

# **PULMONARY & CRITICAL CARE INSIDER**



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# VIEWPOINTS

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ADOPTED FROM PULMCC AND CITED ARTICLES.*

## Value nothing more than Blood! But don't be a Vampire!

When amassed, daily labs on hospitalized patients deplete substantial volumes of blood, almost all of which is wasted. The 4 to 6 mL of blood drawn per standard tube is a legacy of older equipment: modern testing machines only need <0.5 mL per sample, discarding the remaining blood. About a unit of whole blood per week from each patient in the ICU.

By one estimate, 25 million liters (6.6 million gallons) of blood are wasted in this fashion, every year, or near quadruple the total amount of blood transfused annually.

Smaller-volume blood collection tubes are widely available (used by few) at equivalent cost and are compatible with standard blood analyzers with less vacuum suction filling only half the tube.



This led to a rather logical but unproved hypothesis being tested:

*Would removing less blood result in more blood remaining inside patients, thus requiring less blood to be transfused into them?*

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Over 21,000 patients among 25 ICUs in Canada were switched to small-volume blood collection tubes at randomly assigned times from 2019-2021. This led to an absolute (and statistically significant) 9.84 fewer units RBC transfused per 100 patients, relative to the standard-volume tubes.

The individual patient-level effects were exceedingly small. Smaller-volume tubes mitigated the decline in hemoglobin from blood drawn by only about 0.1 g/dL per patient. However, over the two years studied, 30,000 patients may have been spared the transfusion of 1,500 units of blood. The risk and costs occur on a population/systems level. Transfusion harms are usually clinically inapparent, showing up in data sets as slightly worsened outcomes among a few more of the transfused, as compared to the not-transfused.

There is a lack of a clear stakeholder motivated to change the status quo. Health systems will need regulation to encourage change, such as through quality measures or regulations mandating the use of small-volume tubes.

Phlebotomy is not harmful, and neither is ordering daily labs which may be necessary more often. But wasting such vast quantities of patients' blood, and the blood collected at great expense from altruistic donors, seems unacceptable. If it's really this easy to cut the waste by 50%, shouldn't we be doing it already?

# VIEWPOINTS

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## Pamper the Heart : Why Cardiologists Advocate for More Blood Transfusions. MINT Trial

In the history of transfusion cutoffs, recent randomized trials with over 21,000 patients revealed a 50% reduction in blood transfused when restricting red blood cell transfusion until hemoglobin fell below 7 or 8 g/dL in acutely ill, hemodynamically stable patients, compared to the conventional threshold of 9 or 10 g/dL. The 1999 TRICC trial established 7 g/dL as a widely accepted threshold for red cell transfusion in critically ill patients. However, controversy persists, especially in patients with cardiovascular disease, questioning the ideal transfusion thresholds. Three randomized trials on active myocardial ischemia yielded inconsistent results, with the largest trial suggesting safety in restricting transfusion to Hb<8 g/dL in acute MI, although the non-inferiority trial lacked conclusive evidence due to a wide confidence interval.

Now that led to the MINT trial, 3506 patients with acute myocardial infarction and anemia were randomly assigned to either a liberal transfusion threshold (hemoglobin less than 10 g/dL) or a restrictive threshold (permitted at Hb < 8 g/dL, strongly recommended at Hb < 7 g/dL). Conducted across 140 centers in multiple countries, the study included a diverse, real-world patient population with high rates of prior MI, current systolic heart failure, and chronic kidney disease. After 30 days, patients in the liberal transfusion group received over three times as much blood (approximately 4300 units, averaging 2.5 units per patient) compared to the restrictive group (around 1200 units, averaging 0.7 per patient).

