Top 10 Articles from 2016

Neurocritical Care

1. *Qureshi AI, Palesch YY, Barsan WG, et al. Intensive blood-pressure lowering in patients with acute cerebral hemorrhage. N Eng J Med 2016; 375(11)1033-43.*
    - Objective
        - Determine the relative efficacy of intensive versus standard antihypertensive treatment that was initiated within 4.5 hours after symptoms onset and continued for the next 24 hours in patients with spontaneous supratentorial ICH.
    - Study
        - Randomized, multicenter, two-group, open-label trial
        - Patients
            - 18 years of age or older
            - GCS of 5 or more at the time of ED arrival
            - Intraparenchymal hematoma of less than 60 cm
            - At least one reading of SBP of 180 mm Hg or more between symptom onset and initiation of antihypertensive treatment
        - Treatment initiated within 4.5 hours of symptom onset
        - Interventions
            - Goal of treatment was to reduce and maintain the hourly minimum SBP in the range of:
                - 140-170 mm Hg in the standard group
                - 110-139 mm Hg in the intensive treatment group
                - Throughout the period of 24 hours
            - After randomization, IV nicardipine was the first agent used - initiated at 5 mg/hr and titrated by 2.5 mg/hr every 15 min until 15 mg reached; if SBP goal not achieved at max nicardipine dose, could use IV labetalol
            - Primary treatment failure defined as not reaching the target SBP of less than 140 mm Hg in the intensive treatment group and less than 180 mm Hg in the standard treatment group within 2 hours of randomization
        - Trial Assessments
            - CT head obtained at 24 hours after the initiation of treatment
            - Baseline and 24-hr CT scans were read by reader unaware of the assignments, clinical findings, and time points of image acquisition
        - Follow up at 1 m with telephone contact, and in-person evaluation at 3 m
        - Primary outcome: proportion of patients who had moderately severe or severe disability or who had died (dichotomized 3-month mRS 4-6 vs. 0-3)
        - Safety outcomes: neurologic deterioration (decrease from baseline of 2 or more in GCS)
    - Results
        - 110 sites in the US, Japan, China, Taiwan, South Korea, and Germany
        - 1000 patients randomized - 500 each arm
            - 56.2% were Asian; 38% women
            - ICH volume > 30 cm3 9-10%
            - IVH about 25-29%
            - Basal ganglia 51%

        - Primary treatment failure occurred in 12% of intensive-treatment group vs. 0.8% in standard-treatment group
        - Death or disability
            - Intensive treatment group: 38.7%
            - Standard treatment group: 37.7%
        - No significant difference between groups in the ordinal distribution of mRS score at 3 months
        - Serious adverse events
            - Intensive treatment group: 1.6%
            - Standard treatment group: 1.2%
    - Limitations
        - Higher proportion of patients with primary treatment failure in intensive treatment group.
        - Relatively high proportion of Asian patients (no significant difference in treatment group between Asian patients and non-Asian patients)
        - Observed rate of death or disability at 3 months lower than anticipated rate in standard treatment group
        - High proportion of patients with GCS of 15
        - Trial stopped for futility prior to enrolling planned 1280 patients
    - **Take Home Point**
        - **Intensive reduction (110-139 mm Hg) in SBP level does not provide incremental clinical benefit.**

