A more positive fluid balance in patients with septic shock is associated with higher mortality.

**Background:** The mainstays of early treatment in septic shock (antibiotics, infection source control, lung protective ventilation, and aggressive volume resuscitation) remain effective. However, although early goal-directed volume resuscitation and a target central venous pressure (CVP) of 8 to 15 mm Hg has become accepted practice, exactly how much fluids to administer or when to stop has yet to be defined.

**Objective:** To determine whether fluid balance and/or CVP are associated with mortality in septic shock.

**Design:** Retrospective analysis of data from a large randomized, controlled trial.

**Participants:** 778 septic shock patients requiring at least 5 µg/minute of norepinephrine were enrolled in the Vasopressin and Septic Shock Trial.

**Methods:** Cumulative fluid balance (IV plus oral fluid intake minus urine output) and CVP at 12 hours and over the first 4 days was associated with 28-day mortality using Cox hazard regression analysis controlling for age, APACHE II score, and vasopressor dose. Cumulative fluid balance was divided into quartiles, and CVP was divided into <8, 8 to 12, and >12 mm Hg for analysis.

**Results:** Mean cumulative fluid balance was 4.2 liters at 12 hours and 11 liters by day 4. Fluid balance quartile at both 12 hours and day 4 predicted mortality. A dose effect response of fluid balance was seen with patients in the lowest quartile of fluid balance (ie, least positive fluid balance) at 12 hours having a 43% lower risk of dying (HR, 0.569), those in the second lowest quartile having a 42% lower risk of death, and those in the third quartile having a trend for lower mortality (HR, 0.762). Day 4 fluid balance demonstrated a similar effect, with the lowest quartile having 53% lower risk of dying (HR, 0.466), the second quartile having a 48% lower risk of death, and the third 26% having a lower risk of death. Interestingly, although guidelines recommend targeting CVP at 8 to 12 mm Hg, patients with CVP <8 mm Hg at 12 hours experienced the lowest mortality (HR, 0.606 compared to CVP >12 mm Hg), followed by those with CVP 8 to 12 (HR, 0.762). CVP at day 4 was not associated with mortality.

**Conclusions:** A less positive fluid balance, both at 12 hours and day 4, is associated with improved survival, and CVP <8 mm Hg is also associated with lower mortality.

**Reviewer’s Comments:** These data suggest that excessive volume resuscitation is harmful, but what is considered excessive? It appears that volume resuscitation to a goal of 8 to 10 mm Hg is reasonable, but volume resuscitation beyond that may be harmful. In cases where the target CVP is reached, IV fluids should be limited, and vasopressors could be used preferentially to maintain blood pressure. This study also emphasizes that the goals of early resuscitation should not be extrapolated beyond the first 6 hours. (Reviewer-Todd W. Rice, MD, MSc).

**Keywords:** Fluid Balance, Volume Resuscitation, Septic Shock

**Print Tag:** Refer to original journal article
Combination norepinephrine and dobutamine is superior to epinephrine alone with regard to lactic acidosis, dysrhythmias, and gastric mucosal perfusion in patients with cardiogenic shock.

**Background:** Cardiogenic shock often requires catecholamines to maintain adequate perfusing pressure, but adrenergic agents have adverse effects on the heart including tachycardia, arrhythmias, and myocardial ischemia or necrosis. Although data suggest dopamine results in worse outcomes than norepinephrine, no randomized trials have evaluated different adrenergic agents in cardiogenic shock.

**Objective:** To compare systemic hemodynamic and perfusion effects of epinephrine with combined norepinephrine + dobutamine in patients with nonischemic cardiogenic shock.

**Design:** Prospective, randomized, controlled pilot study.

**Participants:** 30 patients with dopamine-resistant cardiogenic shock, defined by ejection fraction of <30% and a cardiac index (CI) <2.2 L/min–1/m–2, absence of hypovolemia, hypotension with systolic BP <90 mm Hg or mean arterial pressure (MAP) <60 mm Hg, low urine output, elevated lactate, and no evidence of cardiac ischemia, were included. Patients with acute myocardial infarction, arrhythmias, or septic shock were excluded.

**Methods:** Participants were randomized to epinephrine or norepinephrine infusion initiated at 0.1 µg/kg/min and titrated every 5 minutes to obtain a MAP of 65 to 70 mm Hg. Dobutamine was discontinued in the epinephrine arm but continued with the norepinephrine.

**Results:** At enrollment, all patients were treated with an average of 10 µg/kg/min of dopamine and 8 µg/kg/min of dobutamine. After 1 hour, there was no difference between groups with regard to hemodynamics, with all patients meeting goals (MAP >65 mm Hg and CI >2.2). Epinephrine resulted in significantly higher heart rates (128 vs 100 beats/min; P <0.05), and there were 3 cases of arrhythmia (2 supraventricular and 1 ventricular tachycardia) compared to none in the norepinephrine group. Oliguria was reversed more frequently with norepinephrine (13 vs 10 patients; P =0.05). At 6 hours, lactate concentrations had decreased in the norepinephrine group but had increased in the epinephrine group (although they recovered by 12 hours). The gastric PCO₂ gap decreased in the norepinephrine group, indicating improved gastric mucosal perfusion, compared to increased gastric pCO₂ in the epinephrine group.

