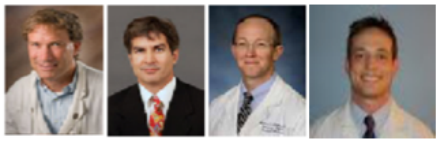
critical care perspectives in emergency medicine



Important Articles from 2018

Rapid Sequence Intubation

Driver BE, et al. Effect of use of a bougie vs endotracheal tube and stylet on first-attempt intubation success among patients with difficult airways undergoing emergency intubation: A randomized clinical trial. JAMA 2018; 319:2179-2189. (BEAM trial)

- Objective
  - Evaluate the bougie in a randomized comparison with an ETT+ stylet in ED patients with at least 1 characteristic predictive of difficult laryngoscopy or intubation
- Study
  - Randomized trial
  - Single center - Hennepin - urban, academic, level 1 trauma center with 109,000 annual ED visits
  - All intubations performed by EM residents or faculty
  - Patients
    - Included
      - 18 years or older
      - Admitted to the ED who would undergo ETI if attending planned to use a Mac laryngoscope blade
    - Excluded
      - Prisoners
      - Pregnant or assumed to be pregnant
      - Known distortion of the upper airway or glottic structures
    - Bougie use with hyperangulated blades not studied
  - Characteristics of Difficult Airway
    - Body fluids obscuring the laryngeal view
    - Airway obstruction or edema
    - Obesity
    - Short nec
    - Small mandible
    - Large tongue
    - Facial trauma
    - Cervical spine immobilization
    - Not formally defined - subjectively determined by physicians
    - Recorded after the procedure - can't ascertain all difficult airway characteristics before intubation
  - Randomization
    - 1:1 ratio to orotracheal intubation using either the bougie or ETT + stylet for the initial attempt
    - 2 strata: obesity or cervical immobilization or no obesity/cervical immobilization
    - Intubation procedure, preoxygenation, use of NMBA, cricoid pressure, choice of laryngoscope, whether to use video screen at discretion of EP

        - ETT+stylet: straight-to-cuff shape and bend of 25-35 degrees
    - Primary outcome
        - First attempt intubation success
    - Secondary outcomes
        - Hypoxemia
        - First attempt duration
        - Esophageal intubation
- Results
    - 757 patients were enrolled
        - 381 patients to bougie
        - 376 to ETT+stylet
    - 380 with difficult airway characteristics
        - 198 to bougie
        - 182 to ETT+stylet
    - Primary outcome (380 patients with at least 1 difficult airway characteristic)
        - Bougie group: 96%
        - ETT+stylet: 82%
    - Secondary outcomes:
        - First attempt success in whole study population
            - Bougie: 98%
            - ETT+stylet: 87%
        - For patients without any difficult airway characteristics, first attempt success
            - Bougie: 99%
            - ETT+stylet: 92%
    - Exploratory analysis
        - First attempt success better with bougie in cervical immobilization (100% vs. 78%), obese patients (96% vs. 75%), and patients with incomplete glottic views on laryngoscopy (97% vs. 60%)
    - Complications
        - Hypoxemia
            - Bougie group: 13%
            - ETT+stylet: 14%
        - Esophageal intubation
            - Bougie group: None
            - ETT+stylet: 3 (1%)
- Limitations
    - Single center institution - may not be generalizable - majority of ED intubations at this institution utilized a bougie prior to the study; more than 96% of patients intubated using the CMAC Mac blade for the initial attempt
    - Difficult airway characteristics were based on subjective assessment
    - Difficult airway characteristics were not all ascertained before intubation - could not stratify randomization by difficult airway characteristics; primary analysis was a postrandomization subgroup analysis
    - 7% of patients randomized to ETT+stylet intubated using a bougie
    - Could not blind or conceal EP to device used for initial intubation attempt
- **Take Home Point**

- **Orotracheal intubation with a bougie on the initial attempt compared with intubation using a stylet and ETT led to improved first-attempt success in patients with at least 1 difficult airway characteristic**
- **Bougie may be beneficial as a primary intubation device rather than solely as a rescue adjunct**

De Jong Audrey, et al. Cardiac arrest and mortality related to intubation procedure in critically ill adult patients: A multicenter cohort study. Crit Care Med. 2018; 46:532-9.

