Top Critical Care Articles - 2022

Cardiac Arrest

- *Cheskes S, et al. Defibrillation Strategies for Refractory Ventricular Fibrillation. N Engl J Med. 2022; 387:1947-56.*
    - Objective
        - To compare DSED and VC Defibrillation to standard defibrillation in patients with refractory VF during OHCA.
    - Methods
        - Cluster-randomized controlled trial with crossover in 6 EMS agencies in Canada.
        - Approx. 4000 paramedics from 3/18-5/22 in a mix of urban/rural communities
        - Trial was stopped early in May 2022 by the DSMB because of paramedic staffing shortages which made response times longer and affecting timely application of assigned type of defibrillation.
    - Patients
        - Adults aged 18 years of age or greater
        - Out-of-hospital cardiac arrest
        - Refractory VF defined as an initial VF rhythm or pulseless VT that was present after 3 intervals of defibrillation with 2-minutes of CPR.
    - Randomization
        - Random treatment sequences were computer-generated
        - Paramedic service clusters crossed over every 6m to a different treatment group
    - Interventions
        - Standard ACLS was provided to all patients
        - First 3 defibrillations had pads placed in the standard anterior-lateral position
        - If still in VF or pulseless VT, patients then received either:
            - Standard Anterior-Lateral Defibrillation
            - Vector Change defibrillation: Anterior-Posterior pads
            - Double-sequential defibrillation: Anterior-Lateral + Anterior-Posterior pads with 2 separate defibrillators
    - Primary Outcome: Survival to hospital discharge
    - Secondary Outcomes
        - Termination of VF
        - Return of spontaneous circulation
        - Good neurologic outcome: Defined as a modified Rankin score of $\leq$ 2 at discharge
    - Results
        - In total, 405 patients were enrolled before DSMB suggested trial be stopped.
            - Standard group: 136 patients (33.6%)
            - VC group: 144 patients (35.6%)
            - DSED group: 125 patients (30.9%)
            - 12.3% of patients did not receive the assigned defibrillation treatment

        - Demographics
            - Age: 64 years old
            - 84% male
            - 68% bystander witnessed arrest
            - 58% received bystander CPR
        - Primary Outcome
            - Results listed as *adjusted relative risk* ratios
            - Survival to hospital discharge
                - Standard defib: 13.3%
                - VC Defib: 21.7%; RR: 1.71 (1.01 – 2.88)
                - DSED group: 30.4%; RR: 2.21 (1.33 – 3.67)
        - Secondary Outcomes
            - Termination of VF
                - Standard defib: 67.6%
                - VC Defib: 79.9%; RR: 1.18 (1.03 – 1.36)
                - DSED group: 84.0%; RR: 1.25 (1.09– 1.44)
            - ROSC
                - Standard defib: 26.5%
                - VC Defib: 35.4%; RR: 1.39 (0.97 – 1.99)
                - DSED group: 46.4%; RR: 1.72 (1.22-2.42)
            - Good neurologic outcome
                - Std: 11.2%
                - VC defib: 16.2%
                - DSED: 27.4%
    - Limitations
        - Stopped early – only enrolled 44% of target participants
        - >10% of patients did not receive assigned treatment arm
        - Vector change group had a fragility index of 1 for the primary outcome
    - **Take Home Point**
        - **There is a signal here of benefit to using DSED and possibly VC defibrillation for refractory VF arrest.**

Post-Arrest Care

- *Kjaergaard J, Møller JE, Schmidt H, et al. Blood-pressure targets in comatose survivors of cardiac arrest. N Engl J Med. 2022; 387:1456-66.*
    - Objective
        - The primary objective was to test whether a MAP of 63 vs. 77 mmHg would be superior in preventing death or severe anoxic brain injury among comatose survivors of OHCA.
    - Methods
        - Randomized clinical trial, 2x2 factorial design
            - MAP target: 63 vs. 77 mmHg (double-blind intervention)
            - O2 target: restrictive or liberal oxygenation (open-label intervention)
        - Location: two medical centers in Denmark
        - Patients
            - Adults aged 18 years or older
            - Comatose after OHCA of presumed cardiac etiology