**Conclusions:** Although both epinephrine alone and combined norepinephrine and dobutamine improve hemodynamics similarly, the norepinephrine-dobutamine combination improves surrogate parameters of tissue perfusion in the first 6 hours.

**Reviewer's Comments:** This is a small pilot study of 2 adrenergic vasopressor regimens in patients with nonischemic cardiogenic shock. Although the very small sample size makes the results less robust, they are intriguing nonetheless. Patients were first started on dobutamine with dopamine added for shock. Once they failed to maintain adequate perfusion on those agents, they were eligible. Despite obtaining similar hemodynamic results, epinephrine alone resulted in more arrhythmias and was inferior to the combination of norepinephrine and dobutamine with regard to surrogates of organ perfusion. Although these are preliminary data, the combination of norepinephrine and dobutamine may be preferable over epinephrine alone in treating these patients until additional data from a larger randomized study are available. (Reviewer-Todd W. Rice, MD, MSc).

Keywords: Epinephrine, Cardiogenic Shock, Lactate, Organ Dysfunction

Print Tag: Refer to original journal article
MALA Has Better Prognosis Than Lactic Acidosis of Other Origins

Outcome of Severe Lactic Acidosis Associated With Metformin Accumulation.

Friesecke S, Abel P, et al:

Crit Care 2010; December 20 (): epub ahead of print

While metformin-associated lactic acidosis leads to worse acid-base derangements, outcomes are better than outcomes with lactic acidosis of other origin.

**Background:** Metformin use can be associated with the development of lactic acidosis in certain subpopulations of patients. Mortality with metformin-associated lactic acidosis (MALA) has been reported to be 30% to 50%. However, it is unclear if MALA differs in outcome from lactic acidosis of other origins.

**Objective:** To compare the outcomes of MALA and lactic acidosis of other origins.

**Design:** Retrospective medical records review of all patients admitted to a single medical ICU during a 5-year period.

**Methods:** Patients with MALA were compared to patients with lactic acidosis of other origins with respect to laboratory measurements, organ dysfunction, and mortality.

**Results:** Over a 5-year period, 197 patients were admitted with lactic acidosis. Of those, 10 (5.1%) were diagnosed with MALA. All 10 participants had previously unrecognized severe renal dysfunction. All MALA patients were in circulatory shock, requiring vasopressors and mechanical ventilation. Compared to patients with lactic acidosis of other origins, patients with MALA had more severe lactate levels (18.7 vs 11.2 mmol/L; \( P < 0.01 \)), lower pH (6.75 vs 7.15; \( P < 0.01 \)), and worse renal failure. Despite this, mortality was significantly lower in MALA patients compared to those with lactic acidosis of other origin (26% vs 50%). In the subgroup with severe acidosis (pH <7.0), survival was significantly higher in patients with MALA compared to patients with lactic acidosis of other origin (50% vs 0%; \( P < 0.01 \)).

**Conclusions:** While MALA patients had the most severe acid-base imbalance, survival was not worse than in patients with lactic acidosis of other origins. It is important to consider the diagnosis of MALA and inquire about metformin use in any patient with very severe lactic acidosis.

**Reviewer’s Comments:** The widespread use of metformin to treat diabetes mellitus, combined with the risk of renal insufficiency associated with diabetic nephropathy, places a large group of patients at risk for MALA. Although this study is limited by the retrospective design and small sample size, Friesecke and colleagues have increased our understanding of the presentation, clinical course, and outcomes associated with MALA. Despite the severe acidosis, these patients appear to fare better than those with lactic acidosis of other etiologies, despite having worse renal function, which is a known predictor of mortality in the ICU. This study highlights the need to consider and inquire about metformin use in any patient with unexplained lactic acidosis.

(Reviewer-M. Bradley Drummond, MD).

Keywords: Metformin, Lactic Acidosis, Survival

Print Tag: Refer to original journal article
Sustained hyperglycemia and seizures requiring therapy are associated with increased mortality when using therapeutic hypothermia to treat out-of-hospital arrest.

**Background:** Therapeutic hypothermia has been implemented as part of routine care for out-of-hospital cardiac arrest patients at many clinical centers. Because therapeutic hypothermia requires sedation, ventilation, and neuromuscular blockade, the risk for adverse events is increased in patients receiving this therapy. Prior publications of therapeutic hypothermia have reported a trend toward more adverse events but have also suggested an overall beneficial effect on survival.

