UTSW ICU LITERATURE BUNDLE

Landmark Clinical Trials and Recommended Reading

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ARDS/ALI

Low tidal volume ventilation

Ventilation with low tidal volumes as compared with traditional tidal volumes for ALI and ARDS

ARDSNet NEJM 2000; 342: 1301

- Rationale: Mechanical ventilation with high TV might result in worsening lung injury in patients with ARDS
- Goal: To determine if low TV mechanical ventilation improves clinical outcomes in patients with ALI/ARDS
- Randomized multi-center study of ventilated patients with P/F < 300, bilateral pulmonary infiltrates, no evidence of left atrial hypertension
- Excluded: ARDS for > 36hrs, age < 18 years, pregnant, increased ICP, neuromuscular disease, sickle cell disease, severe COPD, severe burns, bone/lung transplant, ESLD
- Intervention: Traditional (12 cc/kg body weight, peak plateau < 50) vs. Low (TV 6 cc/kg, peak plateau < 30)
- Primary outcome: In hospital mortality
- 429 pts in traditional arm vs. 432 in low TV arm
- Low tidal volume 31% mortality vs. 39.8% in traditional group (significant); spontaneous respiration at 28 days in low TV group 65.7% vs. 55% in traditional group, vent free days 12 vs. 10 days, barotraumas 10% vs. 11%, days w/out other organ failure 15 vs.12
- **Low TV ventilation in patients with ARDS results in reduced mortality and has become the standard of care in this patient population**. The concept of the "optimal" tidal volume (how low to go) is still unknown

PEEP in ARDS

Higher vs. lower positive end-expiratory pressures in patients with ARDS

ARDS Clinical Trials Network NEJM; 2004; 351: 327

- Rationale: Higher PEEP can improve oxygenation and reduce ventilator induced lung injury (via recruitment) but may also cause circulatory depression and lung injury from over-distension
- Goal: To determine if higher PEEP levels improve clinical outcomes in patients with ALI/ARDS and ARDSNet ventilation
- Randomized, multi-center, patients intubated with P/F ratio of 300 or less, bilateral infiltrates, no left atrial hypertension
- Excluded: ARDS >36 hours, severe chronic respiratory disease, sickle cell disease, neuromuscular disease, vasculitis with DAH, liver disease, s/p BMT or lung transplant
- Intervention: High PEEP (at least 14 of PEEP) vs. Low PEEP (both used ARDSNet ventilation). Recruitment maneuver was part of high PEEP strategy initially but then stopped after 80 pts enrolled (improvements were transient and small)
- Primary outcome: proportion of patients who died before discharge home while breathing without assistance.
- Trial was stopped at early (specified futility stopping rule, even with full enrollment, study would not reach the desired hypothesized outcome)
- Average PEEP in low PEEP group 8.3 vs.13.2 in high PEEP group, P/F higher in high PEEP group than low PEEP group.
- The rates of death before hospital discharge 24.9% and 27.5% (no difference), no difference in unassisted breathing days between groups. No difference in ICU free days, no significant difference in days without circulatory, coagulation, hepatic, or renal failure or incidence of barotrauma
- Higher PEEP did not result in improved clinical outcomes in patients with ARDS on ARDSNet ventilation. Authors suggest lack of benefit might have been due to lack of recruitment as recruitment maneuvers not performed on all patients (although maneuvers did not show sustained benefit.

Positive End-Expiratory Pressure Setting in Adults with Acute Lung Injury and Acute Respiratory Distress Syndrome: A Randomized Controlled Trial

Mercat et al. JAMA 2008;299:646.

- Rationale: Optimal PEEP strategy in patients with ARDS has not been defined.
- Goal: To compare the effect on outcome of a strategy for setting PEEP aimed at increasing alveolar recruitment while limiting hyperinflation to one aimed at minimizing alveolar distension in patients with ALI.
- Randomized multi-center study of ventilated patients with P/F < 300, pulmonary infiltrates, no evidence of left atrial hypertension
- Excluded: ARDS for > 48 hours, known pregnancy, increased intracranial pressure, sickle cell disease, severe chronic respiratory disease requiring long-term oxygen therapy or home mechanical ventilation, actual body weight exceeding 1 kg/cm of height, severe burns, severe chronic liver disease (Child-Pugh class C), bone marrow transplant or chemotherapy-induced neutropenia, pneumothorax, expected duration of mechanical ventilation shorter than 48 hours, and decision to withhold life-sustaining treatment.
- Intervention: Tidal volume was set at 6 mL/kg of predicted body weight in both strategies. Patients were randomly assigned to a moderate PEEP strategy (5-9 cm H_2O) (minimal distension strategy) or to a level of PEEP set to reach a plateau pressure of 28 to 30 cm H_2O (increased recruitment strategy).
- Primary outcome: 28-day mortality
- 382 in minimal distention strategy and 385 in increased recruitment strategy
- 28-day mortality was 31.2% in minimal distension vs 27.8% in increased recruitment (p=0.31). No difference in in hospital mortality rate. Higher median vent free days and organ failure free days in the increased recruitment group. Increased recruitment group also had better compliance, better oxygenation, less use of adjunctive therapies, and larger fluid requirements.
- A strategy for setting PEEP up to a plateau pressure of 28-30 (increased recruitment) did not significantly reduce mortality but did improve lung function and reduced the duration of mechanical ventilation and organ failure.

Fluid management in ARDS

Comparison of two fluid management strategies in ALI **(FACTT trials)**

Weidman et al. NEJM 2006; 354: 2564.

- Goal: To determine the risk/benefit of a conservative fluid protocol in patients with ALI
- Randomized 2X2 design, 20 centers, intubated pts receiving positive pressure ventilation with paO2/FiO2 ≤ 300, bilateral infiltrates, no evidence of left atrial hypertension
- Excluded: PA catheter placement after onset of ALI, lung injury > 48 hrs, impaired weaning or compliance, conditions with 6 months mortality rate > 50%
- Intervention: Patients assigned to a PA catheter or a central venous catheter, lasix or fluids to either CVP < 4, PaOP< 8 (conservative strategy) or CVP 10-14, PAOP 10-18 (liberal strategy) x 7 day
- Primary outcome: Mortality at 60 days
- 1001 pts randomized. 60-day mortality rate was 25.5% vs. 28.4% favoring the conservative strategy (not statistically significant), 7-day fluid balance -136 cc in conservative group, + 6992 cc in liberal group
- Conservative group had more vent. free days (14.6 vs. 12.1), and ICU free days (13.4 vs. 11.2) during first 28 days
- Implication: **Conservative fluid management results in improved oxygenation and shortened the duration of mechanical ventilation and ICU stay in patients with ALI**. Note: this study excluded a large number of patients and was underpowered to detect differences other than primary outcome. However, this study showed that it is safe (and even beneficial) to use a conservative fluid strategy in patients with ALI who are normotensive and not oliguric to improve oxygenation/lung edema

A randomized controlled trial of furosemide with or without albumin in hypoproteinemic patients with acute lung injury

Khan et al. Critical Care 2007; 11:314.

- Rationale: hypoproteinemia is common in critically ill patients and can lead to development of ALI/ARDS
- Randomized, double blinded, placebo control, multi-center (medical, trauma, and surgical ICU) study. 40 patients with ALI/ARDS (randomized w/in 3 days of diagnosis), TP < 6.
- Excluded patients who were hemodynamically unstable or with significant renal or hepatic failure.
- Randomized to furosemide + albumin (25G of 25% solution Q8hrs) vs. furosemide + placebo x 72 hrs titrated to net fluid loss and normalization of serum total protein.
- Primary outcome: change in oxygenation from baseline to day 1
- Results: No differences at baseline, albumin treated patients had improvement in oxygenation (P/F + 43 vs. -24 mm Hg at 24 hrs, + 49 vs. -13 at day 3), higher serum TP (1.5 vs. 0.5 at day 3), and more fluid loss (-5480 vs. -1490 at day 3).
- Control patients had more frequent hypotension and had fewer shock free days, translated to differences in organ failure.
- Overall small study that did not really look at hard clinical outcomes. It is hard to draw too many conclusions but the findings do support the FACTT trial.

Pulmonary-artery vs. central venous catheter to guide treatment of ALI
ARDS Study Network NEJM 2006; 354: 2213.

- Rationale: Role of PA lines in the treatment of ICU patients is controversial
- Multi-center, factorial study (part of the FACTT) of patients with ALI/ARDS for <48 hrs randomized to PAC vs. CVC.
- Primary outcome: Death at 60 days (again part of FACTT trial)
- 1000 patients, no baseline differences
- Rates of death similar at 60 days between the PAC and CVC group (27.4 vs. 26.3)
- No difference in vent-free days, ICU-free days to day 28, kidney or lung function, rates of hypotension, vent. settings, or use of HD or pressors
- PAC had twice as many catheter-associated complications (due to higher number of catheters placed)
- Overall, study indicated the **PAC guided therapy did not improve survival and/or any other clinically important outcomes.** I would note caution with interpreting this as **patients with CHF and renal failure on dialysis were excluded** and it is unclear if PAC would have provided benefit in these patient populations

Neuromuscular blockade in ARDS

***Neuromuscular blockers in early ARDS* (ACURASYS Trial)**
Papazian et al. NJEM 2010; 363: 1107.

- Rationale: Neuromuscular blockade during mechanical ventilation in patients with ARDS may improve mortality
- Goal: To determine whether a short treatment with cisatracurium (neuromuscular blocker) in the course of ARDS improves clinical outcomes
- Randomized, multi center, adults with ARDS for < 48 hrs
- Excluded age < 18, pregnancy, enrollment in another trial, increased ICP, home O2 or vent requirement, obesity liver disease, bone marrow transplant, neutropenia, pneumothorax, liver disease, expected vent time < 48 hrs
- Intervention: cisatracurium vs. placebo for 48 hrs
- Primary outcome: mortality at 90 days
- 340 pts randomized, at baseline lower paO2/FiO2 in cisatracurium group (106 vs. 115)
- Hazard ratio for 90 day- mortality (adjusted for different in P/F ratio, SAPSII, and plateau pressure) in intervention vs. placebo 0.68 (significant), no difference in unadjusted mortality (31.6% cisatracurium vs. 40.7% control)
- Cisatracurium group had a decreased 28-day mortality, more vent free days, more days without organ failure, more days outside the ICU, decreased incident of barotrauma, no difference in muscle strength or ICU paresis between the two groups.
- Conclusion: short course of cisatracurium in early severe ARDS improves mortality at 90 days. A current criticism of this study is that deep sedation was used in both the intervention and control groups. **A future study did not show benefit – see below**

Early neuromuscular blockade in the acute respiratory distress syndrome (ROSE Trial)
PETAL Clinical Trials Network. NEJM 2019: 380:1997

- Background: the benefits of continuous neuromuscular blockade in ARDS patients remains unclear.
- Goal: to determine efficacy of 48 hours of continuous neuromuscular blockade in patients with ARDS
- Inclusion criteria: ARDS with P:F < 150 with PEEP of at least 8 enrolled within 48h
- Intervention 48h of cisatracurium with concomitant deep sedation vs usual care without routine neuromuscular blockade and with lighter sedation targets
- Primary end point: in-hospital death from any cause at 90 days
- 501 assigned to intervention group and 505 assigned to control group
- Results: study was stopped at interim analysis due to futility. 90-day mortality was 42.5% in intervention group and 42.8% in controls (p=0.93). While in the hospital, patients in the intervention group were less physically active and had more adverse cardiovascular events than controls.
- Conclusion: Routine neuromuscular blockade is not beneficial in severe ARDS. Authors speculate whether the positive findings in the ACURASYS trial were related to deeper levels of sedation in the control group of the ACURASYS trial, as lighter sedation was used in controls in this study

Prone positioning in ARDS

Effect of prone positioning on the survival of patients with ARDS

Gattinoni et al. NEJM 2001; 345: 568.

