COVID-19


  o Objective
    ▪ Determine if HFNC reduces intubation rate and mortality in patients with COVID-19 and acute respiratory failure.

  o Study
    ▪ Retrospective study of 379 critically ill patients
    ▪ Multicenter study of 4 ICU’s in France
    ▪ Patients
      ▪ Adults ≥ 18 years of age
      ▪ Acute respiratory failure defined as:
        ▪ RR > 25,
        ▪ bilateral pulmonary infiltrates on CXR/CT
        ▪ need for ≥ 3L/min nasal cannula to keep SpO2 > 92%
      ▪ COVID19 positive
    ▪ Interventions - HFNC (with initial flow rate ≥ 50L/min) vs standard O2 therapy
    ▪ Primary Outcome – need for invasive mechanical ventilation
    ▪ Secondary Outcome 28-day mortality
    ▪ Statistical Analysis
      ▪ Outcomes were risk adjusted for immunosuppression, Admission within 7 days of symptom onset, vasopressors, and AKI
      ▪ Adjusted case matching was performed on 1:1 ratio

  o Results
    ▪ 379 patients were enrolled
      ▪ Median age was 66 years’ old
      ▪ Common co-morbidities of HTN (50%), DM (30%), immunosuppression (18%), CKD, obesity; not different between groups
      ▪ 146 (39%) of patients received HFNC within first 24 hours of ICU admission, compared to 233 (51% who did not); 137 subjects were matched for comparison.
    ▪ Primary Outcome
      ▪ HFNC was associated with a reduced proportion of pts requiring IMV
    ▪ Secondary Outcomes
      ▪ No difference in Day 28 mortality (21% in HFNC group vs. 22% in the other group)

  o Take Home Point
    ▪ This study highlights that HFNC was as safe as standard oxygen in a large cohort of patients with COVID-19

- **Objective**
  - Determine the effect of dexamethasone (multiple treatment arms) on outcomes in patients with COVID19

- **Study**
  - Design: Multicenter, randomized control trial at 176 hospitals
  - Power: Assuming a 28-day mortality of 20%, enrollment of at least 2000 patients in the dexamethasone group and 4000 in the usual care group to provide a power of at least 90% at a two-sided P value of 0.01 to detect a clinically relevant proportional reduction of 20% (an absolute difference of 4 percentage points) between the two groups
  - Inclusion was BROAD
    - Adults >= 18 years of age
    - No medical history that might, in the opinion of the attending clinician, put patients at substantial risk
  - Intervention
    - Eligible and consenting patients were assigned in a 2:1 ratio to receive either the usual standard of care alone or the usual standard of care plus oral or intravenous dexamethasone (at a dose of 6 mg once daily) for up to 10 days (or until hospital discharge if sooner)
  - Primary Outcome
    - All-cause mortality within 28 days
  - Secondary outcome
    - 6-month outcomes
    - Time until discharge from the hospital
    - Need for intubation, ECMO, or death
    - Cause specific mortality, need for hemodialysis, duration of mechanical ventilation

- **Results**
  - 6,425 total patients enrolled (2,104 in the dexamethasone arm; 4321 in usual care arm)
    - Mean age 66 years old; 36% female
    - 16% were receiving mechanical ventilation or ECMO at randomization
    - 60% receiving O2 therapy
  - Primary Outcome
    - Mortality at 28 days was significantly lower in the dexamethasone group than in the usual care group (22.9% in the steroids group vs. 25.7% in the usual care group)
      - Trend showing the greatest absolute and proportional benefit among patients who were receiving invasive mechanical ventilation
      - In the dexamethasone group, the incidence of death was lower than that in the usual care group among patients receiving invasive mechanical ventilation (29.3% vs. 41.4%)
  - Secondary Outcome
• Dexamethasone group had shorter duration of hospitalization and greater probability of discharge alive within 28 days.
• The risk of progression to invasive mechanical ventilation was lower in the dexamethasone group.

- Limitations
  - Comparison group is made of patients receiving “usual care” – 8% of usual care group received dexamethasone.

- Authors Take Home Point
  - The RECOVERY trial provides evidence that treatment with dexamethasone at a dose of 6 mg once daily for up to 10 days reduces 28-day mortality in patients with Covid-19 who are receiving respiratory support. There was no benefit (and the possibility of harm) among patients who did not require oxygen.