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Despite sparing a significant amount of blood, the results raised concerns:

- Recurrent myocardial infarction or death, the composite primary outcome (~17% in restrictive, 14.5% in liberal)
- Death (~10% in restrictive, ~8% in liberal)
- Recurrent MI (8.5% in restrictive, ~7% in liberal)
- Cardiac death (5.5% in restrictive, ~3% in liberal)

While confidence intervals generally included 1.0, the proximity suggested potential harm, with a rough estimate of a number needed to harm of about 50 by restricting transfusion in acute MI. Interestingly, there was no increased rate of heart failure symptoms among the liberally-transfused patients. The trial's unblinded nature may have influenced differences in care due to attendings' knowledge of intervention assignments.

Experts predict the MINT trial will value the advocacy of the usual practice of more-liberal red blood cell transfusion in patients with active myocardial ischemia and anemia.

# VIEWPOINTS

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## CODE BLUE... More Epi Means More Death!

In a study involving 2,792 patients, the analysis revealed the following outcomes: 8.7% survivors at hospital discharge, 35.9% deaths from cardiocirculatory causes, 44.2% deaths from neurological causes, and 11.2% deaths from other etiologies.

The group experiencing cardiocirculatory death received higher doses of epinephrine during CPR compared to other groups. The proportion of cardiocirculatory death increased linearly ( $R^2=0.92$ ,  $p<0.001$ ) with cumulative epinephrine doses during CPR (17.7% in subjects who did not receive epinephrine and 62.5% in those who received  $>10$  mg). In multivariable analysis, a cumulative dose of epinephrine was strongly associated with cardiocirculatory death (adjusted odds ratio of 3.45, 95% CI [2.01–5.92] for 1 mg of epinephrine; 12.28, 95% CI [7.52–20.06] for 2–5 mg; and 23.71, 95% CI [11.02–50.97] for  $>5$  mg; reference 0 mg; population reference: alive at hospital discharge).

The cumulative dose of epinephrine remained significantly associated with cardiocirculatory death; seven times more likely with multivariate analysis after adjusting for the duration of resuscitation.

Also noted associations between epinephrine use and other modes of death (neurological and other causes), though to a lesser extent. This study indicates we should consider evaluating futility of care and continued resuscitation after 3 to 5 rounds of epinephrine.

# VIEWPOINTS

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## Intubation for airway protection is a myth and maybe even a contraindication. NICO says Naaa to intubation!!

**“For GCS of 8, intubate.”  
It’s an age-old adage of  
emergency medicine.**



Both the American College of Surgery and the Eastern Association for the Surgery of Trauma recommend intubation for trauma patients with a GCS of 8 or less, based on the assumption that comatose patients face a high risk of aspiration pneumonitis or pneumonia, and that intubation reduces this risk. However, the evidence supporting this practice is weak and equivocal. Intubation and mechanical ventilation carry inherent risks, including aspiration and pneumonia. This approach is commonly applied to comatose non-trauma patients (e.g., intoxicated), yet data supporting it are scarce and mostly retrospective.

The Non-invasive Airway Management of Comatose Poisoned Emergency Patients (NICO) randomized trial challenged this practice in intoxicated patients. Among 225 patients with a GCS < 9 due to suspected intoxication or poisoning, immediate intubation was compared to intubation at the discretion of the treating physician. Most patients were young (mean 33 years) and male (62%), with median GCS 6, usually intoxicated with alcohol (67%). Many also had ingested gamma-hydroxy-butyrate (GHB or its analogues), a “club drug” with a very short half-life. Only 16% of those in the intervention group were eventually intubated, vs 58% in the immediate intubation group. (Enough of the “immediate” intubation patients improved quickly enough after enrollment to not need intubation).

# VIEWPOINTS

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The delayed-intubation group had significantly fewer adverse events of intubation, shorter hospital [(21 hours vs 37 hours length of stay) and avoid the ICU entirely (median zero hours vs 24 hours)] stays, and lower risks [including pneumonia (7% vs 15%) or adverse events of intubation (6% vs 15%)]. Delaying intubation did not seem to result in more-difficult intubations, if they became necessary.