2. *Baharoglu MI, Cordonnier C, Al-Shahi Salman R, et al. Platelet transfusion versus standard care after acute stroke due to spontaneous cerebral haemorrhage associated with antiplatelet therapy (PATCH): a randomized, open-label, phase 3 trial. Lancet 2016; 387:2605-13.*
    - Objective
        - Assess whether platelet transfusion would reduce death or dependence compared to standard care by reducing ICH growth
    - Study
        - Multicenter, randomized, open-label, parallel-group trial
        - 36 hospitals in Netherlands, 13 hospitals in the UK, 11 hospitals in France
        - Patients
            - 18 years of age or older
            - Nontraumatic supratentorial ICH
            - GCS of 8-15
            - Platelet transfusion could be initiated within 6 hours of symptom onset and within 90 min of brain imaging
            - Taking antiplatelet therapy (COX inhibitors-aspirin; ADP receptor inhibitor-clopidogrel; adenosine-reuptake inhibitor-dipyridamole) for at least 7 days
            - Had preICH mRS of 0 or 1
        - Intervention
            - Randomized 1:1
            - Standard care
                - Not defined in protocol
                - Assumed to be given according to contemporary European and National guidelines
            - Standard care plus platelet transfusion
                - Leukocyte-depleted

        - Initiated within 6 hours of ICH symptom onset and within 90 min of diagnostic brain imaging
        - COX inhibitor - got one platelet concentrate
        - ADP receptor inhibitor - got 2 platelet concentrates
    - Brain imaging done at 24 hours
  - Primary outcome
    - Difference in functional outcome at 3 months after randomization scored with mRS
- Results
  - 41 sites enrolled 190 patients
    - 97 assigned to standard care + platelets
    - 93 assigned to standard care
    - None lost to follow up at 3 months
    - Baseline characteristics balanced
    - 19% had at least one exclusion criteria
    - Follow up imaging missing for 17 patients in platelet group and 20 in control group
  - Primary outcome
    - Shift towards death or dependence at 3 months higher in platelet transfusion group (OR 1.84)
    - More participants in the platelet group had poor outcome with a mRS score of 4-6 at 3 months
  - Secondary outcomes
    - Survival and proportion of patients with an mRS of 3-6 at 3 months weren't significantly different nor did ICH volume change at 24 hours
  - Serious adverse events
    - Platelet group: 42%
    - Standard group: 29%
    - Most were ICH enlargement, UTI, and pulmonary infections
- Limitations
  - Small size
  - Most were taking aspirin; relatively few clopidogrel
  - 19% met at least one exclusion criteria
- **Take Home Point**
  - **Platelet transfusion cannot be recommended for treatment of ICH in patients taking antiplatelet therapy**

<u>Cardiac Arrest</u>

3. *Kudenchuk PJ, Brown SP, Daya M, et al. Amiodarone, lidocaine, or placebo in out-of-hospital cardiac arrest. N Engl J Med 2016; 374:1711-22.*
   - Objective
     - Compare the effects of amiodarone, lidocaine, and placebo on survival to hospital DC after OHCA due to shock-refractory VF or pVT
   - Study
     - Randomized, double-blind, placebo-controlled prehospital trial
     - 55 EMS agencies enrolled patients with OHCA at 10 North American sites participating in ROC
     - Patients
       - 18 years of age or older
       - Nontraumatic OHCA
       - Shock-refractory VF or pVT

        - Required to have IV or IO access
    - Treatment protocol
        - After failure of one or more shocks to terminate VF or pVT or prevent its recurrence, patients received a vasopressor and study drug kit
        - Patients, investigators, trial personnel unaware of trial-drug assignments
        - If VF or pVT persisted after initial dose of drug, standard resusc measures, additional shock, and supplemental dose of drug were administered
        - Post-cardiac arrest care -all interventions completed before hospital arrival; post arrest care provided in accordance with AHA guidelines and include open-label amio or lidocaine
        - Components of hospital care not standardized
    - Primary outcome
        - Survival to hospital DC
        - Main aim was to compare amio vs. placebo, lido vs. placebo, and amio vs. lidocaine
    - Secondary outcome
        - Survival with favorable neurologic status at DC (mRS)
- Results
    - 3,026 patients included in per-protocol population
        - Amiodarone: 974
        - Lidocaine: 993
        - Placebo: 1059
    - Survival to hospital DC
        - Amiodarone: 24.4%
        - Lidocaine: 23.7%
        - Placebo: 21%
    - Favorable neurologic status
        - Amiodarone: 18.8%
        - Lidocaine: 17.5%
        - Placebo: 16.6%
    - Subgroup
        - Higher rate of survival with drugs vs. placebo when arrest was witnessed
            - Amiodarone: 27.7%
            - Lidocaine: 27.8%
            - Placebo: 22.7%
    - Placebo patients more likely to require additional dose of blinded drug than recipients of amio or lidocaine; received greater number of shocks and other rhythm control medications
- Limitations
    - Selection bias - may have influenced trial enrollment
    - Trial tested only 1 administration strategy without crossover
    - Enrollment of patients whose conditions may have afforded little to no chance of survival may have diluted presence of more robust treatment effect
- **Take Home Point**
    - **The use of amiodarone or lidocaine did not improve survival to hospital DC in OHCA patients with shock-refractory ventricular fibrillation or pulseless ventricular tachycardia.**

