A Year in Review: Key Articles from the 2019 Critical Care Literature

Septic Shock

Hernandez G, et al. Effect of a resuscitation strategy targeting peripheral perfusion status vs serum lactate levels on 28-day mortality among patients with septic shock. The ANDROMEDA-SHOCK randomized clinical trial. JAMA. 2019; 321:654-64.

- Objective
  - Compare a peripheral perfusion targeted resuscitation to lactate level targeted resuscitation in patients with early septic shock
- Study
  - Multicenter, randomized clinical trial
  - 28 hospitals in 5 countries (Argentina, Chile, Colombia, Ecuador, Uruguay)
  - Patients
    - Adults ≥ 18 years of age
    - Septic shock
    - Admitted to an ICU
    - Recruited within 4 hours of fulfilling criteria
  - Interventions - Peripheral perfusion-targeted
    - Capillary Refill Time (CRT)
    - Firm pressure to ventral surface of R index finger distal phalanx with microscope slide; increased until skin blank - maintained for 10 s
    - Used chronometer to record time to normal
    - CRT > 3 seconds abnormal
    - Goal CRT - normalize CRT
  - Interventions - Lactate level-targeted
    - Lactate assessed every 2 hrs until normalization
    - Goal - normalize or decrease by 20% every 2 hours
  - Step 1 - Assess fluid responsiveness
    - Each center used its standard technique - followed by fluid challenges with 500 ml of crystalloids every 30 min in responders until goal was achieved
    - In patients who could not be assessed for responsiveness, fluids were continued until the goal was met or safety limit reached
  - Step 2 – Vasopressor Test
    - In patients with chronic hypertension, if the previous interventions did not meet the goals, a vasopressor test was conducted, transiently increasing NE until reaching a MAP of 80-85 mm Hg, followed by reassessment of CRT or lactate after 1 to 2 hours
    - If goal was met, the MAP was maintained throughout the intervention period
    - If not, NE dose was decreased to previous dose and moved to next step
  - Step 3 - Inodilator test
    - Low dose dobutamine or milrinone administered if target was not reached
    - CRT and lactate reassessed every 1 to 2 hours

        - If end points were not met or a safety issue arose, the inodilator was DCd
    - Primary Outcome - all-cause 28-day mortality
    - Secondary Outcomes
        - Death in 90 days
        - Organ dysfunction during the first 72 hours
        - Mechanical ventilation free days within 28 days
        - Vasopressor free days within 28 days
        - ICU and hospital LOS
    - Tertiary Pre-specified exploratory outcomes
        - Resuscitation fluids during the intervention period
        - Total fluid balance within 8, 24, and 72 hours
        - Occurrence of IAH within 72 hours
        - RRT within 28 days
        - In-hospital mortality
    - Statistical Analysis
        - Plan to enroll 420 pts to detect a reduction in 28-day mortality from 45% to 30%
- Results
    - 424 patients were enrolled
        - 212 assigned to each group
        - All patients included in the ITT analysis for primary outcome
        - Baseline characteristics similar
        - 71% admitted from the ED
    - Primary Outcome
        - CRT: 34.9%
        - Lactate: 43.4%
        - HR 0.75, CI 0.55-1.02; p=0.06
    - Secondary Outcomes
        - Less organ dysfunction at 72 hours in the CRT group (SOFA -1.00)
        - No differences in the other 6 outcomes
    - Tertiary
        - Patients in the CRT group received less fluids in first 8 hours (-408 ml)
- Limitations
    - ICU-based study
    - Non-blinded
    - Study may have been underpowered to exclude a clinically meaningful difference between groups
    - Interrater variability for CRT was not evaluated
    - Worth noting: 2nd analysis using a Bayesian Analysis using initial SOFA Score as a probability for response found peripheral perfusion-targeted resuscitation may result in lower mortality and faster resolution of organ dysfunction when compared to a lactated-targeted resuscitation strategy. (AJRCCM; doi: 10.1164/rccm.201905-0968OC)
- **Authors Take Home Point**
    - **A resuscitation strategy targeting normalization of CRT compared with lactate did not reduce all-cause 28-day mortality**

