./total no. (%)	534/645 (82.8)	535/656 (81.6)	1.2 (−2.9 to 5.4)
Median time from induction to intubation (IQR) — seconds	115 (89 to 150)	113 (85 to 152)	2 (−5 to 9)
Exploratory safety outcomes			
Operator-reported aspiration — no./total no. (%)**	6/645 (0.9)	9/656 (1.4)	−0.4 (−1.6 to 0.7)
New infiltrate on chest imaging — no./total no. (%)††	144/509 (28.3)	148/497 (29.8)	−1.5 (−7.1 to 4.1)
New pneumothorax — no./total no. (%)‡‡	7/509 (1.4)	7/497 (1.4)	0.0 (−1.5 to 1.4)
Median oxygen saturation at 24 hr (IQR)§§	97 (95 to 100)	97 (95 to 100)	0 (−1 to 1)
Median F_{IO_2} at 24 hr (IQR)¶¶	0.40 (0.30 to 0.40)	0.40 (0.30 to 0.40)	0.01 (−0.05 to 0.05)
Exploratory clinical outcomes‖‖			
Median ventilator-free days (IQR)	21 (0 to 26)	17 (0 to 25)	4 (−1 to 9)
Median ICU-free days (IQR)	16 (0 to 23)	14 (0 to 23)	2 (−1 to 8)
In-hospital death — no./total no. (%)	209/645 (32.4)	217/656 (33.1)	−0.7 (−5.8 to 4.4)

Gibbs KW, Semler MW, Driver BE, et al. Noninvasive Ventilation for Preoxygenation during Emergency Intubation. N Engl J Med. 2024;390(23):2165-2177.

PREOXI

Limitations

Generalizability:

- Excluded patients who needed emergent intubation (20% of patients)

Specific indication for intubation was not disclosed in the study.

Bias:

- Unblinded pragmatic study

While there was no increase risk of aspiration, those at highest risk (e.g., those who were vomiting, at risk of vomiting, etc.) were excluded from the study.

Unclear if PEEP valves were used with BVM for the O2 only group.

It is unclear how much oxygen flow the O2 only group received, as it was not recorded.

Does not inform use of heated high-flow nasal cannula for pre-oxygenation strategy.

Gibbs KW, Semler MW, Driver BE, et al. Noninvasive Ventilation for Preoxygenation during Emergency Intubation. N Engl J Med. 2024;390(23):2165-2177.

Author's Conclusions:

Among critically ill adults undergoing tracheal intubation, preoxygenation with noninvasive ventilation resulted in a lower incidence of hypoxemia during intubation than preoxygenation with an oxygen mask.

Are you more likely to use BiPAP to pre-oxygenate prior to intubation now?

STEROIDS/ PNEUMONIA

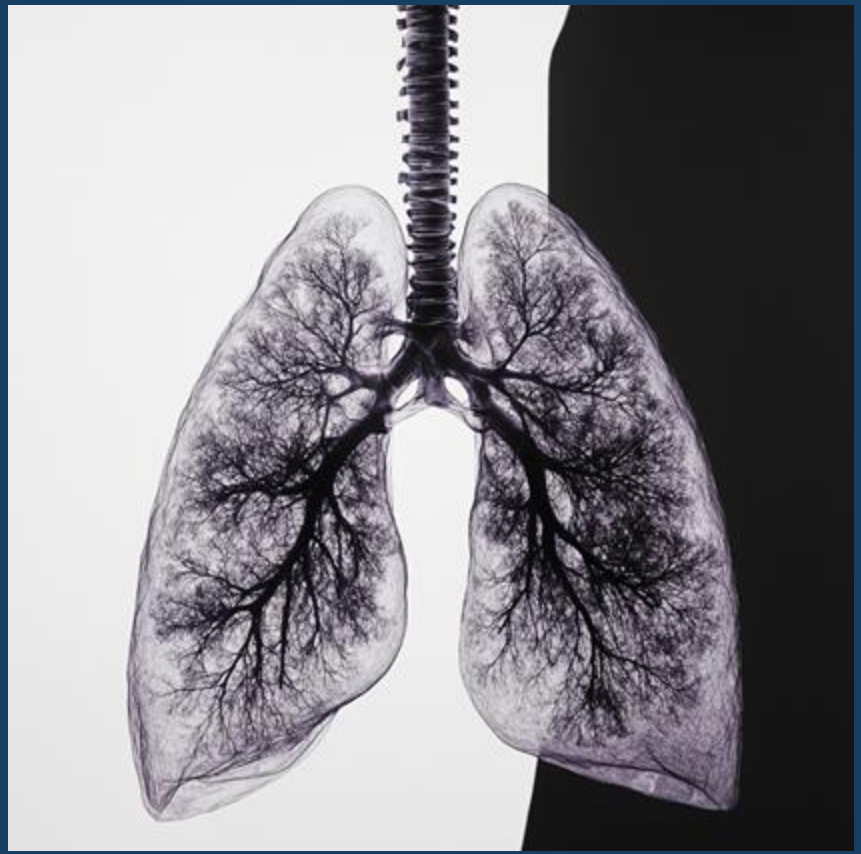


Image created using MidJourney

In patients with severe community-acquired pneumonia requiring ICU level care, does hydrocortisone lower risk of death by day 28?

CAPE COD

Hydrocortisone in Severe Community-Acquired Pneumonia

Population: ICU patients with severe community-acquired pneumonia admitted within the previous 48 hours*

Intervention: IV hydrocortisone starting at 200mg daily

Comparison: Placebo

Outcomes: Primary outcome death from any cause at day 28

Secondary: Death at 90 days, length of ICU/hospital stay, incidence of intubation, incidence of vasopressor use, cumulative incidence of hospital-acquired infections, cumulative incidence of GI bleeding

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 25, 2023 VOL. 388 NO. 21

Hydrocortisone in Severe Community-Acquired Pneumonia

P.-F. Dequin, F. Meziani, J.-P. Quenot, T. Kamel, J.-D. Ricard, J. Badie, J. Reignier, N. Heming, G. Plantefève, B. Souweine, G. Voiriot, G. Colin, J.-P. Frat, J.-P. Mira, N. Barbarot, B. François, G. Louis, S. Gibot, C. Guitton, C. Giacardi, S. Hraiech, S. Vimeux, E. L'Her, H. Faure, J.-E. Herbrecht, C. Bouisse, A. Joret, N. Terzi, A. Gacouin, C. Quentin, M. Jourdain, M. Leclerc, C. Coffre, H. Bourgoin, C. Lengellé, C. Caille-Fénérol, B. Giraudeau, and A. Le Gouge, for the CRICS-TriGGERSep Network*

Double-blind
Multicenter
Randomized
Location: 31 ICUs in France

*Severity defined by at least one of the following :
1. Pneumonia Severity Index (PSI) > 130
2. Patient placed on mechanical ventilation (invasive or not) for acute respiratory failure, with a PEEP level of 5 cm of water or more
3. Patient treated by high-flow oxygen therapy with a FiO2 of 50% or more and a PaO2/FiO2 (P/F) ratio lower than 200

Dequin PF, Meziani F, Quenot JP, et al. Hydrocortisone in Severe Community-Acquired Pneumonia. N Engl J Med. 2023;388(21):1931-1941.

CAPE COD

Demographics and Characteristics

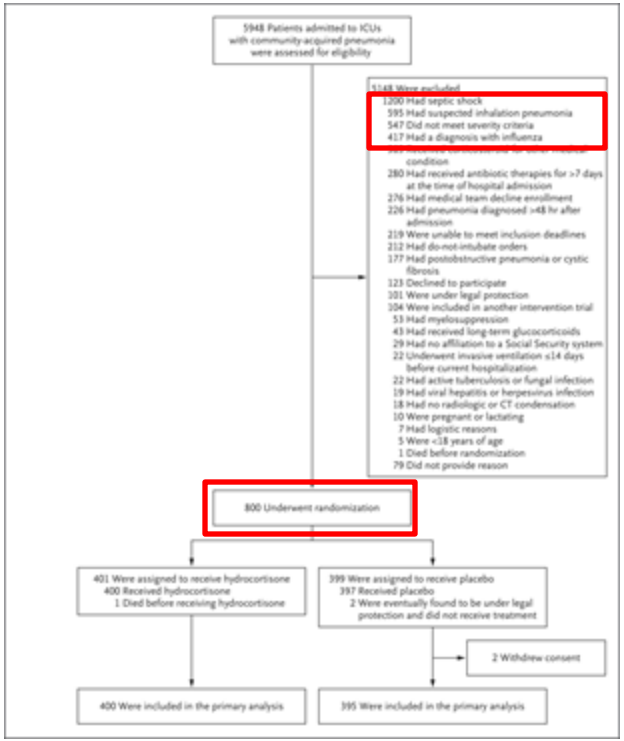


Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Hydrocortisone (N=400)	Placebo (N=395)
Median age (IQR) — yr	67 (58–77)	67 (58–78)
Sex — no. (%)		
Male	281 (70.2)	271 (68.6)
Female	119 (29.8)	124 (31.4)
Coexisting condition — no. (%)		
COPD	86 (21.5)	105 (26.6)
Asthma	22 (5.5)	17 (4.3)
Diabetes	95 (23.8)	86 (21.8)
Immunosuppression	24 (6.0)	27 (6.8)
Type of respiratory support — no. (%)		
Mechanical ventilation	178 (44.5)	175 (44.3)
Invasive	92 (23.0)	85 (21.5)
Noninvasive	86 (21.5)	90 (22.8)
High-flow nasal cannula	169 (42.2)	162 (41.0)
Nonrebreathing mask	53 (13.2)	58 (14.7)
Median Pulmonary Severity Index (IQR)†	127 (102–153)	130 (103–150)
Distribution — no./total no. (%)		
Class I	5/396 (1.3)	4/392 (1.0)
Class II	15/396 (3.8)	15/392 (3.8)
Class III	45/396 (11.4)	47/392 (12.0)
Class IV	150/396 (37.9)	133/392 (33.9)
Class V	181/396 (45.7)	193/392 (49.2)
Median SAPS II score (IQR)‡	37 (30–45)	38 (31–47)
Median SOFA score (IQR)§	4 (3–6)	4 (3–6)
Treatment with vasopressors — no. (%)	41 (10.2)	51 (12.9)
Laboratory data		
C-reactive protein		
Median (IQR) — mg/dl	26.3 (11.7–35.6)	23.8 (11.7–35.0)
Value of >15 mg/dl — no./total no. (%)	208/298 (69.8)	215/312 (68.9)
Median procalcitonin (IQR) — ng/ml	3.2 (0.5–16.4)	4.1 (0.6–16.0)
Median cortisol (IQR) — nmol/liter	302 (24–785)	307 (25–697)
Timing of treatment		
Median interval from hospital admission to ICU admission (IQR) — hr	5.5 (2.8–10.9)	5.2 (2.4–10.9)
Median interval from ICU admission to initiation of trial agent (IQR) — hr	15.3 (7.0–20.5)	14.6 (5.9–20.5)

Dequin PF, Meziani F, Quenot JP, et al. Hydrocortisone in Severe Community-Acquired Pneumonia. N Engl J Med. 2023;388(21):1931-1941.