        - Intervention
            - Experimental arm(s)
                - Clinical staff, investigators, patients, and outcome assessors were unaware of the assigned blood-pressure targets, but were told to target a MAP of 70 mmHg
                    - Actual BP targets were achieved by assigning patients to an electronic module that was set to show either 10% higher or lower value than the actual MAP, so clinicians would achieve 63 vs. 77 mmHg groups.
                - Resuscitation to MAP target of 70 mmHg was achieved using a 3-stage approach, starting with IV fluids to achieve a CVP of 10 mmHg, norepinephrine infusion (dopamine as second line pressor)
        - Primary Outcome
            - Composite of death or discharge from the hospital with a Cerebral Performance Category of 3 or 4 within 90 days or at time of discharge.
        - Secondary Outcomes
            - Death from any cause within 90 days
            - Time to renal-replacement therapy
            - Neuron specific enolase levels at 48 hours after randomization
            - Multiple different cognitive scores at 3 months
    - Results
        - In total, 802 patients were enrolled from March 2017 – December 2021
            - 789 patients were included
            - High BP Group: 393 patients
            - Low BP Group: 396 patients
        - In general, the trial appears to have achieved a MAP difference of 10.7 points starting at randomization – 65 vs. 75 mmHg (randomization usually took place in ICU, not ED).
        - Primary Outcome
            - High BP Group: 34%
            - Low BP Group: 32%
            - Not statistically significant
        - No difference in any of the secondary outcomes, including
            - Death from any cause at 90 days
                - High BP Group: 31%
                - Low BP Group: 29%
            - 3-month CPC or other neurologic assessment scores
        - No difference in any of the recorded complications (infection, arrhythmia, bleeding, metabolic disorders, or seizures).
    - Limitations
        - Did not achieve the separation of 14 points that was initially targeted
        - BP targets were not titrated based on degree of anoxic injury – perhaps those with worse anoxic injury need higher BP targets?
        - Long-term neurologic outcomes were only measured in 65% of surviving patients – limited by the COVID-19 pandemic.
    - **Take Home Point**

        - **A MAP of 65 vs. 75 mm Hg did not result in a significant difference in death or severe disability after OHCA from a likely cardiac cause.**

- *Schmidt H, Kjaergaard J, Hassager C, et al. Oxygen targets in comatose survivors of cardiac arrest. N Engl J Med. 2022; 387:1467-76.*
    - Objective
        - Evaluate whether a restrictive or liberal oxygen target was superior in patients who remain comatose from OHCA.
    - Methods
        - Investigator-initiated, open-label, randomized trial with 2-by-2 factorial design
        - 2 tertiary cardiac arrest centers in Denmark
        - Patients
            - Adults aged 18 years or older
            - Comatose after OHCA of presumed cardiac etiology
        - Intervention
            - Restrictive Target Group
                - PaO_2 68-75 mm Hg
                - Initial FiO_2 set at 30% and adjusted to assigned target
            - Liberal Target Group
                - PaO_2 98-105 mm Hg
                - Initial FiO_2 set at 60% and adjusted to assigned target
        - Primary Outcome
            - Composite of death or discharge from the hospital with a Cerebral Performance Category of 3 or 4 within 90 days or at time of discharge.
        - Secondary Outcomes
            - Plasma neuro-specific enolase levels at 48 hours
            - Death from any cause
            - 90-day scores on the Montreal Cognitive Assessment, mRS, and CPC
    - Results
        - In total, 802 patients were enrolled from March 2017 – December 2021
            - 789 patients were included
            - Restrictive Target Group: 394
            - Liberal Target Group: 395
            - Characteristics of patients were well balanced
        - Oxygen Intervention
            - On arrival to ICU, pts in both groups had similar PaO_2 and FiO_2 values
            - Separation between the groups was seen within 2-4 hours and remained there through the first 48 hours
            - Median duration of mechanical ventilation
                - Restrictive Target Group: 57 hours
                - Liberal Target Group: 61 hours
        - Primary Outcome
            - Restrictive Target Group: 32%
            - Liberal Target Group: 33.9%
            - No statistical difference
        - Secondary Outcomes - no statistical difference
        - Adverse Events - No significant difference between the groups