The Freund et.al study challenges the "GCS of 8, intubate" dogma, particularly in alcohol-intoxicated patients. Early intubation appeared to increase the intended outcome, aspiration pneumonia, without averting catastrophes. The trial suggests a potential shift towards delaying intubation, aligning with the existing practice in opioid intoxication cases in the U.S. This study makes me want to have a much higher threshold to intubate solely for airway protection regardless of etiologies including the likes of alcohol/drug overdose or hepatic encephalopathy etc.



# ORIGINAL STUDY SUMMARIES:

## ANGIOTENSIN II FOR THE TREATMENT OF REFRACTORY SHOCK: A MATCHED ANALYSIS, 2023

**Background & Aim:** This is a retrospective matched cohort study of adult patients with shock admitted to an ICU at a large, university-based health system over a 6 year period. The goal of this trial was to determine if, in patients with severe, refractory shock requiring high doses of vasopressors, does the addition of angiotensin II (AT2) improve 30-day and 90-day mortality?

### **Clinical Features & Methods & Inclusion/Exclusion:**

Retrospective, matched analysis data was gathered from 813 adult patients with shock admitted to an ICU and requiring vasopressor support. Comparison of patients receiving angiotensin II compared with both historical and concurrent controls receiving equivalent doses of nonangiotensin II vasopressors.

#### Inclusion:

- Adult patients ( $\geq 18$  yr old)
- Received an IV infusion in the ICU between 1/1/2016 and 2/28/2022 of:
  - norepinephrine
  - epinephrine
  - phenylephrine
  - vasopressin
  - dopamine
  - AT2

#### Exclusion:

- If Patient was given AT2 in the operating room.

Two control populations were identified, one historical and the other concurrent. Study defined historical controls as patients who received vasopressors before AT2 was available (to account for possible changes in practice with AT2 use). Patients who received vasoconstrictors (outside of AT2) after 3/18/2018 (when AT2 first became available in hospital) were defined as concurrent controls.

# ORIGINAL STUDY SUMMARIES:

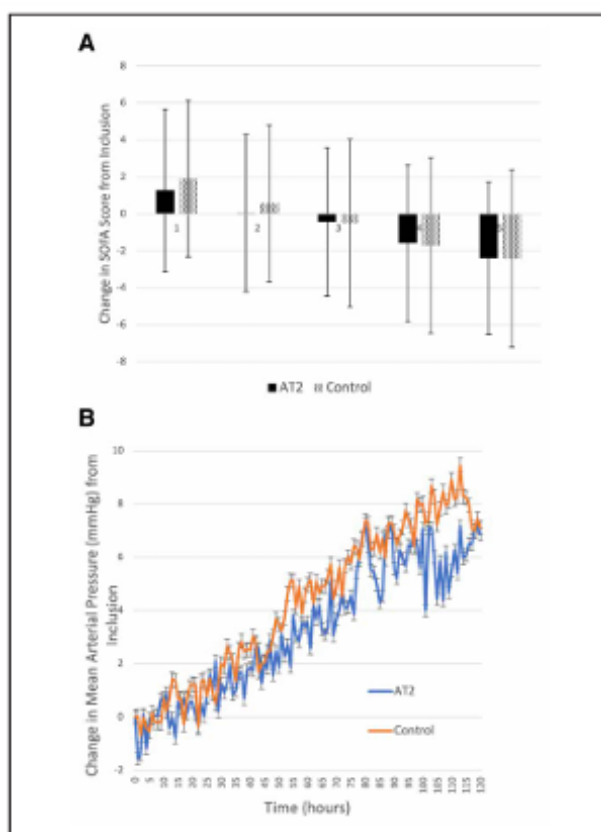
## ANGIOTENSIN II FOR THE TREATMENT OF REFRACTORY SHOCK: A MATCHED ANALYSIS, 2023

Doses of epinephrine, phenylephrine, vasopressin, and dopamine were converted to NEs. **See table.** Changes in blood pressure and organ failure. **See Figure 1.**