Rapid Sequence Intubation

Casey JD, et al. Bag-mask ventilation during tracheal intubation of critically ill adults. NEJM. 2019; 380:811-821. (The PREVENT Trial)

- Objective
    - Determine the effect of BMV on hypoxemia during tracheal intubation of critically ill adults
- Study
    - Multicenter, parallel-groups, unblinded, pragmatic, randomized trial comparing BMV with no ventilation during the interval between induction and laryngoscopy during tracheal intubation of critically ill adults
    - 7 academic ICUs across the US
    - Patients
        - Adults >= 18 years of age
        - Undergoing induction and tracheal intubation in the ICU
    - Randomized in 1:1 fashion to receive:
        - BMV
            - Provided by treating clinicians during the interval from induction until the initiation of laryngoscopy
            - PEEP valve to deliver 5-10 cm H_2O, oropharyngeal airway, two-handed seal, head-tilt/chin-lift maneuver
            - Ventilated at 10 breaths per minute
            - Smallest volume required to generate a visible chest rise
        - No Ventilation
            - BMV between induction and laryngoscopy not permitted
            - Except during after failed attempt at laryngoscopy and treatment for hypoxemia $SpO_2 < 90\%$
        - NIV not allowed in either group
        - All methods of preoxygenation were allowed in either group before induction
        - Apneic oxygenation not mandated, but was allowed
    - Primary Outcome
        - Lowest oxygen saturation observed during interval between induction and 2 min after tracheal intubation
    - Secondary outcome
        - Incidence of severe hypoxemia ($SpO_2 < 80\%$)
    - Safety Outcome
        - Worst value for SpO_2, FiO_2, and PEEP between 6 and 24 hours after intubation
    - Procedural Outcomes
        - Presence of new opacity on CXR within 48 hours
        - Operator-reported oropharyngeal or gastric aspiration
- Results
    - 401 patients
        - Median age 60 years
        - 50% had sepsis or septic shock
        - 60% had hypoxemic respiratory failure as indication for intubation
        - 199 assigned to BMV and 202 assigned to no ventilation
    - Primary Outcome
        - Median lowest SpO_2 was 96% in BMV group and 93% in No Ventilation group
        - Mean difference in lowest SpO_2 between BMV group and No Ventilation group 4.7 % points
    - Secondary Outcome

        - 10.9% of patients in the BMV group had an SpO2 < 80% compared with 22.8% in the No Ventilation group
    - Additional Outcomes
        - Lower % of patients in the BMV group had SpO2 < 90% (29.5%) compared to No Ventilation group (40.1%)
        - No difference with regard to incidence of operator-reported aspiration or presence of new opacity on CXR in first 48 hours after intubation
- Limitations
    - No blinding
    - Involved only ICU patients
    - Did not examine use of NIV during interval between induction and laryngoscopy
- **Authors Take Home Point**
    - **For every 9 critically ill adults undergoing tracheal intubation providing BMV between induction and laryngoscopy would prevent severe hypoxemia in 1 patient**
    - **Patients receiving BMV had higher SpO2 levels and lower rates of severe hypoxemia**

Mechanical Ventilation

ICU-ROX Investigators and the Australian and New Zealand Intensive Care Society Clinical Trials Group, et al. Conservative oxygen therapy during mechanical ventilation in the ICU. N Engl J Med. 2019. [epub ahead of print]

- Objective
    - Test the hypothesis that conservative oxygen therapy would result in more ventilator-free days than usual oxygen therapy in adults expected to undergo mechanical ventilation in the ICU beyond the day of recruitment
- Study
    - Multicenter, randomized, controlled trial
    - 21 ICUs in New Zealand and Australia
    - Patients – Included
        - Adult patients expected to receive mechanical ventilation in the ICU beyond the day after recruitment
    - Patients – Excluded
        - Pregnant
        - Long-term ventilated patients
        - Moribund
        - Patients were hyperoxia was indicated – CO poisoning
        - Patients were avoidance of hyperoxia was indicated – acute COPD exacerbation
    - Intervention – Randomized 1:1
        - Conservative Oxygen Therapy group
            - If SaO2 was 97% or higher, FiO2 reduced by 10% every 5 min until SaO2 < 97%
            - If SaO2 < 90%, FiO2 was increased
            - Lowest possible FiO2 to achieve SaO2 91-96%
        - Usual Oxygen Therapy group
            - Any SaO2 > 90% allowed
            - Any FiO2 < 0.3 discouraged
            - No upper limit for SaO2
    - Primary Outcome