CAPE COD

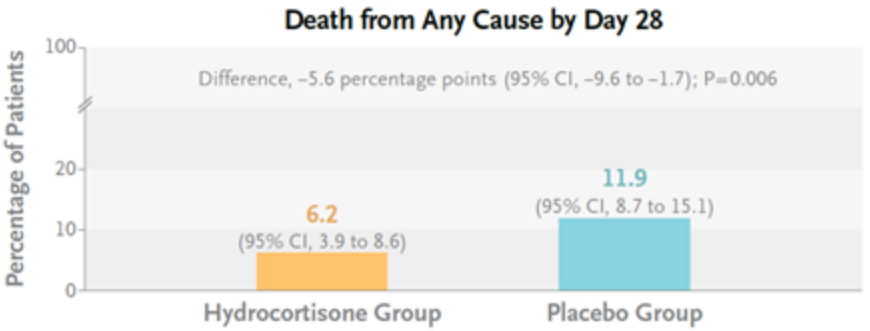
Results: Primary and Secondary Outcomes

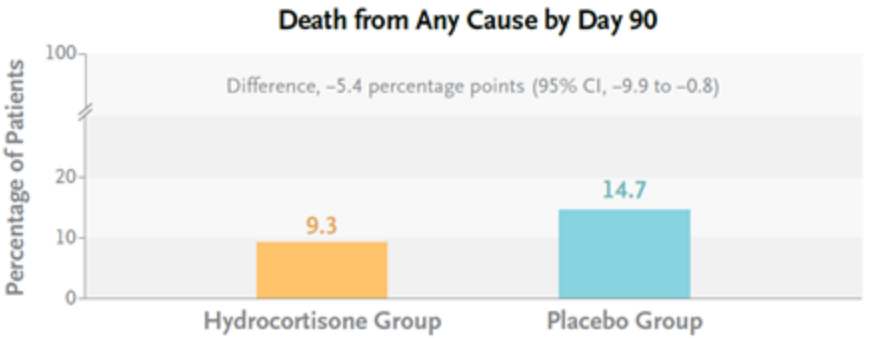
Primary outcome:

- The hydrocortisone group showed significantly lower mortality rate at 28 days
- Hydrocortisone group: 6.2%
- Placebo group: 11.9%
- Absolute difference: -5.6% (95% CI, -9.6 to -1.7; P = 0.006)

Secondary outcome:

- The hydrocortisone group showed significantly lower mortality rate at 90 days
- Hydrocortisone: 9.3%
- Placebo: 14.7%
- Absolute difference: -5.4% (95% CI, -9.9 to -0.8) – not adjusted for multiplicity





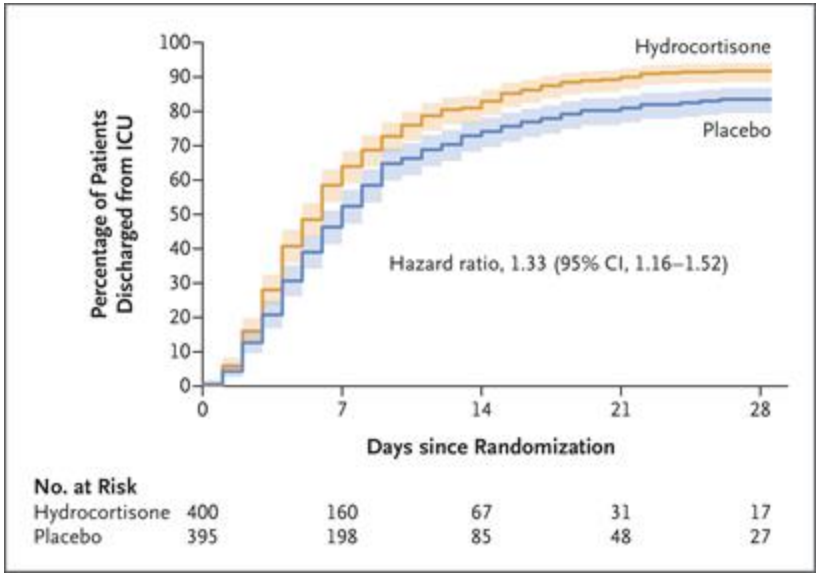
Dequin PF, Meziani F, Quenot JP, et al. Hydrocortisone in Severe Community-Acquired Pneumonia. N Engl J Med. 2023;388(21):1931-1941.

CAPE COD

Secondary Outcomes

Secondary outcome: ICU discharge by day 28

- Hydrocortisone group were more likely to be discharged from the ICU by day 28 compared to placebo.



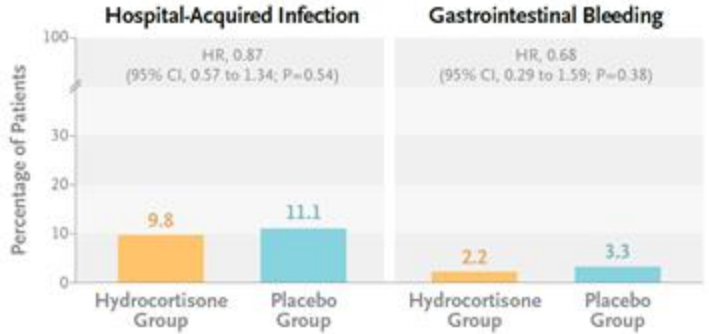
No adjustment for multiplicity and therefore these results are more exploratory

Dequin PF, Meziani F, Quenot JP, et al. Hydrocortisone in Severe Community-Acquired Pneumonia. N Engl J Med. 2023;388(21):1931-1941.

CAPE COD

Results: Safety Outcomes

GI Bleeding and hospital-acquired infections were comparable between the two groups.



The hydrocortisone group required high median daily dose of insulin in patients receiving insulin therapy.

Safety outcomes‡				
Cumulative incidence of hospital-acquired infection by day 28 — no./total no. (%)§	39/400 (9.8)	44/395 (11.1)	HR, 0.87 (0.57 to 1.34)	0.54
Ventilator-associated pneumonia	32/152 (21.0)	38/171 (22.2)		
Bloodstream infection	5/400 (1.2)	9/395 (2.3)		
Cumulative incidence of gastrointestinal bleeding by day 28	9/400 (2.2)	13/395 (3.3)	HR, 0.68 (0.29 to 1.59)	0.38
Median daily dose of insulin by day 7 in patients receiving insulin therapy (IQR) — IU/day¶	35.5 (15.0 to 57.5)	20.5 (9.4 to 48.5)	Median difference, 8.7 (4.0 to 13.8)	<0.001
Median weight change from baseline to day 7 (IQR) — kg‖	2.0 (−0.5 to 5.0)	1.0 (−3.0 to 6.0)	Median difference, 1.0 (0 to 2.0)	0.18

Dequin PF, Meziani F, Quenot JP, et al. Hydrocortisone in Severe Community-Acquired Pneumonia. N Engl J Med. 2023;388(21):1931-1941.

CAPE COD

Limitations

Generalizability:

- Conducted in France (31 hospitals)
- Small number of immunocompromised patients enrolled

Early termination: trial stopped early after enrolling 800 of the planned 1200 patients

Less than 15% of screened patients were enrolled

Excluded patients who were on vasopressors for septic shock at time of enrollment.

Secondary endpoints did not adjust for multiplicity.

Mortality in the study (11.9%) was less than anticipated (27%), indicating a possible lower severity of illness.

Did not evaluate other downstream effects of hyperglycemia such as neuropsychological and neuromuscular side effects.

Recent study which did not show mortality benefit, although this could be due to study being predominantly men (97%), different steroids (methylpred) and timing (up to 96 hours after admission). (Meduri 2022).

Dequin PF, Meziani F, Quenot JP, et al. Hydrocortisone in Severe Community-Acquired Pneumonia. N Engl J Med. 2023;388(21):1931-1941.

Author's Conclusions:

Among patients with severe community-acquired pneumonia being treated in the ICU, those who received hydrocortisone had a lower risk of death by day 28 than those who received placebo.

Have you already modified your practice to include IV steroids in patients with severe CAP?

INFECTIOUS DISEASE/ ANTIBIOTICS

Image from https://blogs.jwatch.org/hiv-id-observations/index.php/a-brilliant-strategy-for-conducting-clinical-trials-the-acorn-study/2023/10/17/

Does choosing between cefepime and piperacillin-tazobactam affect the risk of acute kidney injury or neurological dysfunction?

ACORN

Cefepime vs Piperacillin-Tazobactam in Adults Hospitalized with Acute Infection

Population: Hospitalized patients with suspected or confirmed gram-negative bacterial infections

Intervention: Cefepime

Comparison: Piperacillin-tazobactam (extended infusion)

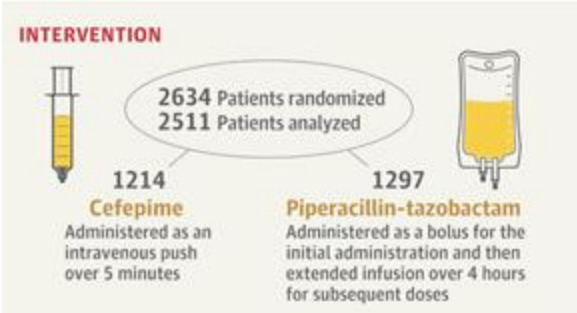
Outcomes:

- Primary: Highest stage of AKI or death by day 14 on a 5-level ordinal scale ranging from no AKI to death
- Secondary:
  - Incidence of major adverse kidney events at day 14
  - Number of days alive and free of delirium and coma within 14 days

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Cefepime vs Piperacillin-Tazobactam in Adults Hospitalized With Acute Infection

The ACORN Randomized Clinical Trial



Pragmatic
Parallel-group
Open-label
Randomized
Location: ER or ICU at Vanderbilt

Qian ET, Casey JD, Wright A, et al. The ACORN Randomized Clinical Trial. JAMA. 2023;330(16):1557-1567.