**Table S1. Equivalent Vasoconstrictor Doses to Norepinephrine.**

Drug	Drug Dose	Norepinephrine Equivalent
Norepinephrine	0.1 µg/kg/min	0.1 µg/kg/min
Epinephrine	0.1 µg/kg/min	0.1 µg/kg/min
Phenylephrine	1 µg/kg/min	0.1 µg/kg/min
Dopamine	15 µg/kg/min	0.1 µg/kg/min
Vasopressin	0.04 U/min	0.1 µg/kg/min

The conversion table was derived from the cardiovascular Sequential Organ Failure Assessment score and previously published data comparing vasopressin equivalence to norepinephrine<sup>9,19-22</sup>.



**Figure 1.** Change in organ failure and blood pressure. **A,** Plot showing the mean with one sd in daily change in Sequential Organ Failure Assessment (SOFA) score from pre-inclusion values in daily survivors who received angiotensin II (AT2) (solid) or did not (half-tone). *p* values between the groups are 0.318, 0.364, 0.207, 0.424, and 0.435 for days 1–5, respectively. **B,** Plot showing the mean with one sd change in mean arterial blood pressure (mm Hg) from pre-inclusion values during the 5-d monitoring period in patients receiving AT2 and controls.

# ORIGINAL STUDY SUMMARIES:

## ANGIOTENSIN II FOR THE TREATMENT OF REFRACTORY SHOCK: A MATCHED ANALYSIS, 2023

### Results:

Angiotensin II use **was not** associated with:

- 30-day mortality
- 90-day mortality
- Sequential Organ Failure Assessment scores
- Increased rates of kidney replacement therapy
- Receipt of mechanical ventilation
- The rate of thrombotic events
- Improve hypotension
- Improved SOFA scores

### Clinical Interpretation:

Angiotensin II, when used as a salvage therapy, was not associated with improved outcomes (30-day or 90-day mortality). Nor was AT2 associated with an increased rate of adverse events, such as organ dysfunction.

Further studies are needed to determine if AT2 improves outcomes as a first- or second-line vasopressor.

# CORRESPONDING EDITORIAL: IS IT TIME TO RECONSIDER THE CONCEPT OF “SALVAGE THERAPY” IN REFRACTORY SHOCK?

## RE: ANGIOTENSIN II FOR THE TREATMENT OF REFRACTORY SHOCK: A MATCHED ANALYSIS, 2023

Although the diagnostic criteria, risk factors, and frequency of refractory shock are not universally accepted, most clinicians would consider the requirement of high doses of vasopressor agents to be an important part of the diagnosis. Indeed, shock refractory to high doses of vasopressors is associated with extraordinarily high mortality rates, ranging from 60% to greater than 90%. These high mortality rates are consistent with those observed by this study (mean baseline NEE vasopressor dose of approximately 0.62 mcg/kg/min).

### Many questions arise:

- If the opportunity to meaningfully intervene has passed, making concept of a “salvage therapy” inherently flawed?
- Are the opportunities for reversing organ hypoxia and restoring vascular integrity the same in refractory shock as they are in shock that has not progressed to this extent?
- Is it plausible for discrete interventions to drastically alter the course of refractory shock?

Answers to the above questions suggest that “salvage therapy” is *potentially flawed*. Compiling it all, the data suggest that contrary to the environment in the Smith et al. study assessed angiotensin II (AT2), potential benefits of the addition of alternative vasopressors, including AT2, to catecholamine vasopressors such as norepinephrine, maybe realized in settings where progression to refractory shock has not yet occurred, implying earlier addition of secondary or tertiary vasopressors and adjunct treatments (for example, corticosteroids) may be more appropriate. While most will respond to this first line vasopressor, those not achieving goals—at some specified timepoint and vasopressor dose—a secondary vasopressor agent is added and adjunct treatments are considered. Preeminent limitations of this strategy is the time lost in providing satisfactory perfusion when allowing each vasopressor an opportunity to restore hemodynamics. Therefore, once the time has come to add a secondary, tertiary, quaternary agent, there has been greater exposure to hypotension, sub-satisfactory perfusion, tissue hypoxia, and organ failure.