        - Number of ventilator-free days from randomization to day 28
    - Secondary Outcomes
        - Death from any cause at day 90 and day 180
        - Duration of survival
        - Cognitive function at day 180
        - Health-related quality of life at day 180
- Results
    - I000 patients underwent randomization
        - 965 included in the analysis
        - Conservative Oxygen Therapy: 484
        - Usual Oxygen Therapy: 481
    - Primary Outcome
        - Conservative Oxygen Therapy: 21.3 days
        - Usual Oxygen Therapy: 22.1 days
        - No difference
    - Secondary Outcomes
        - Death from any cause at day 90 and day 180
            - Conservative Oxygen Therapy: 34.7%
            - Usual Oxygen Therapy: 32.5%
            - No difference
        - Death from any cause at day 180
            - Conservative Oxygen Therapy: 35.7%
            - Usual Oxygen Therapy: 34.5%
            - No difference
        - Cognitive function at day 180
            - No difference
        - Health-related quality of life at day 180
            - Conservative Oxygen Therapy had less problems with mobility and personal care
- Limitations
    - Clinicians unblended
    - Usual Oxygen Therapy group had low doses of O2 – does not preclude harm if more liberal O2 therapy given
    - Ventilator-free days may not be the right end-point to assess potential harm of hyperoxia
- **Authors Take Home Points**
    - **Conservative oxygen therapy did not affect the number of ventilator-free days compared with usual oxygen therapy in ventilated ICU patients**

Post-Cardiac Arrest Management

Lemkes JS, et al. Coronary angiography after cardiac arrest without ST-segment elevation. The COACT Trial. NEJM. 2019; 380:1397-1407.

- Objective
    - Test the hypothesis that in patients with ROSC after CA in the absence of STEMI, a strategy of immediate angiography would be better than a strategy of delayed angiography with respect to overall survival
- Study

- Investigator-initiated, randomized, open-label, multicenter trial
- 19 centers in the Netherlands
- Patients – Included
  - OHCA
  - Initial shockable rhythm
  - Unconscious after ROSC
- Patients – Excluded
  - Signs of STEMI on ECG in the ED
  - Shock
  - Obvious non-coronary cause of arrest
- Randomization
  - 1:1 ratio
  - Immediate angiography
    - Performed as soon as possible and within 2 hours after randomization
  - Delayed angiography
    - Performed after neurologic recovery - usually after DC from the ICU
    - If patient was assigned to this group but showed signs of cardiogenic shock, recurrent life-threatening arrhythmias, recurrent ischemia, urgent angiography was performed
  - Further post-arrest care included TTM and in-line with international guidelines
- Primary outcome
  - Survival at 90-days
- Secondary outcomes
  - Survival at 90 days with good cerebral performance or mild/moderate disability
  - Acute kidney injury
  - Need for RRT
  - Duration of catecholamine or inotropic therapy
  - Neurologic status at ICU DC
  - Duration of MV
  - Major bleeding

- Results
  - 538 patients had data available for assessment
    - 273 assigned to immediate angiography group
    - 265 assigned to delayed angiography group
  - Angiography
    - 265 of 273 in immediate group (97.1%)
    - 172 of the 265 patients in the delayed group (64.9%)
    - Median time in immediate group was 0.8 hours
    - Median time in the delayed group was 120 hours
    - Acute thrombotic occlusion found in 3.4% in the immediate group and in 7.6% of delayed group
    - PCI performed in 33% of immediate group
    - PCI performed in 24.2% of delayed group
  - Crossover
    - 13 patients assigned to the immediate group got delayed angiography
    - 3 patients assigned to the delayed group treated with immediate angiography
  - Other
    - More than 90% treated with TTM and MV

