9-2023

# Pulmonary & Critical Care Insider: Issue 2

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# PULMONARY & CRITICAL CARE INSIDER

## Issue 2

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# VIEWPOINTS:
# FEEDING THE ICU (INTENSIVE CARE UNIT)

***VIEWPOINTS COMPILED BY BHARAT BAJANTRI, MD.***
***ADOPTED FROM PULMCC AND CITED ARTICLES.***

## *Make sure tube feeds are held for the Spontaneous Breathing Trial (SBT)... or not?*

At 22 ICUs (Intensive Care Unit) in France, 1130 mechanically ventilated patients already receiving enteral feedings were cluster-randomized (i.e., by center) to have feeds stopped 6 hours before and their gastric tubes suctioned prior to extubation, compared to continued feedings and no suctioning.

- At 7 days after extubation, identical numbers of patients (in the intention-to-treat analysis) had been reintubated or had died (17.2% vs 17.5%)
- Patients whose enteral feedings continued received significantly more calories.
- Lower incidence of pneumonia among those with continued enteral feeds (1.6% vs 2.5%)

Because the trial was unblinded and intended as a non-inferiority trial, you cannot put too much stock in the findings unless it is replicated.

**This study makes me less worried about aspiration in recently extubated patients, and less anxious about extubating without a period of fasting or gastric suctioning.**

## *Is there a reason to document severe malnutrition other than the coders request? EFFORT Protein trial.*

Protein requirements in supplemental nutrition during critical illness remain unknown, and multiple high-quality randomized trials have shown no benefit to any altered nutritional product, versus its control.
In the EFFORT Protein trial, ~1300 - critically ill patients at considerable risk for malnutrition defined as:

1. BMI (Body Mass Index) <25 or > 35
2. Moderate to Severe Malnutrition by assessment
3. Frailty
4. Sarcopenia
5. Projected MV days > 4 days

Patients were randomized to receive either high dose protein (≥2.2 g/kg per day) or usual dose (≥1.2 g/kg per day). **There was no benefit observed (in time-to-discharge-alive from the hospital or overall mortality), and patients with acute kidney injury and additional organ failure who received high protein doses appeared to be harmed.**

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***Trickle the feed or fill the stomach?***
***NUTRIREA-3 trial***

In the NUTRIREA-3 trial conducted in France, 3044 patients receiving invasive mechanical ventilation and vasopressors were randomized to receive either standard calorie and protein feedings (6 vs 25 kcal/kg per day and 0·2–0·4 vs 1·0–1·3 g of protein/kg per day) in the first 7 ICU days.

- Patients were receiving high-dose norepinephrine (median 0.5 µg/kg/min, or 35 mcg/min for a 70 kg person) and enteral feedings were started and advanced without regard to the vasopressor dose
- There was no observed difference in 90-day mortality (41% vs 43%), but the restricted calorie group were ready for ICU discharge one day sooner and had fewer adverse effects attributable to enteral feedings (vomiting, diarrhea, bowel ischemia and liver dysfunction)
- Usual practice in the U.S. is to restrict caloric delivery in patients with this degree of shock which is validated by these findings.

Because overall acuity of the patients was remarkably high with high vasopressor requirements and high overall mortality, it is difficult to conclude that feeding less is superior but **clearly not inferior to feeding more.**

## Announcements

**We would like to welcome a new provider starting with our group.**

**Welcome Dr. Matthew Paparo!**

# ACUTE HYPOXEMIC RESPIRATORY FAILURE AFTER TREATMENT WITH LOWER TIDAL VOLUME VENTILATION FACILITATED BY EXTRACORPOREAL CARBON DIOXIDE REMOVAL: LONG-TERM OUTCOMES FROM THE REST RANDOMIZED TRIAL

**Aim of Study**

Evaluation of the effectiveness of lower tidal volume ventilation, facilitated by veno-venous extracorporeal carbon dioxide removal (vv-ECCO2 R), on long term outcomes for ICU patients with acute hypoxemic respiratory failure (AHRF).

**Clinical Features/Methods/Inclusion/Exclusion**

N= 412. Patients were eligible if they were within 48 hours of onset of an acute and potentially reversible cause of hypoxemic respiratory failure (PF ratio<150 mm Hg) while receiving invasive mechanical ventilation with a PEEP of at least 5 cm H2O.
Mortality to 2 years was assessed, while respiratory function, post-traumatic stress disorder, cognitive function and health-related quality of life were evaluated in survivors at 1 year using standardized questionnaires.

- Randomized Patients for Intervention: vv-ECCO2 R was commenced with sweep gas flow of 10 L/min was given. Goal Tidal volume ≤3 mL/kg predicted body weight. Duration 2-7 days.
- Randomized Patients for Standard Care: Received mechanical ventilation with a tidal volume 6 mL/kg predicted body weight, with PEEP titrated according to the ARDSNet protocol.