- Limitations
  - Open label
  - Enrolled only patients with a presumed cardiac etiology of CA
  - PaO2/FiO2 ratio was higher in this trial than others – suggests that hypoxic respiratory failure was infrequent in this trial. For some, the spontaneous PaO2 values were higher that target values without supplemental O2
  - Limited by the number of patients who could be evaluated in person at 90 days
- **Take Home Point**
  - **Authors found no difference in a composite outcome of death or severe disability at 90 days in OHCA patients randomized to a restrictive or liberal oxygen target.**

Sepsis

- *Meyhoff TS, et al. Restriction of Intravenous Fluids in ICU Patients with Septic Shock. NEJM. 2022; 386:2459-70.*
  - Objective
    - Evaluate the effects of restriction of IVFs on mortality and other outcomes in adult patients with septic shock admitted to the ICU.
  - Methods
    - International, stratified, parallel-group, open-label, randomized clinical trial
    - 31 ICUs in Denmark, Norway, Sweden, Switzerland, Italy, Czech Republic, UK, and Belgium
    - Patients
      - Adults aged 18 years or older
      - Admitted to the ICU
      - Had septic shock
        - Lactate 2 mmol/L or higher
        - Ongoing infusion of vasopressor or inotrope
        - Received at least 1 L of IVF before screening
      - Onset of shock within 12 hrs of screening
    - Intervention
      - Patients randomized in a 1:1 ratio to restrictive IVFs or standard IVFs
      - Restrictive IVF Group
        - Patients were given <u>250-500 ml crystalloid bolus</u>
        - IVFs could only be given for the following conditions:
          - <u>Severe hypoperfusion</u>
            - Lactate > 4 mmol/L
            - MAP < 50 mm Hg despite vasopressor or inotropic agent
            - Mottling beyond the edge of the kneecap
            - Urine output < 0.1 ml/kg during first 2 hours of randomization
          - Given to replace documented fluid losses (GI or drain losses)
          - Given to correct dehydration or electrolytes deficiency
          - Given to ensure a total daily fluid intake of 1 L
      - Standard IVF Group

        - No restriction on the amount of IVFs
        - IVFs could be given for the following conditions:
            - To improve hemodynamic factors
            - Given to replace expected or observed losses or to correct dehydration or electrolyte imbalances
            - Given for maintenance fluid in the ICU
    - Primary Outcome: 90-day mortality
    - Secondary Outcomes
        - Number of patients who had one or more serious adverse events in the ICU or had a new episode of severe AKI
        - Number of serious adverse reactions to IV crystalloids
        - Number of days alive without life support at day 90
        - Number of days alive and out of the hospital at day 90
- Results
    - In total, 1545 patients were analyzed
        - Restrictive IVF Group: 764 patients
        - Standard IVF Group: 781 patients
        - Patient characteristics well balanced between the groups
    - Median volume of IVFs 24 hours before randomization
        - Restrictive IVF Group: 3,200 ml
        - Standard IVF Group: 3000 ml
    - IVF Interventions
        - Median volume of IVFs administered in the ICU
            - Restrictive IVF Group: 1798 ml
            - Standard IVF Group: 3811 ml
            - Difference of 2013 ml
        - Median cumulative volume of all fluids given in the ICU
            - Restrictive IVF Group: 10,433 ml
            - Standard IVF Group: 12,747 ml
            - Difference of 2314 ml
        - Median cumulative fluid balance
            - Restrictive IVF Group: 1645 ml
            - Standard IVF Group: 2368 ml
            - Difference of 723 ml
        - Protocol violations
            - Restrictive IVF Group: 162 patients (21.5%)
            - Standard IVF Group: 101 (13%)
    - Primary Outcome: 90-day mortality
        - Restrictive IVF Group: 42.3%
        - Standard IVF Group: 42.1%
        - Adjusted absolute difference 0.1%
    - Secondary Outcomes – no change
- Limitations
    - Unblinded trial: patients and personnel aware of group assignments
    - Data regarding co-interventions and hemodynamic factors not recorded
    - Patients received IVFs before enrollment
    - Some protocol violations occurred

- **Take Home Points**
  - **Among adult patients in the ICU with septic shock, a restrictive IVF strategy did not improve 90-day mortality compared with standard IVF therapy.**