        - Median time to TTM in immediate group was 5.4 hours
        - Median time to TTM in delayed group was 4.7 hours
    - Primary Outcome – 90-day survival
        - 64.5% survival in the immediate angiography group
        - 67.2% in the delayed group
- Limitations
    - Majority of pts had stable lesions; thrombotic occlusions found in only 5%
    - Physicians were aware of the assigned group - unblinded
    - Did not evaluate those with shock or persistent STEMI
    - Actual percentage of patients who survived was higher than anticipated - may have affected the power of the trial
- **Authors Take Home Point**
    - **Patients resuscitated from OHCA secondary to a shockable rhythm and no signs of STEMI on ECG did not benefit from a strategy of immediate angiography in terms of 90-day survival.**

Lascarrou JB, et al. Targeted temperature management for cardiac arrest with nonshockable rhythm. N Engl J Med. 2019; 381:2327-2337. (The HYPERION Trial)

- Objective
    - Assess whether moderate therapeutic hypothermia at 33C, as compared with targeted normothermia at 37C, would improve neurologic outcome in patients with coma who were successfully resuscitated from cardiac arrest with a nonshockable rhythm
- Study
    - Investigator-initiated, open-label, blinded-outcome-assessor, pragmatic, multicenter, randomized controlled trial
    - 25 ICUs in France (11 university hospitals; 14 community hospitals)
    - Patients
        - Included
            - Adults $\geq$ 18 years of age
            - Resuscitated from OHCA or IHCA
            - Nonshockable rhythm due to any cause
            - Coma (GCS $\leq$ 8) at ICU admission
        - Excluded
            - No-flow time of more than 10 min before CPR
            - Low-flow time of more than 60 min from time of CPR to ROSC
            - Hemodynamic instability (NE or epi infusion > 1 mcg/kg/min)
            - Moribund condition
            - Severe hepatic dysfunction
            - Pregnancy
            - Inmate or under guardianship
            - Lack of health insurance
            - Next of kin for the patient declined to participate
    - Randomized 1:1
        - Moderate therapeutic hypothermia group
            - Target 33C
            - Maintained for 24 hours
            - Each center followed its own protocol

                - Slow rewarming to 36.5-37.5C maintained over 24 hours
                - Sedation and NMBA administered according to each center's protocol
            - Normothermia group
                - Target 36.5-37.5C
                - Maintained for 48 hours
                - Sedation given routinely only during first 12 hours after randomization
    - Primary Outcome
        - Survival with favorable 90-day neurologic outcome (assessed using CPC and defined as a CPC of 1 or 2)
        - Assessed using a semi-structured telephone interview
    - Secondary Outcomes
        - Mortality
        - Mechanical ventilation duration
        - ICU and hospital LOS
        - Infection
        - Adverse events
- Results
    - 584 patients underwent randomization – 581 patients in final analysis
        - Moderate hypothermia group: 284 patients
        - Normothermia group: 297 patients
        - Characteristics evenly balanced between the two groups
        - Case of cardiac arrest was noncardiac in two-thirds of patients
        - Circulatory shock present in almost 60%
        - Most common cause of death – withdrawal of life support
    - Primary Outcome – Favorable neurologic survival at 90-days
        - Moderate hypothermia group: 10.2%
        - Normothermia group: 5.7%
        - P=0.04
    - Secondary Outcomes
        - Mortality
            - Moderate hypothermia group: 81.3%
            - Normothermia group: 83.2%
        - Duration of mechanical ventilation – no difference
        - ICU LOS – no difference
        - Adverse events – no difference
- Limitations as described by Authors
    - Primary outcome assessed using a phone interview rather than face-to-face interview
    - Substantial portion of patients had body temps above 38C in the period after TTM
    - Used TTM for 56-64 hours in the hypothermia group and in 48 hours in the Normothermia group to avoid rebound hyperthermia
    - Fragility Index value for the study was 1 – suggests that an outcome change in 1 patient could make the difference in primary outcome results nonsignificant
- **Take Home Points**
    - **Use of moderate hypothermia at 33C led to higher percentage of patients who survived with favorable neurologic outcome at 90 days.**
    - **NNT from this trial is 22, to achieve a CPC of 1 or 2 with TTM in patients with a nonshockable rhythm.**