- Objective
  - Establish the prevalence of cardiac arrest during intubation procedure, the mortality rate of patients suffering cardiac arrest, immediately and at day 28, and to assess risk factors for cardiac arrest and 28-day mortality in a large cohort of ICU intubations
- Study
  - Retrospective analysis of intubation procedures in 6 prospective randomized and observational studies using 5 databases in 64 ICUs
  - Inclusion
    - All intubation procedures performed in 64 ICUs
    - Adults >= 18 years of age
  - Primary Outcome
    - Intubation-related cardiac arrest during or within 5 minutes after intubation requiring CPR
- Results
  - 1,918 intubations from the 5 datasets in 64 ICUs
  - Total of **1,847 intubations were included**
  - Most common indication for intubation was acute respiratory failure and coma
  - Anesthesiologists first provider in 68%
  - **Intubation related CA occurred in 2.7%**
  - **Factors** associated with intubation-related cardiac arrests
    - Arterial hypotension (SBP <90 mm Hg) prior to intubation (OR 3.406)
    - Hypoxemia prior to intubation (OR 3.991)
    - Absence of preoxygenation (OR 3.584)
    - Obesity (OR 2)
    - Age over 75 years (OR 2.251)
  - **Outcomes**
    - Patients without intubation-related CA - significantly lower mortality rate at day 28 (30.1%) vs. those who had CA (with ROSC - 62.8%)
    - Intubation-related CA was an independent risk factor for 28-day mortality (HR 3.9)
- Limitations
  - Reporting bias and inaccuracy of studies
  - Cohort study - can't eliminate effect of unmeasured confounders
  - Some data missing in oldest datasets
  - All 5 databases not specifically designed to assess CA outcomes
- **Take Home Points**
  - **Intubation-related CA occurred in 2.7% of patients; 1 out of every 40**
  - **Main risk factors: obesity, age over 75 years, low SBP prior to intubation, hypoxemia prior to intubation, absence of preoxgyenation**

Mechanical Ventilation

Simonis, et al. Effect of a low vs intermediate tidal volume strategy on ventilator-free days in intensive care unit patients without ARDS. The PReVENT Trial. JAMA 2018. Published online October 24, 2018.

- Background
  - MV is increasingly recognized as a potentially harmful intervention
  - Lung-protective ventiation using a low-tidal volume improves survival in patients with ARDS
  - It is less certain whether tidal volume restriction benefits pateints without ARDS
  - Use of low tidal volumes could lead to an increased need for sedation because of high RR and ventilator asynchrony, possibly self-inflicted lung injury due to compensatory injurious inspiratory effort
- Objective
  - Test whether a ventilation strategy using low tidal volumes is superior to a ventilation strategy using intermediate tidal volumes with respect to the number of ventilator-free days and alive at day 28
- Study
  - Randomized trial in 6 ICUs in the Netherlands
  - Patients
    - Received invasive ventilation shortly before or after admission to the ICU
    - Expected not to be extubated within 24 hours of randomization
    - Randomized within 1 hour of initiation of ventilation in the ICU
    - Exclusion
      - Presence of ARDS
      - Age < 18 years
      - Pregnancy
      - Ventilation lasting longer than 12 hours before admission to the ICU
      - Increased and uncontrollable ICP
      - History of pulmonary disease
      - New PE
  - Randomization
    - 1:1 ratio of low or intermediate tidal volume ventilation strategy group
  - Interventions
    - Low-tidal volume group
      - Started at 6 ml/kg PBW
      - Received either VC or PS ventilation
      - TV decreased by 1 ml/kg PBW every hour to a minimum of 4 ml/kg PBW
      - With PSV, lowest level of pressure support was used to target a tidal volume minimum of 5 cmH2O
      - Severe dyspnea, increasing levels of discomfort with or without need for more sedation, a RR > 35 bpm, uncontrollable acidosis, patient-ventilator asynchrony - tidal volume could be increased in increments of 1 ml/kg PBW per hr in patients receiving VC or PSV
    - Intermediate tidal volume group
      - Started at 10 ml/kg PBW using VCV
      - If Pplat > 25, tidal volumes decreased in increments of 1 ml/kg PBW per hour