- Rationale: Previous study had reported that putting patients with ARDS in the prone position improves oxygenation possibly by improving end-expiratory lung volume, improving V/Q matching, or changing chest wall mechanics
- Goal: to determine if prone positioning improved survival in patients with ALI/ARDS
- Multicenter, randomized trial, patients with ARDS or ALI.
- Excluded: CHF, cerebral edema, ICH, severe hemodynamic instability, spine fractures
- Intervention: Prone group (prone position for 6 or more hrs daily for 10 days) vs. supine group
- Primary outcome: death at 10 days, at time of discharge from ICU, and at 6 months.
- 12 pts in supine group were placed in prone position despite randomization because of severity of hypoxemia, 41 patients had non-compliance leading to 91 missed periods of pronation over 10 days
- No difference in mortality at any time point between prone vs. supine group (21.1 vs. 25%). Similar results when they excluded patients that violated the protocol. Major respiratory variables better in prone positioning, no difference in organ dysfunction. No difference in position related complications between the groups.
- Implications: Although prone positioning improves oxygenation, it did not lead to overall improved survival; however, patients were only proned for average of 7.0 hours. Note: **post-hoc analysis in patients with p/f ratio < 88, there was a lower 10-day mortality (23.1% vs. 47.2%) indicating that sicker patients might benefit from prone positioning.**

Prone positioning in severe acute respiratory distress syndrome (PROSEVA)

Guerin et al. NEJM 2013;368:2159.

- Background: Previous trials have failed to show benefit of prone positioning
- Goal: to determine whether early application of prone positioning affected outcomes in patients with severe ARDS
- Intubated patients with ARDS for < 36 hours with P:F <150 on FiO2 > 60% with PEEP >/=5 and 6cc/kg VT.
- Exclusion: ICP > 30 or CPP < 60, massive hemoptysis requiring a procedure, tracheal surgery or sternotomy within 15d, severe facial trauma or surgery within 15d, DVT treated for < 2d, PPM inserted within 2d, unstable spine/femur/pelvic fracture, MAP < 65, pregnancy, single anterior chest tube with air leak, iNO use, ECMO
- Intervention: 12–24-hour stabilization period after eligibility determined. Intervention group proned for at least 16 consecutive hours. Proning was stopped if P:F > 150 with PEEP < 10 and FiO2 < 0.6 for 4 hours after the end of last proning session, complications during a prone session leading to its immediate interruption, or decrease in P:F of more than 20% relative to supine ratio.
- Primary outcome: Mortality at 28 days
- 237 assigned to prone group and 229 in supine group
- 28d mortality was 16% in prone group and 32.8% in supine group ($p<0.001$). HR for death with proning was 0.39. Unadjusted 90-day mortality was 23.6% in prone and 41.0% in supine ($p<0.001$). Cardiac arrests higher in supine group but no other difference in complications
- Implications: **In patients with P:F < 150, early application of prolonged proning sessions decreased 28d mortality.**

Of note, multiple metanalyses have suggested benefit in mortality of prone positioning when used in severe ARDS. Guidelines recommend prone positioning as rescue therapy for severe ARDS

Corticosteroids in ARDS

Efficacy and safety of corticosteroids for persistent ARDS **(ARDS Net Trial)**

ARDS Clinical trial Network NEJM 2006; 354: 1671.

- Background: Many trials of short courses of steroids in early ARDS did not show a survival benefit
- Goal: RCT evaluating the safety and efficacy of moderate dose steroids in patients with persistent ARDS
- Intubated patients with ARDS (onset 7-28 days prior) with PaO2/FiO2 ratios <200 and bilateral infiltrates
- Intervention: 2mg/kg IV solumedrol followed by 0.5mg/kg Q6hrs x 2 weeks followed by 0.5mg/kg Q12hrs x 7 days followed by taper over 4 days if completed or over 2 days if severe infection vs. placebo
- Primary outcome: Mortality at 60 days
- At 60 days, hospital mortality rate was 28.6% in placebo and 29.2% in methylprednisolone ($p=1.0$). At 180 days, there was also no mortality difference. Patients enrolled 14 or more days after ARDS onset had increased 60-day mortality and 180-day mortality (35% vs. 8% placebo, $p = .02$)

- There was a significant increase in number of vent free days and shock-free days in patients who got steroids. There was more steroid myopathy in patients who got steroids. No increase in infection rate in steroid group.
- Implications: Overall, steroids did not improve mortality in patients with ARDS. They did increase vent free time. Avoid starting steroids for ARDS after day 14 due to possible increase in mortality.

Methylprednisolone infusion in early severe ARDS: results of a randomized controlled trial.
Meduri et al. Chest 2007; 131:954.
- Objective: To determine the effects of low-dose prolonged methylprednisolone infusion on lung function in patients with early severe ARDS.
- Inclusion criteria: patients with severe early ARDS (</= 72 h),
- Interventions: Patients were randomized (2:1 fashion) to methylprednisolone infusion vs placebo. Dosing of methylpred was 1 mg/kg/d from day 1 to day 14, 0.5 mg/kg/d from day 15 to day 21, 0.25 mg/kg/d from day 22 to day 25, and 0.125 mg/kg/d from day 26 to day 28. If the patient was extubated between days 1 and 14, the patient was advanced to day 15 of drug therapy and tapered according to schedule
- Primary outcome**:** a 1-point reduction in lung injury score (LIS) or successful extubation by day 7.
- Results: In intention-to-treat analysis, the response of the two groups (63 treated and 28 control) clearly diverged by day 7, with twice the proportion of treated patients achieving a 1-point reduction in LIS (69.8% vs 35.7%; p = 0.002) and breathing without assistance (53.9% vs 25.0%; p = 0.01). Treated patients had significant reduction in CRP levels, and by day 7 had lower LIS and multiple organ dysfunction syndrome scores. Treatment was associated with a reduction in the duration of mechanical ventilation (p = 0.002), ICU stay (p = 0.007), and ICU mortality (20.6% vs 42.9%; p = 0.03). Treated patients had a lower rate of infections (p = 0.0002), and infection surveillance identified 56% of nosocomial infections in patients without fever.
- Conclusions: Methylprednisolone was associated with significant improvement in pulmonary and extrapulmonary organ dysfunction and reduction in duration of mechanical ventilation and ICU LOS. The higher proportion of patients with catecholamine-dependent shock among controls, cross over from control to steroids in “non-responders” at day 7, and 2:1 randomization of treatment to control are among the concerns raised since its publication.

Inhaled nitric oxide in ARDS

Inhaled nitric oxide for acute respiratory distress syndrome (ARDS) and acute lung injury in children and adults.
Gebistorf et al. Cochrane Database Syst Rev 2016 6:CD002787.
- Background: Role of iNO in ARDS remains controversial
- Objectives: TO examine effects if iNO on mortality in adults and children with ARDS.
- Selection criteria: all RCTs
- Results: There were no significant effects of iNO on 28d mortality in adults (34.4% in iNO group vs 32.0 in controls). There was an improvement in P:F ratio at 24h. No difference in ventilator free days. Increase in renal failure in iNO group.
- Conclusion: **inhaled nitric oxide improves oxygenation and increases risk of renal failure but does not change mortality in ARDS.**

ECMO in ARDS

Efficacy and economic assessment of conventional ventilator support vs ECMO for severe adult respiratory failure: a multicenter randomized controlled trial. (CESAR Trial)
Peek et al. Lancet 2009;374:1351.
- Background: Respiratory failure has high mortality despite maximal medical therapy so ECMO is investigated here as an ancillary treatment.
- Objectives: to determine the utility of ECMO compared with conventional ventilator support
- Inclusion: 18-65 years old with severe (defined by Murray score > 3 or pH < 7.2) but potentially reversible respiratory failure. Of note, low TV ventilation strategy not mandated
- Exclusion: Peak pressure > 30 or FiO2 > 80% for more than 7d, intracranial bleeding, contraindication to anticoagulation
- Intervention: transfer to referral center for consideration of ECMO vs conventional management
- Primary outcome: death or severe disability at 6 months after randomization or before discharge from hospital
- 90 patients in intervention group and 90 in control
- Only 75% of patients transferred actually received ECMO. Survival higher in patients in intervention group (63% vs 47%, p=0.03). **93% of those transferred received low tidal volume ventilation compared to 70% in the control group**

- Conclusion: Compared to standard of care, **transfer to an ECMO-ready facility reduced mortality with an NNT of 6 to prevent 1 death or severe disability at 6 months**. Study was limited by the difference in use of low tidal volume ventilation between groups and the use of ECMO only in 75% of intervention group.

Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome **(EOLIA Trial)**
*C*ombes et al. NEJM 2018;378:1965.
- Background: efficacy of ECMO for ARDS remains controversial
- Objective: to determine mortality benefit from ECMO vs conventional mechanical ventilation with ECMO available as rescue therapy in patients with very severe ARDS
- Inclusion: had to meet 1 of 3 criteria: P:F < 50 for more than 3 hours, P:F < 80 for more than 7 hours, or pH < 7.25 with PaCO2 of at least 60 for more than 6 hours
- Outcome: 60-day mortality
- 124 randomized to ECMO group and 125 to control group
- No difference in 60d mortality between ECMO group (35%) and control group (46%) (p=0.09). Crossover to ECMO occurred at a mean of day 6.5 after randomization in 28% of controls, with 57% of those dying. More thrombocytopenia and more bleeding events requiring transfusion in ECMO group than controls. More cases of ischemic stroke in the control group.
- Conclusion: the routine use of ECMO in patients with severe ARDS is not superior to the use of ECMO as a rescue maneuver.