Fluid Resuscitation

- *Finfer S, et al. Balanced multielectrolyte solution versus saline in critically ill adults. N Engl J Med. 2022*; 386:815-26.
  - Objective
    - To determine if 90-day mortality would be lower in critically ill adults who received a balanced multielectrolyte solution (BMES) compared with saline.
  - Methods
    - Investigator-initiated, double-blind, parallel-group, randomized, controlled trial conducted at 53 ICUs in Australia and New Zealand.
    - Patients
      - 18 years of age or older
      - Admitted to the ICU
      - Fluid resuscitation deemed necessary by the treating physician
      - Expected to be in the ICU on 3 consecutive days
    - Interventions
      - Patients received assigned trial fluid for all fluid resuscitation and compatible crystalloid therapy for up to 90 days after randomization.
      - Treating clinician decided the amount and rate of fluid administration.
      - Once the patient was outside of the ICU, the type of fluid administered was not dictated
      - All other treatments were at the discretion of the treating clinicians
    - Primary Outcome - Death from any cause within 90 days of randomization
    - Secondary Outcomes
      - Receipt of RRT
      - Receipt and duration of vasopressor medications
      - Duration of mechanical ventilation
      - ICU and hospital LOS
      - Death from any cause during the ICU stay
  - Results
    - A total of 5037 patients underwent randomization
      - BMES Group: 2515
      - Saline Group: 2522
    - Baseline characteristics similar
      - 45% were admitted to the ICU from the OR or PACU
      - 79% were intubated
      - 42% had sepsis
    - Fluids administered
      - 96% of patients got IVFs
      - Median duration of treatment with assigned fluid was 6 days
      - Median volume of fluid was 3.9 liters in the BMES Group and 3.7 liters in the Saline Group
    - Primary Outcome – 90-day all-cause mortality
      - BMES Group:21.8%

        - Saline Group: 22%
        - Results were similar after adjusting for baseline risk factors and secondary analyses
        - No heterogeneity in the effect of IVFs based on subgroups
    - Secondary Outcomes - No differences
    - No difference in adverse events between the groups
- Limitations
    - Initially estimated that 8800 patients would be needed to show an absolute difference of 2.9% in 90-day all-cause mortality from an estimated baseline mortality of 23%. In August 2020, the trial-management committee and the sponsor decided to stop enrollment. They then estimated a sample size of 5000 patients to detect an absolute difference of 3.8%.
    - Use of Plasma-Lyte 148
    - Did not control for all fluid patients received outside of the ICU
- **Take Home Point**
    - **The PLUS study found no evidence that the use of Plasma-Lyte 148 reduced 90-day all-cause mortality in critically ill ICU patients compared with those who received saline.**

Rapid Sequence Intubation

- *Russell DW, et al. Effect of fluid bolus administration on cardiovascular collapse among critically ill patients undergoing tracheal intubation: A randomized clinical trial. JAMA. 2022; 328:270-9.*
    - Objective
        - Examine the effect of IVF bolus on CV collapse among critically ill adults undergoing intubation with positive pressure ventilation.
    - Methods
        - Multicenter, parallel group, unblinded, pragmatic RCT
        - 11 ICUs across the US
        - Patients
            - Adults aged 18 years or older
            - Undergoing tracheal intubation
            - Were to receive medications to induce anesthesia
            - Positive pressure ventilation with either a BVM or NIV between induction and laryngoscopy
    - Intervention
        - Patients randomized in a 1:1 ratio to receive an IVF bolus or not
        - Fluid Bolus Group
            - Operators instructed to infuse 500 ml of isotonic crystalloid of choice
            - Infuse as much as possible before induction, and then administer any of the remaining amount after induction and during the intubation.
        - No Fluid Bolus Group
            - Initiation of a new IVF bolus was not permitted except as treatment for hypotension or if the operator determined that IVFs were necessary
        - All other aspects of the intubation were left to the operator
            - Choice of induction agents
            - Use of vasopressors
        - Primary Outcome

- Cardiovascular collapse – 1 or more of the following
    - New or increased receipt of vasopressors between induction and 2 min after intubation
    - A SBP of less than 65 mm Hg between induction and 2 min after intubation
    - Cardiac arrest between induction and 1 hour after intubation
    - Death between induction and 1 hour after intubation
- Secondary Outcome - Death prior to day 28