            - With PSV, PS was adjusted to reach a target tidal volume while keeping max airway pressure < 25
        - Vent settings measured every 8 hours
        - Use of analgosedation or muscle relaxants with purpose of allowing assigned vent strategy was not allowed
    - Primary Outcome
        - Number of ventilator-free days and alive at day 28
    - Secondary Outcomes
        - ICU and hospital LOS
        - ICU, hospital, 28-day, and 90-day mortality
        - Occurrence of pulmonary complications - development of new ARDS, VAP, severe ATX, and PTX
        - Amount of sedatives prescribed
        - Use of analgesics and NMBAs
        - Transfusion of blood products
- Results
    - 3659 patients screened
    - 2734 patients excluded
    - **961 patients included**
        - 477 allocated to low-tidal volume group
        - 484 to the intermediate group
        - Groups well balanced
        - More than 80% were admitted to ICU for medical reason
        - Most frequent reason for mechanical ventilation was cardiac arrest
    - Intervention
        - Median time between start of ventilation and randomization was 0.88 hours
        - Median time between start of ventilation in the ICU and randomization was 0.57 hours
        - During first 3 days - tidal volumes and airway pressures were significantly different among the groups
        - Pplat and driving pressure were lower and RR higher in the low-tidal volume group
        - PaO2 and FiO2 did not differ
        - PaCO2 was higher and pH lower in low tidal volmue group
    - Outcomes
        - 28 days after randomization
            - **Low tidal volume group: median of 21 ventilator free days**
            - **Intermediate group: median of 21 ventilator**
        - Median ICU and hospital LOS did not differ
        - ICU and hospital mortality rates did not differ
        - 28-day and 90-day mortality rates did not differ
        - Occurrence of ARDS, pneumonia, severe ATX, and PTX did not differ
        - No difference between the groups with respect to need for, duration of, and amount of sedatives, analgesics, and NMBAs
- Limitations
    - Not blinded
    - Heterogeneous group of patients without ARDS was included
    - Substantial number of patients were missed for randomization!

    - Randomization within 1 hour was in some cases impractical or impossible
- **Take Home Point**
    - **In this trial of adult patients in the ICU without ARDS who received ventilation and were expected not to be extubated within 24 hours of randomization, a ventilation strategy using low tidal volumes was <u>not more effective</u> than a strategy using intermediate tidal volumes with respect to ventilator-free days and alive at day 28**

Fluid Resuscitation

Semler MW, Balanced crystalloids versus saline in critically ill adults. N Engl J Med 2018; 378:829-39.

- Background
    - Question of whether crystalloid composition affects patient outcomes remains unanswered
    - Data suggest that IV saline may be associated with hyperchloremic metabolic acidosis, acute kidney injury, and death
    - Several observational studies and a before and after trial suggested that the use of balanced crystalloids is associated with lower rates of AKI, RRT, and death
- Objective
    - Determine the effect of isotonic crystalloid composition on clinical outcomes in critically ill adults
    - Compared the use of balanced crystalloids with the use of saline in patients in medical and nonmedical ICUs
- Study
    - Pragmatic, unblinded, cluster-randomized, multiple crossover trial
    - Use of balanced crystalloids compared with saline
    - Vanderbilt University Medical Center (5 ICUs)
    - Patients
        - All adults 18 years of age or older
        - Admitting to a participating ICU during trial time and enrolled at the time of ICU admission
    - Randomization
        - For each month - participating ICUs were assigned to use either balanced crystalloids or saline for any IV administration of isotonic crystalloids
        - ICUs were randomly assigned to used saline during even-numbered months and balanced crystalloids during odd-numbered months
        - Coordinated with the ED and OR
    - Treatments
        - Saline - 0.9% sodium chloride
        - Balanced - LR or Plasma-Lyte A according to physician preference
        - Hyperkalemia and brain injury - relative contraindications to use of balanced solutions
    - Primary Outcome
        - Proportion of patients who met one or more criteria for major adverse kidney event within 30 days (composite outcome of death, new receipt of RRT, or persistent renal dysfunction
    - Secondary outcomes
        - In-hospital death before ICU discharge or at 30d or 60d
        - ICU free days
        - Ventilator-free days