SEPSIS/SHOCK:

Early Goal Directed Therapy

Early goal directed therapy in the treatment of severe sepsis and septic shock
Rivers et al. NEJM 2001; 345: 1368.
- Goal: To determine whether early goal directed therapy (EGDT) before admission to the ICU reduces the incidence of multi-organ dysfunction and mortality in patients with septic shock
- Randomized single center, pts 2 of 4 SIRS criteria and either SBP < 90 after a fluid challenge or lactate > 4.
- Excluded: pregnancy, age < 18, acute stroke, ACS, acute pulmonary edema, status asthmaticus, arrhythmia, contraindication for a central line, active GI bleed, seizure, drug overdose, burns, trauma, need for immediate surgery, ongoing chemo, immunosuppression, DNR.
- Intervention: standard hemodynamic resuscitation vs. EGDT (CVP 8-12, MAP>65, CVO2>70, UOP>0.5cc/kg/hr in first 6 hours). ScvO2 monitoring with CVC, CVP 8-12 mmHg with IVF boluses, MAP >65 with vasopressors, and ScvO2>70% with PRBC and dobutamine.
- Primary outcome: In-hospital mortality
- 263 randomized. In hospital mortality in EGDT 30.5% vs. 46.5% control, less organ dysfunction at 72 hrs in EGDT, 60-day mortality with EGDT 44.3% vs. 56.9% in standard therapy.
- Overall, EGTD did improve in house mortality by 16% possibly by improving oxygen delivery. Limitations include that this was a single center study and Manny Rivers was at the bedside caring for the patients. Was it just Manny Rivers that improved mortality? **These findings have been refuted in more recent publications**

Trial of Early, Goal-Directed Resuscitation for Septic Shock **(ProMISe trial)**
Mouncey PR, et al. *The New England Journal of Medicine*. 2015. 372(14):1301-1311.
- Goal: Does EGDT reduce mortality compared to standard of care in severe sepsis and septic shock in a multicenter trial
- Randomized, multicenter trial with cost-effectiveness analysis in 56 hospitals in England.
- 1260 patients randomized to EGDT or usual care (630 in each group). Similar targets in the Rivers trial for EGDT. Followed for 6 hours and then went to care as determined by physician
- Primary end point: Mortality at 90 days

Inclusion criteria: Within 6 hours of ED presentation with known or presumed infection, two or more SIRS criteria, and either lactate > 4 or refractory hypotension (SBP<90 or MAP <65 despite at least 1 L IVF)
- Results: By 90 days, 184 of 623 patients (29.5%) in the EGDT group and 181 of 620 patients (29.2%) in the usual-care group had died (relative risk in the EGDT group, 1.01; 95% confidence interval [CI], 0.85 to 1.20; P=0.90)
- There was increased treatment intensity in the EGDT group with more IVF, vasoactive medications, and RBC transfusions with worse organ failure scores, and longer ICU stays. No differences in health care related quality of life or rates of serious adverse events.

- Conclusions: There was no significant mortality difference with possible increased costs.
- Criticism: not blinded, and mortality was less than predicted (29% versus 40%), thus limiting power of the study

***A Randomized Trial of Protocol-Based Care for Early Septic Shock* (ProCESS trial)**
Angus DC, et al. NEJM. 2014. 370(10):1683-1693
- Goal: In patients with early septic shock, is EGDT or a new protocol-based therapy superior to usual care in decreasing all cause in hospital mortality at 60 days
- Randomized, multicenter trial in 31 ER in the United States
- 1341 patients were randomly assigned to one of three groups: protocol-based EGDT; protocol-based standard therapy that did not require blood transfusions, CVC placement of inotropes; or usual care.
- Primary end point: All cause in hospital mortality at 60 days
- Results: At 60 days, 92/439 died in the EGDT group (21.0%), 81/446 in the protocol-based standard-therapy group died (18.2%), and 86/456 in the usual-care group died (18.9%) (RR w/ protocol-based therapy vs. usual care, 1.04 (0.82 to 1.31: P=0.83); RR with protocol-based EGDT vs. protocol-based standard therapy, 1.15 (0.88 to 1.51; P=0.31).
- Conclusion: There were no significant differences in 60-day, 90-day or 1-year mortality in all-cause-in hospital mortality.
- Criticisms: underpowered

***Goal-Directed Resuscitation for Patients with Early Septic Shock* (ARISE trial)**
ARISE and ANZICS writers. *The New England Journal of Medicine*. 2014. 371(16):1496-1506.
- Goal: Does EGDT versus usual care decrease all-cause mortality in severe sepsis or septic shock
- Randomized, multicenter trial 51 centers (mainly Australia and New Zealand)
- 1600 patients randomized to EGDT group to usual care group
- Primary end point: All -cause mortality at 90 days
- Results: EGDT group received a larger volume of IVF in the first 6 hours after randomization than did those in the usual-care group (1964±1415 ml vs. 1713±1401 ml) and were more likely to receive vasopressors (66.6% vs. 57.8%), RBCs (13.6% vs. 7.0%), and dobutamine (15.4% vs. 2.6%) (P<0.001 for all comparisons). (which is what EGDT suggests anyways). At 90 days, 147 deaths had occurred in the EGDT group (18.6%) and 150 had occurred in the usual-care group (18.8%) (absolute risk difference with EGDT vs. usual care, −0.3 percentage points; 95% confidence interval, −4.1 to 3.6; P=0.90).
- Conclusion: There was no significant difference in survival time, in-hospital mortality, duration of organ support, or length of hospital stay.

Overall, studies suggest that septic shock should be identified early, and treated early with early antibiotics, adequate fluid resuscitation, and consideration of early vasopressors

Steroids in Septic Shock

Effect of Treatment with Low Doses of Hydrocortisone and Fludrocortisone on Mortality in Patients with Septic Shock
Annane et al. JAMA 2002; 288: 862
- Rationale: Severe sepsis might be associated with relative adrenal insufficiency leading to decrease response to pressors
- Goal: To determine whether replacement therapy with hydrocortisone and fludrocortisones improves 28-day mortality in patients with septic shock
- Multicenter, double blind RCT. Patients with documented infection; fevers; HR>90, SBP<90 despite 1 hour of fluid or pressors; PaO2/FiO2 <280; dropping UOP; lactate>2, vented
- Excluded: patients who were given etomidate (interferes with cortisol response to corticotrophin), shock duration>8 hours before randomization, cancer, AIDS
- Intervention: Hydrocortisone 50 Q6, fludrocortisone 50 mg daily x 7 days vs. placebo
- Corticotropin test performed on all patients prior to getting treatment. Relative AI/non-responders defined as response of </=9
- Primary endpoint: Mortality at 28 days
- In non-responders (relative AI), there was a 33 % reduction in mortality at 28 days in steroid group compared to placebo. NNT 7. No difference in responder group
- In non-responder group, there was a shorter time to pressor withdrawal. No difference in adverse events
- Implications: Steroids improved mortality, especially in patients with relative AI by possibly helping to restore responsiveness to catecholamines. Issues include that patients did not receive EGTD which is often performed in these patients. Steroids in sepsis remains controversial and debatable.

***Hydrocortisone therapy for patients with septic shock* (CORTICUS Trial)**

CORTICUS Study group NEJM 2008; 358:111

- Follow up to the JAMA/Annane study in 2002 to assess role of steroids in sepsis
- Randomized multi center, adults admitted to the ICU with clinical evidence of infection, evidence of systemic response to infection, and onset of shock SBP < 90 despite fluid or need for vasopressors > 1 hr
- Excluded: chronic steroid use, pts likely to die within 24 hrs
- Intervention: hydrocort 50 vs. placebo for 5 days, then tapered over one day
- Primary outcome: 28-day mortality
- 500 pts enrolled and randomized, 233 pts (46.7%) no response to corticotropin
- Hydrocortisone did not improve overall 28-day mortality (34.3% vs. 31.5%). No benefit seen in non-responders (39.2 % vs. 36.1%) or responders (28.8% vs. 28.7%.)
- No difference in proportion of patients in whom shock was reversed. Time to reversal was shorter in the hydrocortisone group (3.3 vs. 5.8 days significant). No difference in hospital stay or ICU stay.
- Harms: increased incidence of new sepsis/septic shock (RR 1.37) hyperglycemia RR 1.18, hypernatremia (RR1.58) in hydrocortisone group.
- Overall, steroids did not improve survival or reversal of shock in pts with septic shock regardless of response to corticotropin, but hastened reversal of shock in pts in whom shock was reversed.
- Note: study was under-powered and stopped early. Steroids in sepsis remains controversial and debatable.

***Hydrocortisone plus fludrocortisone for Adults with Septic Shock* (APPROCCHSS Trial)**

Annane, D et al. NEJM 2018. 378(9):809-818

- Rationale: Effect of corticosteroids on septic shock is controversial. This study was performed to assess low dose corticosteroid and fludrocortisone x 7 days to see if this affected mortality
- Goal: To determine if corticosteroids and fludrocortisone x 7 days affected mortality
- Design: Randomized, multi-center, double blind trial with 2 x 2 factorial design using hydrocortisone and fludrocortisone, drotrecogin alfa, all three together, or none of them in patients with septic shock
- 1241 patients randomized with 7 days or less in the ICU with septic shock for less than 24 hours defined as documented infection, ongoing treatment with catecholamines for at least 6 hours and less than 24 hours to maintain MAP >65, at least 2 organ failures with SOFA organ score >3
- Excluded: septic shock presence for at least 24 hours, high risk of bleeding, pregnancy/lactation, underlying conditions that could affect short term survival, previous tx with steroids.
- Intervention: 50 mg IV bolus Q 6 hours for hydrocortisone and 50 ug tablet of fludrocortisone through NG tube in the AM x 7 days, drotrecogin alfa, all three together, or none of them
- Primary outcome: 90-day all-cause mortality
- Secondary outcomes: mortality at ICU and hospital discharge and at day 28 and 180; number of days alive and free of vasopressors, mechanical ventilation, and organ failure.
- After drotrecogin alfa was withdrawn from the market, the trial continued with a two-group parallel design comparing those that received hydrocortisone + fludrocortisone with those that did not (placebo group)
- Results: 90day mortality was 43% (264 of 614) in the hydrocortisone/fludrocortisone group and 49.1% (308 of 627) in the placebo group (P=0.03). Relative risk of death 0.88 (CI 0.78-0.99). Mortality was significantly low in intervention group than in placebo at ICU discharge (35.4% v 41%), hospital discharge (39.0% v 45.3%) and day 180 (46.6% v 52.5%) but not at day 28 (33.7% v 38.9%). Number of vasopressors free days was similar.
- Conclusion: 90-day mortality was lower in the hydrocortisone + fludrocortisone group. Of note, this is in stark contrast two several other major trials (ADRENAL and CORTICUS). Difference between ADRENAL is less patients, and sicker patients in this trial. Note: steroids in sepsis remains controversial and debatable.

***Adjunctive Glucocorticoid Therapy in Patients with Septic Shock* – (ADRENAL Trial)**

NEJM 2018:378:797-808

- Rationale: Effect of corticosteroids on septic shock is controversial. This study was performed to assess hydrocortisone on reduction of mortality in septic shock requiring mechanical ventilation
- Goal: To determine if corticosteroids affected mortality at 90 days
- Design: Randomized, multi-center, double blind placebo trial including 3800 patients randomized that were over age 18, who were undergoing mech ventilation, with documented or strong clinical suspicion of infection, 2 or more SIRS criteria, and were on vasopressors or inotropes for minimum of 4 hours at time of randomization
- Excluded: prior steroids for other indication, etomidate used during hospitalization, or were considered likely to die from pre-existing disease within 90 days after randomization
- Intervention: continuous infusion of hydrocortisone 200 mg per day x 7 days or until death or discharge from the ICU

- Primary outcome: 90-day all-cause mortality
- Results: 90-day mortality was 27.9% in hydrocortisone group and 28.8% in placebo group (P=0.50 with CI 0.82-1.10). Subgroup analysis showed faster resolution of shock in hydrocortisone group (3 v 4 days)
- Conclusion: 90-day mortality was not different. Possible reasons for the difference between this trial and APROCCHSS is the lower mortality and larger number of patients. Note: steroids in sepsis remains controversial and debatable.