ACORN

Demographics and Characteristics

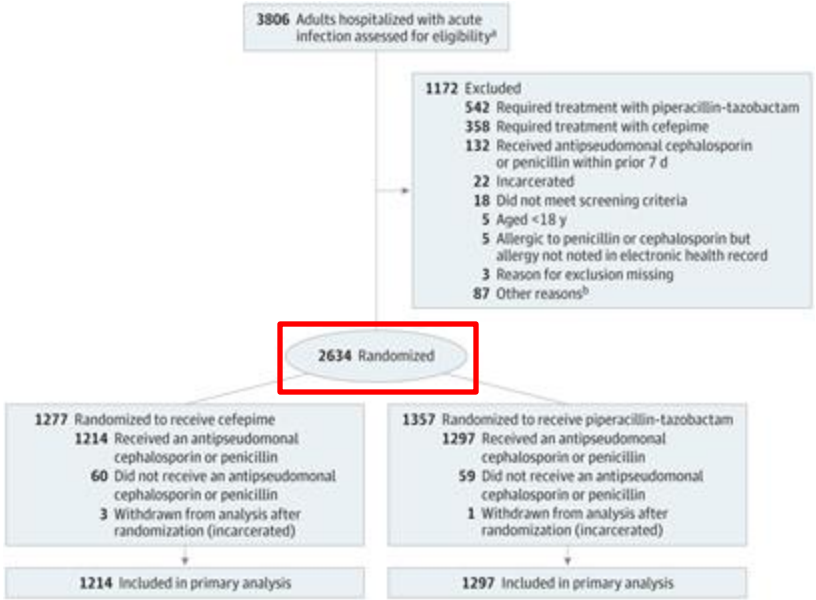


Table 1. Patient Characteristics at Baseline

Patient characteristics[a]	Cefepime (n = 1214)	Piperacillin-tazobactam (n = 1297)
Age, median (IQR), y	57 (42 to 68)	59 (44 to 69) [n = 1296]
Sex, No. (%)		
Female	523 (43.1)	548/1296 (42.3)
Male	691 (56.9)	748/1296 (57.7)
Race and ethnicity, No./total (%)		
Hispanic	59/1186 (5.0)	73/1264 (5.8)
Non-Hispanic Black	190/1186 (16.0)	209/1264 (16.5)
Non-Hispanic White	913/1186 (77.0)	950/1264 (75.2)
Other race[b]	24/1186 (2.0)	32/1264 (2.5)
Hours from hospital presentation to enrollment, median (IQR)	1.3 (0.5 to 3.7)	1.1 (0.4 to 3.2)
Location at enrollment, No. (%)		
Emergency department	1135 (93.5)	1243 (95.8)
Intensive care unit	79 (6.5)	54 (4.2)
Sepsis, No. (%)[c]	658 (54.2)	704 (54.3)
Suspected source of infection at enrollment, No. (%)[d]		
Intra-abdominal	319 (26.3)	293 (22.6)
Lung	257 (21.2)	300 (23.1)
Skin and soft tissue	201 (16.6)	245 (18.9)
Genitourinary	100 (8.2)	144 (11.1)
Other	104 (8.6)	97 (7.5)
Unknown	233 (19.2)	218 (16.8)
Sequential Organ Failure Assessment score, median (IQR)[e]	2 (0 to 5)	2 (0 to 4)
Type of treatment, No. (%)		
Mechanical ventilation	110 (9.1)	95 (7.3)
Vancomycin on day of enrollment	942 (77.6)	997 (76.9)
Charlson Comorbidity Index, median (IQR)[f]	4 (2 to 7) [n = 1191]	4 (2 to 6) [n = 1276]
Chronic kidney disease, No./total (%)[g]	243/1191 (20.4)	259/1276 (20.3)
Assessment at enrollment, No. (%)[h]		
No acute kidney injury	623 (51.3)	652 (50.3)
Stage 1 acute kidney injury	231 (19.0)	311 (24.0)
Stage 2 acute kidney injury	134 (11.0)	123 (9.5)
Stage 3 acute kidney injury	148 (12.2)	144 (11.1)
Prior receipt of kidney replacement therapy (ineligible for acute kidney injury)	78 (6.4)	67 (5.2)
Creatinine level, median (IQR), mg/dL[i]		
Lowest in prior 12 mo (between 365 d and 12 h before enrollment)	0.7 (0.6 to 0.8) [n = 1136]	0.8 (0.6 to 0.9) [n = 1229]
At enrollment	1.0 (0.8 to 1.6) [n = 1136]	1.0 (0.8 to 1.5) [n = 1229]
Richmond Agitation-Sedation Scale score, median (IQR)[j]	0 (−1 to 0) [n = 1158]	0 [n = 1211]
Coma, No. (%)[j]	84 (6.9)	77 (5.9)
Delirium, No. (%)[k]	62 (5.1)	51 (3.9)

Qian ET, Casey JD, Wright A, et al. The ACORN Randomized Clinical Trial. JAMA. 2023;330(16):1557-1567.

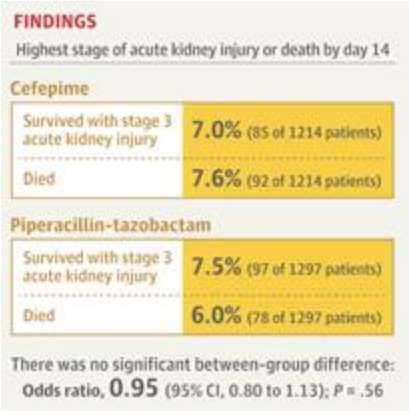
ACORN

Results – Primary Outcome

Primary outcome:

- No significant difference in the highest stage of AKI or death by day 14
- OR 0.95 [95% CI, 0.80-1.13, *P* = 0.56]

	Cefepime (n = 1214)	Piperacillin-tazobactam (n = 1297)
Primary outcome		
Acute kidney injury or death by day 14, No. (%)		
No stage (survived)	910 (75.0)	952 (73.4)
Stage 1 (survived)	86 (7.1)	100 (7.7)
Stage 2 (survived)	41 (3.4)	70 (5.4)
Stage 3 (survived)	85 (7.0)	97 (7.5)
Stage 4 (died)	92 (7.6)	78 (6.0)



Qian ET, Casey JD, Wright A, et al. The ACORN Randomized Clinical Trial. JAMA. 2023;330(16):1557-1567.

ACORN

Secondary outcomes

No significant difference in major adverse kidney events at day 14

- 10.2% in the cefepime group
- 8.8% in the pip-tazo group
- Risk difference 1.4 (-1.0 to 3.8)

Patients in the cefepime group experienced **fewer days alive and free of delirium and coma**

- mean 11.9 days in cefepime group
- mean 12.2 days in the pip-tazo group
- OR 0.79, 95% CI 0.65-0.95

	Cefepime (n = 1214)	Piperacillin-tazobactam (n = 1297)	Between-group difference expressed as RD or OR (95% CI)[a]
Secondary outcomes			
Major adverse kidney events at day 14, No. (%)[b]	124 (10.2)	114 (8.8)	RD, 1.4 (−1.0 to 3.8)
Death, No. (%)	92 (7.6)	78 (6.0)	RD, 1.6 (−0.5 to 3.6)
New kidney replacement therapy, No./total (%)	37/1136 (3.3)	28/1230 (2.3)	RD, 1.0 (−0.4 to 2.4)
Final creatinine level ≥2 times the baseline level, No./total (%)	15/1136 (1.3)	29/1230 (2.4)	RD, −1.0 (−2.2 to 0.1)
Delirium- and coma-free days within 14 d[c]			
Median (IQR)	14 (14 to 14)	14 (14 to 14)	OR, 0.79 (0.65 to 0.95)
Mean (SD)	11.9 (4.6)	12.2 (4.3)	
Delirium, No. (%)[d]	200 (16.5)	181 (14.0)	RD, 2.5 (−0.4 to 5.4)
Coma, No. (%)[d]	164 (13.5)	162 (12.5)	RD, 1.0 (−1.7 to 3.7)
Delirium or coma, No. (%)[d]	252 (20.8)	225 (17.3)	RD, 3.4 (0.3 to 6.6)
Exploratory outcomes			
Major adverse kidney events at day 28, No. (%)[b]	135 (11.1)	132 (10.2)	RD, 0.9 (−1.6 to 3.4)
Death, No. (%)	104 (8.6)	106 (8.2)	RD, 0.4 (−1.9 to 2.6)
New kidney replacement therapy, No./total (%)	44/1136 (3.9)	28/1230 (2.3)	RD, 1.6 (0.1 to 3.1)
Final creatinine level ≥2 times the baseline level, No./total (%)	14/1136 (1.2)	26/1230 (2.1)	RD, −0.9 (−2.0 to 0.2)
Delirium- and coma-free days within 28 d[c]			
Median (IQR)	28 (28 to 28)	28 (28 to 28)	OR, 0.80 (0.66 to 0.97)
Mean (SD)	24.4 (8.6)	24.8 (8.2)	
Kidney replacement therapy–free days within 28 d[c]			
Median (IQR)	28 (28 to 28)	28 (28 to 28)	OR, 0.78 (0.62 to 0.98)
Mean (SD)	24.4 (9.1)	25.0 (8.5)	
Vasopressor-free days within 28 d[c]			
Median (IQR)	28 (28 to 28)	28 (28 to 28)	OR, 0.96 (0.80 to 1.16)
Mean (SD)	24.8 (8.3)	25.1 (7.9)	
Ventilator-free days within 28 d[c]			
Median (IQR)	28 (28 to 28)	28 (28 to 28)	OR, 0.84 (0.68 to 1.03)
Mean (SD)	24.8 (8.4)	25.0 (8.2)	
Intensive care unit–free days within 28 d[c]			
Median (IQR)	28 (25 to 28)	28 (26 to 28)	OR, 0.92 (0.77 to 1.09)
Mean (SD)	23.9 (8.6)	24.2 (8.4)	
Hospital-free days within 28 d[c]			
Median (IQR)	22 (15 to 24)	22 (15 to 24)	OR, 0.99 (0.86 to 1.13)
Mean (SD)	18.1 (8.6)	18.3 (8.5)	
Allergic reaction to study antibiotic, No. (%)[e]	16 (1.3)	15 (1.2)	RD, 0.2 (−0.8 to 1.1)

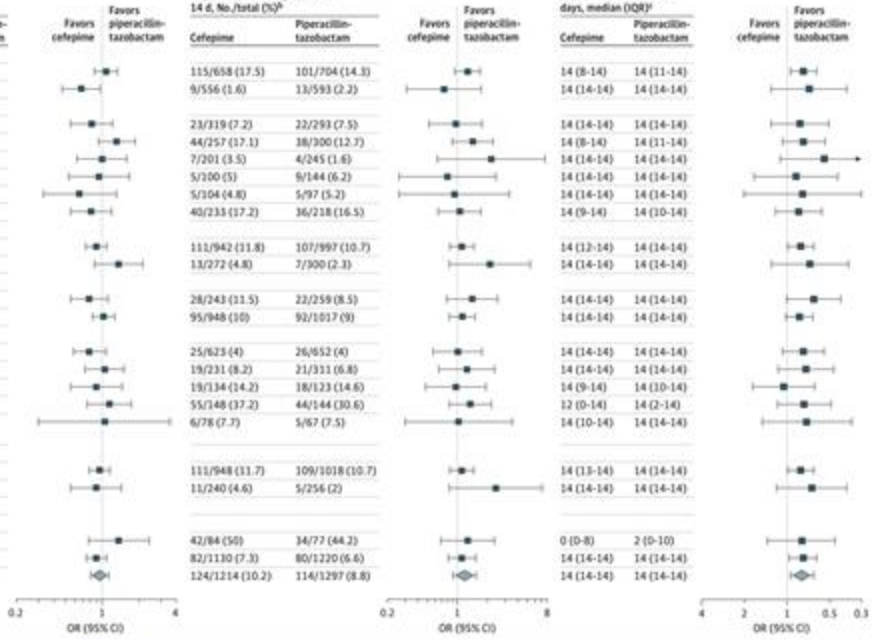
Qian ET, Casey JD, Wright A, et al. The ACORN Randomized Clinical Trial. JAMA. 2023;330(16):1557-1567.

ACORN

Results

Figure 3. Effect Modification of the Primary and Secondary Outcomes

Subgroup	No. of patients	Acute kidney injury ordinal scale, median (IQR)[a] Cefepime	Acute kidney injury ordinal scale, median (IQR)[a] Piperacillin-tazobactam	Major adverse kidney events at 14 d, No./total (%)[b] Cefepime	Major adverse kidney events at 14 d, No./total (%)[b] Piperacillin-tazobactam	Delirium- and coma-free days, median (IQR)[c] Cefepime	Delirium- and coma-free days, median (IQR)[c] Piperacillin-tazobactam
Sepsis							
Yes	1362	0 (0-2)	0 (0-2)	115/658 (17.5)	101/704 (14.3)	14 (8-14)	14 (11-14)
No	1149	0	0	9/556 (1.6)	13/593 (2.2)	14 (14-14)	14 (14-14)
Source of infection							
Intra-abdominal	612	0	0	23/319 (7.2)	22/293 (7.5)	14 (14-14)	14 (14-14)
Lung	557	0 (0-2)	0 (0-1)	44/257 (17.1)	38/300 (12.7)	14 (8-14)	14 (11-14)
Skin and soft tissue	446	0	0	7/201 (3.5)	4/245 (1.6)	14 (14-14)	14 (14-14)
Urinary	244	0 (0-1)	0 (0-1)	5/100 (5)	9/144 (6.2)	14 (14-14)	14 (14-14)
Other	201	0	0	5/104 (4.8)	5/97 (5.2)	14 (14-14)	14 (14-14)
Unknown[d]	451	0 (0-1)	0 (0-2)	40/233 (17.2)	36/218 (16.5)	14 (9-14)	14 (10-14)
Vancomycin							
Yes	1939	0 (0-1)	0 (0-1)	111/942 (11.8)	107/997 (10.7)	14 (12-14)	14 (14-14)
No	572	0	0	13/272 (4.8)	7/300 (2.3)	14 (14-14)	14 (14-14)
Chronic kidney disease							
Yes	502	0 (0-1)	0 (0-2)	28/243 (11.5)	22/259 (8.5)	14 (14-14)	14 (14-14)
No	1965	0	0	95/948 (10)	92/1017 (9)	14 (14-14)	14 (14-14)
Acute kidney injury[e]							
No	1275	0	0	25/623 (4)	26/652 (4)	14 (14-14)	14 (14-14)
Stage 1	542	0 (0-1)	0 (0-1)	19/231 (8.2)	21/311 (6.8)	14 (14-14)	14 (14-14)
Stage 2	257	0 (0-3)	0 (0-2)	19/134 (14.2)	18/123 (14.6)	14 (9-14)	14 (10-14)
Stage 3	292	3 (0-3)	3 (0-3)	55/148 (37.2)	44/144 (30.6)	12 (0-14)	14 (2-14)
Prior kidney replacement therapy	145	0	0	6/78 (7.7)	5/67 (7.5)	14 (10-14)	14 (14-14)
Admission type							
Medical	1966	0 (0-1)	0 (0-1)	111/948 (11.7)	109/1018 (10.7)	14 (13-14)	14 (14-14)
Surgical	496	0	0	11/240 (4.6)	5/256 (2)	14 (14-14)	14 (14-14)
Post hoc subgroup							
Coma							
Yes	161	3 (0-4)	2 (0-4)	42/84 (50)	34/77 (44.2)	0 (0-8)	2 (0-10)
No	2350	0	0	82/1130 (7.3)	80/1220 (6.6)	14 (14-14)	14 (14-14)
Overall	2511	0 (0-1)	0 (0-1)	124/1214 (10.2)	114/1297 (8.8)	14 (14-14)	14 (14-14)



The results of tests for interaction appear in eTables 14, 21, and 22 in Supplement 2.