        - Vasopressor free days
        - Days alive and free of RRT during 28 days after enrollment
- Results
    - 15,802 patients from 5 ICUs were enrolled
        - 1/3rd receiving mechanical ventilation
        - ¼ receiving vasopressors
    - Fluid therapy and electrolytes
        - Majority of pre-ICU fluid patients received was consistent with trial group
        - Median volume of balanced fluids between ICU admission and hospital DC or 30d - 1000 ml
        - Median volume of 0.9% NS was 1020 ml
        - Fewer patients in the balanced fluid group had measured chloride levels > 110 mmol/L and plasma bicarbonate concentration less than 20 mmol/L
    - Primary outcome
        - Balanced crystalloid group: 14.3%
        - Saline group: 15.4%
        - OR 0.91
        - Difference in rate of primary outcome between balanced and saline group greater among those with larger volumes of crystalloid and among patients with sepsis
        - Sepsis
            - Balanced group: 25.2% in-hospital mortality
            - Saline: 29.4% in-hospital mortality
    - Secondary outcomes
        - Died before hospital DC or within 30d of ICU admission
            - Balanced group: 10.3%
            - Saline group: 11.1%
        - Highest stage of AKI and incidence of persistent renal dysfunction did not differ
- Limitations
    - Single academic center
    - Clinicians aware of composition of assigned crystalloids
    - Decision to initiate RRT may be susceptible to treatment bias
    - Evaluated LR and Plasma-Lyte together
- **Take Home Point**
    - **IV administration of balanced crystalloids, rather than saline, had a favorable effect on composite outcome of death, new RRT, or persistent renal dysfunction**

Cardiac Arrest

Perkins GD, et al. A randomized trial of epinephrine in out-of-hospital cardiac arrest. N Engl J Med. 2018; 379:711-21.

- Background
    - Epi has potential beneficial effects in cardiac arrest
        - Alpha-adrenergic effects: increases aortic diastolic BP during CPR and augments coronary blood flow, increasing the chances of ROSC; can cause platelet activation which promotes thrombosis and impairs microvascular blood flow
        - Beta-adrenergic effects: can cause dysrhythmias and increased myocardial oxygen demand, increases the risk of recurrent cardiac arrest

    - Observational trials involving more than 500,000 patients have reported higher rates of ROSC but worse neurologic outcomes in patients treated with epi
    - These studies have produced conflicting results
    - ILCOR called for the initiation of a placebo-controlled trial to establish whether epi is safe and effective in cardiac arrest
- Objective
    - Determine whether epinephrine is beneficial or harmful as a treatment for OHCA
- Study
    - Multicenter, randomized, double-blind, placebo-controlled trial
    - 5 National Health Service ambulance services in the UK
    - Patients
        - Inclusion
            - Adults with OHCA for which ALS was provided by trial-trained paramedics
        - Exclusion
            - Pregnancy
            - Age < 16 years
            - Anaphylaxis or asthma as etiology
            - Administration of epi prior to arrival of trial-trained paramedic
    - Randomization and Treatment
        - If initial attempts at resuscitation (CPR and defibrillation) were unsuccessful, patient randomly assigned to receive epi or saline placebo
        - Trial packs (10 prefilled syringes) of 1 mg of epi or 0.9% saline
        - Single doses given every 3 to 5 minutes
        - Assigned in a ratio of 1:1
        - Treatment was continued until a sustained pulse was achieved, resus discontinued, or care handed over to clinicians in the hospital
        - Hospital care (TTM, hemodynamic, oxygenation/ventilation, prognostication) not specified
    - Primary outcome: 30-day survival
    - Secondary outcomes
        - Rate of survival until hospital admission
        - ICU and hospital LOS
        - Rates of survival at hospital DC and at 3 months
        - Neurologic outcomes at hospital DC and 3 months (defined using mRS)
- Results
    - 8014 patients assigned (8103 of 10,623 eligible and trial packets opened)
        - Epi group: 4015 patients
        - Placebo group: 3999 patients
        - Characteristics well balanced
        - Concurrent treatments similar
        - Median time from call to EMS arrival 6.6 minutes
        - Median time from arrival to trial agent administration 13.8 minutes
        - Proportion of patients with ROSC during prehospital phase 36.3% vs. 11.7%
    - Primary Outcome
        - 30-day survival
            - Epi group: 130/4012 patients: 3.2%
            - Placebo group: 94/3995 patients: 2.4%