Activated Protein C for Septic Shock

***Efficacy and Safety of Recombinant Human Activated Protein C for Severe Sepsis* (PROWESS)**
Bernard et al. NEJM 2001; 344:699
- Goal: To determine if APC (activated protein C) improves survival in patients with severe sepsis
- Randomized multi-center, adult patients with 3 SIRS criteria and organ dysfunction for < 24 hours
- Intervention: Placebo vs. APC X 96 hrs
- Primary outcome: Mortality at 28 days
- 1728 randomized, mean age 60, no significant differences in severity of illness or comorbidities
- 30.8% death rate in the placebo vs. 24.7% in activated protein c (p=0.005), NNT = 16, similar in stratified, pre-stratified, non-stratified subgroup analyses
- Absolute risk reduction of 6% present within days and persistent throughout the study period
- APC group, lower d-dimer levels and greater decreases in IL-6 levels days 1-7.
- Serious bleeding 3.7% in APC vs. 2.0% (significant)
- Implications: Among patients with severe sepsis, APC reduced mortality. Most of benefit seen in sicker patients (patients with higher APACHE scores or multi-organ dysfunction).

Drotrecogin Alfa (Activate) for Adults with Severe Sepsis and a Low Risk of Death
Abraham et al. NEJM 2005; 353: 1332
- Follow up to PROWESS, RCT looking at APC in patients with severe sepsis and low risk of death
- Trial terminated early secondary to futility (would not meet reduction and risk of bleeding high)
- No significant difference in mortality between the 2 groups and trend towards increased death from bleeding causes in APC group with significant increase in serious bleeding events. ***APC is NOT recommended***

Vasopressors in Septic Shock

***Vasopressin vs. Norepinephrine infusion in patients with septic shock* (VASST trial)**
Russell et al. NEJM 2008; 358: 877 (VASST Trial)
- Rationale: patients with septic shock have relative vasopressin deficiency and administering it would restore vascular tone/BP and reduce the need for catecholamines
- Goal: To determine whether vasopressin reduced mortality as compared with norepinephrine in patients with septic shock
- Multicenter, randomized, double-blind trial. Patients with septic shock refractory to fluids (only 500cc!) and a minimum of 5 ug of norepinephrine
- Exclusion: Unstable angina or class III or IV CHF
- Intervention: Lose dose vasopressin vs. more norepinephrine (in addition to open-labeled vasopressors)
- Primary outcome: mortality at 28 days
- 778 randomized, no differences at baseline between the two arms
- There was no difference in mortality at 28 days between the vasopressin and norepinephrine groups (35.4% vasopressin vs. 39.3% norepinephrine p = 0.26). No difference in rates of serious adverse events (10.3% vs. 10.5%)
- In subgroup analysis, patients with less severe septic shock, there was a trend in favor of the vasopressin group (mortality 26.5% vs. 35.7% p=0.05). In more severe septic shock patients, there was no difference between the two groups
- No difference in adverse events although there was a trend toward a higher rate of cardiac arrest in norepinephrine arm and a trend toward higher digital ischemia in vasopressin arm
- Implications: Vasopressin can be used as an adjunct to norepinephrine in patients with septic shock. **Addition of this agent can be considered in attempt to help reduce dose of norepinephrine, especially in patients with arrhythmias**. Main limitations include that the overall mortality rate in this study was lower than what the authors anticipated (underpowering the study significantly). In addition, they excluded patients who had acute coronary syndrome and severe CHF, which could alter their findings.

***Comparison of dopamine vs. norepinephrine in the treatment of shock* (SOAP II trial)**
De Backer et al. NEJM 2010; 362: 779

- Rationale: SOAP study showed that the administration of dopamine was an independent risk factor for death in the ICU
- Goal: To evaluate whether norepinephrine over dopamine as first line pressor could reduce mortality in patient with shock
- Multicenter, randomized trial, assigned patients with shock (MAP<70 or SBP,100 despite 1000cc IVF)
- Excluded: Pts with CVP>12, PCWP>14, arrhythmia, already received pressor
- Intervention: dopamine vs. norepinephrine as first-line pressor therapy to restore BP.
- Primary outcome: mortality at 28 days, target BP determined by MD in charge of each individual patient.
- 858 pts assigned to dopamine 821 to norepinephrine. Baseline no differences, most patients with septic shock. No differences in amount of fluid given although more fluid given to dopamine group on day 1
- Trial was stopped early, **no significant differences in mortality at any time point between the two groups, more arrhythmia seen in the dopamine group** (207 events vs. 102 $p < 0.001$, mainly atrial fibrillation)
- Subgroup analysis **dopamine increased risk of death at 28 days among patients with cardiogenic shock** (? Increased heart rate leading to more ischemia), but not among patients with septic or hypovolemic shock. ****This study showed dopamine is not the preferred pressor in septic shock****

***High versus low BP target in patients with septic shock. (*SEPSISPAM trial)**
Asfar, P et al. NEJM 2014. 370(17): 1583-1593

- Rationale: The optimal MAP goal for sepsis in not clear, and a higher MAP goal may improve organ perfusion, especially in patients with HTN.
- Goal: To evaluate outcomes with higher MAP goal in septic shock
- Multicenter, open-label randomized control trial randomized 776 patients with septic shock to MAP goal 65-70 or 80-85 for up to 5 days through vasopressor administration
- Excluded:
- Intervention: 65-70 versus 80-85 MAP
- Primary outcome: mortality at 28 days
- Results: no difference in mortality at 28 or 90 days. In the high MAP goal, there was increases in new onset atrial fibrillation and decreased need for dialytic therapy but those were not associated with changes in mortality.
- Conclusion: Patient with chronic hypertension may benefit from higher MAP goal to prevent dialysis

Some trials have suggested earlier administration of vasopressors may be more beneficial in preventing prolonged hypotension, increasing CO, improving microcirculation, preventing fluid overload, and possibly improving outcomes. More randomized trials are needed.

Volume resuscitation in septic shock

Fluid resuscitation in septic shock: Positive fluid balance and elevated CVP associated with increased mortality
Boyd et al. Crit Care Med 2001; 39: 2259.

- Objective: To determine whether CBP and fluid balance after resuscitation for septic shock are associated with mortality
- Design: retrospective review of use of IVF during 4 days of care in the VASST multicenter randomized controlled trial
- Patients: they reviewed the 778 patients in the VASST trial and split them into quartiles based on fluid balance.
- At enrollment (on average 12 hours after presentation), average fluid balance was 4.2 L and by day 4, the average was 11 L net positive.
- Results: A more positive fluid balance was associated with higher mortality. CVP did not correlate with fluid balance after 12 hours. At 12 hours, lower CVP was associated with low mortality.
- Conclusion: A more positive fluid balance both early in resuscitation and cumulatively was associated with increase mortality.
- Criticism: retrospective review can only show correlation

Early Lactate-guided therapy in ICU patients
Jansen et al. Am J Resp Crit Care Med 2010; 182: 752

- Background: Increased lactate levels are associated with significant morbidity and mortality. Many studies have emphasized the importance of lactate as a prognostic tool and its prognostic value seems to be independent of the underlying cause. Despite this, studies have shown that improving lactate metabolism does not improve outcomes, indicating that a high lactate level is an indicator of severe underlying illness/tissue hypoxia. If this is the case, improving hemodynamics/tissue oxygenation in patients with high lactate levels or poor lactate clearance would improve clinical outcomes

- Goal: To determine whether serial lactate monitoring aimed to reduce lactate levels by 20% Q2hrs would improve clinical outcomes in ICU patients with high lactate levels (>3)
- A multicenter, open labeled, randomized trial, patients admitted to ICU with lactate >/= 3
- Excluded: Liver failure, seizures, other cause of hyperlactatemia, DNR
- Intervention: Treatment group (treatment was guided by lactate levels to decrease by 20% per 2 hrs for initial 8 hrs + standard parameters of control group) vs. control group (goal MAP>60, CVP 8-12, CVO2>/= 70, blinded to lactate level). If lactate not decreased and CVO2>70, vasodilators were used in attempt to improve microvascular perfusion
- Primary outcome: In-hospital mortality
- There were no significant differences in lactate levels between groups (lactate reduced in both groups). MAP, HR, CVP, hg also similar
- The lactate group received more fluids and vasodilators than control, other characteristics the same
- In-hospital mortality in control group 43.5% vs. 33.9% in lactate group (p = 0.067), adjusted for pre-defined risk factors, lactate group had significantly lower hospital mortality (HR 0.61). Sequential organ failure assessment scores were also lower, also earlier discharge from ICU and earlier weaning from the ventilator
- Overall, lactate group had improved mortality but lactate levels were similar between the two groups. The big difference between the two groups was fluids (and vasodilators). Can lactate be used as a target for hemodynamic therapy-this study might actually argue against this and highlights the difficulties of using lactate as a marker of tissue hypoperfusion/damage.

Lactate clearance vs. central venous oxygen saturation as goals of early sepsis therapy

Jones et al. JAMA 2010; 303: 739

- Background: Treatment of septic shock is often driven by objective hemodynamic parameters (CVP, MAP). As well as measures of O2 tissue delivery CVO2. Measurement of the CVO2 can be cumbersome and studies have attempted to look at lactate clearance as a surrogate marker for tissue oxygen delivery.
- Goal: To determine if lactate clearance can serve as a surrogate maker for O2 delivery (CVO2) in patients with early septic shock
- Multicenter, randomized, non-inferiority trial in patients with severe sepsis. Or septic shock (SBP<90 after 20cc/kg fluid challenge or lactate.4)
- Excluded: CPR, contraindication to CVC, need for surgery, DNR
- Intervention: 1 of 2 resuscitation protocols. ScVO2 group (CVP >8, MAP >65, and ScVO2 >70, essentially Rivers protocol) vs. lactate clearance group (normalize CVP >8, MAP >65, lactate clearance of at least 10%, measured at 2-hour intervals. Rivers protocol except lactate instead of CVO2)
- Primary outcome: absolute-in-hospital mortality rate (non-inferior threshold set at 10%)
- 300 pts enrolled 150 in each group. No baseline differences including baseline lactate levels. No difference in treatments during initial 72 hours of hospital stay
- There were no differences in treatments rendered in first 3 days between the 2 groups. Objective parameters (CVP, MAP, CVO2/lactate clearance) were met in a similar number of patients. Note: 95% of patients in lactate clearance group achieved appropriate lactate clearance.
- ScVO2 group in hospital mortality rate was 23% compared to 17% in lactate clearance group (difference of 6%), no difference in treatment-related adverse events between groups.
- Implication: Among patients with septic shock who were treated to normalize central venous and mean arterial pressure, additional management to normalize lactate clearance compared with management to normalize ScvO2 did not result in significantly different in-hospital mortality.

Effect of a resuscitation strategy targeting peripheral perfusion status vs serum lactate levels on 28-day mortality among patients with septic shock (ANDROMEDA-Shock Trial).

Hernandez et al. Jama 2019; 321:654-664.