[a] The primary outcome was the highest stage or death by day 14 (score range, 0 [alive without acute kidney injury] to 4 [dead]). An odds ratio (OR) <1.0 indicates a better outcome with cefepime.

[b] Defined as a composite of death, receipt of new kidney replacement therapy, or final creatinine level that was at least 2 times the baseline level. An OR <1.0 indicates a better outcome with cefepime.

[c] The number of days from randomization to day 14. An OR >1.0 indicates a better outcome with cefepime.

[d] Clinician uncertain about the suspected source of infection at enrollment.

[e] Presence or absence at enrollment.

Qian ET, Casey JD, Wright A, et al. The ACORN Randomized Clinical Trial. JAMA. 2023;330(16):1557-1567.

ACORN

Limitations

Generalizability:

- Limited to single, university-associated hospital in the US

Bias:

- Unblinded and open label (may affect the clinical assessments such as RASS and CAM-ICU)

Short duration of antibiotic exposure (median 3 days)

About 20% of patients in each group received at least one dose of the unassigned antibiotic within the first 14 days, and about 7% of patients received another extended-spectrum gram-negative antibiotc

Did not collect data on agitation, myoclonus and seizures, which has been associated with cefepime.

Pip-tazo was delivered as extended infusion which is not a widely applicable approach.

A trial that compares 2 treatments with 2 safety outcomes increases the risk of type 1 error.

Did not assess long-term complications as outcomes were only assessed up to 14 days.

Qian ET, Casey JD, Wright A, et al. The ACORN Randomized Clinical Trial. JAMA. 2023;330(16):1557-1567.

Author's Conclusions:

Among hospitalized adults in this randomized clinical trial, treatment with piperacillin-tazobactam did not increase the incidence of acute kidney injury or death. Treatment with cefepime resulted in more neurological dysfunction.

Does this change your preferred go to broad spectrum antibiotic in the ICU?

COPD/ Respiratory Failure/ Intubation

Image created using MidJourney

In patients with acute exacerbation of COPD and hypercapnia, does aiming for higher tidal volumes with BiPAP reduce the need for endotracheal intubation?

HAPPEN

Effect of High-Intensity vs Low-Intensity Noninvasive Positive Pressure Ventilation on the Need for Endotracheal Intubation in Patients with an Acute Exacerbation of COPD

Population: Patients with exacerbation of COPD and persistent hypercapnia on low-intensity NPPV in non-ICU setting in China.

Intervention: High-intensity NPPV (IPAP adjusted for goal tidal volume 10-15 cc/kg IBW)

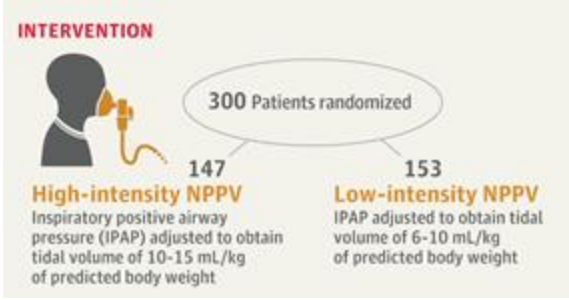
Comparison: Low-intensity NPPV (IPAP adjusted for goal tidal volume of 6-10 cc/kg IBW)

Outcomes: Need for endotracheal intubation during hospitalization*

JAMA | Original Investigation

Effect of High-Intensity vs Low-Intensity Noninvasive Positive Pressure Ventilation on the Need for Endotracheal Intubation in Patients With an Acute Exacerbation of Chronic Obstructive Pulmonary Disease
The HAPPEN Randomized Clinical Trial

Zujin Luo, MD; Yichong Li, PhD; Wenjun Li, MD; Ying Li, MD; Qingrong Nie, MD; Yu Shi, PhD; Juan Wang, BSN; Qiuling Ji, MD; Xuefeng Han, MD; Sijie Liu, MD; Dongmei Li, MD; ShaSha Wang, MD; Zhijun Li, MD; Dong Jia, MD; Huiqing Ge, MD; Peifeng Xu, BSc; Zhijun Feng, MD; Fengjie Li, MD; Fucheng An, MD; Na Tai, MD; Lili Yue, MD; Hongwei Xie, MD; Xiuhong Jin, MD; Hongru Liu, MD; Qiang Dang, MD; Yongxiang Zhang, MD; Li Sun, MD; Jinxiang Wang, MD; He Huang, MD; Liang Chen, MD; Yingmin Ma, MD; Zhixin Cao, MD; Chen Wang, MD, PhD; for the HAPPEN Investigators



Single-blind
Multicenter
Randomized
Location: 30 non-ICU units in China

*Pre-specified intubation criteria:
1. Arterial pH level of less than 7.25 with PaCO2 level that increased by more than 20% compared with baseline level or PF of less than 100 mmHg AND
2. The presence of at least 1 of the following: clinical signs suggestive of severely decreased consciousness (coma, delirium), use of accessory muscles or abdominal paradoxical movement, excessive respiratory secretions, aspiration or vomiting, bleeding in upper gastrointestinal tract, severe hemodynamic instability without response to fluid resuscitation and low-dose vasoactive agents, or ventricular or supraventricular arrhythmias; or
3. cardiac or respiratory arrest.

Luo Z, Li Y, Li W, et al. The HAPPEN Randomized Clinical Trial. JAMA. Published online September 16, 2024.

HAPPEN

Demographics and Characteristics

Table 1. Baseline Characteristics of the Participants

	Noninvasive positive pressure ventilation (NPPV)	
	High intensity (n = 147)	Low intensity (n = 153)
Age, mean (SD), y	73 (9)	73 (10)
Sex, No. (%)		
Male	100 (68)	103 (67)
Female	47 (32)	50 (33)
Height, mean (SD), cm	165 (8)	164 (8)
Body weight, mean (SD), kg		
Actual	65 (13)	64 (14)
Predicted[a]	60 (9)	59 (9)
Body mass index, mean (SD)[b]	24 (5)	24 (5)
COPD-related characteristics[c]		
Smoking history		
Ever smoked, No. (%)	90 (61)	98 (64)
Currently smoke, No. (%)	48 (33)	63 (41)
Median (IQR) [total], pack-years	40 (20-60) [n = 90]	30 (20-50) [n = 98]
Pulmonary function[d]		
FEV_1, mean (SD) [total], % predicted	35 (17) [n = 116]	38 (12) [n = 127]
Ratio of FEV_1 to FVC, mean (SD) [total]	47 (17) [n = 116]	48 (11) [n = 127]
Measured within previous 1 y, No. (%)	47 (32)	52 (34)
Measured at hospital discharge, No. (%)	69 (47)	75 (49)
Disease course, median (IQR), y	15 (10-20)	10 (5-30)
Treatment use, No. (%)		
Long-acting inhaled bronchodilators	124 (84)	133 (87)
Inhaled corticosteroids	116 (79)	122 (80)
Long-term oxygen therapy[e]	85 (58)	98 (64)
Long-term home NPPV[f]	28 (19)	32 (21)
Previous NPPV	81 (55)	89 (58)
Comorbidities, No. (%)[g]		
Chronic heart failure	73 (50)	70 (46)
Hypertensive heart disease	65 (44)	73 (48)
Ischemic heart disease	44 (30)	44 (29)
Diabetes	21 (14)	25 (16)
Obstructive sleep apnea	18 (11)	12 (8)
Atrial fibrillation	15 (10)	10 (7)
Cerebrovascular disease	10 (7)	14 (9)
Chronic kidney failure	5 (4)	3 (2)
Prior myocardial infarction	4 (3)	1 (1)
Peripheral vascular disease	2 (1)	3 (2)
Prior percutaneous coronary intervention	2 (1)	1 (1)
Exacerbation-related characteristics, No. (%)		
Respiratory infection	103 (70)	100 (65)
Pneumonia	31 (21)	38 (25)
Heart failure	50 (34)	46 (30)
Exposure to air pollutants	3 (2)	4 (3)
Undetermined	10 (7)	13 (9)
Time from exacerbation to randomization, median (IQR), d[h]	6 (3-10)	6 (3-10)
Arterial blood gas levels at randomization, mean (SD)[i]		
pH	7.31 (0.06)	7.31 (0.05)
$PaCO_2$, mm Hg	79 (15)	79 (15)
PaO_2/FiO_2, mm Hg	206 (63)	200 (53)
Bicarbonate, mmol/L	38 (7)	38 (7)
Disease status score, mean (SD)		
Modified Medical Research Council dyspnea scale[j]	3 (1)	3 (1)
COPD Assessment Test[k]	25 (6)	26 (7)
Acute Physiology and Chronic Health Evaluation II[l]	17 (4)	17 (4)

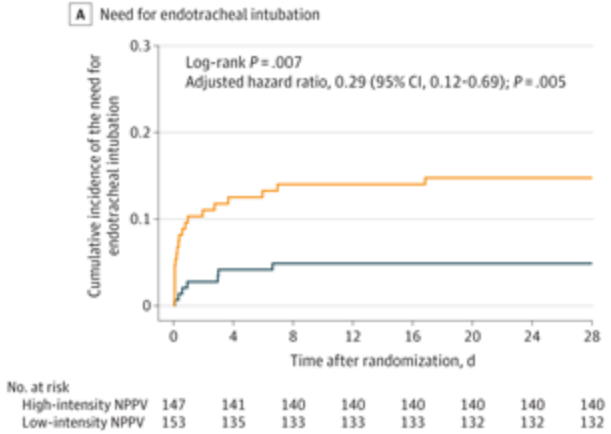
Luo Z, Li Y, Li W, et al. The HAPPEN Randomized Clinical Trial. JAMA. Published online September 16, 2024.

HAPPEN

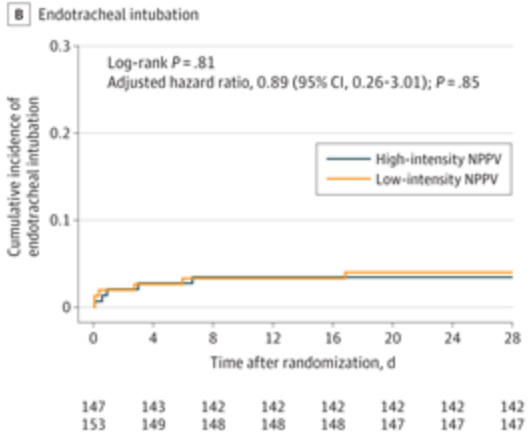
Results

Primary outcome:

- Patients in high-intensity NPPV group were significantly less likely to meet criteria for intubation compared to low-intensity NPPV (4.8% vs 13.7%)



Despite differences in meeting criteria for intubation, the actual rates of intubation did not significantly differ between the groups



Adjusted for respiratory tract infection, days from exacerbation to randomization, pH level at randomization, and ratio of PaO2 to fraction of inspired oxygen (FIO2) at randomization.