4. *Bernard SA, Smith K, Finn J, et al. Induction of therapeutic hypothermia during out-of-hospital cardiac arrest using a rapid infusion of cold saline: The RINSE Trial (Rapid Infusion of Cold Normal Saline). Circulation 2016; 134:797-805.*
    - Objective
        - Compare induction of TH during CPR in OHCA patients using a rapid IV infusion of large-volume cold saline with standard care
    - Methods
        - Study
            - December 2010 - December 2014
            - Multicenter, randomized, controlled trial
            - EMS in 3 cities in Australia (Melbourne, Adelaide, Perth)
                - Followed the recommendations of the Australian Resuscitation Council for treatment of OHCA
            - EMS carried 2 L of normal saline in an insulated cooler that maintained the temperature at 3 C using a chilled ice block
        - Patients
            - Adults > 18 years of age
            - Cardiac arrest upon EMS arrival
            - IV access
            - Were still in cardiac arrest after defibrillation, IV access, ventilation with 100% O2, and an initial dose of epinephrine
        - Randomization
            - If patient remained in CA after initial interventions, patients randomized to rapid infusion of 30 ml/kg cold saline (max 2L) or standard care
            - Cold saline was stopped if the tympanic temp reached 33 C or pulm edema was suspected
            - Patients with ROSC were transported to nearest hospital with an ED and ICU
            - Standard care at most hospitals included lytics or cath for STEMI and a TTM protocol targeted to 33 C
        - Primary Outcome: survival at hospital DC
        - Secondary Outcome: proportion of patients in shockable and nonshockable rhythms with ROSC
    - Results
        - 1198 patients for primary analysis
            - 618 to intra-arrest TH
            - 580 to standard prehospital care
        - Characteristics
            - Over 60% had bystander CPR performed
            - 75% arrested at private residence
            - 96% suspected cardiac cause
            - 46% VF/pVT
            - 33% Asystole
            - > 50% from Melbourne area
            - About 6 mg of epi given to both groups
            - 25% had post-arrest epi infusion
        - Outcomes
            - Overall no difference in survival at hospital DC
                - Intra-arrest cooling: 10.2%
                - Standard care: 11.4% (p=0.51)
                - Shockable rhythm

        - Intra-arrest cooling: 18.9%
        - Standard care: 23.2% (p=0.21)
    - Significant decrease in number of patients with an initial shockable rhythm allocated to cold saline who had ROSC as the scene (41% vs. 51%)
- Limitations
    - Study stopped prior to first planned interim analysis because a number of hospitals changed their TTM protocol to 36 C after the TTM trial
    - EMS was not blinded to treatment
    - Tympanic membrane temps used; other methods not feasible
    - Enrolled approximately 10% of all arrests undergoing CPR
    - Primary outcome was survival to hospital DC, not neurologic survival
- **Take Home Points**
    - **Pre-hospital Intra-arrest cooling with cold saline did not improve survival to hospital DC**
    - **Reduction in rate of ROSC for patients with an initial shockable rhythm**