- Results
  - In total, 1065 patients were included in the primary analysis
    - Fluid Bolus Group: 538 patients
    - No Fluid Bolus Group: 527 patients
    - Patient characteristics well balanced between the groups
  - Receipt of IVF
    - Fluid Bolus Group
      - 99.4% of group received bolus
      - Majority of bolus was administered prior to induction
      - Medan volume of IVF was 500 ml
    - No Fluid Bolus Group - 1.1% of patients received bolus
  - Intubation
    - Approach to preoxygenation, choice of induction agents, SBP and SpO2 at induction were not significantly different between groups.
    - Approximately 12% of patients in both groups had a vasopressor bolus or infusion administered between enrollment and induction.
    - Approximately 97.5% of patients in both groups received positive pressure ventilation between induction and laryngoscopy.
  - Primary Outcome:
    - Cardiovascular collapse
      - Fluid Bolus Group: 21%
      - No Fluid Bolus Group: 18.2%
      - Did not differ significantly between groups in the sensitivity analysis
      - Did not decrease the incidence of CV collapse in any prespecified subgroup
  - Secondary Outcome
    - Death at 28 days
      - Fluid Bolus Group: 40.5%
      - No Fluid Bolus Group: 42.3%
- Limitations
  - Used a composite outcome
  - May not be generalizable to those with cardiac arrest, respiratory arrest, or other urgent needs for intubation.
  - Would the results have been different if a volume > 500 ml was used?
  - This trial evaluated fluid bolus prior to induction to prevent CV collapse. It did not evaluate a fluid bolus used to treat hypotension during intubation.
- **Take Home Point**

        - **Among critically ill adult patients undergoing intubation in the ICU, the administration of a 500 ml fluid bolus did not decrease the incidence of CV collapse.**

Mechanical Ventilation

- *Semler MW, et al. Oxygen-saturation targets for critically ill adults receiving mechanical ventilation. N Engl J Med. 2022; 387:1759-69.*
    - Objective
        - Determine the effects of lower, intermediate, and higher SpO2 targets on outcomes in critically ill patients received mechanical ventilation.
    - Methods
        - Pragmatic, unblinded, cluster-randomized, cluster-crossover trial
        - Conducted in the ED and ICU at Vanderbilt University Medical Center
            - Initial enrollment began 7/1/2018
            - Paused from 4/1/20-5/31/20 due to COVID
            - Resumed on 6/1/20 and concluded on 8/31/21
        - Patients
            - Adults aged 18 years of age or greater
            - Located in the ED or MICU
            - Enrolled at the time of first receipt of mechanical ventilation
        - Randomization
            - All eligible patients (ED and ICU) were assigned together as a single cluster to an SpO2 target
            - Every 2 months the ED and ICU switched together between lower, intermediate, and higher SpO2 targets in a random sequence
        - Interventions
            - Low SpO2 target 90% (goal range 88%-92%)
            - Intermediate SpO2 target 94% (goal range 92%-96%)
            - High SpO2 target 98% (goal range 96%-100%)
            - Adjusting of FiO2 to target SpO2 was initiated within 15 min of initiation of MV and ended at discontinuation of MV, transfer out of the unit, or end of the 2-month study period
            - If continuous SpO2 monitoring was unavailable, O2 was adjusted to a PaO2 target of 60 mm Hg, 70 mm Hg, and 110 mm Hg in the low, intermediate, and high target groups respectively.
        - Primary Outcome - Numbers of days alive and free of MV through day 28
        - Secondary Outcome - All-cause mortality at day 28
    - Results
        - A total of 2541 patients in the primary analysis.
            - Low SpO2 group: 808 patients
            - Intermediate SpO2 group: 859 patients
            - High SpO2 group: 874 patients
        - Primary Outcome
            - Low SpO2 group: 20 days
            - Intermediate SpO2 group: 21 days
            - High SpO2 group: 21 days

            - Results did not differ in any prespecified subgroups (including sepsis and post-arrest)
        - Secondary Outcome
            - Low SpO2 group:34.8%
            - Intermediate SpO2 group: 34%
            - High SpO2 group: 33.2%
        - Safety Outcomes
            - Incidence of cardiac arrest, arrhythmia, MI, ischemic stroke, and pneumothorax were similar in all 3 groups
    - Limitations
        - Single center – limits generalizability
        - Given they started intervention immediately after intubation and initiation of MV, this precluded assessment of severity of lung injury
        - Clinicians not blinded to oxygen target assignments
        - Did not control for other interventions such as PEEP, sedation, and approach to weaning.
    - **Take Home Point**
        - **Among critically ill patients in the ED and ICU receiving mechanical ventilation, the use of a low, intermediate, or high oxygenation target did not affect the number of ventilator free days.**