Luo Z, Li Y, Li W, et al. The HAPPEN Randomized Clinical Trial. JAMA. Published online September 16, 2024.

HAPPEN

Safety Outcomes

Abdominal distension occurred more frequently in the high-intensity NPPV group (37.4%) compared to the low-intensity NPPV group (25.5%)

Severe alkalosis was seen in patients in the high-intensity NPPV group (4.1%).

Table 3. Safety Outcomes and Serious Adverse Events

	Noninvasive positive pressure ventilation (NPPV), No. (%)	
	High intensity (n = 147)	Low intensity (n = 153)
Safety outcomes[a]		
Complications related to NPPV		
Abdominal distension	55 (37.4)	39 (25.5)
Nasal or oral dryness	44 (29.9)	46 (30.1)
Severe air leakage[b]	26 (17.7)	17 (11.1)
Severe intolerance to NPPV[c]	11 (7.5)	6 (3.9)
Inability to remove respiratory secretions	8 (5.4)	9 (5.9)
Nasal or facial skin necrosis	3 (2.0)	6 (3.9)
Claustrophobia	3 (2.1)	4 (2.6)
Intolerance to NPPV because of abdominal distension	5 (3.4)	1 (0.7)
Aspiration	1 (0.7)	1 (0.7)
Hypotension	2 (1.4)	0
Conjunctivitis	0	1 (0.7)
Serious adverse events		
Severe alkalosis	6 (4.1)	0
Gastrointestinal tract bleeding	0	3 (2.0)
Nosocomial pneumonia	0	2 (1.3)
Septic shock	1 (0.7)	1 (0.7)
Multiple organ failure	1 (0.7)	1 (0.7)
Cardiac arrest	0	2 (1.3)

Luo Z, Li Y, Li W, et al. The HAPPEN Randomized Clinical Trial. JAMA. Published online September 16, 2024.

HAPPEN

Limitations

Generalizability:

- Conducted in China
- Patients with bullae and pulmonary infiltrates were excluded.

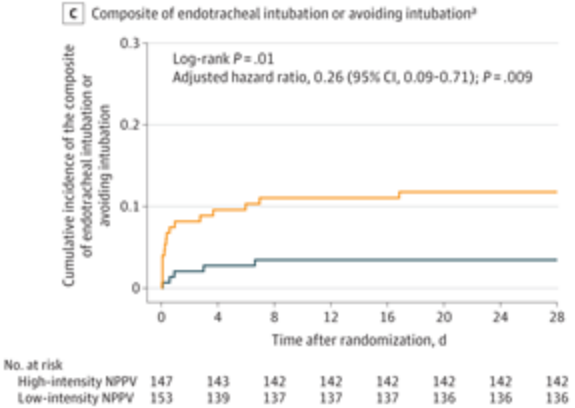
Bias:

- Single blind (blinded to the independent statistician)

Trial was terminated early after interim analysis of first 300 patients. This could overestimate treatment effect.

Crossover design where patients in the low-intensity NPPV group could crossover into the high-intensity NPPV group could reduce the differences between the two groups.

Question of clinical relevance of primary outcome given the significant difference in meeting criteria for intubation which did not translate into difference in actual intubation rates. However, the avoidance of intubation in the low-intensity group could be due to crossover into high-intensity NPPV



Luo Z, Li Y, Li W, et al. The HAPPEN Randomized Clinical Trial. JAMA. Published online September 16, 2024.

Author's Conclusions:

Patients with COPD and persistent hypercapnia in the high-intensity NPPV group (vs patients in the low-intensity NPPV group) were significantly less likely to meet criteria for the need for endotracheal intubation; however, patients in the low-intensity NPPV group were allowed to crossover to high-intensity NPPV, and the between-group rate of endotracheal intubation was not significantly different.

Will you aim for higher tidal volumes to avoid intubation in your COPD patients based on these results?

SUMMARY SLIDE

	Population	Intervention	Comparison	Outcome
PREOXI	ED/ICU pt needing emergent intubation	Preoxygenation with BiPAP	Preoxygenation with oxygen mask	Hypoxia seen in 9.1% pt with BiPAP vs 18.5% in patients with oxygen
CAPE COD	Severe CAP in the ICU	IV Hydrocortisone	Placebo	6.2% of pt in steroid arm died at 28 days versus 11.9% of pt in the placebo arm
ACORN	Pt suspected of gram-negative bacterial infection	Cefepime	Piperacillin-tazobactam (extended infusion)	No significant difference in primary outcome of AKI or death between groups
HAPPEN	AECOPD with hypercarbia needing BIPAP	High-intensity NPPV (higher IPAP)	Low-intensity NPPV (lower IPAP)	High-intensity NPPV less likely to meet pre-specified criteria for need for intubation

NOTABLE MENTIONS

	Population	Intervention	Comparison	Outcome
ARiE	Cirrhosis patients with acute hepatic encephalopathy in ICU	Antibiotics + Rifaximin	Abx only	No effect on encephalopathy resolution or in-hospital mortality
STRESS-L	ICU patients with septic shock and tachycardia	Landiolol infusion	Standard care	No difference in mean SOFA score
DanGer Shock	Pt with STEMI-related cardiogenic shock	Microaxial flow pump (Impella CP device) plus standard care	Standard care	45.8% of pt with microaxial flow pump died from any cause at 180 days versus 58.5% of patient with standard care
HOT-COVID	ICU patients with severe hypoxemic from COVID-19	Targeting lower PaO2	Targeting a higher PaO2	Lower O2 group had more median days alive without life support
REVISE	Mechanically ventilated patients in ICU	IV Pantoprazole	Placebo	HR 0.30 favoring IV PPI for clinically significant bleeding but no improvement in mortality and no increased side effects (CDI, VAP)

Citations

Bill Barker, MD, MMM, FCCP
Briana DiSilvio, MD
Collin Flanagan, DO, FACP

Samantha S. Kunvatanagarn

Richard Zou, MD, MS

Tariq Cheema, MD, FCCP, MMM

Acknowledgements

Bill Barker, MD, MMM, FCCP
Briana DiSilvio, MD
Collin Flanagan, DO, FACP

Samantha S. Kunvatanagarn

Richard Zou, MD, MS

Tariq Cheema, MD, FCCP, MMM

Questions

Perry.Tiberio@ahn.org

INTUBATION QUICK HIT

VIDEO LARYNGOSCOPY VS DIRECT LARYNGOSCOPY FOR ENDOTRACHEAL INTUBATION IN THE OPERATING ROOM

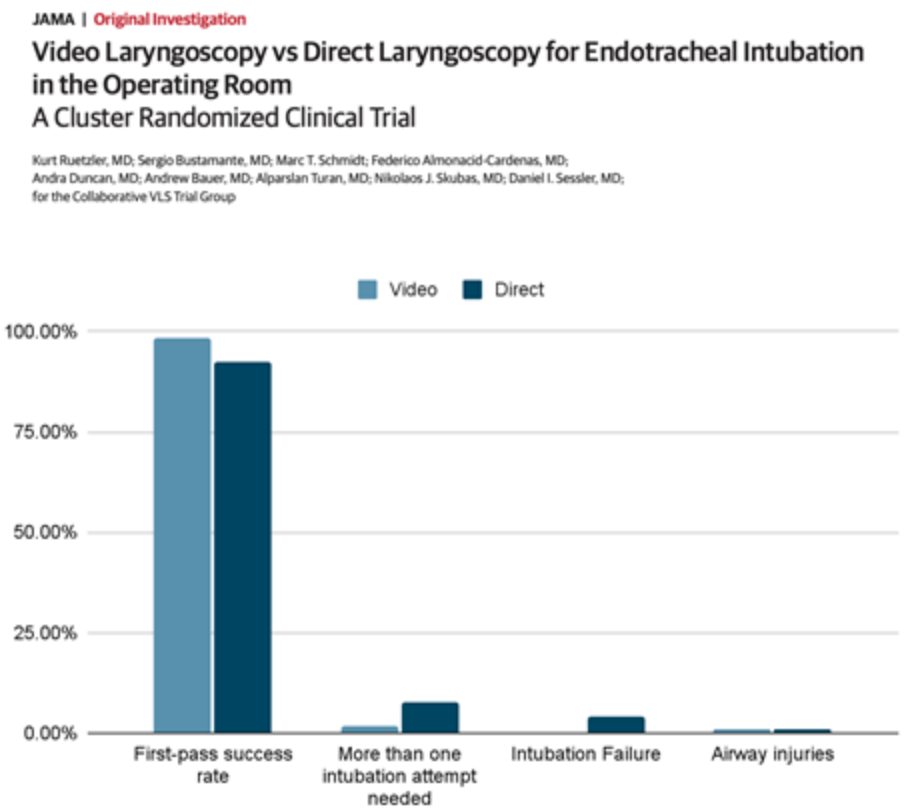
A Cluster Randomized Clinical Trial

Population: Adult patients undergoing elective or emergent surgical procedures requiring single-lumen endotracheal intubation for general anesthesia

Intervention: Use of hyperangulated video laryngoscopy for endotracheal intubation

Comparison: Use of direct laryngoscopy for endotracheal intubation.

Outcomes: Number of attempts needed to achieve successful endotracheal intubation, first-pass success rates, and incidence of intubation-related complications.



OXYGENATION QUICK HIT

ICONIC

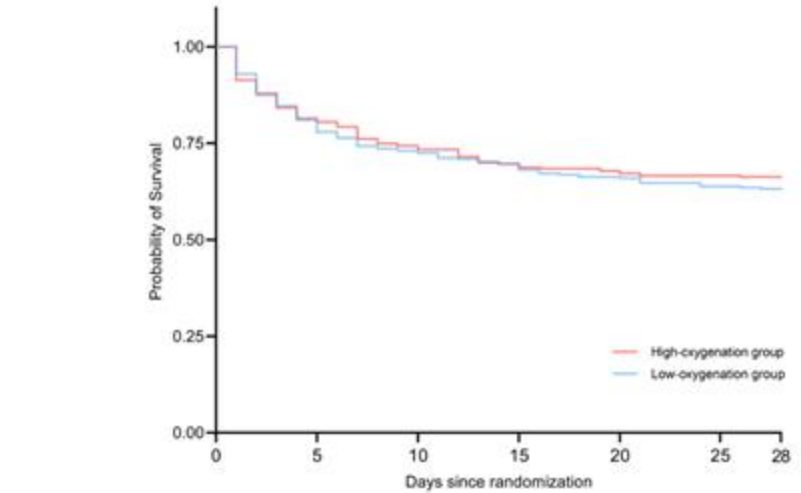
Conservative versus Liberal Oxygenation Targets in Intensive Care Unit Patients (ICONIC): An RCT

Population: Patients receiving invasive mechanical ventilation in the ICU.