# **CORRESPONDING EDITORIAL: *IS IT TIME TO RECONSIDER THE CONCEPT OF “SALVAGE THERAPY” IN REFRACTORY SHOCK?***

## **RE: ANGIOTENSIN II FOR THE TREATMENT OF REFRACTORY SHOCK: A MATCHED ANALYSIS, 2023**

Longer the MAP is less than 65 mm Hg, higher the odds of AKI, MI and death. There is also increased odds of death with increase in every 10 mcg/min and decline in vasopressor responsiveness for every 1mmol/L increase in lactate concentrations. It may be prudent to consider early multimodal vasopressor strategy where vasopressors bearing differing mechanisms, and adjunctive treatments, are instituted in concert early in shock. Patients randomized to vasopressin when the norepinephrine dose was low ( $< 15$  mcg/min), had a lower risk of death (risk ratio, 0.78; 95% CI, 0.61–0.99) than those who received continued escalation of norepinephrine, an effect not seen at higher vasopressor doses. Also, delayed addition of vasopressin to catecholamine vasopressors is associated with worse outcomes: the odds of death rise by over 20% (OR, 1.21; 95% CI, 1.09–1.34) for every 10 mcg/min increase in vasopressor dose at the time vasopressin is added to catecholamine vasopressors. Similarly, when the vasopressor dose at the time of randomization to angiotensin II was low ( $\leq 0.25$  mcg/kg/min), the hazard of death was nearly half that of continued escalation of other vasopressors

The goals of deploying such a strategy are to maximize the number of treatment responders and minimize the time spent under sub-satisfactory perfusion targets. Having said that there is much to learn about different endotypes of shock and their responses to specific vasopressors.

Now I think we must critically reconsider the potentially flawed concept of “salvage therapy” and seek every opportunity possible to prevent progression to refractory shock. At a personal experience level for what it's worth, the few times I have had some success with AT2 in refractory shock has been in patients with severe acidosis and renal failure while they were on some form of renal replacement therapy, but do not take my work for it. Please feel free to let us know your experience.

# SNAPSHOTS

## When does a smoker become a never smoker?

When Does Excess Smoking-Related Mortality Subside After Quitting?

Paul S. Mueller, MD, MPH, FACP, reviewing Thomson B and Islami F. *JAMA Intern Med* 2023 Nov 27

*Thirty years after quitting, former smokers avoided nearly all excess cardiovascular-, cancer-, and respiratory-related deaths.*

Smoking cessation results in lower risk for early death compared with continued smoking. However, the time frame during which this benefit accrues is unclear. Researchers analyzed nationally representative data on 440,000 adults (mean age, 47) from the U.S. National Health Interview Survey and National Death Index and determined the association between years since quitting and death. During a mean 11 years of follow-up, current smokers' risks for cardiovascular-, cancer-, and respiratory-related deaths were 2, 3, and 13 times higher, respectively, than never smokers' risks. Former smokers who had quit <10 years before enrollment avoided roughly 50% to 60% of these excess risks. Thirty years after quitting, excess mortality was virtually eliminated.

## Comment

This study shows that smoking cessation's effects on cardiovascular, cancer, and respiratory mortality are large and accrue over time: After 30 years of sustained cessation, former smokers have death rates for these causes that are comparable to those in never smokers. These findings should be helpful when counseling former smokers who are concerned about lingering adverse effects of prior smoking.