        - p=0.02
        - NNT with Epi to prevent one death at 30-days: 112
    - Secondary Outcomes
        - Proportion of patients who survived to hospital DC with favorable neurologic outcome
            - Epi group: 87/4007 patients: 2.2%
            - Placebo group: 74/3994 patients: 1.9%
        - Severe neurologic impairment
            - Epi group: 39/126 patients: 31%
            - Placebo group: 16/90 patients: 17.8%
        - No difference in survival at 3 months and neurologic outcomes at 3 months
        - No difference in LOS in the hospital or ICU
        - No evidence of difference in treatment effect based on age, witnessed cardiac arrest, bystander CPR, initial rhythm, or response time to trial agent administration
- Limitations
    - Earlier administration may have influenced results?
    - Did not collect info on patient's baseline neuro status
    - Information about quality of CPR only during first 5 minutes and in less than 5% of cases
    - No information or specification of hospital care
- **Take Home Point**
    - **In patients with OHCA, use of epi resulted in higher rate of 30-day survival but no difference in rate of favorable neuro outcome with more severe impairment**

Post-Arrest Care

Roberts BW, et al. Association between early hyperoxia exposure after resuscitation from cardiac arrest and neurological disability: a prospective multi-center protocol-directed cohort study. Circulation 2018; 137:2114-24.

- Background
    - PCAS characterized by systemic post-resuscitation ischemia/reperfusion injury commonly resulting in neurologic damage
    - In-hospital mortality over 50%
    - Many who survive are left with permanent and severe neurological disability
    - Exposure to hyperoxia previously demonstrated to amplify the production of oxygen free radicals - neuronal injury and death
    - Current post-resuscitation guidelines recommend titrating FiO2 in post-arrest patients to avoid hypoxia and prolonged exposure to hyperoxia (PaO_2 > 300 mm Hg)
    - Observational studies, however, have produced conflicting results - all studies have had methodological limitations - mostly retrospective and most evaluated ABG measurements over first 24 hours after ROSC
- Objective
    - Test the association between early post-resuscitation hyperoxia and poor neurological outcome among adult patients successfully resuscitated from cardiac arrest
- Study
    - Prospective cohort study
    - 6 hospitals in the US - Cooper, UPenn, Penn-Presbyterian, Methodist in Indianapolis, University of Mississippi, and BID in Boston
    - Patients