Intervention/Comparison: Low-oxygenation (PaO2, 55-80 mmHg, O2 sat 91-94%) vs high-oxygenation (PaO2, 110-150 mmHg, O2 sat 96-100%)

Outcome: 28-day mortality

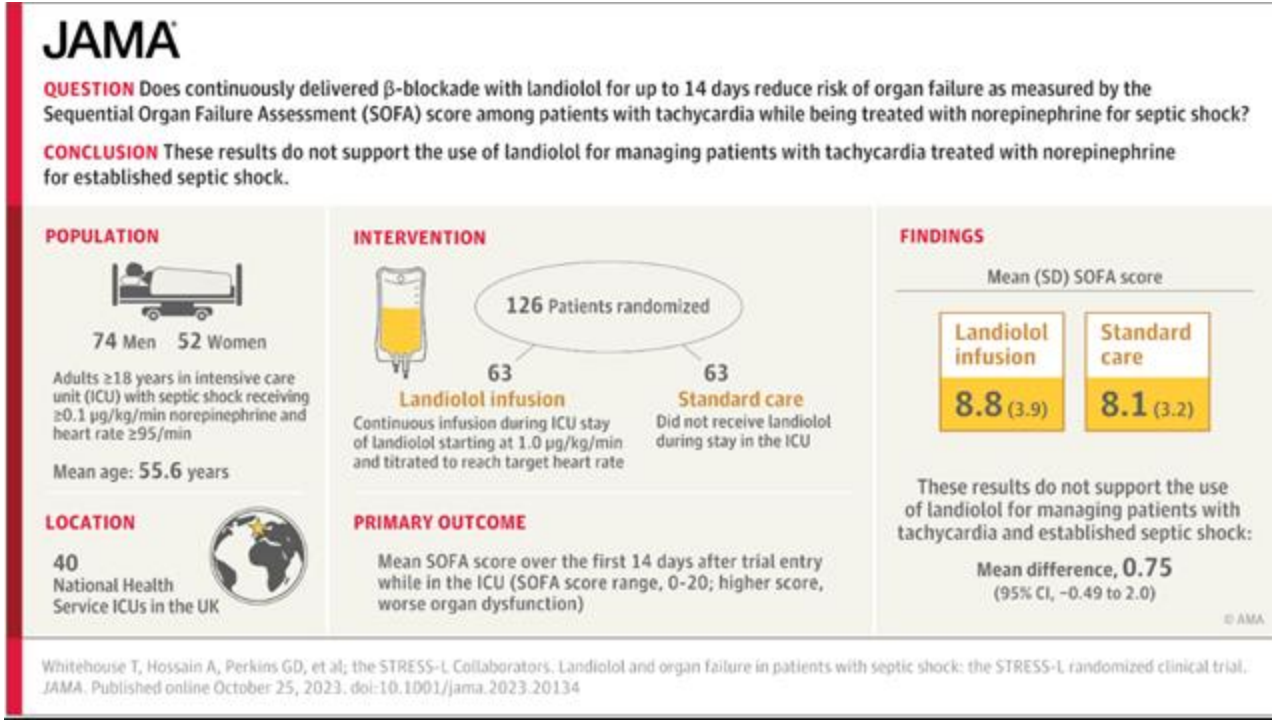
Study stopped prematurely due to COVID-19 pandemic, when 664 of the planned 1,512 patients were included.



CARDIOLOGY QUICK HIT

STRESS-L

Landiolol and Organ Failure in Patients With Septic Shock



Do you use beta blockers during septic shock?

GI QUICK HIT

ARiE

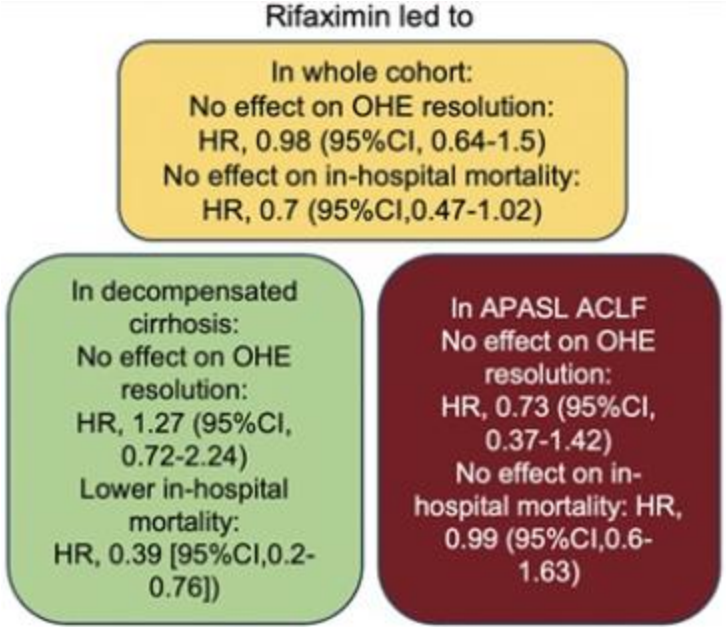
Antibiotics With or Without Rifaximin for Acute Hepatic Encephalopathy in Critically Ill Patients with Cirrhosis

Population: Patients with cirrhosis with acute hepatic encephalopathy admitted to the ICU

Intervention: Antibiotics + Rifaximin

Comparison: Antibiotics only

Outcomes: Resolution (or 2 grade reduction) of HE, time to resolution of HE, in-hospital mortality, nosocomial infection, and changes in endotoxin levels.



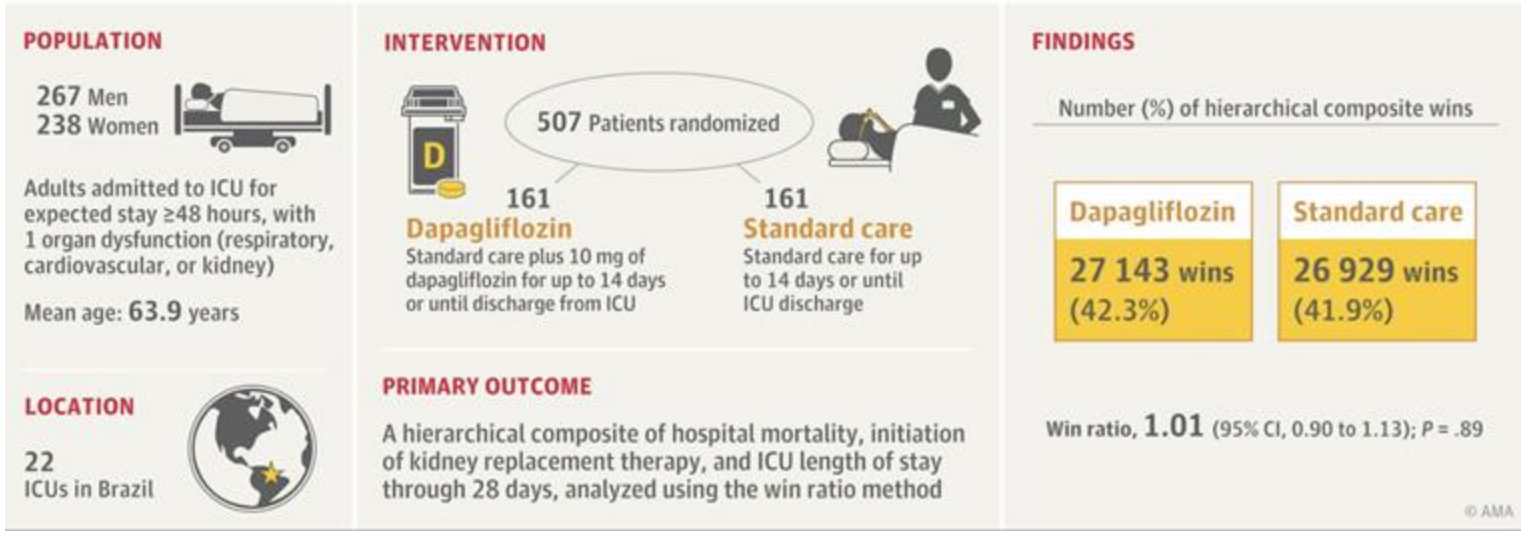
RANDOM QUICK HIT

DEFENDER

Dapagliflozin for Critically Ill Patients With Acute Organ Dysfunction

QUESTION Does the addition of dapagliflozin to standard care improve hierarchical outcomes of hospital mortality, initiation of kidney replacement therapy, and the length of stay in the intensive care unit (ICU) among critically ill patients with acute organ dysfunction?

CONCLUSION The addition of dapagliflozin to standard care for individuals with critical illness and acute organ dysfunction did not improve clinical outcomes.



OMITTED STUDIES

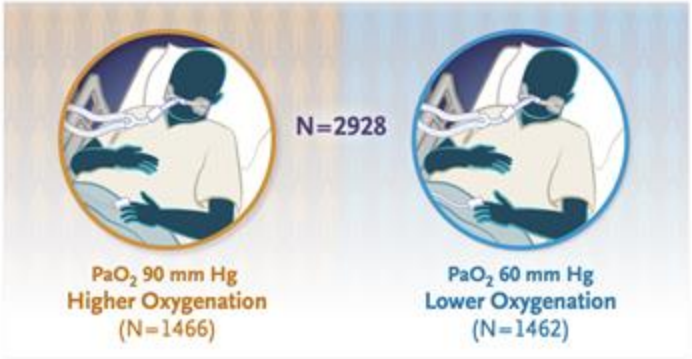
HOT-ICU

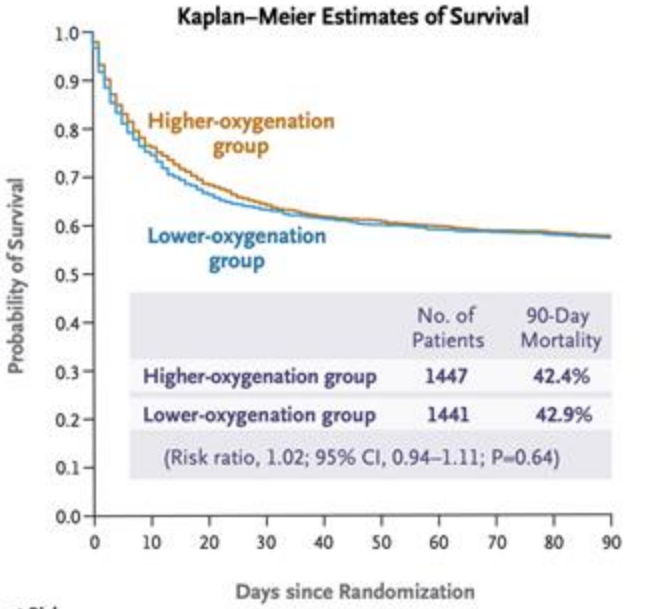
Lower or Higher Oxygenation Targets for Acute Hypoxemic Respiratory Failure

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Lower or Higher Oxygenation Targets for Acute Hypoxemic Respiratory Failure





	No. of Patients	90-Day Mortality
Higher-oxygenation group	1447	42.4%
Lower-oxygenation group	1441	42.9%

(Risk ratio, 1.02; 95% CI, 0.94–1.11; P=0.64)

No. at Risk

Higher oxygenation	1447	933	865	834
Lower oxygenation	1441	912	851	824

HOT-COVID

Lower vs Higher Oxygenation Target and Days Alive Without Life Support in COVID-19

Population: Patients with COVID-19 and severe hypoxemia (at least 10LNC or mechanical ventilation) admitted to ICUs in Europe

Intervention: Targeting a lower arterial partial pressure of oxygen of 60 mmHg

Comparison: Targeting a high arterial partial pressure of oxygen of 90 mmHg

Outcomes: Number of days alive without life support (mechanical ventilation, circulatory support, or kidney replacement therapy) at 90 days

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Lower vs Higher Oxygenation Target and Days Alive Without Life Support in COVID-19

The HOT-COVID Randomized Clinical Trial

HOT-COVID

Results

Primary Outcome: Median number of days alive without life support

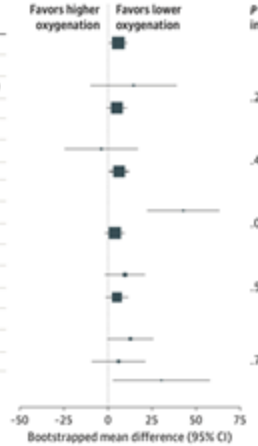
- Lower O2 group: 80 days
- Higher O2 group: 72 days
- P = 0.009