5. *Gaspari R, Weekes A, Adhikari S, et al. Emergency department point-of-care ultrasound in out-of-hospital and in-ED cardiac arrest. Resuscitation 2016; 109:33-39.*
    - Objective
        - Determine the association between US visible cardiac activity and survival for patients with PEA or asystole
    - Study
        - Multicenter, prospective, protocol-driven observational study
        - 20 sites in the US and Canada
        - Patients
            - Presented to the ED in nontraumatic CA
            - Found to be in PEA or asystole
            - Had US imaging performed during their resuscitation
        - Protocol
            - Required US imaging at the beginning of ACLS in the ED and a second US exam at the end of resuscitation efforts
            - All USs performed during pauses in resuscitation
            - Used subxiphoid or parasternal long axis views to identify cardiac activity during resuscitation
            - Cardiac activity defined as any visible movement of the myocardium; excluded blood movement within the chambers or isolated valve movement
            - USs performed by credentialed EM physicians
        - Primary outcome
            - Percentage of patients that survive to hospital admission
        - Secondary outcomes
            - % of patients that survive to hospital DC
            - % of patients with ROSC
    - Results
        - 953 patients enrolled from 2011 to 2014
            - ROSC: 26.2%
            - Survival to hospital admission: 14.4%
            - Survival to hospital DC 1.6%
        - 33% had cardiac activity on initial US
            - ROSC: 51%

- Survival to hospital admission: 28.9%
- Survival to hospital DC: 3.8%

- Patients without cardiac activity
  - ROSC: 14.3%
  - Survival to hospital admission: 7.2%
  - Survival to hospital DC: 0.6%
- Rapidly reversible causes
  - 34 patients with pericardial effusion
    - 13 pericardiocentesis
      - Survival to hospital DC: 15.4%
  - 15 patients with suspected PE
    - Got tPA
    - 1 patient survived to hospital DC
- Lack of cardiac activity on POCUS and asystole strongly associated with lack of survival

- Limitations
  - Lack of blinding: those with cardiac activity on US demonstrated longer resus times
  - Did not assess survival to hospital DC with neurologic function
  - Did not protocolize all aspects of resuscitation
  - Possibility of selection bias
- **Take Home Points**
  - **PEA, cardiac activity strongly associated with survival to hospital admission and DC**
  - **Lack of cardiac activity and asystole strongly associated with lack of survival**

Rapid Sequence Intubation

6. *Khandelwal N, et al. Head-elevated patient positioning decreases complications of emergent tracheal intubation in the ward and intensive care unit. Anesth Analg 2016; 122:1101-7.*
   - Background
     - Incidence of difficult intubation and airway-related complications is greater with ETI performed outside of the OR
     - Patient positioning is crucial
     - Studies suggest that preoxygenation is improved and apnea time prolonged when patients are in a back-up head-elevated (BUHE) position versus supine; BUHE > 30 degrees
     - Data regarding the efficacy of BUHE position in reducing ETI-related complications lacking
   - Objective
     - Determine if BUHE position is associated with a decrease in complications related to ETI outside of the OR
   - Study
     - Retrospective cohort
     - 2 large academic medical centers affiliated with University of Washington
     - Out of OR intubations (except ED) performed by preassigned anesthesia airway team
     - Patients
       - ETI outside of the OR or PACU
       - ETI attempts had to be made using DL
       - Excluded