For long-term follow up of the cohorts: SGRQ, PTSS, MoCA and EuroQol questionnaires used. Limitations included Significant Bias; only 40% of eligible patients provided responses to the questionnaires, and 33% of those were fully completed and may not fully reflect the health status of all survivors to 1 year. Additionally, questionnaires were self-reported or completed by proxy.

**Results**

Lower-tidal volume ventilation, facilitated by vv-ECCO2 R, does not affect long-term mortality. There was no statistically significant difference between treatment arms in 90-day mortality or other long-term outcomes in patients with moderate-to-severe AHRF who completed follow-up. It has been demonstrated that the intervention studied in the REST trial did not reduce mortality at either 6 months or 1 year from randomization. In the patients who provided questionnaire responses, the intervention did not significantly reduce the long-term physical or neuropsychological symptoms, nor improve their health-related quality of life.

**Clinical Interpretation**

These findings reinforce that a lower tidal volume ventilation strategy, facilitated by vv-ECCO2 R as delivered in the REST trial, should not be used in the management of patients with moderate-to-severe AHRF, and should not be used routinely (outside the setting of clinical trials).

# EFFICACY OF A CLINICAL DECISION RULE TO ENABLE DIRECT ORAL CHALLENGE IN PATIENTS WITH LOW-RISK PENICILLIN ALLERGY: THE PALACE RANDOMIZED CLINICAL TRIAL

## *I am allergic to penicillin …. just kidding !!!*

**Aim of Study**

To verify or disprove a penicillin allergy in adults by comparing allergy testing methods. The Penicillin Allergy Clinical Decision Rule (PALACE) study evaluated whether risk-stratified direct oral challenge with penicillin was noninferior to penicillin prick and intradermal skin testing followed by an oral challenge in patients with low-risk penicillin allergy (PEN-FAST score <3).

**Clinical Features/Methods**

The PALACE study, a multicenter, parallel, 2-arm, noninferiority, international, open-label, randomized clinical trial, was conducted in outpatient clinics at 6 centers, (US, Cananda, Australia). Eligible adults had a PEN-FAST score lower than 3. Study had 382 Patients were randomly assigned to either direct oral challenge with penicillin (intervention arm) or a standard-of-care arm of penicillin skin testing followed by oral challenge with penicillin (control arm).

| PEN-FAST Score | % Risk of Penicillin Allergy |
|---|---|
| 0 | <1% (very low risk) |
| 1-2 | 5% (low risk) |
| 3 | 20% (moderate risk) |
| 4-5 | 50% (high risk) |


**Results:**

1 of 187 patients in the intervention group and 1 of 190 patients in the control group had an immune-mediated reaction to the oral penicillin, which presented as a mild cutaneous skin reaction. This was resolved with a single dose of antihistamine.

Adverse Events: The 5-day adverse events occurred after an average of 4 hours following the oral penicillin challenge in the intervention group and an average 6 hours in the control group. All reported adverse events were subcategorized into immune or nonimmune mediate. No adverse events led to hospitalization or emergency department presentation.

**Clinical Interpretation:** This study suggests that fewer than 5% of patients labeled with a penicillin allergy are truly allergic. In low-risk penicillin allergy adult patients, direct oral penicillin challenge is a safe and effective procedure that may facilitate the removal of a larger number of penicillin allergy labels and provide better patient treatment. This was a trial in the outpatient setting but could be extrapolated to inpatient population in the right clinical setting.

# ETOMIDATE AS AN INDUCTION AGENT FOR ENDOTRACHEAL INTUBATION IN CRITICALLY ILL PATIENTS: A META-ANALYSIS OF RANDOMIZED TRIALS

## *Etomidate increases mortality – does it though?*

**Aim of the study:** Meta-analysis of randomized controlled trials to evaluate if etomidate impacted mortality in critically ill adults when compared with other induction agents.

**Materials and methods**: Included 11 randomized controlled trials comprising 2704 patients which compared etomidate with any other induction agent in critically ill adult patients undergoing endotracheal intubation. The primary outcome was mortality at the main timepoint defined by the study.

**Findings**: Etomidate increased mortality (319/1359 [23%] vs. 267/1345 [20%]; risk ratio (RR) = 1.16; 95% confidence interval (CI), 1.01–1.33; P = 0.03)

**Conclusion**: This meta-analysis found a high probability that etomidate increases mortality when used as an induction agent in critically ill patients with a number needed to harm of 31.

**Clinical interpretation**: At least 50% of the trials included had a control arm receiving midazolam. Only two RCTs had only ketamine in the control arm, and both showed no difference in 28 mortality with one of them suggesting increased 7-day mortality with etomidate was an open label RCT.

This meta-analysis suggests need for further studies to establish if there are truly worse outcomes associated with etomidate as an induction agent, there certainly is not enough evidence to change current practice of using etomidate as an induction agent at this time.