Secondary Outcomes:

- **Death by day 90:**
  - Lower O2: 30.2%
  - Higher O2: 34.7%
- **Days alive and out of hospital over 90 d, median (IQR):**
  - Lower O2: 59 (0-75)
  - Higher O2: 48 (0-74)
- **Serious adverse events:**
  - Lower O2: 47.5%
  - Higher O2: 51.4%

B Days alive without life support by subgroup

Subgroup	No. of patients		Days alive without life support, median (IQR)		Bootstrapped mean difference (95% CI)	*P* value for interaction
	Lower oxygenation	Higher oxygenation	Lower oxygenation	Higher oxygenation		
All patients	351	346	80 (9-89)	72 (2-88)	5.8 (0.2 to 11.5)	
COPD						.21
Yes	27	24	64 (7-86)	7 (0-64)	14.5 (-10.1 to 39.1)	
No	324	322	81 (10-89)	76 (2-88)	5.0 (-0.8 to 10.6)	
Hematological malignancy						.45
Yes	26	35	18 (5-87)	50 (2-89)	-3.8 (-24.7 to 17.1)	
No	325	311	80 (14-89)	73 (2-87)	6.3 (0.5 to 12.0)	
Shock						.001
Yes	18	19	75 (2-86)	0 (0-18)	42.8 (22.2 to 63.4)	
No	333	327	80 (11-89)	76 (3-88)	3.9 (-1.8 to 9.5)	
Invasive mechanical ventilation						.53
Yes	87	79	69 (1-83)	49 (0-78)	9.6 (-1.8 to 21.1)	
No	264	267	84 (14-90)	79 (4-89)	5.1 (-1.4 to 11.6)	
$Pao_2:Fio_2$ ratio						.77
<100	64	53	64 (2-79)	27 (0-77)	12.7 (-0.4 to 25.9)	
100 to 199	45	62	77 (2-84)	51 (0-79)	6.0 (-9.3 to 21.3)	
200 to 300	13	9	80 (21-84)	4 (0-77)	30.4 (2.7 to 58.0)	



HOT-COVID

Limitations

Generalizability:

- Limited to 13 ICUs in Denmark, Switzerland, Norway, Iceland and Wales. Practice may vary elsewhere.
- Only applies to COVID-19, early in the pandemic.

Bias:

- Unblinded and open label

Trial stopped early, due to slow enrollment, with 726 patients out of planned 780 patients.. This could lead to underpowered study.

No specific protocols for intubation or weaning from mechanical ventilation.

The authors note that “no adjustments for multiplicity on the basis of the conducted interim analysis were included”. (see comments). They state that the risk of type I statistical error is low.

COVID-19 is a different disease than it was when this study was initially performed.

No specific protocol was required to meet the oxygenation target, but at least 4 measurements per day were expected. It is not standard of care to check routine ABGs.

GI


CC124812
"I wanted you to meet our colon specialist before we miniaturized him."

Does daily pantoprazole, used as stress ulcer prophylaxis in ventilated ICU patients, reduce the incidence of clinically significant upper GI bleeding without increase 90-day all cause mortality? Does it carry higher rate of C diff infection and VAP?

REVISE

Stress Ulcer Prophylaxis during Invasive Mechanical Ventilation

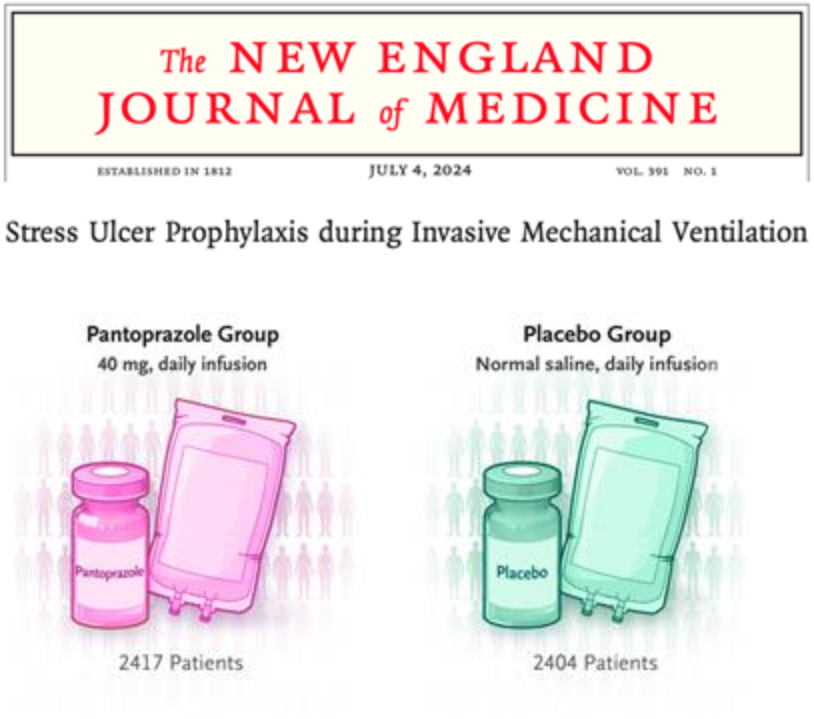
Population: Mechanically ventilated adult patients in the ICU

Intervention: Stress ulcer prophylaxis with intravenous pantoprazole 40mg daily

Comparison: Placebo (normal saline)

Outcomes: Clinically important GI bleeding at 90 days

Primary safety outcome was death from any cause at 90 days. Multiplicity-adjusted secondary outcomes included VAP, *Clostridium difficile* infection, and patient-important bleeding



REVISE

Results

Primary outcome: Clinically important GI bleeding at 90 days

- Pantoprazole group: 1.0%
- Placebo: 3.5%
- HR, 0.30; 95% CI, 0.19 to 0.47; P<0.001

Primary safety outcome (death at 90 days):

- Pantoprazole group: 29.1%
- Placebo: 30.9%
- HR, 0.94; 95% CI, 0.85 - 1.04; P=0.25

Table 2. Primary Efficacy and Safety Outcomes.

Outcome	Pantoprazole (N=2417)	Placebo (N=2404)	Absolute Difference (95% CI)	Hazard Ratio (95% CI)*	P Value
	no./total no. (%)		*percentage points*		
Primary efficacy outcome: clinically important upper gastrointestinal bleeding	25/2385 (1.0)	84/2377 (3.5)	2.5 (1.6 to 3.3)	0.30 (0.19 to 0.47)	<0.001
Primary safety outcome: 90-day mortality	696/2390 (29.1)	734/2379 (30.9)	1.7 (−0.9 to 4.3)	0.94 (0.85 to 1.04)	0.25

* Hazard ratios were adjusted for prehospital use of histamine 2–receptor antagonists or proton-pump inhibitors. Mortality analyses were also adjusted for the baseline APACHE II score.

REVISE

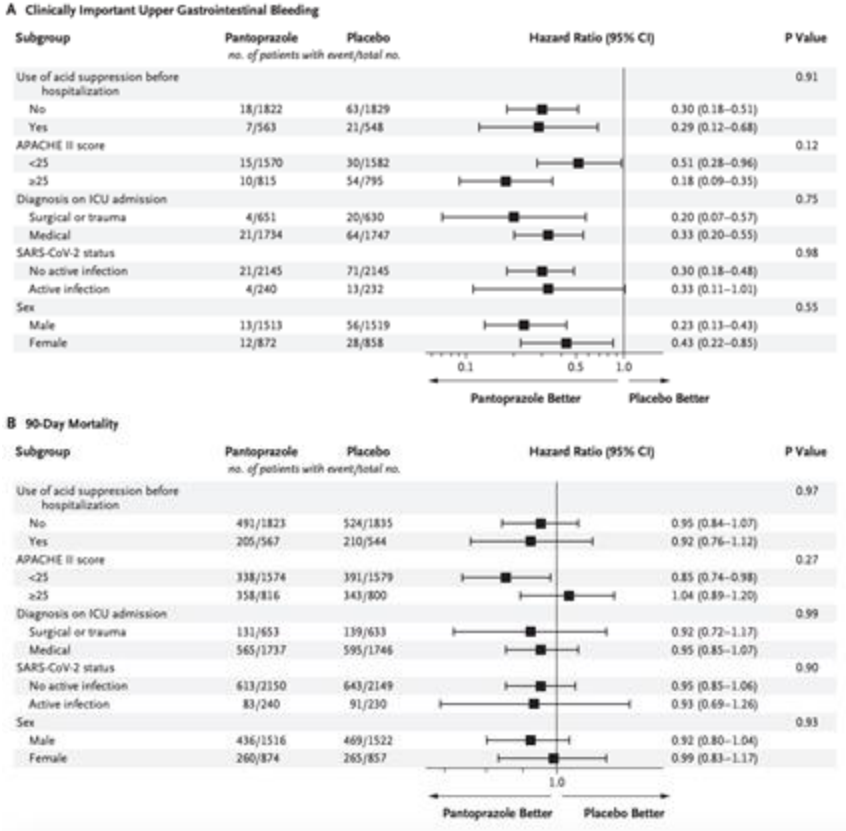
Results

Primary outcome:

- Pantoprazole group: 1.0%
- Placebo: 3.5%
- HR, 0.30; 95% CI, 0.19 to 0.47; P<0.001

Primary safety outcome (death at 90 days):

- Pantoprazole group: 29.1%
- Placebo: 30.9%
- HR, 0.94; 95% CI, 0.85 - 1.04; P=0.25



REVISE

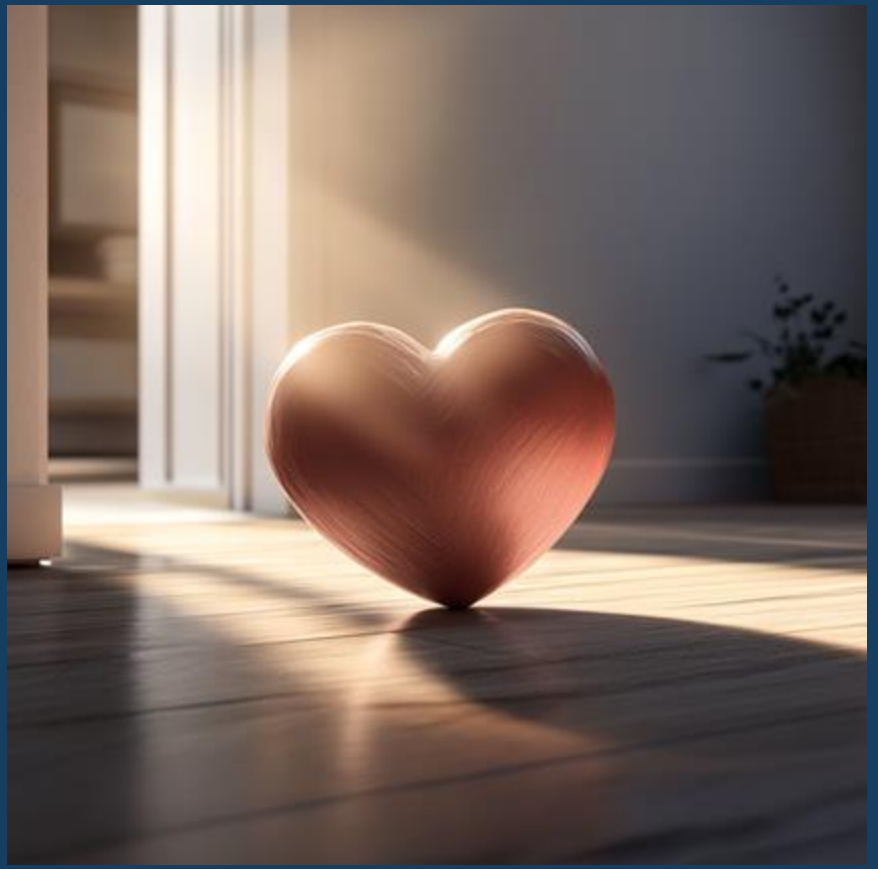
Stress Ulcer Prophylaxis during Invasive Mechanical Ventilation