Neuro Critical Care

CRASH-3 Trial Collaborators. Effects of tranexamic acid on death, disability, vascular occlusive events and other morbidities in patients with acute traumatic brain injury (CRASH-3): a randomised, placebo-controlled trial. Lancet. 2019;

- Objective: Determine if the administration of tranexamic acid (TXA) under 3 hours from injury in patients with TBI, compared with placebo, reduces head injury associated in-hospital mortality within 28 days?
- Study
    - Randomized, Placebo Control Trial
    - 175 hospitals in 29 countries, enrolled between 2012 - 2019
    - Patients
        - Included
            - Adults with TBI within 3 hrs of injury (changed from within 8 hrs of injury in Sep 2016)
            - GCS <=12 or intracranial bleeding on CT
            - No major external bleeding
            - The treating clinician had to be substantially uncertain as to the appropriateness of TXA as a treatment
        - Exclusions: None listed
    - Study groups
        - Experimental arm: Received TXA
            - Dose: 1g over 10 minutes followed by IV infusion of 1g over 8 hours
            - 12737 patients randomized
                - 6406 to TXA of which 4649 were randomized < 3 hours
                - 4613 / 4649 analyzed
        - Control: Received placebo
            - 0.9% NaCl used, identical packaging
            - 6331 to placebo of which 4553 were randomized < 3 hours
            - 4514 / 4553 analyzed
        - Clinical care: Locally provided, no constraints
- Results
    - Primary Outcome
        - 28 day in-hospital head injury associated mortality in patients assigned within 3 hours of injury: **NO significant difference**
            - TXA group 855/4613 (18.5%) vs. 892/4514 (19.8%) in placebo
            - RR 0.94 (95% CI 0.86 – 1.02)
            - ARR 1.23% (95% CI -0.39 – 2.84%)
    - Pre-specified Subgroup Analysis of Primary Outcome
        - **Excluding those with GCS 3 or bilateral unreactive pupils: NO significant difference**
            - 28 day in hospital TBI associated mortality in TXA group 485/3880 (12.5%) vs. 525/3757 (14.0%) in placebo
            - RR 0.89 (95% CI 0.80 – 1.00)
            - ARR 1.47% (95% CI -0.05 – 2.99%)

        - **Patients with Mild to Moderate TBI (GCS 9-15): Significantly reduced mortality in the TXA group**
            - 28 day in hospital TBI associated mortality in TXA group 166/2846 (5.8%) vs. 207/2769 (7.5%) in placebo
            - RR 0.78 (95% CI 0.64 – 0.95)
            - ARR 1.64% (95% CI 0.34 – 2.95%)
- **Complications**: No increased risk of VTE events (1.6% in both groups) or seizures (3.2% in TXA group vs 3.0% in placebo)
- **Take Home Point**
    - **Use of TXA in TBI appears to be safe and may reduce mortality in patients with Mild to Moderate TBI**
    - **Compare results to TICH trial (TXA for spontaneous ICH – Lancet 2018) which found TXA does not affect functional status at 90 days**

Take Home Points

- Lactate-guided or peripheral perfusion guided resuscitation strategy for septic shock?
- BMV probably safe to perform on case-by-case basis during RSI in critically ill patients.
- Conservative oxygen therapy did not reduce the number of ventilator-free days in ICU patients.
- Immediate coronary angiography did not benefit patients resuscitated from OHCA secondary to a shockable rhythm and who did not have evidence of a STEMI on ECG.
- Moderate hypothermia led to a higher percentage of patients with a nonshockable rhythm who survived with favorable neurologic outcome.
- TXA appears to be safe to use in patients with TBI and may have a mortality impact in patients with mild to moderate TBI.