# SPICE 3: PRECEDEX WITH CAUTION: HEALTH ALERT BY NATIONAL AGENCIES IN EUROPE AND NEW ZEALAND

SPICE III was a randomized controlled trial that included 4000 patients and evaluated the mortality among ICU patients receiving dexmedetomidine at a maximum dose of 1.5 mcg/kg/h adjusted to reach a targeted Richmond Agitation and Sedation Scale (RASS) score of − 2 to+1, compared to usual care involving propofol and benzodiazepines. The study reported no significant difference in 90-day mortality.

- The Dexmedetomidine group needed more sedative agents when compared with the control group, reflecting a potential and considerable efficacy issue of the agent.

- Significantly higher incidence of adverse effects including bradycardia (5.1% vs. 0.5%, p= <0.0001), hypotension (2.7% vs. 0.5%, p= <0.0001), and persistent asystole (0.7% vs. 0.1%, p=0.003), indicating a potential major flaw of the indiscriminate use of dexmedetomidine.

- Although exploratory results from subgroup and post-hoc Bayesian analysis should be taken cautiously, a subgroup analysis revealed a significantly higher mortality observed in patients younger than 65 years. Another subgroup analysis from the study also indicated that increasing the dexmedetomidine dose was associated with elevated 90-day mortality in younger (age < 65 years) patients.

- Finally, a systematic review and meta-analysis of controlled randomized trials evaluated the use of dexmedetomidine in patients with sepsis reported a lower mortality associated with dexmedetomidine.

**Takeaways**

1. Nonetheless, this reduction in mortality was only consistently observed when compared only to benzodiazepines, but not with propofol.
2. Dexmedetomidine was also not found to be associated with a lower risk of delirium compared to other sedatives. Additionally, dexmedetomidine did not demonstrate a reduction in ICU days compared to other sedatives, nor did it reduce the duration of mechanical ventilation or increase ventilator free days
3. Dexmedetomidine presented a higher risk of arrhythmias but not hypotension.

# SNAPSHOTS

## Albumin for cirrhotic patients in septic shock

(from "*Identification of indications for albumin administration in septic patients with liver cirrhosis*. Critical Care. 2023)

| Indications for albumin infusion | Good outcome threshold | Best mortality outcome threshold |
|---|---|---|
| Serum Albumin levels | 2.5 – 3.0 g/dL | < 2.7 g/dL |
| Serum Lactate | ➢ 2.0 mmol/L | ➢ 2.2 mmol/L |
| MAP | < 60 mm Hg | |
| Vasopressor use | < 60 mm Hg, regardless of vasopressor choice or dose | Norepinephrine equivalent dose 0.2 to 0.3 mcg/kg/min |

- Effects maintained with both 5% and 25% albumin.
- Secondary analysis showed the beneficial effects of albumin infusion were compromised when daily dose of albumin exceeds 1.0 mg/Kg.

## Myositis ILD (Interstitial Lung Disease) associations. Hallowell, R. W., & Danoff, S. K. (2023)

**TABLE 1** ] Antisynthetase Antibodies

| Antibody | Target Antigen | ARS-Abs Detected, %[23,26,27,31,32] | Patients With Lung Involvement,[a] %[11,12,26-28,33-37,31,38-45] | Patients With Muscle Involvement,[a] %[11,12,26-28,33-37,31,38-45] | Distinct Clinical Features[21,26,27,36,37,31,46,47] |
|---|---|---|---|---|---|
| Anti-Jo-1 | Histidyl-tRNA synthetase | 22-73 | 69 | 84 | Arthralgias, mechanics hands, myositis |
| Anti-PL-12 | Alanyl-tRNA synthetase | 6-17 | 91 | 33 | Raynaud's, isolated ILD |
| Anti-PL-7 | Threonyl-tRNA synthetase | 10-18 | 75 | 66 | Heliotrope rash, severe ILD, myositis, pericardial effusions |
| Anti-EJ | Glycyl-tRNA synthetase | 2-23 | 98 | 56 | |
| Anti-OJ | Isoleucyl-tRNA synthetase | 2-5 | 100 | 44 | Severe myopathy, lower incidence of Raynaud's |
| Anti-KS[b] | Asparaginyl-tRNA synthetase | 3-8 | 100% | 5% | Isolated ILD |
| Anti-ZO[b] | Phenylalanyl-tRNA synthetase | Rare | ... | ... | ... |
| Anti-HA/YRS[b] | Tyrosyl-tRNA synthetase | Rare | ... | ... | ... |

ARS-Ab = antisynthetase antibody; ILD = interstitial lung disease.
[a]Values shown are the average of studies listed.
[b]These antibodies are not commercially available.

## Blood cultures from A lines... Duhhhh just do it!!!!

(from "*Contamination of Blood Cultures From Arterial Catheters and Peripheral Venipuncture in Critically Ill Patients: A Prospective Multicenter Diagnostic Study*". Chest. 2023)

Prerequisites:

- Closed sampling system
- Sterile technique
- In the ICU not ED (Emergency Department)
- Avoid collection from femoral A lines (only 1.9% of patients (11/590) in the trial had femoral A lines for risk of contamination)

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