Table 3. Secondary and Tertiary Outcomes.*

Outcome	Pantoprazole (N=2417)	Placebo (N=2404)	Treatment Effect (95% CI)†	P Value‡
Secondary outcome				
Ventilator-associated pneumonia in ICU — no./total no. (%)§	556/2394 (23.2)	567/2381 (23.8)	1.00 (0.89–1.12)	0.93
Clostridioides difficile infection in hospital — no./total no. (%)	28/2385 (1.2)	16/2377 (0.7)	1.78 (0.96–3.29)	0.50
New renal-replacement therapy in ICU — no./total no. (%)	146/2385 (6.1)	142/2380 (6.0)	1.04 (0.83–1.31)	0.98
Death — no./total no. (%)				
In ICU	488/2402 (20.3)	515/2392 (21.5)	0.98 (0.87–1.11)	0.94
In hospital	630/2399 (26.3)	677/2381 (28.4)	0.96 (0.86–1.07)	0.91
Patient-important upper gastrointestinal bleeding in ICU — no./total no. (%)	36/2385 (1.5)	100/2377 (4.2)	0.36 (0.25–0.53)	<0.001
Tertiary outcome				
Median no. of red-cell units transfused in first 14 days in ICU (IQR)	0 (0–1)	0 (0–1)	0.87 (0.74–1.02)	0.51
Median peak serum creatinine level in ICU (IQR) — μmol/liter	99 (70–190)	99 (69–184)	NA	0.91
Median no. of days of mechanical ventilation (IQR)	6 (3–11)	6 (3–11)	NA	0.73
Median no. of days in ICU (IQR)	10 (6–16)	10 (6–16)	NA	0.48
Median no. of days in hospital (IQR)	20 (11–35)	21 (11–38)	NA	0.47

Does this convince you that PPIs do not have an increased infection risk?

CARDIOLOGY



Does the use of microaxial flow pumps improve outcomes in patients with STEMI-related cardiogenic shock?

DanGer Shock

Microaxial Flow Pump or Standard Care in Infarct-Related Cardiogenic Shock

Population: Patients with STEMI-related cardiogenic shock

Intervention: Microaxial flow pump (Impella CP device) plus standard care

Comparison: Standard care

Outcomes: Death from any cause at 180 days.

Secondary end points*

A composite safety end point was severe bleeding, limb ischemia, hemolysis, device failure, or worsening aortic regurgitation.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Microaxial Flow Pump or Standard Care in Infarct-Related Cardiogenic Shock

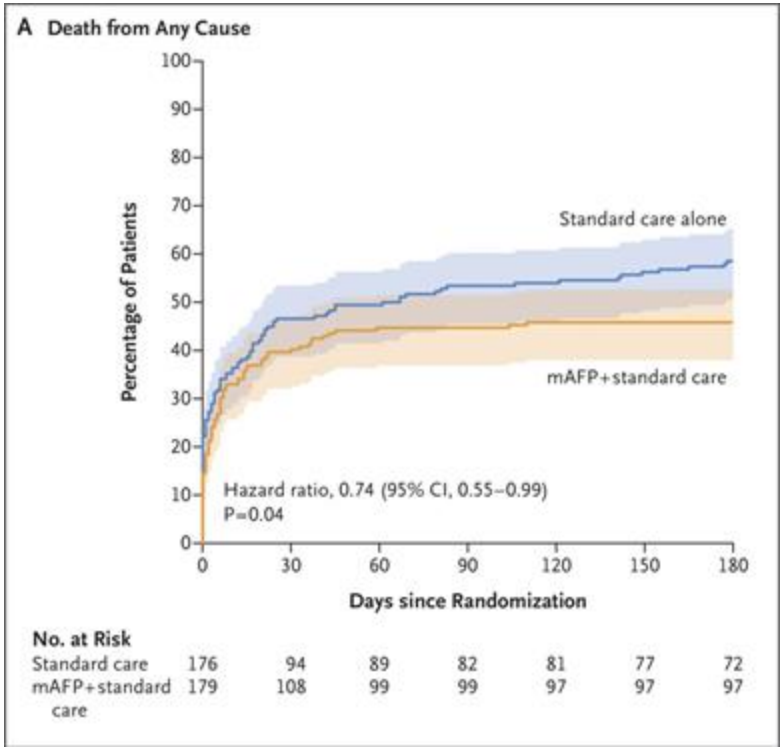
J.E. Møller, T. Engstrøm, L.O. Jensen, H. Eiskjær, N. Mangner, A. Polzin, P.C. Schulze, C. Skurk, P. Nordbeck, P. Clemmensen, V. Panoulas, S. Zimmer, A. Schäfer, N. Werner, M. Frydland, L. Holmvang, J. Kjærgaard, R. Sørensen, J. Lønborg, M.G. Lindholm, N.L.J. Udesen, A. Junker, H. Schmidt, C.J. Terkelsen, S. Christensen, E.H. Christiansen, A. Linke, F.J. Woitek, R. Westenfeld, S. Möbius-Winkler, K. Wachtell, H.B. Ravn, J.F. Lassen, S. Boesgaard, O. Gerke, and C. Hassager, for the DanGer Shock Investigators*

International, multicenter
Unblinded
Randomized
Open-label
Location: 14 centers in Denmark, Germany and the UK

N ENGL J MED 390;15 NEJM.ORG APRIL 18, 2024

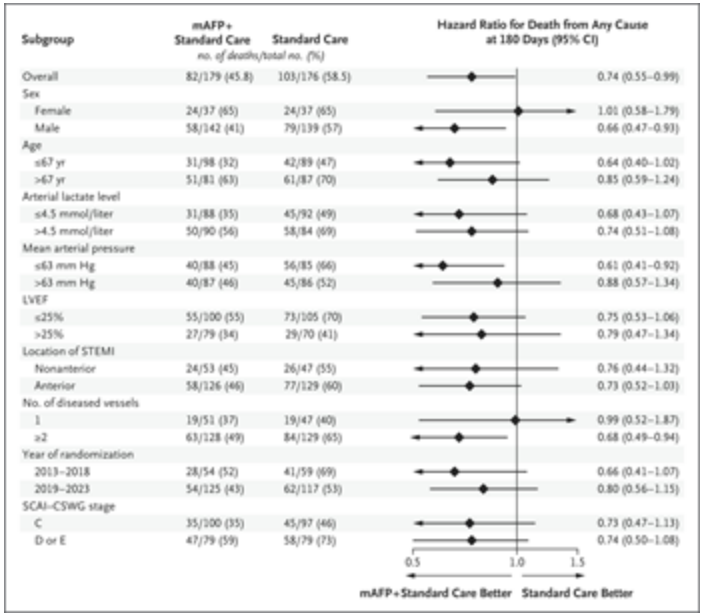
DanGer Shock

Results



Primary Outcome: Death from any cause within 180 days

- Microaxial flow pump: 45.8%
- Standard Care: 58.5%
- HR 0.74 (95% CI, 0.55 - 0.99; p=0.04)



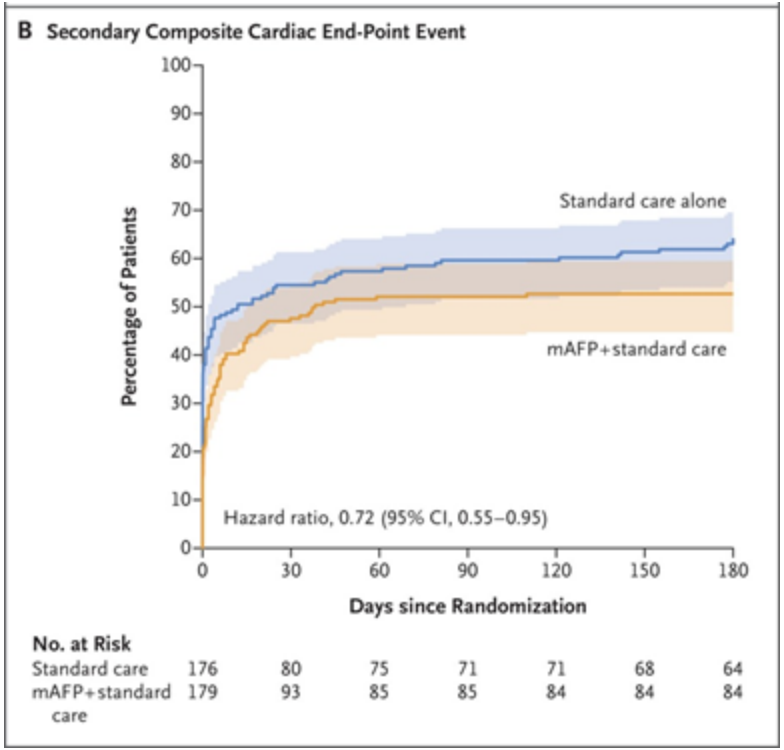
DanGer Shock

Results: Secondary Composite Cardiac End-Point

Secondary Composite Cardiac End-Point

- Microaxial flow pump: 52.5%
- Standard Care: 63.6%
- HR 0.72 (95% CI, 0.55 - 0.95; p=0.04)

Defined as escalation of treatment to additional mechanical circulatory support (short or long-term), heart transplantation, or death from any cause, whichever came first.



DanGer Shock

Results

Number of days alive and out of the hospital

- Microaxial flow pump: 82 (0 to 177)
- Standard Care: 73 (0 to 179)

Composite safety end point:

- Microaxial flow pump: 24.0%
- Standard Care: 6.2%
- RR 4.74; 95% CI, 2.36 to 9.55

Table 3. End Points and Adverse Events in the Intention-to-Treat Population.*

Event	Microaxial Flow Pump plus Standard Care (N=179)	Standard Care Alone (N=176)	Effect Size (95% CI)†
Primary end point: death from any cause at 180 days — no. (%)	82 (45.8)	103 (58.5)	0.74 (0.55 to 0.99)‡
Secondary end point			
Composite cardiac end point — no. (%)§	94 (52.5)	112 (63.6)	0.72 (0.55 to 0.95)
No. of days alive and out of the hospital (range)¶	82 (0 to 177)	73 (0 to 179)	8 (−8 to 25)
Adverse events			
Composite safety end point — no. (%)‖	43 (24.0)	11 (6.2)	4.74 (2.36 to 9.55)
Moderate or severe bleeding — no. (%)**	39 (21.8)	21 (11.9)	2.06 (1.15 to 3.66)
Limb ischemia — no. (%)	10 (5.6)	2 (1.1)	5.15 (1.11 to 23.84)
Renal-replacement therapy — no. (%)	75 (41.9)	47 (26.7)	1.98 (1.27 to 3.09)
Stroke — no. (%)	7 (3.9)	4 (2.3)	1.75 (0.50 to 6.01)
Cardioversion after ventricular tachycardia or fibrillation — no. (%)	59 (33.0)	52 (29.5)	1.17 (0.75 to 1.83)
Sepsis with positive blood culture†† — no. (%)	21 (11.7)	8 (4.5)	2.79 (1.20 to 6.48)

DanGer Shock

Limitations

Generalizability:

- Limited to 14 centers in Denmark, Germany and the UK limits external validity
- Practice variation is dependent on exposure at each center
- 79% study participants were male and White
- Strict inclusion criteria

Bias:

- Unblinded and open label

Slow enrollment over 10 years. Likely there will be evolution of practice in critical care over that time period.

Safety outcomes did not take into account competing risks.

How would you balance the safety profile with the mortality data presented in the DanGer Shock trial?