Highlights from the 2020 Critical Care Literature

COVID-19

- *Demoule A, Vieillard Baron A, Darmon M, et al. High-flow nasal cannula in critically iii patients with severe covid-19. Am J Respir Crit Care Med. 2020;202(7):1039-1042.*
    - Objective
        - Determine if HFNC reduces intubation rate and mortality in patients with COVID-19 and acute respiratory failure.
    - 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
    - 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)
    - **Take Home Point**
        - **This study highlights that HFNC was as safe as standard oxygen in a large cohort of patients with COVID-19**

- *Horby, et al. Dexamethasone in hospitalized patients with COVID-19 – Preliminary Report. NEJM. 2020; online ahead of print.*
    - 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.**

- *Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the treatment of covid-19 — final report. N Engl J Med. 2020;383(19):1813-1826.*
    - 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

- *Roberts, et al. Effects of a high-dose 24-h infusion of tranexamic acid on death and thromboembolic events in patients with acute gastrointestinal bleeding (HALT-IT): an international randomized, double-blind, placebo-controlled trial. Lancet. 2020; 395:1927-1936.*
    - 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**

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

        - 798 received 0.9% NS
        - 476 received balanced crystalloid (mostly LR)
    - 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.**

- *Li, et al. Timing of norepinephrine initiation in patients with septic shock: a systematic review and meta-analysis. Crit Care. 2020; 24:488.*
    - 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**

- *Fujii, et al. Effect of vitamin C, hydrocortisone, and thiamine vs hydrocortisone alone on time alive and free of vasopressor support among patients with septic shock: the VITAMINS randomized clinical trial. JAMA. 2020; 323:423-431.*
  - 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**

- *Chang, et al. Combined treatment with hydrocortisone, vitamin C, and thiamine for sepsis and septic shock: a randomized controlled trial. Chest. 2020; 158:174-182. (HYVCTTSSS)*
    - 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**

- *Moskowitz, et al. Effect of ascorbic acid, corticosteroids, and thiamine on organ injury in septic shock: the ACTS randomized clinical trial. JAMA. 2020; 324:642-650.*
    - Objective:
        - To determine whether the combination of ascorbic acid, corticosteroids, and thiamine attenuates organ injury in patients with septic shock.
    - Study

        - 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**

- *Hwang, et al. Combination therapy of vitamin C and thiamine for septic shock: a multicenter, double-blinded randomized, controlled study. Intensive Care Med. 2020; 46:2015-2025.*
    - Objective
        - Evaluate the effects of vitamin C and thiamine in the <u>early phase</u> 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

- *Lamontagne, et al. Effect of reduced exposure to vasopressors on 90-day mortality in older critically ill patients with vasodilatory hypotension: a randomized clinical trial. JAMA. 2020; 323:938-49.*
    - 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

- *Fernando, et al. Lung-protective ventilation and associated outcomes and costs among patients receiving invasive mechanical ventilation in the ED. Chest. 2020. Online ahead of print.*
    - Objective
        - Evaluate the relationship of lung-protective ventilation in ventilated ED patients and mortality and duration of MV
    - 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
    - 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
    - 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
    - **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

- *Mohr, et al. Boarding of critically ill patients in the emergency department. Crit Care Med. 2020; 48:1180-7.*
- *Self WH, Semler MW, Leither LM, et al. Effect of hydroxychloroquine on clinical status at 14 days in hospitalized patients with covid-19: a randomized clinical trial. JAMA. 2020;324(21):2165.*
- *Spiegel, et al. The utility of midline intravenous catheters in critically ill emergency department patients. Ann Emerg Med. 2020; 75:538-545.*
- *Shaker, et al. Anaphylaxis – A 2020 practice parameter update, systematic review, and grade of recommendations, assessment, development and evaluation (GRADE) analysis. J Allergy Clin Immunol. 2020; 145:1082-1123.*

- *April, et al. Ketamine versus etomidate and peri-intubation hypotension: A National Emergency Airway Registry Study. Acad Emerg Med. 2020; 27:1106-1115.*