- Background: The role of clinical assessment of peripheral perfusion as a target during resuscitation during early septic shock has not been determined
- Multicenter RCT
- Patients were randomized to a resuscitation protocol that either aimed to normalize capillary refill time or normalize / decrease lactate levels at a rate > 20% every 2 hours
- Primary outcome: 28d mortality
- Results: no statistically significant difference in 28d mortality between groups but trend toward improved mortality in cap refill group (p=0.06). Cap refill group had less organ dysfunction at 72h.
- Outcome: no change in mortality between cap refill guided resuscitation and lactate guided resuscitation

A comparison of albumin and saline for fluid resuscitation in the ICU (SAFE Trial)
Finfer et al. NEJM 2004; 350:2247

- Goal: To determine if there is a mortality difference using 4% albumin vs. NS for fluid resuscitation in ICU patients
- Randomized multi center, adult surgical and medical ICU pts with clinician identified (and>/= 1 objective criteria of intravascular hypovolemia requiring fluids)
- Excluded: post-cardiac surgery, post-liver transplant or for burns.
- Intervention: 4% albumin vs. 0.9% normal saline used for all fluid resuscitation
- Primary outcome: Mortality w/in 28 days
- 6997 enrolled, 67 withdrew. There was a higher mean initial central venous pressure in albumin group (9.0 vs. 8.6 saline group.) No difference in 28-day mortality (20.9% albumin vs. 21.1 NS p=0.87), no significant differences in secondary outcomes
- In subgroups trauma pts receiving albumin RR of death 1.36 p =0.06 and was more pronounced in severe brain injury. In patients with severe sepsis, RR of death in pts w/ albumin was 0.87 (p=0.09 favoring the albumin group)
- Albumin group received 71 cc more RBC over the first 2 day than NS group
- **Overall, there were no differences in outcomes between the two groups**. Given the greater expense of albumin, albumin may not be warranted. This study also shows that caution should be given to the use of albumin in patients with TBI.

Balanced Crystalloids versus Saline in Critically Ill Adults
Semler et al, "Balanced Crystalloids versus Saline in Critically Ill Adults" – NEJM 2018; 378:829-839

- Goal: Both saline and balanced crystalloids are used for IV fluid administration in critically ill adults, but it is not known which results in better clinical outcomes. Saline has been associated with hyperchloremic metabolic acidosis and renal injury in the past.
- Cluster randomized, single center, multiple-crossover trial conducted in 5 ICU in an academic center
- Assigned 15,802 adults to receive either saline or LR/plasmalyte according to the randomization of the unit to which they were admitted
- Intervention: saline versus LR or plasmalyte
- Primary outcome: major adverse kidney event during 30 days – a composite of death from any cause, new RRT, or persistent renal dysfunction (creatinine >200% of baseline) at hospital discharge or 30 days whichever occurred first
- 15,802 patients were randomized
- Results: The composite endpoint was reached in 14.3% in the balanced-crystalloids group vs. 15.4% in the saline group (p = 0.04) with a trend toward a small improvement in mortality in the balanced crystalloid group (2.5 vs 2.9%).
- Conclusion: Balanced crystalloids may be superior to normal saline in critically ill patients by reducing rate of death, RRT, and/or persistent renal dysfunction

****Overall, it is now recommended that LR be used over normal saline in most situations. Albumin can be considered if patients are not responding to crystalloids but should be avoided in patients with TBI****

WEANING/EXTUBATION/SEDATION:

Discontinuation of mechanical ventilation

Noninvasive Positive-Pressure Ventilation for Respiratory Failure after Extubation
Esteban et al. NEJM 2004; 350: 2452

- Background: Current guidelines recommend SBT trials prior to extubation to decrease the need for re-intubation. With this method, the need for re-intubation is roughly 15%. Patients who require reintubation have higher mortality rates and extubation failure is an independent predictor of death.
- Goal: To determine whether NIPPV in patients with respiratory failure <48hrs from extubation reduces mortality as compared to medical therapy alone
- RCT, patients: on vents 48 hours, with successful extubation after SBT. Patients were extubated when pt was afebrile, no pressors, FiO2 40%, PEEP 5, PaO2>60, passed SBT's. If patients failed extubation w/in 48 hours after extubation, they were assigned to either medical therapy (O2, bronchodilators) or NIPPV
- Primary outcome: Mortality
- 980 patients, 25% had failure requiring intubation prior to 48 hours
- **All-cause mortality was higher in NIPPV group compared to standard group** (just met statistical significance) RR 1.78, NNH 9. This was driven by differences in death rate among patients who required re-intubation.

- There were no differences in the rate of reintubation between the two groups. Reasons for intubation were also not different. Time to re-intubation from onset of respiratory failure was significantly longer in NIPPV group compared to control (12 hours compared to 2)
- Implications: **NIPPV post extubation in *unselected patients who develop respiratory failure* can result in delay in re-intubation that can have negative effect on survival.**

****Key point is that NIPPV should not be used <u>after</u> people develop post extubation respiratory failure, but in other trials it can be used to <u>prevent</u> post extubation respiratory failure****

A Comparison of Four Methods of Weaning Patients from Mechanical Ventilation

Esteban et al. NEJM 1995; 332: 345

- Prospective, randomized, multicenter study
- 546 patients receiving mechanical ventilation for 7.6 days considered ready to be weaned.
- Patients randomized to four weaning techniques (intermittent mandatory ventilation rate set at 10 and decreased if possible, twice a day by 2-4 breaths, pressure support ventilation (initially set at 18 and then reduced 2-4 water at least twice a day), and intermittent trials of spontaneous breathing twice or more a day, or a once-daily SBT.
- Mean duration of weaning 5 days intermittent mandatory vent vs. 4 days PS vs. 3 days intermittent multiple SBT vs. 3 days for once daily SBT. After adjustment of covariates, the rate of successful weaning was higher in once-daily SBT than intermittent mandatory vent or PS, no difference in rate of success between once daily trials and multiple times a day SBT.
- Once daily SBT extubated 3 times more quickly than SIMV and twice as quickly as PS. ***Once daily SBT it preferred over these methods due to this trial***

12-h pretreatment with methylprednisolone versus placebo for prevention of post-extubation laryngeal oedema: a randomized double-blind trial

Francois B, Bellissant E, Gissot V, et al. Lancet 2008; 369:1083-89.

- Background: the efficacy of steroids in reducing post-extubation laryngeal edema is controversial. This study aimed to assess efficacy of steroids in this setting
- Design: placebo-controlled, double-blinded, multicenter, randomized trial or 698 adults intubated >36 hrs received methylprednisolone (20 mg IV) or placebo every 4 hours for 12 hours (3 doses) preceding extubation.
- Results: Laryngeal edema was significantly reduced (22% vs 3%, $p<0.0001$), as were overall reintubation rate (8% vs 4%, $p=0.02$) and reintubation due to laryngeal edema (54% vs 8%, $p=0.005$).
- Conclusion: steroids significantly reduced laryngeal edema and reintubation (mainly from laryngeal edema) in patients intubated for >36 hours. **guidelines suggest all patients high risk of post-extubation laryngeal edema/stridor undergo bedside cuff leak test. If no cuff leak, they recommend IV methylprednisolone 40 mg at least 4 hours before extubation**

Efficacy and safety of a paired sedation and ventilator weaning protocol for ventilated patients in ICU (ABC Trial)

Girard et al. Lancet 2008; 371:126

- Goal: To determine the efficacy and safety of a protocol of daily spontaneous awakening trials (SAT's) and SBT's and to see if this combination can reduce the duration of mechanical ventilation
- Randomized, unblinded, multi-center trial. Adults who require intubation > 12 hrs.
- Excluded: Admission post cardiac arrest, continuous mechanical ventilation >/=2 weeks, imminent death, profound neurological deficits, withdrawal of life support
- Intervention: Paired SAT and SBT protocols vs. SBT protocol only
- During SAT, all sedatives and analgesics used for sedation were interrupted. Analgesics needed for pain were continued.
- Primary outcome: Ventilator free days during 28-day study period
- 168 pts randomized to each group. 90% of intervention group did actually undergo SAT. There were significantly more ventilator free days in intervention group (14.7 vs. 11.6) than control. The intervention group also had a shorter time to discharge from ICU (9.1 d vs. 12.9 days), and hospital (14.9 vs. 19.2 days), shorter duration of coma (2 days vs. 3 days). There was a trend toward fewer tracheostomies in the intervention group, no difference in 28-day mortality but improved 1 year survival in intervention group (HR 0.68).
- There were more self-extubations in the intervention group (16 vs. 6), but no difference in reintubations, 1.6% more dysrhythmias during SBT in intervention group $p=0.02$).
- **Implications: Compared to usual care (SBT alone), daily SAT and SBT resulted in more ventilator free days, less time in the ICU and hospital, less time in coma, and improved 1 year survival. Daily SAT's and SBT's should be encouraged in the ICU.**

A prospective study of indexes predicting the outcome of trials of weaning from mechanical ventilation
Yang KL, Tobin MJ. N Engl J Med 1991; 324:1445-50.

- Background: traditional predictors of success after weaning from mechanical ventilation are frequently inaccurate. This trial developed the rapid shallow breathing index and CROP (compliance, RR, arterial oxygenation, and Plmax) indices to assess success
- Methods: 36 patients were assessed with threshold values calculated that discriminated between a successful and unsuccessful outcome of weaning and tested prospectively in 64 patients.
- Results: Sensitivity was highest for Plmax (1.00) and RR/VT (0.97) *(RSBI score). Specificity was highest for RR/VT (0.64). The f/VT was best predictor of successful weaning.
- Conclusions: Rapid shallow breathing index (RSBI) measured by RR/VT ratio was most accurate in predicting failure, and the absence of rapid shallow breathing was the most accurate predictor of success. (sensitivity 0.97, specificity 0.64).

Tracheostomy

Effect of early vs late tracheostomy placement on survival in patients receiving mechanical ventilation: the TracMan randomized trial
Young D, Harrison DA, Cuthbertson BH. JAMA. 2013; 309;2121-2129.

- Background: tracheostomy is a widely used intervention in the ICU with little evidence to guide timing of the procedure.
- Design: Open, randomized, multicenter clinical trial in 72 ICU and hospitals in the UK randomized 909 patients predicted to require >7 days of ventilation to early (day 4) or late (day 10) tracheostomy.
- Primary Outcome: 30-day mortality.
- Results: There was no change in mortality. Importantly, only 44.9% of patients randomized to the late tracheostomy group required it, as opposed to 94% of the early tracheostomy group
- Conclusion: Early trach did not improve outcomes, and may have caused people to undergo tracheostomy when they may not have needed it at 10 days.

Our typical time frame is to trach someone if they are expected to be on mech vent for over 10-14 days

Effect of pressure support versus unassisted breathing through a tracheostomy collar on weaning duration in patients requiring prolonged mechanical ventilation: A randomized trial
Jubran A, Grant BJB, Duffner LA, et al. JAMA. 2013;309:671–677.

- Background: Patients needing prolonged mechanical ventilation (over 21 days) are commonly weaned at LTACHs, and the most effective method for weaning such patients has not been addressed
- Design: randomized trial between 200 and 2020 in trached patients transferred to a single LTACH for weaning. 500 patients underwent a 5-day screening period where they were placed on trach collar. If they did not develop distress over 120-hour period they were considered weaned and excluded. The 316 who failed were randomized to pressure support trial (PS) or trach collar (TC) trial. (see article for the full protocol)
- Primary outcome: weaning duration
- Results: there was a shorter weaning time (19 days versus 15 days, p=0.004) when using unassisted breathing via tracheostomy ("T-piece") as opposed to a pressure support method with no mortality benefit at 6 and 12 months. Greater than 50% of patients in both groups had died after 6 months.
- Conclusions: among patients needing mech vent at LTACH, unassisted "T-piece" resulted in shorter weaning when compared to pressure support without effect on survival.