        - < 18 years of age
        - ETI for cardiac arrest
        - ED intubations
        - Initial ETI attempts using VL or fiberoptic scope
    - Primary outcome
        - Occurrence of a complication of any intubation-related complication among patients intubated in supine position vs. BUHE position
            - Difficult intubation
            - Hypoxemia
            - Esophageal intubation
            - Pulmonary aspiration
- Results
    - 528 patients included in study
    - Intubation-related complications
        - Supine position: 76/332 (22.6%) of patients
        - BUHE position: 18/192 (9.3%) of patients
            - OR 0.42
            - Primary reason is a decrease in composite of hypoxemia, aspiration, or esophageal intubation
- Limitations
    - Intubation data self-reported - subject to reporting bias
    - Performance of intubation by experienced anesthesia providers may have driven down the DI rate
    - Could not guarantee that the patient was in the BUHE position for preoxygenation
    - Retrospective design
    - Several things could have affected whether patients needed supine position - hemodynamic instability, intracranial hypertension
- **Take Home Point**
    - **Placing patients in a BUHE position during ETI, compared with a supine position, reduced odds of hypoxemia, aspiration, and esophageal intubation.**

<u>Mechanical Ventilation</u>

7. *Faust AC, et al. Impact of an analgesia-based sedation protocol on mechanically ventilated patients in the medical intensive care unit. Anesth Analg 2016; 123:9903-9.*
    - Objective
        - Evaluate the impact of an analgosedation protocol on duration of mechanical ventilation, ICU LOS, sedation levels, and medication costs.
    - Study
        - Retrospective cohort study
        - MICU at Texas Health Presbyterian Hospital of Dallas - large, teaching, community hospital with 24-bed MICU
        - Preimplementation Group
            - Adult MICU patients ventilated between June 1, 2011-December 1, 2011
            - Managed by their 2009 sedation policy and protocol
            - RASS 0-(-2)
            - CPOT used for analgesia management
            - Typically given propofol for sedation, then IV narcotics (morphine) or a second sedative agent (midazolam)
        - Postimplementation Group

- Adult MICU patients ventilated between June 1, 2010-December 1, 2013
- Changed approach in 2012
- Focused on treating pain before sedative or antipsychotic use
- Same RASS and CPOT targets
- Used IV fentanyl first, then propofol or dexmetomidine afterwards

▪ Primary outcome: duration of mechanical ventilation
▪ Secondary outcomes
- MICU LOS
- RASS scores
- CPOT scores
- Sedative and analgesic medications use and costs
- Self-extubation
- Mortality

o Results
▪ 237 patients
- 65 in the preimplementation group
- 79 in the post implementation group

▪ Postimplementation group
- Lighter levels of sedation
- Decreased mechanical ventilation (45 hours)
- Decreased ICU LOS (51 hours)
- Better pain management

o Limitations
▪ Single center
▪ MICU
▪ Noncontrolled
▪ Retrospective

o **Take Home Point**
▪ **An analgosedation based sedation protocol using fentanyl resulted in better pain management, lighter sedation levels, reduced duration of MV, and reduced LOS in the ICU.**

8. *Girardis M, et al. Effect of conservative vs conventional oxygen therapy on mortality among patients in an intensive care unit. The Oxygen-ICU Randomized Clinical Trial. JAMA 2016. [epub ahead of print]*
   a. Objective
      i. Determine whether the application of a strict conservative protocol for oxygen supplementation to maintain PaO2 within physiologic limits could improve outcomes in critically ill ICU patients
   b. Study
      i. Single-center, open-label, parallel-group, randomized clinical trial
      ii. Modena University hospital
      iii. Patients
- 18 years or older
- Admitted to the ICU with expected LOS 72 hours or more

▪ Randomized 1:1
- Conventional
  - Oxygen therapy was administered according to standard ICU practice
  - Patients received an FiO2 of at least 40%, allowing PaO2 values up to 150 mmHg and an SpO2 97%-100%

- Conservative
    - Oxygen administered at the lowest possible FiO2 to maintain the PaO2 between 70-100 mm Hg
    - Only got supplemental oxygen if SpO2 < 94%
    - Target 94-98%
- Primary outcome: ICU mortality
- Secondary outcomes: new-onset respiratory, cardiovascular, liver, and renal failure occurring 48 hours or more after ICU admission