        - Adults >= 18 years
        - Cardiac arrest
        - ROSC > 20 min
        - Mechanically ventilated after ROSC
        - Intent to perform TTM
        - Included both in-patient and OHCA
    - Standard Care
        - Routine across all sites
            - TTM for 24 hours
            - Controlled rewarming to avoid hyperpyrexia with TTM
            - Goal-directed hemodynamic support interventions
            - Interventional cardiac cath (if needed)
            - Continuous EEG
            - Evidence-based approach to neurologic prognostication, waiting > 72 hours after ROSC
    - Data Collection
        - Obtained initial ABG 1 hour after ROSC and a second 6 hours after ROSC
        - Also recorded plateau pressures
        - SaO2 and FiO2 were continuously monitored and recorded every 15 min
        - Calculated time-weighted average for SaO2 and FiO2
    - Primary Outcome
        - Poor neurologic function or death at hospital DC, defined a priori as mRS > 3
    - Secondary outcomes
        - In-hospital mortality
        - Early neurologic injury defined as FOUR Score <= 6 at 72 hours after ROSC
    - A Priori
        - Defined hyperoxia as PaO2 > 300 mm Hg on 1 or more ABGs
        - Also examined associated between PaO2 and outcome across thresholds to define hyperoxia - 100, 150, 200, 250, 300, 350, and 400 mm Hg
- Results
    - 280 patients included in the final cohort
        - OHCA with PEA/asystole was initial rhythm in 39%, followed by OHCA with pulseless VT/VF in 31%
        - Excluded 326 due to no informed consent
        - Study cohort had higher rate of Vf/VT 37% vs. 21% and longer duration of CPR
    - 38% had exposure to hyperoxia
    - Primary outcome
        - 70% of patients with poor neurologic outcome or death at hospital DC
        - Subjects with exposure to hyperoxia had a higher incidence of poor neurologic function at hospital DC than patients with no exposure (77% vs. 65%)
    - Hyperoxia was an independent predictor of poor neurological function at hospital DC as well as early neurologic injury
    - 1-hour longer duration of hyperoxia was associated with a 3% increase in risk of poor neurologic outcome
- Limitations
    - Observational study - only report association
    - Included both in-patient and OHCA
    - 326 subjects excluded due to lack of consent

    - Found discordance between measured PaO2 and corresponding SaO2
    - Does hyperoxia reflect a patient population that is more ill - higher likelihood to have poor neurologic outcome
- **Take Home Point**
    - **Early hyperoxia after resuscitation from cardiac arrest is independently associated with death and poor neurologic function**
    - **Increased risk appears to begin at a PaO2 of 300 mm Hg**

Roberts BW, et al. Association between elevated mean arterial blood pressure and neurologic outcome after resuscitation from cardiac arrest: results from a multicenter prospective cohort study. Crit Care Med. 2018. Epub ahead of print.

- Objective
    - Test the association between elevated post-resuscitation MAP and neurologic outcome among adult patients successfully resuscitated from CA
- Study
    - Preplanned analysis of a prospective cohort study
    - 6 US hospitals - prospectively compiled and maintained a CA registry
    - Included
        - Age >= 18 years
        - Cardiac arrest
        - ROSC >= 20 minutes
        - Unresponsive (GCS motor < 6) and mechanical ventilation
        - Intent to perform TTM
        - Both IHCA and OHCA
    - Excluded
        - Presumed etioogy of arrest secondary to trauma, hemorrhage, sepsis
        - Residents of nursing home or long-term care facility
        - Pregnancy
        - Prisoners
        - Persistent hypotension during the initial 6 hours after ROSC
    - Data Collection
        - Measured MAP immediately after ROSC and hourly thereafter using NIV cuff for the first 6 hours (most critical time period for hemodynamic optimization after CA)
    - Primary Outcome
        - Good neurologic function at hospital DC (mRS <= 3)
    - Secondary Outcomes
        - Survival to hospital DC
        - Good early neurologic response (FOUR score > 6 at 72 hours)
    - Data Analysis
        - A priori grouped subjects into
            - MAP 70-90 mm Hg
            - MAP > 90 mm Hg
        - Multiple preplanned subgroup analysis
- Results
    - 280 subjects
        - 11 excluded for MAP < 70 mm Hg
        - 269 ultimate subjects