  - Objective
    - Determine the efficacy and safety of Remdesivir on outcomes in patients with COVID19
  - Study
    - Design: Phase 3, Randomized, double-blind, international, placebo-controlled trial
    - Inclusion
      - Adults >= 18 years of age
      - COVID (+) with severe disease
        - Patients were considered to have severe disease if they required mechanical ventilation, if they required supplemental oxygen, if the oxygen saturation as measured by pulse oximetry ($SpO_2$) was 94% or lower while they were breathing ambient air, or if they had tachypnea (respiratory rate ≥24 breaths per minute)
    - Intervention
      - Eligible patients were randomly assigned in a 1:1 ratio to receive either intravenous remdesivir (given as a 200mg loading dose on day 1 followed by a 100mg maintenance dose on days 2-10) vs placebo
      - All patients received supportive care according to the standard of care for the trial site hospital.
    - Primary Outcome
      - Time to recovery, defined as the first day (during 28 days after enrollment) which patients met a prespecified recovery category (either discharged or not requiring supplemental oxygen)
    - Secondary outcome
      - Clinical status at day 15 using same clinical outcome scale
  - Results
    - 1062 subjects randomized (521 to placebo, 541 to remdesivir)
      - Mean age 59 years old; 36% female
• Median number of days between symptom onset and randomization was 9 days
• 90% had severe disease at enrollment

Primary Outcome
• Patients in the remdesivir group had a shorter time to recovery than patients in the placebo group (median, 10 days, as compared with 15 days)
• In the severe disease stratum (957 patients) the median time to recovery was 11 days, as compared with 18 days
• Kaplan–Meier estimates of mortality by day 15 were 6.7% in the remdesivir group and 11.9% in the placebo group

Secondary outcome
• Patients receiving oxygen at enrollment, those in the remdesivir group continued to receive oxygen for fewer days than patients in the placebo group (median, 13 days vs. 21 days)

Limitations
○ The primary outcome of the current trial was changed early in the trial, from a comparison of the eight-category ordinal scale scores on day 15 to a comparison of time to recovery up to day 29.

Authors Take Home Point
○ Remdesivir was superior to placebo in shortening the time to recovery in adults who were hospitalized with Covid-19 and had evidence of lower respiratory tract infection.

Acute GI Bleed

Objective
○ Quantify the effects of TXA on death and thromboembolic complications in patients with an acute gastrointestinal hemorrhage

Study
○ International, randomized, multi-center, double-blind placebo-controlled pragmatic trial
○ 15 countries including 164 hospitals
○ Inclusion criteria were clinical: adult (either 16 or 18 years) and treating clinician was “substantially uncertain” whether to use TXA for patients with a significant GI bleed
○ Significant GI bleed defined as: “risk of bleeding to death and included patients with hypotension, tachycardia, or signs of shock, or those likely to need transfusion or urgent endoscopy or surgery”

Intervention
○ Intervention group: loading dose of 1 g TXA was added to a 100 mL infusion bag of 0.9% sodium chloride and infused by slow intravenous injection over 10 min, followed by a maintenance dose of 3 g tranexamic acid added to 1 L of any isotonic intravenous solution and infused at 125 mg/h for 24 h
- **Control group:** 100 mL infusion bag of 0.9% sodium chloride and infused by slow intravenous injection over 10 min, followed by a maintenance dose of 1 L of any isotonic intravenous solution and infused at 125 mg/h for 24 h

- **Outcomes**
  - Primary: death due to bleeding within 5 days of randomization

- **Results**
  - 12,009 total patients were enrolled (10,190 prior to change in primary outcome) of which 5994 (49.9%) were randomized to TXA and 6015 (50.1%) were in placebo group
  - Primary outcome: NO DIFFERENCE in death due to bleeding at 5 days (3.7% vs. 3.8%, RR 0.99) in TXA and placebo group, respectively

- **Secondary Outcomes**
  - No difference in death from bleeding at 24 hours and 28 days
  - No difference in all-cause mortality at 28 days
  - Similar proportion of patients with rebleeding, surgery, radiological intervention, and blood product transfusion
  - No change in ICU duration or Katz score