- Statistical analysis
    - Planned 660 patients
    - Stopped after 480 patients - violent earthquake seriously damaged hospital, with temporary evacuation of ICU and 20-25% reduction in hospital beds - resulted in low inclusion rates
    - Concerned about high risk of bias related to changes in standard practice
    - Used a modified intent-to-treat population
- Results
    - 480 patients included
        - Conventional: 244
        - Conservative: 236
        - MITT analysis
            - Conventional 218
            - Conservative 216
    - Mortality
        - Conventional group: 20.2%
        - Conservative group: 11.6%
    - Hospital mortality also lower in the conservative group
    - No difference between the 2 groups with respect to occurrence of new respiratory or renal failure
    - Lower incidence of new shock, liver failure lower in conservative group
    - Lower risk of developing bloodstream infection in conservative group
    - Analysis of primary and secondary outcomes in intention to treat population confirmed data in MITT
- Limitations
    - Single center
    - Open label
    - Stopped early
- **Take Home Point**
    - **Among ICU patients with a LOS of 72 hours or longer, a conservative approach for O2 therapy resulted in lower ICU mortality**

Fluid Responsiveness

9. *Cherpanath TG, et al. Predicting fluid responsiveness by passive leg raising: A systematic review and meta-analysis of 23 clinical trials. Crit Care Med 2016; 44:981-91.*
    - Objective
        - Investigate available literature on PLR and fluid responsiveness to provide an overview of the predictive value of PLR in various settings
    - Study
        - Meta-analysis
        - Included
            - Fluid challenge was given as gold standard to delineate fluid responders from non-responders

        - PLR was performed
        - Data available to calculate sensitivity, specificity, and AUROC
    - Results
        - 23 articles
            - 1,013 patients
            - 1,034 fluid challenges
            - Mostly in sinus rhythm
            - Mean age 60 years
        - Most frequent indication for IVFs - circulatory failure in setting of sepsis
        - PLR mostly performed from the semirecumbent starting position
        - All studies prospectively performed in the ICU except 1 study in the ED, 1 in anesthesiology, and 1 retrospective study in the ICU
        - 4 methods used as primary measurement technique for fluid challenge
            - Esophageal Doppler
            - TTE
            - Pulse contour analysis
            - Bioreactance
        - Cutoff of 15% used to identify responders from non-responders
        - Sensitivity: 86%
        - Specificity: 92%
        - AUROC: 0.95
        - Similar performance in spontaneously breathing patients versus mechanical ventilation
        - No difference when performed from supine starting position versus semirecumbent
        - Pulse pressure had sensitivity of just 58%
    - Limitations
        - Meta-analysis
        - Studies used different cutoff values, different measurement techniques
        - No studies on whether PLR to guide fluid administration improves outcome
    - **Take Home Point**
        - **PLR is a reliable tool to predict fluid responsiveness in various clinical settings**

Sepsis

10. *Singer M, Deutschman CS, Seymour CW, et al. The third international consensus definitions for sepsis and septic shock (Sepsis 3). JAMA 2016; 315:801-810.*
    - ESICM and SCCM
    - 19-member Task Force
        - Critical care, infectious disease, surgical, and pulmonary specialists
        - Tasked with:
            1. Differentiating sepsis from infection
            2. Updated definitions of sepsis/septic shock
            3. Identify clinical criteria that identifies all elements of infection, host response, and organ dysfunction
    - Sepsis
        - "Life-threatening organ dysfunction caused by dysregulated host response to infection"
        - Organ dysfunction defined as SOFA score >= 2 resulting from infection
    - qSOFA
        - Altered mental status (GCS < 13)

        - RR >= 22 bpm
        - SBP <= 100 mm Hg
    - Septic Shock
        - "A subset of sepsis in which profound circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality"
        - Criteria
            1. Vasopressors to maintain MAP > 65 mm Hg
            2. Lactate >= 2 mmol/L
            3. Adequate fluid resuscitation
    - "Severe sepsis" and SIRS are gone