        - 150 (59%) had MAP > 90 mm Hg during the initial 6 hours
    - Primary outcome
        - 82 subjects (30%) had good neurologic function at hospital DC
            - MAP 70-90 mm Hg: 15%
            - MAP > 90 mm Hg: 42%
    - Survival to hospital DC
        - 122 subjects
            - MAP 70-90 mm Hg: 28%
            - MAP > 90 mm Hg: 57%
        - MAP > 90 mm Hg was an independent predictor of good neurologic function at hospital DC as well as survival to hospital DC and early neurologic response
        - Difference between MAP > 90 mm Hg and good neurologic outcome was found to be stronger among subjects with a previous diagnosis of HTN compared with those w/o HTN
    - For every additional hourly BP measurement with MAP > 90 mm Hg there was a 15% increase in the probability of good neurologic outcome
- Limitations
    - Observational study - only associations
    - Did not require invasive BP monitoring
    - No standardized BP target - goals varied between clinicians
    - 42% (25 of 59) patients with MAP > 90 mm Hg had exposure to hypotension during initial 6 hours
    - Potential for unmeasured confounders
    - Did not collect data on number of vasopressor agents administered
- Take Home Points
    - **MAP > 90 mm Hg independently associated with good neurologic outcome at hospital DC**
    - **PostROSC MAP > 110 mm Hg had strongest association**
    - **Elevated MAP during early period after ROSC associated with good neurologic outcome**
    - **Stronger association among patients with a previous diagnosis of HTN**

Septic Shock

Venkatesh B, et al. Adjunctive glucocorticoid therapy in patients with septic shock. N Engl J Med. 2018.

- Background
    - Steroids have been used as adjuvant therapy for septic shock for more than 40 years
    - Uncertainty remains about their safety and efficacy
    - 1980s - RCTs demonstrating harm with high-dose methylprednisolone
    - 2 RCTs examining lower-dose hydrocortisone had conflicting results on mortality among patients with septic shock
    - Current clinical practice guidelines recommend the use of hydrocortisone in patients with septic shock if adequate fluid resuscitation and vasopressors have not restored hemodynamic stability - Recommendation WEAK based on low quality of evidence
    - Much variation in clinical practice
- Objective
    - Test the hypothesis that hydrocortisone results in lower mortality than placebo among patients with septic shock
- Study

- Investigator-initiated, international, pragmatic, double-blind, parallel-group, randomized, controlled trial
- Australia, UK, New Zealand, Saudi Arabia, and Denmark
- Patients
  - Included
    - Adults >= 18 years of age
    - Undergoing mechanical ventilation
    - Documented or strong suspicion of infection
    - 2 or more SIRS criteria
    - Treated with vasopressors or inotropic agents for a minimum of 4 hours
  - Excluded
    - Receive treatment with systemic steroids for an indication other than septic shock
    - Received etomidate
    - Were considered likely to die from a pre-existing disease within 90 days after randomization
    - Met all inclusion criteria for more than 24 hours
- Randomized
  - IV infusion of hydrocortisone at a dose of 200 mg per day
  - Placebo
  - Administered over a period of 24 hours for a maximum of 7 days or until ICU discharge or death
  - Patients, treating clinicians, trial personnel unaware of trial-group assignments and sequence
- Outcomes
  - Primary outcome: 90-day mortality
  - Secondary
    - 28-day mortality
    - Time to resolution of shock
    - Recurrence of shock
    - Length of ICU stay
    - Length of hospital stay
    - Frequency and duration of MV
    - Frequency and duration of RRT
    - Incidence of new bacteremia or fungemia between 2-14 days
    - Receipt of blood transfusion

- Results
  - 3800 patients were enrolled in 69 medical-surgical ICUs
    - 1898 assigned to hydrocortisone
    - 1902 assigned to placebo
  - Ultimately 3658 included in study
    - 1832 to hydrocortisone
    - 1825 ot placebo
  - Characteristics of patients similar
- Primary outcome
  - 90-day mortality
    - 27.9% in hydrocortisone group
    - 28.8% in placebo

        - No difference based on admission type (med vs. surgical), dose of catecholamine infusion, primary site of sepsis, gender, APACHE II score, and duration of shock
    - Secondary
        - No difference in 28-day mortality
        - Time to resolution of shock shorter in hydrocortisone group
        - Time to ICU DC shorter in hydrocortisone group
        - Shorter duration of initial episode of MV in hydrocortisone group
        - Fewer patients in the hydrocortisone group received a blood transfusion
- Adverse events
    - 33 reported in trial population
        - 1.1% in hydrocortisone group
        - 0.3% in placebo
    - 6 serious adverse events - 4 in hydrocortisone group, 2 in placebo
- Limitations
    - Only adverse events judged by the treating clinician to be related to trial regimen were recorded
    - Did not adjudicate appropriateness of ABX
    - Did not collect data regarding all possible secondary infections
- **Take Home Point**
    - **A continuous infusion of hydrocortisone did not lower 90-day mortality in septic shock patients undergoing mechanical ventilation**