- **Complications**
  - Higher rates of venous thromboembolic events [0.8% vs. 0.4%, OR 1.85 (1.15 to 2.98)] in TXA group

- **Limitations**
  - Primary outcome was changed from all-cause mortality at 5 days to death due to bleeding at 5 days of randomization on 11/2018 due to a high percentage of deaths from non-bleeding causes
  - Clinical diagnosis of GI bleed and inclusion of wide spectrum of bleeds
  - Potential for misclassification of location and type of bleed by study teams
  - Patients without equipoise for TXA were excluded

- **Take Home Point**
  - TXA does not reduce death from GI bleeding and should not be used as part of a uniform approach to treat GI bleeding

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**Sepsis**

- **Jackson, et al. Effect of early balanced crystalloids before ICU admission on sepsis outcomes. Chest. 2020; online ahead of print.**

  - **Objective**
    - What is the impact on sepsis outcomes of fluid composition during early resuscitation in the ED vs after ICU admission?

  - **Study**
    - A secondary analysis of the SMART data set
      - Recall the SMART study was a cluster-crossover trial comparing balanced crystalloids vs saline among critically ill adults
      - This particular study examined the final 15 months of the trial, when fluid choice was coordinated between the ED and ICU.
    - **Patients**
      - 15,802 patients in the SMART study
      - 1,641 with sepsis
      - 1,247 sepsis patients admitted during the final 15 months
Primary Outcome

- 30-day in-hospital mortality

Results

- 30-day in-hospital mortality
  - Balanced crystalloid group: 24.9%
  - 0.9% NS group: 30.6%
  - OR 0.68

Secondary outcomes all favored balanced crystalloid group

- More ICU-free days
- More ventilator-free days
- More vasopressor-free days
- More RRT-free days

Limitations

- SMART study was unblinded and from single center
- The evaluation of fluid choice in sepsis was not a primary outcome of SMART
- This was not a randomized trial

Take Home Point

- The use of balanced crystalloids early in sepsis resuscitation (i.e., in the ED) may have a greater effect on survival than if selected once admitted to the ICU.


Objective

- Evaluate the impact of early and late start of norepinephrine support on clinical outcomes in patients with septic shock

Study

- Systematic review and meta-analysis
- Included RCTs, prospective cohorts, and retrospective cohorts that evaluated adult patients in septic shock, compared early vs. late norepinephrine initiation, and reported on short-term mortality
- Primary outcome was short-term mortality: in-hospital mortality, 28-day mortality, 30-day mortality
- Secondary outcomes: ICU LOS, time to achieve MAP > 65 mm Hg, and volume of IVFs within 6 hours

Results

- Included 5 studies: 2 RCTs, 3 cohort studies; all were single-center studies
- 929 patients
- Short-term mortality
  - Early norepinephrine group: 21.6%
  - Late norepinephrine group: 37%
  - OR 0.45
- Secondary outcomes favored early norepinephrine group
  - Shorter time to achieve target MAP
  - Overall lower volume of IVFs
**Limitations**
- Definition of early vs late differed between studies: one defined as < 1 hr, some defined as < 2 hrs, some defined as < 6 hrs
- Overall were only able to find 5 studies, all of which were single-center
- Heterogeneity among patient populations in the studies

**Take Home Point**
- Early administration of norepinephrine in patients with septic shock may be associated with decreased short-term mortality, shorter time to target MAP, and less use of IVFs

  - **Objective**
    - Does vitamin C, high-dose thiamine, and hydrocortisone resolve septic shock?
  - **Study**
    - Open-label, parallel-group, RCT
    - 10 ICUs in Australia, New Zealand, and Brazil
    - Included adult patients admitted to the ICU with septic shock (lactate > 2 mmol/L, 2 hrs of vasopressors, and 2-point increase in SOFA score)
    - Randomized
      - **Intervention Group**
        - Vitamin C: 1.5 grams every 6 hrs
        - Hydrocortisone: 50 mg every 6 hrs
        - Thiamine: 200 mg every 12 hrs
      - **Control Group**
        - Hydrocortisone: 50 mg every 6 hrs
        - Thiamine could be given at discretion of treating physician
  - **Primary outcome**: time alive and free of vasopressors at 7 days
  - **Results**
    - 211 Patients
    - **Primary outcome**
      - Intervention group: 122.1 hrs
      - Control group: 124.6 hrs
    - **Secondary outcomes**
      - No difference in all-cause, 28-day, or 90-day mortality
      - No difference in 28-day cumulative vasopressor-free days
      - No difference in vasopressor-free days
      - No difference in RRT-free days
  - **Limitations**
    - Open-label, non-blinded to outcome
    - Did not assess individual effects of vitamin C
    - Trial not powered to detect mortality difference
  - **Take Home Point**
    - The combination of vitamin C, hydrocortisone, and thiamine did not affect time alive and free of vasopressors at day 7