- *Fuller BM, et al. Awareness with paralysis among critically ill emergency department patients: a prospective cohort study. Crit Care Med. 2022; 50:1449-1460.*
    - Objective
        - Estimate the frequency of awareness with paralysis (AWP) in vented ED patients
        - Identify risk factors associated with AWP
        - Compare perceived threat between patients experiencing AWP and those without AWP
    - Methods
        - A priori planned secondary analysis of AWP events collected during the ED-SED Pilot Trial (multicenter, prospective, before-and-after pilot that examined the impact of ED-based targeted sedation for vented patients)
        - 3 academic tertiary medical centers
        - Patients
            - Adults greater than or equal to 18 years of age
            - Mechanical ventilations in the ED via an ETT
            - Received a neuromuscular blocker during RSI or postintubation period
        - AWP
            - Patients had to report a memory of wakeful paralysis
            - Used Brice questionnaire
            - Assessed by a study team member after extubation either before hospital DC or via telephone after hospital DC
            - 3 independent reviewers reviewed questionnaire responses

            - Adjudicated as definite AWP, possible AWP, or no AWP
        - Primary Outcome – AWP
        - Secondary Outcome – perceived threat
    - Results
        - 388 patients included in the final study population
        - Baseline differences – patients with AWP
            - Generally younger
            - Greater proportion male
            - History of alcohol abuse and psychiatric illness
            - Less severely ill
        - Primary Outcome – 3.4% of patients experienced AWP
        - Risk Factors
            - Rocuronium use
            - 92% of patients with AWP received rocuronium
            - Exposure to rocuronium in the ED was statistically significant predictor of AWP
        - Secondary Outcome
            - Patients with AWP had higher mean threat perception
    - Limitations
        - Overall sample size is small
        - May not be generalizable to sites that do not routinely use rocuronium
        - Exact timing of questionnaire was not standardized
        - Brice questionnaire not been extensively used outside of the OR
    - **Take Home Points**
        - **AWP was present more than 3% of survivors of ED mechanical ventilation**
        - **Rocuronium use was associated with increased risk of AWP**

- *Driver BE, et al. Recall of awareness during paralysis among ED patients undergoing tracheal intubation. Chest. 2022.*
    - Objective
        - Estimate the prevalence of recalled awareness during paralysis in patients who underwent emergency tracheal intubation and mechanical ventilation
    - Methods
        - Prospective observational study using data from a continuous quality improvement database
        - Single center – Hennepin County Medical Center
        - Patients
            - Adult patients greater than or equal to 18 years of age
            - Underwent orotracheal intubation in the ED
            - Received a NMB agent
        - Measurement

        - Trained staff used the modified Brice questionnaire
        - 3 independent reviewers adjudicated the case – when 2 or more reviewers agreed with definite or possible recall, the patient was adjudicated as experiencing that outcome
    - Primary Outcome – awareness of paralysis in the ED
    - Secondary Outcome – memory of the intubation procedure
- Results
    - 866 patients were included in the primary cohort for this analysis
    - Primary Outcome
        - Following adjudication – 66 patients (7.4%) were deemed to possibly or definitely have awareness of paralysis
    - Secondary Outcome
        - Following adjudication – 34 patients (3.8%) were deemed to possibly or definitely have memory of the intubation
    - Risk Factor
        - Depressed mental status prior to intubation was independently associated with lower odds of awareness of paralysis
    - Class of NMB agent, sedative, shock index, and postintubation sedation were not associated with awareness with paralysis
- Limitations
    - Single center
    - Adjudicating awareness of paralysis is subjective
    - Patient memories can be uncertain
    - Tried to focus only on events in the ED or early ICU period
    - Only focused on patients who received an NMB agent
    - Excluded 231 patients who were DC'd and unable to be contacted
- **Take Home Point**
    - **Awareness of paralysis occurred in a significant number of patients undergoing ED intubation and mechanical ventilation**