Sedation in the ICU

Monitoring sedation status over time in ICU patients: Richmond Agitation-Sedation Scale
Ely et al. JAMA 2003; 289: 2983

- In order to appropriately titrate sedation, there needs to be a quantitative and reproducible measurement of agitation and sedation
- Goal: To test the reliability and validity of RASS
- Prospective cohort study, ICU patients, intubated
- Excluded: History of psychosis or neurologic disease, non-English speaking/deaf, extubated or died before nursing screen
- Intervention: reliability and validity of the RASS tested
- Primary outcomes: Inter-rater reliability between RASS, GCS and Ramsay Scale
- Both RASS and Ramsey showed excellent inter-rater reliability across nurses, intensivists and neuropsychiatric experts, superior to GCS.

- RASS showed excellent discrimination between levels of consciousness. RASS correlated with onset of inattention, GCS, and with cumulative sedative medications, successful extubation and with EEG.
- This study showed that RASS is reproducible and valid compared to other measures of sedation and can be used to titrate sedation

Daily Interruption of Sedation in critically ill patients undergoing mechanical ventilation

Kress et al. NEJM 2000; 342: 1471

- Goal: To determine whether daily interruption of sedative infusions in critically ill patients receiving mechanical ventilation would decrease the duration of mechanical ventilation and length of ICU stay
- Randomized, single center, intubated, mechanically ventilated ICU patients deemed to require continuous IV sedatives
- Excluded: pregnant, transfers from outside institution, admission after cardiac arrest
- Intervention: Daily interruption of sedatives starting 48 hours after enrollment vs. interruption at the discretion of the team.
- Primary outcome: duration of mechanical ventilation, length of ICU stay, length of hospital stay.
- 68 pts in intervention group vs. 60 in control group.
- Intervention group had shorter duration of mechanical ventilation (4.9 vs. 7.3 d p = 0.004), decreased ICU stay 6.4 vs. 9.9, decreased cumulative dose of midazolam 229.8 vs. 425.5, fewer diagnostic tests to evaluate neurologic status. There was no difference in in-hospital mortality, adverse events, dosage of propofol required.
- Implications: **A daily awakening trial can lead to earlier extubation, shorter ICU stay and lower total dosage of midazolam with no apparent increase in re-intubation or adverse events due to early extubation** (not powered to see a difference for this).
- Limitations: unclear if truly blinded, more attention was paid to the intervention arm.

Daily sedation interruption in mechanically ventilated critically ill patients cared for with a sedation protocol: a randomized controlled trial

Mehta S, Burry L, Cook D, et al. SLEAP Investigators. JAMA 2012; 308:1985-92.

- Objective: To compare protocolized sedation with protocolized sedation plus daily sedation interruption in critically ill patients
- Design: Multicenter trial conducted in 16 tertiary ICUs in Canada and US. They randomized 430 critically ill, mechanically ventilated adults to protocolized sedation vs protocolized sedation plus daily sedation interruption.
- Results: Median time to extubation was 7 days in both groups. There was no difference in time to successful extubation, length of ICU stay, length of hospital stay, or incidence of delirium. The daily sedation interruption group received higher doses of sedatives and opiates, and required greater nursing care based on a visual analog scale.
- Conclusion: Daily sedation breaks did not reduce ICU stay or length of mechanical ventilation. **This is in contrast to prior studies. The difference is that this study had a lighter sedation strategy as "usual care" compared with prior studies. Suggesting that prior usual care consisted of too heavily sedating patients, thus delaying extubation**

Dexmedetomidine vs midazolam for sedation of critically ill patients: a randomized trial.

Riker RR, Shehabi Y, Bokesch PM, et al. JAMA 2009; 301:489-99.

- Background: GABA receptor agonists are most commonly used in ICU (at this time), but alpha agonists like dexmedetomidine may have distinct advantages
- Objective: to compare the efficacy and safety of prolonged sedation with dexmedetomidine versus midazolam for mechanically ventilated patients
- Desing: prospective, double-blind, randomized trial conducted in 68 centers in 5 countries in 375 ICUs in patients with expected mech vent for over 24 hours. RASS and CAM ICU scores were used.
- Intervention: dexmedetomidine (0.2-1.4 mcg/kg/hour) or midazolam (0.02-0.1 mg/kg/hour) titrated to achieve light sedation (RASS -2 to +1) from enrollment until extubation or 30 days
- Measures: percentage of time in target RASS with secondary endpoints of duration of delirium, use of fentanyl and open label midazolam, nursing assessments, duration of mech vent, and ICU LOS
- Results: There was no difference in the primary outcome, time spent at target level of sedation. Presence of delirium was less in dex group (54% versus 76.6% ($p<0.001$). Duration of mechanical ventilation was shorter with dexmedetomidine (3,7 days versus 5.6 days ($p=0.01$) but length of ICU stay was similar.
- Conclusion: **dexmedetomidine patients had less delirium and less time on the ventilator, and is safe for prolonged infusion (main side effect bradycardia)**

Dexmedetomidine vs midazolam or propofol for sedation during prolonged mechanical ventilation: two randomized controlled trials

Jakob SM, Ruokonen E, Grounds RM, et al. JAMA. 2012; 307:1151-60.

- Background: propofol and midazolam can have serious side effects. Dexmedetomidine may reduce duration of mech vent and enhance patient comfort

- Objective: to compare propofol with dexmedetomidine for sedation in the ICU
- Two phase 3 multicenter, randomized, double blind trials were conducted between 2007 and 2020. The MIDEX trial compared midazolam (n=251) with dexmedetomidine (n=249) and the PRODEX trial compared propofol (n=247) with dexmedetomidine (n=251).
- Inclusion: adult ICU patients receiving mech vent who needed light to moderate sedation for more than 24 hours.
- Results: Time spent at target sedation was similar between all medications. Duration of mechanical ventilation (including invasive and noninvasive) did not differ between dexmedetomidine and propofol (97 hrs vs 118 hrs, p=0.24). Dexmedetomidine shortened duration of mech vent compared with midazolam (123 hrs vs 164 hrs, p=0.03)
- Conclusion: This article is the first to directly compare sedation with propofol vs. dexmedetomidine in patients requiring prolonged mechanical ventilation.

Early sedation with dexmedetomidine in critically ill patients

Shehabi Y, Howe BD, Bellomo R, et al**.**. N Engl J Med. 2019; 380:2506-17.

- Objective: To assess dexmedetomidine as the sole agent in critically ill patients undergoing mechanical ventilation
- Design: Open-labeled, RCT of 4000 critically ill patients undergoing ventilation in the ICU for less than 12 hours to receive dexmedetomidine as sole or primary agent vs usual care with target RASS score of -2 to +1.
- Results: The primary outcome (rate of death) was the same (29.1%) in both groups. To achieve the prescribed level of sedation, 65% of the dexmedetomidine group had to receive propofol. Bradycardia and hypotension were more common in dexmedetomidine group.
- Conclusion: There was no difference in all-cause mortality at 90 days but bradycardia and hypotension were more common in dexmedetomidine group and nearly ⅔ of dexmedetomidine group received supplemental propofol to reach target sedation.

Delirium in the ICU

Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit

Ely EW, Shintani A, Truman B, et al. JAMA 2004;291:1753-62.

- Objective: Delirium is common, yet underdiagnosed form of organ dysfunction in the ICU. To determine if delirium is an independent predictor of clinical outcomes, including 6-month mortality and LOS in ICU patients
- Design: prospective cohort enrolling 275 consecutive mech vent patients admitted to ICUs of a single-center. Patients were assessed for development of delirium with CAM ICU and RASS scores
- Primary outcomes: 6-months mortality, overall hospital LOS and LOS in post ICU period. Secondary outcomes ventilator free days and cognitive impairment at hospital discharge.
- Results: of the 275 patients, 51 (18.5%) had persistent coma and died. Among the remaining 224 patients, 183 (81.7%) developed delirium. Patients who developed delirium had higher 6-month mortality (34% vs 15%, P=0.03) and spent 10 days longer in the hospital (p<0.001). Delirium was associated with longer post-ICU stay (adjusted HR, 1.6; 95% CI, 1.2-2.3; *P* = .009), fewer median days alive and without mechanical ventilation (19 [interquartile range, 4-23] vs 24 [19-26]; adjusted *P* = .03), and a higher incidence of cognitive impairment at hospital discharge (adjusted HR, 9.1; 95% CI, 2.3-35.3; *P* = .002).
- Conclusion: ICU delirium was associated with much higher 6-month mortality. Delirium was also associated with prolonged ICU and hospital stays, as well as cognitive impairment at hospital discharge.

Long-term cognitive impairment after critical illness

Pandharipande PP, Girard TD, Jackson JC, et al. N Engl J Med. 2013;369:1306-16.

- Objective: To assess the long-term effects of delirium in the ICU
- Design: A prospective, two center study of patients with respiratory failure or shock in ICU. They were assessed for in-hospital delirium, global cognition and executive functioning at 3 and 12 months after discharge with the Repeatable Battery of the Assessment of Neuropsychological Status, and the track making test.
- Results: of the 821 patients enrolled, 74% developed delirium during the hospital stays. At 3 months, 40% had global cognition scores 1.5 SD below the mean (similar to those seen in moderate traumatic brain injury), and 26% had deficits 2 SD below the mean (similar to mild Alzheimer's disease). A similar pattern was evident at 12 months. Longer duration of delirium was associated with worse global cognition and executive function at 3 and 12 months.
- Conclusion: **ICU patients are at extremely high risk of delirium and high risk of long-term cognitive impairment.**

Low-dose nocturnal dexmedetomidine prevents ICU delirium: A randomized, placebo-controlled trial

Skrobik Y, Duprey MS, Hill NS et al. Am J Respir Crit Care Med. 2018; 197:1147-1156.

- Objective: to determine if nocturnal dexmedetomidine prevents delirium and improves sleep in critically ill adults

- Design: Two-center, double-blind, placebo-controlled trial which randomized 100 delirium-free critically ill adults receiving sedatives to receive nocturnal (9:30 p.m. to 6:15 a.m.) IV dexmedetomidine or placebo until ICU discharge.
- Primary outcome: delirium assessed using the Intensive Care Delirium Screening Checklist every 12 hours throughout the ICU admission and sleep evaluated each morning by the Leeds Sleep Evaluation Questionnaire.
- Results: The dexmedetomidine group was free of delirium in 80% of patients compared with 54% for placebo. Patient-reported sleep quality did not differ.
- Conclusion: dexmedetomidine can decrease incidence of delirium but has no change in sleep quality.