Objective
- Evaluate the efficacy and safety of hydrocortisone, vitamin C, and thiamine in sepsis and septic shock

Study
- Randomized, single-blind, controlled trial
- Single center in China
- Patients
  - Adults > 18 years of age
  - Admitted to the ICU
  - Met Sepsis-3 criteria
  - Procalcitonin > 2 ng/ml
- Randomized
  - Treatment Group
    - Vitamin C: 1.5 gm every 6 hrs for 4 days
    - Hydrocortisone: 50 mg every 6 hrs for 4 days
    - Thiamine: 200 mg every 12 hrs for 4 days
  - Control Group
    - Matched normal saline infusions
- Primary outcome: 28-day all-cause mortality

Results
- 80 patients: 40 in each group
- Primary Outcome
  - Treatment Group
  - Control Group
  - No statistical difference
- Subgroup analysis: patients with sepsis < 48 hrs at ICU admission had improved 28-day mortality (13.6% vs. 47.6%)
- Secondary outcomes
  - No difference in ICU LOS
  - No difference in duration of vasopressor use
  - No difference in mean procalcitonin clearance rate

Limitations
- Study terminated early - underpowered
- Single center with small sample size
- 28 patients in the Control group did not receive matched saline infusions

Take Home Point
- Hydrocortisone, vitamin C, and thiamine did not reduce 28-day all-cause mortality


Objective:
- To determine whether the combination of ascorbic acid, corticosteroids, and thiamine attenuates organ injury in patients with septic shock.
Randomized, blinded, multicenter clinical trial of ascorbic acid, corticosteroids, and thiamine vs placebo for adult patients with septic shock.

**Inclusion**
- Adults >= 18 years of age, suspected or confirmed infection and receiving vasopressors
- Excluded if taken hydroxychloroquine prior to hospital presentation, QTc > 500 ms or medications that prolong QTc
- COVID (+) with severe acute respiratory distress syndrome

Randomized in a 1:1 ratio, block sizes (2 and 4) with concealed allocation.

**Intervention**
- Intravenous Vitamin C (1500 mg), hydrocortisone (50 mg), and thiamine (100 mg) every 6 hours for 4 days (n = 103) or placebo in matching volumes at the same time points (n = 102).
- Enrolled within 24 hours of identification as meeting inclusion

**Primary Outcome**
- Change in the Sequential Organ Failure Assessment (SOFA) score between enrollment and 72 hours

**Results**
- 205 patients were randomized out of 4569 that met inclusion (831 were eligible, 224 consented)
- 100 patients were in the intervention group, 99 were analyzed in the placebo group
- Mean age ~67 years old; 44% female
- Median number of days between symptom onset and randomization was 5 days

**Primary Outcome**
- There was no statistically significant interaction between intervention group and time over 72 hours for the primary outcome of change in SOFA score

**Secondary outcomes**
- There was no statistically significant difference in kidney failure incidence between groups (31.7% in the intervention group vs 27.3% in the placebo group)
- There was no statistically significant difference in 30-day mortality between the intervention and placebo groups

**Additional comments**
- Compared with the VITAMINS study, this trial did not include corticosteroids in the control group. (VITAMINS was also a negative trial)

**Limitations noted by Authors**
- Ongoing or planned corticosteroid use was the most common exclusion criterion
- A large number of patients were screened but not randomized, which potentially reduces generalizability
- Was not powered for mortality

**Take Home Point**
- Combination of vitamin C, hydrocortisone, and thiamine did not attenuate organ injury after 72 hrs

Objective
- Evaluate the effects of vitamin C and thiamine in the early phase of septic shock