Annane D, et al. Hydrocortisone plus fludrocortisone for adults with septic shock. N Engl J Med. 2018; 378:809-18. APROCCHSS Trial (Activated Protein C and Corticosteroids for Human Septic Shock)

- Objective
    - Test the hypothesis that hydrocortisone plus fludrocortisone therapy or drotrecogin alfa would improve the clinical outcomes of patients with septic shock
- Study
    - Placebo-controlled trial with four parallel groups organized in a 2x2 factorial design
        - After withdrawal of Xigris from the market - trial continued with 2 parallel groups
    - 34 centers: September 2008 to June 2015
    - Patients
        - Admitted to the ICU
        - Indisputable or probable septic shock for less than 24 hours
        - SOFA score of 3 or 4 for at least 2 organs for at least 6 hours
        - Vasopressor therapy for at least 6 hours to maintain SBP of at least 90 or MAP of at least 65 mm Hg
    - Randomization
        - Assigned in permuted blocks of eight to receive hydrocortisone plus fludrocortisone, drotrecogin alfa, the combination of the 3 drugs, or their respective placebos
        - Hydrocortisone given in 50 mg IV boluses every 6 hours; fludrocortisone given as 50 mcg tablet once a dail
        - Treatment for 7 days
    - Measurements

        - Plasma total cortisol levels measured before, 30 min, and 60 min after corticotropin test
    - Treatment according to the 2008 SSC Guidelines
    - Primary Outcome: 90-day all cause mortality
    - Secondary outcomes
        - All cause mortality at ICU DC, hospital DC, day 28, and day 180
        - % of patients weaned from vasopressors at day 28 and 90
        - Time to weaning from vasopressors
        - % of patients weaned from mechanical ventilation at day 28 and day 90
        - Time to weaning from MV
        - Ventilator free days up to day 28 and day 90
        - Others
    - Safety outcomes
        - Superinfection up to day 180
        - GIB up to day 28
        - Hyperglycemia up to day 7
- Results
    - Trial suspected twice
    - Sponsor terminated trial when expiration dates of meds were reached - 1241 patients
    - 90-day all cause mortality
        - Hydrocortisone plus fludrocortisone: 43%
        - Placebo: 49.1%
        - P=0.03; RR of death 0.88
    - Secondary outcomes
        - ICU DC mortality
            - Hydrocortisone plus fludrocortisone: 35.4%
            - Placebo: 41%
            - P=0.04
        - Hospital DC mortality
            - Hydrocortisone plus fludrocortisone: 39%
            - Placebo: 45.3%
            - P=0.02
        - 180 day mortality
            - Hydrocortisone plus fludrocortisone: 46.6%
            - Placebo: 52.5%
            - P=0.04
    - Hydrocortisone plus fludrocortisone group
        - Shorter time to weaning from mechanical ventilation
        - Shorter time to weaning from vasopressor therapy
        - More vasopressor free days
        - More organ failure free days
    - Serious Adverse Events
        - Hydrocortisone plus fludrocortisone: 53.1%
        - Placebo: 58%
        - P=0.08
        - Risk of GIB or superinfection not higher
- Limitations

    - Some imbalance between groups - slightly more viral pathogens in the hydrocortisone plus fludrocortisone group
    - Drotrecogin alfa removed from market and impacted statistical power calculation
    - Used 2008 SSC Guidelines
    - Did not report all secondary outcomes included in original trial
- **Take Home Point**
    - **7-day treatment course of hydrocortisone plus fludrocortisone resulted in lower mortality at day 90, ICU DC, and hospital DC compared with placebo**