Haloperidol and ziprasidone for treatment of delirium in critical illness
Girard TD, Exline MC, Carson SS et al. N Engl J Med. 2018; 379:2506-2516.
- Background: there are conflicting date on antipsychotics in the ICU
- Objective: to study the effect of antipsychotics on mortality in the ICU
- Design: Randomized, double-blind, placebo-controlled trial of patients with acute respiratory failure or shock with delirium. During the study, 566 patient developed delirium hypoactive (89%) / hyperactive delirium (11%) and were randomized to receive intravenous boluses of haloperidol (maximum dose, 20 mg daily), ziprasidone (maximum dose, 40 mg daily), or placebo.
- Primary endpoint: number of days alive without delirium or coma during the 14-day intervention period
- Results: There were no differences in primary outcome of number of days alive without delirium or coma during the 14-day intervention period.
- Conclusion: antipsychotics do not alter delirium course in the ICU

Other Selected ICU Topics

Glucose management in the ICU

Intensive Insulin Therapy in Critically Ill Patients
Van Den Berghe et al. NEJM 2001; 345: 1359
- Rationale: Hyperglycemia is common in critically ill patients and it can lead to complications
- Goal: To determine whether normalization of blood glucose levels with intensive insulin therapy reduces mortality and morbidity among critically ill patients
- RCT of post cardiac surgery ICU patients
- Intervention: intensive therapy (insulin started if glucose >110, goal 80-110) or conventional insulin therapy (insulin pump started when glucose>215, goal 180-200)
- Primary outcome: All-cause mortality during ICU stay
- There was a significant reduction in mortality at ICU stay and in hospital in intensive treated group compared to control. Findings were the same across all degrees of illness
- Intensive glucose control patients had less RRT and prolonged ventilation as well as decreased number of septic episodes
- Overall, **intensive glucose control reduced morbidity and mortality <u>but this was not a MICU population</u>**, making data difficult to extrapolate.

Intensive Insulin Therapy in the Medical ICU
Van den Berghe et al. NEJM 2006; 354:449
- FU to strict glucose control in post-surgical patients, looking at MICU patients
- Goal: determine if tight glucose control in MICU patients improves mortality
- RCT; MICU patients who needed to be there for at least 3 days
- Intervention: Intensive vs. control group same as previous study
- Primary outcome: All cause in hospital mortality
- Hypoglycemia occurred more often in intensive treatment group. Morbidity was reduced with intensive treatment group (fewer days on the vent etc.). No effect on rates of bacteremia (was seen in surgical group). In hospital mortality was not significantly reduced with intensive control
- Implications: **Intensive insulin therapy did not improve mortality in MICU patients**. Authors felt results might have been due to the fact that long term effects of tight glucose control might not have been seen given the study set up. Furthermore, both liver and renal failure are more common in MICU patients, which can lead to more hypoglycemia/effects on glucose control.

Intensive vs. conventional glucose control in critically ill patients **(NICE-Sugar Trial)**
NICE-Sugar Study Investigators NEJM 2009; 360: 1283

- Follow up study to the two previous studies looking to finally determine if intensive glucose control in ICU patients reduces 90-day mortality
- Randomized multinational, adult medical and surgical ICU pts with expected stay > 3days
- Excluded: in ICU > 24 hrs, expected to be eating the next day.
- Intervention: Intensive glucose control (target 81-108) vs. conventional (target < 180 using IV insulin)
- Primary outcome: death from any cause at 90 days
- 6104 randomized, 3010 intensive group and 3012 in conventional group. Study discontinued prematurely. No baseline differences.
- There was a significant increase in mortality at 90 days in the intensive glucose control group (27.5% intensive vs. 24.9% conventional p=0.02 number needed to harm 38) There was a trend toward lower 90-day mortality with intensive control among trauma patients (p=0.07) and among pts receiving steroids at baseline (p=0.06).
- Excess deaths in the intensive control group mostly from cardiovascular causes. Severe hypoglycemia occurred in 6.8% of intensive group vs. 0.5% in conventional group (significant).
- **This was the definitive trial that showed that intensive glucose control increased mortality among ICU patients, with more adverse events. This was the largest trial in MICU patients and settled the debate.**

Transfusion in the ICU

A multicenter, randomized, controlled trial of transfusion requirement in critical care (TRICC)
Hebert et al. NEJM 1999; 340: 409
- Goal: To determine whether a restrictive approach to RBC transfusion (Hgb<7) is equivalent to a more liberal strategy (Hgb10-12)
- Multi-center, randomized, controlled trial
- 838 ICU patients (euvolemic) with hgb</=9 w/in first 72 hours of ICU admission
- Excluded: chronic anemia, active blood loss, pregnancy, or expected imminent death
- Intervention: Restriction transfusion strategy (Hgb < 7 goal 7-9), vs. liberal strategy (Hgb < 10, goal 10-12).
- Primary outcome: 30-day mortality.
- Similar mortality between the two groups (8.7% vs. 23.3% liberal, trend that restrictive is better, p = 0.11).
- The mortality rates were significantly lower with the restrictive transfusion strategy among patients who were less ill (APACHE < 20), 8.7% restrictive vs. 16.1% liberal p = 0.03), and among patients less than 55 years of age (5.7% restrictive vs. 13% liberal p = 0.02), but not among patients with clinically significant cardiac disease (20.5% restrictive vs. 22.9 liberal p = 0.69).
- Implications: **Based on this trial, transfusion requirement in critically ill changed to Hgb<7.** Note: this number does not apply to patients with chronic blood loss prior to ICU, acute blood loss, or patients with active ischemia.

Transfusion strategies for acute upper gastrointestinal bleeding.
Villanueva C, Colomo A, Bosch A, et al. N Engl J Med. 2013; 368:11-21.
- RCT of restrictive transfusion strategy with Hb goal 7 vs liberal strategy with goal of 9 in patients with GI bleed
- Exclusion: massive exsanguinating bleeding; patients who declined transfusion; an acute coronary syndrome, symptomatic peripheral vasculopathy, stroke, transient ischemic attack, or transfusion within the previous 90 days; a recent history of trauma or surgery; lower gastrointestinal bleeding; a previous decision on the part of the attending physician that the patient should avoid specific medical therapy; and a clinical Rockall score of 0 with a hemoglobin level higher than 12 g per deciliter.
- Primary outcome: rate of death from any cause within the first 45 days
- Probability of survival at 6 weeks was higher in the restrictive group (95% vs 91%, p=0.02). Less rebleeding and fewer adverse events in restrictive group. The mortality benefit was greatest in patients with Child-Pugh class A or B cirrhosis. Portal pressure gradient higher at 5d in patients with liberal strategy. Fewer patients in restrictive strategy group received transfusion.
- **Conclusion: goal Hg of 7 versus 9 Hg in this patient population decreases rebleeding and mortality.**

Antibiotics in the ICU

Comparison of 8 vs. 15 days of antibiotic therapy for VAP in adults
Chastre et al. JAMA 2003; 290: 2588
- Prospective randomized, double-blinded, multi-center trial 401 pts diagnosed with VAP
- 197 randomized to 8 days of abx vs. 15 days of therapy
- Outcome: death from any cause, microbiologically documented pulmonary infection recurrence, and abx free days assessed at 28 days

- No difference in mortality (18.8% vs. 17.2%), or recurrent infections (28.9% vs. 26.0%). There was a significant difference in antibiotic free days (13.1 vs. 8.7)
- **EXCEPTION: patients with pseudomonas treated with 8 days had higher pulmonary infection recurrence compared to those treated with15 days (40.6% vs. 25.4%).** There was also less antibiotic resistance in general in the group that got a shorter course of antibiotics (significant). Another exception to note is that this study had very little MRSA pneumonia so be wary.

Methicillin-resistant Staphylococcus aureus nasal colonization is a poor predictor of intensive care unit-acquired methicillin-resistant Staphylococcus aureus infections requiring antibiotic treatment
Sarikonda et al. Crit Care Med 2010; 38:1990-95.
- Single center prospective cohort study evaluated 749 consecutive patients admitted to ICU
- Nasal swabs obtained at ICU admission and weekly for MRSA
- 21.9% had nasal colonization with MRSA at ICU admission. Positive predictive value for ICU-acquired lower respiratory tract infection was 17.7% and negative predictive value was 84.4%. PPV for ICU-acquired bloodstream infection 11% and NVP 89.7%.
- **Negative MRSA swabs do not exclude MRSA infection in the ICU.**

Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock.
Kumar A, et al. Crit Care Med. 2006 Jun: 34(6):1589-96
- Objective: to determine the prevalence and impact on mortality of delays of initiation of effective antimicrobial therapy in patients with septic shock
- Retrospective cohort study between 1989 and 2004 in 14 ICUs in Canada and the US
- Patients: 2,731 adult patients with septic shock were reviewed
- Results: Among the 2,154 septic shock patients (78.9% total) who received effective antimicrobial therapy only after the onset of recurrent or persistent hypotension, a strong relationship between the delay in effective antimicrobial initiation and in-hospital mortality was noted (adjusted odds ratio 1.119 [per hour delay], 95% confidence interval 1.103-1.136, p<.0001). Administration of an effective antimicrobial within the first hour of documented hypotension was associated with a survival rate of 79.9%. **Each hour of delay in antimicrobial administration over the ensuing 6 hrs was associated with an average decrease in survival of 7.6%**. In multivariate analysis, **time to initiation of effective antimicrobial therapy was the single strongest predictor of outcome.**
- Conclusion: Effective antimicrobial administration within the first hour of documented hypotension was associated with increased survival to hospital discharge in adult patients with septic shock. *and is likely one of the most important interventions in septic shock*

Nutrition in the ICU

Early versus late parenteral nutrition in critically ill adults.
Casaer MP, Mesotten D, Hermans G, et al. N Engl J Med 2011;365: 506-17.
- Randomized, multicenter trial
- Inclusion: nutritional risk screening >/= 3 indicating that patient was at risk
- Exclusion: < 18yo, moribund, short bowel, home vent, diabetic coma, referred with nutritional regimen, pregnant or nursing, had no central catheter, taking oral nutrition, readmitted to ICU, BMI < 17, NRS score < 3
- In 2312 patients parenteral nutrition was initiated within 48h of ICU admission (early initiation group) and in 2328 patients parenteral nutrition was not initiated before day 8 (late-initiation groups)
- In both groups, enteral nutrition was attempted, and in early initiation group parenteral nutrition was titrated to meet expected caloric goal through combined enteral and parenteral nutrition. In the late group, 5% glucose solution was used in a volume equal to that of parenteral nutrition in the early group to provide hydration with delivered volume of enteral nutrition taken into account; if enteral nutrition was insufficient after 7d, parenteral nutrition was initiated on day 8 to reach caloric goal.
- The primary end point was the duration of dependency on intensive care, assessed as the number of ICU days (for survivors and non-survivors) and the time to discharge from the ICU.
- Similar rates of death in ICU and the hospital and at 90 days between groups. Proportion of patients discharged alive from ICU within 8d was higher in late group. More patients with hypoglycemia in late group. Patients in the late-initiation group, as compared with the early-initiation group, had fewer ICU infections (22.8% vs. 26.2%, P=0.008) and a lower incidence of cholestasis (P<0.001). The late-initiation group had a relative reduction of 9.7% in the proportion of patients requiring more than 2 days of mechanical ventilation (P=0.006), a median reduction of 3 days in the duration of renal-replacement therapy (P=0.008), and a mean reduction in health care costs of €1,110 (about $1,600) (P=0.04).

- Note: The study has been criticized for including patients with low risk of malnutrition and for the composition of the parenteral nutrition delivered.

Trial of the route of early nutritional support in critically ill adults.
Harvey SE, Parrott F, Harrison DA, et al. New Engl J Med. 2014; 371:1673-84. CALORIES trial
- Multicenter RCT in the UK
- Randomly assigned patients who could be fed through either the parenteral or the enteral route to a delivery route, with nutritional support initiated within 36 hours after admission and continued for up to 5 days
- The primary outcome was all-cause mortality at 30 days.
- 2388 patients included
- No difference in 30d mortality between groups.
- Parenteral group had less hypoglycemia and vomiting. No difference in treated infections, 90d mortality, or adverse events. Caloric intake similar between the 2 groups.