Study
- Randomized, double-blind, controlled trial
- 4 academic EDs in South Korea
- Patients
  - Adults 19-89 years of age
  - Presented to the ED in septic shock
- Randomized
  - Treatment Group
    - Vitamin C: 50 mg/kg
    - Thiamine: 200 mg
    - Every 12 hrs for a total of 48 hrs
  - Placebo Group
    - Matched 0.9% NS infusions
- Primary outcome: change in SOFA score at 72 hrs from ED enrollment

Results
- 111 patients included in the final analysis: 53 in Treatment Group, 58 in Placebo Group
- Primary outcome – change in SOFA score
  - Treatment group: 3
  - Placebo group: 3
  - No statistical difference
- Secondary outcomes
  - No difference in mortality
  - No difference in shock reversal
  - No difference in vasopressor-free days
  - No difference in duration of MV
  - No difference in new RRT need
  - No difference in ICU or hospital LOS

Limitations
- Primary outcome was not patient-centered
- Vitamin C not assessed separately
- Large number of patients in this study had malignancies

Take Home Point
- The combination of vitamin C and thiamine given in the first 48 hrs of ED presentation with septic shock did not improve SOFA scores

Vasopressors

Objective
- Determine the effect of reducing vasopressor exposure in ICU patients 65 years of age and older on 90-day mortality
Study

- Multicenter, pragmatic, randomized trial
- 65 ICUs in the UK

Patients

- Adults > 65 years of age
- Admitted to the ICU
- With vasodilatory shock
- Had received < 6 hrs of vasopressor infusion and expected to need vasopressors for at least 6 more hours

Randomized

- Permissive Hypotension group
  - Vasopressors administered to target a MAP 60-65 mm Hg
- Usual Care group
  - Vasopressors administered and titrated at discretion of the treating clinician

Primary outcome: 90-day all-cause mortality

Results

- 2,598 patients
  - Permissive Hypotension group: 1,291
  - Usual Care group: 1,307
- Primary outcome
  - Permissive Hypotension group: 41%
  - Usual Care group: 43.8%
  - No statistical difference
- Secondary outcomes
  - No difference in ICU mortality
  - No difference in mortality at hospital DC
  - No difference in ICU or hospital LOS
- Adverse Events
  - Permissive Hypotension: 6.2%
  - Usual Care: 5.8%
  - No statistical difference
- Chronic HTN Subgroup
  - 90-day all-cause mortality
    - Permissive Hypotension group: 38.2%
    - Usual Care group: 44.3%
    - Adjusted OR 0.67

Limitations

- Not blinded
- Mortality of patients not adjudicated

Take Home Point

- Permissive hypotension did not reduce 90-day mortality in older ICU patients with vasodilatory shock. There was no increase in adverse events or harm and a signal that those with chronic HTN may actually benefit from a lower MAP

Mechanical Ventilation
  
  o **Objective**
    - Evaluate the relationship of lung-protective ventilation in ventilated ED patients and mortality and duration of MV
  
  o **Study**
    - Retrospective analysis
    - 8 EDs in Canada
    - Patients
      - Adults > 18 years of age
      - Received mechanical ventilation in the ED
      - LPV defined as Vt < 8 ml/kg PBW
    - Primary outcome: hospital mortality
  
  o **Results**
    - 4,174 patients
    - 2,437 (58.4%) received LPV in the ED
    - Primary outcome
      - LPV Group: 26.6%
      - No LPV Group: 30.6%
      - P < 0.1
      - aOR 0.91
    - Secondary outcomes – LPV Group
      - Lower incidence of ARDS
      - Shorter duration of MV
      - Shorter ICU and hospital LOS
      - Lower mean total costs
  
  o **Limitations**
    - Observational trial
    - Ventilator parameters (plateau pressure) were not often available
    - No data regarding adjunctive treatment therapies for patients
    - No data regarding duration of ventilation at initial ED vent settings
  
  o **Take Home Point**
    - LPV was only used 58% of the time. Similar to other studies, the use of LPV was associated with lower hospital mortality, lower incidence of ARDS, shorter duration of mechanical ventilation, LOS, and lower costs.
  
**Additional Important Articles to Note**