# SNAPSHOTS

**Confused about eligibility of different pneumococcal vaccines in the clinic?  
Maybe give any and all vaccines !**

2023 Guidelines for Pneumococcal Vaccination of Adults aged  $\geq 19$  years.

**Target Group:** Healthcare practitioners who provide care for adults.

## Key Recommendations

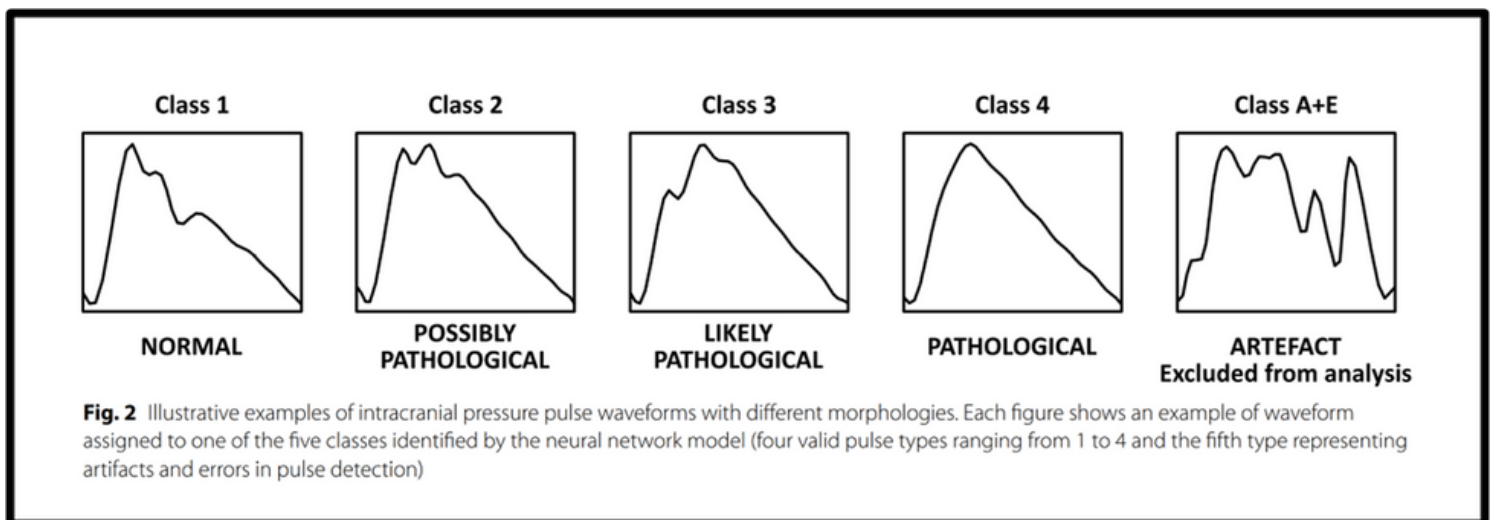
- Pneumococcal vaccination is not recommended in healthy adults younger than 65.
- Adults aged 19–64 with underlying medical conditions who have not previously received a pneumococcal conjugate vaccine should receive either PCV20 alone or PCV15 followed by PPSV23 given  $\geq 1$  year later. No PPSV23 is needed if PCV20 is given.
- Adults aged 19–64 with underlying medical conditions who have received only one dose of PPSV23 should receive either PCV15 or PCV20 at least 1 year after their PPSV23 vaccination.
- Adults aged 19–64 with underlying medical conditions (or healthy adults aged  $\geq 65$ ) who have received PCV13 alone should receive either PCV20 or PPSV23 at least 1 year later.
- Vaccine-naïve adults aged  $\geq 65$  should receive either PCV20 alone or PCV15 followed by PPSV23 given  $\geq 1$  year later.

Although these vaccines provide successive overlap in the covered serotypes, the nature and duration of immunity varies; thus, some vaccines require re-immunization. Previous guidelines in 2021 recommended use of PPSV23 alone (2 doses) or PCV13 followed by PPSV23.

# SNAPSHOTS

Now would be a good time to wake up the Neurointensivist or Neurosurgeon.

*Intra cranial pressure pulse (ICP) waveforms of concern or not?*





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