Initial trophic vs full enteral feeding in patients with acute lung injury: the EDEN randomized trial.
Rice TW, Wheeler AP, Thompson BT, et al. JAMA 2012;307: 795-803. (EDEN trial)
- Randomized, open label multicenter trial
- Participants were 1000 adults within 48 hours of developing acute lung injury requiring mechanical ventilation whose physicians intended to start enteral nutrition at 44 hospitals in the National Heart, Lung, and Blood Institute ARDS Clinical Trials Network.
- randomized to receive either trophic or full enteral feeding for the first 6 days. After day 6, the care of all patients who were still receiving mechanical ventilation was managed according to the full feeding protocol.
- Outcome: vent-free days to study day 28
- 508 were in trophic feeding group and 492 to full feeding group.
- Full feeding group received more enteral calories for the first 6d. Initial trophic feeding did not increase vent free days or reduce 60d mortality compared with full feeding. No differences in infections between groups.
- Full feeding group experienced more vomiting, constipation, and elevated gastric residuals.

Permissive underfeeding or standard enteral feeding in critical illness.
Arabi YM, Aldawood AS, Solaiman O, et al. New Engl J Med. 2015; 372:2398-2408.
- Multicenter nonblinded RCT of critically ill adults with medical, surgical, or trauma admission. The study population was not limited to patients with high baseline nutritional risk. Patients were eligible for the trial if they were fed enterally within 48 hours after ICU admission
- Randomized to permissive underfeeding with 40-60% calculated caloric requirements or standard enteral feeding with 70-100% for up to 14d while maintaining similar protein intake between groups
- Primary outcome: 90d mortality
- No difference in 90d mortality. No serious adverse events, and no difference in feeding intolerance, diarrhea, ICU infections, or LOS between groups. Permissive underfeeding group received fewer calories and protein intake was stable.
- Post-hoc analysis showed that permissive underfeeding group had a significantly lower rate of renal replacement therapy.

Effect of not monitoring residual gastric volume on risk of ventilator-associated pneumonia in adults receiving mechanical ventilation and early enteral feeding: a randomized controlled trial.
Reignier J, Mercier E, Le Gouge A, et al. JAMA. 2013; 309:249-56.
- Randomized, noninferiority, open label multicenter trial
- Included adults requiring invasive mechanical ventilation for more than 2 days and given enteral nutrition within 36h
- Intervention group did not have gastric residual volumes monitored; intolerance to enteral nutrition was based on regurgitation and vomiting in the intervention group and based on residual gastric volume > 250cc or regurgitation/vomiting in the control group
- Outcome: proportion of patients with at least 1 VAP within 90d after randomization.
- No difference in VAP occurrence between groups. No differences in other ICU infections, duration of mechanical ventilation, ICU LOS, or mortality. A significantly greater proportion of patients in the intervention group met their calorie goal.

Renal Critical Care

Continuous venovenous hemodiafiltration versus intermittent hemodialysis for acute renal failure in patients with multiple-organ dysfunction syndrome.
Vinsonneau C, Camus C, Combes A, et al. Lancet 2006;368:379-85

- Randomized, multicenter trial of adults in ICU requiring renal replacement therapy
- Randomized patients with MODS and renal failure needing renal replacement to iHD vs CVVHD. Of note, mean duration of HD treatments was 5.5 hours.
- Excluded: pregnancy, age younger than 18 years, chronic renal failure (serum creatinine >180 μmol/L before acute renal failure), acute renal failure of obstructive or vascular origin, continuing treatment with an angiotensin-converting-enzyme inhibitor, coagulation disorders (prothrombin time <20%, platelet count <30 000/μL), uncontrolled hemorrhage, simplified acute physiology score (SAPS) II of 37 or less, moribund state, or severe underlying disease with survival expectancy of less than 8 days
- Primary outcome: 60-day survival
- 360 patients. Rate of survival at 60-days did not differ between the groups (32% in the intermittent hemodialysis group versus 33% in the continuous renal replacement therapy group
- These data suggest that, provided strict guidelines to improve tolerance and metabolic control are used, almost all patients with acute renal failure as part of multiple-organ dysfunction syndrome can be treated with intermittent hemodialysis.

Initiation strategies for renal-replacement therapy in the intensive care unit.
Gaudry S, Hajage D, Schortgen F, et al. N Engl J Med. 2016 ;375:122-33.
- A randomized trial of early RRT [KDIGO 3: serum creatinine more than 4 mg/dl, greater than 3 times baseline, anuria > 12 hours, or oliguria (<0.3 ml/kg/h or below 500 ml/day) for more than 24 hours] vs late RRT (specified lab changes, or anuria/oliguria lasting > 72 hours).
- Primary outcome: 60-day mortality
- Results - no difference in the primary outcome of 60-day mortality. **Nearly 50% of late group avoided HD, had fewer line infections, and experienced an earlier return of renal function than the early group**.

Timing of renal replacement therapy in patients with acute kidney injury and sepsis.
Barbar et al. N Engl J Med 2018; 379:1431-1442
- Multicenter RCT
- Primary outcome death at 90 days
- With the early strategy, renal-replacement therapy was started within 12 hours after the onset of acute kidney injury that was determined to be at the failure stage of the RIFLE classification. With the delayed strategy, RRT was initiated after a delay of 48 hours if renal function did not spontaneously recover and if no condition meeting the criteria for emergency renal-replacement therapy developed
- Trial stopped early for futility after second planned interim analysis.
- 488 randomized – 58% in early group and 54% in delayed group died. In delayed group, 38% did not receive RRT. Criteria for emergent RRT met in 17% of patients in delayed strategy group.
- **For patients with no emergent indications for RRT, early initiation of RRT doesn't lead to mortality benefit.**

Pulmonary Topics

COPD

Early use of non-invasive ventilation for acute COPD exacerbation
Plant et al. Lancet 2000; 355:1931
- Randomized study of patients in the hospital ward with acute mild-moderate COPD flare with RR>23, pH 7.25-7.35, paCO2 > 45, within 12 hrs of admission
- **Excluded: pH< 7.25, GCS <8)**
- Randomized to standard of care vs. standard of care + NIV.
- Primary outcome: need for intubation at 14 days
- Results: 27.1% needed intubation in control vs. 15.3% in NIV (NNT 8), in hospital mortality 20.3% control vs. 10.2% NIV
- NIV group had more rapidly corrected acidosis in first hr, RR over 4 hrs, more rapid relief in breathlessness and did not alter length of stay
- NIV arm 25 more mins/patient nursing workload w/in the first 8 hrs.
- Conclusion: **The early use of NIV for mild/moderate acidotic patients with COPD in general ward settings leads to more rapid improvement in physiologic variables, decreased intubation (NNT=8) and decreased in-hospital mortality (NNT=10).**

Effect of systemic glucocorticoids on exacerbations of chronic obstructive pulmonary disease (SCOPE)
Niewoehner et al. NEJM 1999; 340: 1941

- Randomized study, pts hospitalized with acute COPD flares (excluded use of steroids in the past 30 days, and co-existing conditions) randomized to placebo vs. 2 weeks vs. 8 weeks of steroids during acute flare (started with solumedrol X 72 hrs then prednisone taper).
- Treatment failure defined as (death from any cause, need for intubation and ventilation, readmission for COPD, intensification of therapy)
- Treatment failure occurred less frequently in the steroid groups compared to placebo. (37% vs. 48%), no difference between 2 weeks vs. 8 weeks steroids. The most common reason for treatment failure was intensification of therapy
- Length of hospital stay was longer in the control group (9.7 vs. 8.5 days.)
- **Conclusion: steroids decreased length of stay and treatment failure with no difference between 2- and 8-week regimens.**

Short-term vs conventional glucocorticoid therapy in acute exacerbations of chronic obstructive pulmonary disease: the REDUCE randomized clinical trial.
Leuppi JD, Schuetz P, Bingisser R, et al. JAMA. 2013; 309:2223-31.

- Randomized, noninferiority multicenter trial
- Enrolled 314 patients presenting to ED with acute COPD exac, > 20 pack year current or former smokers without a history of asthma
- Randomized to pred 40 for 5-14d
- Outcome: time to next exacerbation within 180 days
- **5d steroid course is noninferior to 14d treatment course for 6 m re-exacerbation rate.** No difference in time to death, combined endpoint of exacerbation, death, or both and recovery of lung function. Mean prednisone dose is higher in conventional group but no difference in treatment-associated adverse events.

Pulmonary Embolism

Heparin + alteplase compared to heparin alone in pts w/ submassive PE
Konstantinides et al. NEJM 2002; 347: 1143

- Goal: To compare heparin +TPA vs. heparin alone in patients with submassive PE
- Randomized multi-center study, pts with confirmed PE with RV dysfunction or pulmonary hypertension by TTE, RV strain on EKG or pulm. htn by right heart cath
- Excluded: SBP<90 (massive PE), age>80, GI bleed, CVA
- Intervention: TPA +heparin vs. heparin + placebo
- Primary Outcome: in-hospital mortality or deterioration requiring escalation (pressors, intubation, embolectomy, CPR)
- 256 pts randomized, mortality rate in both groups low and similar (3.4% vs. 2.2%, nonsignificant), rates of escalation of care lower in alteplase group (10.2% vs. 24.6%) mostly due to the need for secondary thrombolysis in the placebo group, event-free survival higher in the alteplase group, rates of recurrent PE, major bleeding, stroke, were low and similar in the two groups
- Implications: TPA + heparin in submassive PE resulted in less escalation of care (need for secondary thrombolysis). Overall, mortality rates were lower than expected. Note: other studies have shown increased risk of bleeding with thrombolytics and no improvement in survival→be thoughtful

Eight-year follow up of patients w/ permanent vena cava filters in the prevention of PE
PREPIC Study Group Circulation 2005; 112: 416

- Randomized multi center, adults w/ DVT with or without PE at high risk for PE
- Excluded: prior filter, contraindication to thrombolysis, shift life expectancy, hereditary thrombophilia, severe renal or hepatic failure, pregnancy
- Randomized to filter vs. no filter.
- 282 pts, symptomatic PE less frequent in filter group (6.2% vs. 15.1%), DVT more frequent in filter group (35.7% vs. 27.5%), no difference in posthrombotic syndrome or death, no difference in major bleeding.
- IVC filter reduced risk of PE, increased risk of DVT, no difference in mortality (follow up over 8 yrs)

Fibrinolysis for patients with intermediate-risk pulmonary embolism.
Meyer G, Vicaut E, Danays T, et al. PLEITHO investigators. N Engl J Med 2014; 370:1402-11.

- RCT of Tenecteplase + heparin vs placebo + heparin in normotensive patients with intermediate risk PE (RV dysfunction on TTE or CT as well as positive troponin)

- Primary outcome – death or hemodynamic compensation within 7d of randomization. The main safety outcomes were major extracranial bleeding and ischemic or hemorrhagic stroke within 7 days after randomization.
- 1006 randomized
- Death or hemodynamic compensation occurred in 2.6% of Tenecteplase group vs 5.6% placebo (p=0.02). No difference in death. Extracranial bleeding and stroke were more common in Tenecteplase group. No difference in 30d mortality.
- **In patients with intermediate risk PE, fibrinolytics reduce hemodynamic complications but increase risk of major hemorrhage and stroke**. There is no difference in all-cause mortality between groups.