**Objective:** To investigate the association between adverse events and mortality in a large cohort of patients treated with therapeutic hypothermia for out-of-hospital cardiac arrest.

**Design:** Prospective, observational, registry-based study of 22 European and U.S. hospitals between October 2004 and October 2008.

**Participants:** 765 consecutive out-of-hospital cardiac arrest patients who were comatose after return of spontaneous circulation and treated with therapeutic hypothermia.

**Methods:** Patient characteristics, cardiac arrest-related factors, and treatment covariates were collected. Univariate and multivariate models were generated to determine the association of these covariates with 6-month mortality and neurological outcomes.

**Results:** At 6 months, 391 patients (52%) had died. Among the 363 still alive, 268 (74%) had good neurological outcomes. Arrhythmias, pneumonia, seizures, and electrolyte disorders were common adverse events associated with therapeutic hypothermia. In a multivariate model, sustained hyperglycemia was associated with increased mortality (OR, 2.3; 95% CI, 1.6 to 3.6; \( P < 0.01 \)). Patients with seizures treated with anticonvulsants also had higher mortality (OR, 4.7; 95% CI, 3.0 to 7.4; \( P < 0.001 \)). Bleeding was not associated with increased mortality.

**Conclusions:** Adverse events are common in the treatment of out-of-hospital cardiac arrest with therapeutic hypothermia. Only sustained hyperglycemia and seizures requiring treatment were associated with higher mortality.

**Reviewer's Comments:** In this well-designed, large, multisite study, Nielsen and colleagues have examined the association of adverse events related to therapeutic hypothermia with 6-month mortality. Although adverse events were common, only hyperglycemia and seizures appeared to be related to worse mortality. While not designed to compare the effectiveness of therapeutic hypothermia in improving survival, this study suggests that many of the adverse events associated with this intervention do not impact mortality and therefore should not impede the initiation of therapeutic hypothermia. The study is also notable for the unusually low 50% 6-month mortality and good neurologic outcomes among survivors. (Reviewer-M. Bradley Drummond, MD).

**Keywords:** Cardiac Arrest, Therapeutic Hypothermia, Mortality, Complications

**Print Tag:** Refer to original journal article
Rivaroxaban Effective for Acute and Extended Tx of Venous Thrombosis

Oral Rivaroxaban for Symptomatic Venous Thromboembolism.

The EINSTEIN Investigators:

N Engl J Med 2010; 363 (December 23): 2499-2510

Rivaroxaban appears to be a promising alternative for the treatment of deep-vein thrombosis.

**Background:** New oral agents have been developed that may replace warfarin for many indications.

**Objective:** To compare the efficacy and safety of the oral factor Xa inhibitor, rivaroxaban, with enoxaparin and vitamin K antagonists for the treatment of deep-vein thromboembolism (DVT).

**Design:** 2 of 3 planned studies are reported (The EINSTEIN studies). The first study is an open-label, randomized trial of 2 anticoagulation strategies in acute DVT, and the second study is a double-blind, randomized trial of active drug versus placebo in continued treatment of DVT.

**Participants:** This international, multicenter trial included adults with acute DVT. Patients with a creatinine clearance <30 mL/minute, liver disease, receiving a strong cytochrome P-450 3A4 inhibitor or inducer, or with a vena cava filter were excluded.

**Methods:** The first trial compared the oral factor Xa inhibitor rivaroxaban with enoxaparin followed by vitamin K antagonists for a period of 3, 6, or 12 months after an acute clot. The second trial compared rivaroxaban with placebo for a period of 6 or 12 months in patients who had completed 6 to 12 months of treatment for DVT or pulmonary embolism (PE).

**Results:** Approximately 3400 patients were enrolled in the first trial and 1200 in the second. For acute DVT management, 2.1% and 3% of patients had recurrent clot in patients with rivaroxaban and enoxaparin/warfarin, respectively. Major bleeding occurred in 0.8% and 1.2%, respectively. For the continuation trial, 1.3% of patients on rivaroxaban developed recurrent clot compared with 7.1% of patients on placebo.

**Conclusions:** Rivaroxaban, an oral factor Xa inhibitor, is a viable and simple treatment with a favorable risk-benefit profile.

**Reviewer's Comments:** This report is highly encouraging and will no doubt be the basis for a submission to the Food and Drug Administration (FDA) for approval for this indication. As noted by the authors, a third study specifically examining use in acute PE is in progress. If you review the clinicaltrials.gov website, you will find 20 trials of rivaroxaban that are underway or have been completed. Rivaroxaban for DVT prevention after hip and knee surgery went before the FDA in 2009, but no action was taken due to concerns for potential liver toxicity. Although rivaroxaban is not yet on the market, it does appear to be very promising. Concerns with this agent include the lack of a specific reversal agent and its renal elimination. In this trial, patients did not have a high burden of comorbidities. Safety in actual practice may not be as good as in the trial, but the same could be said for warfarin. Use in patients on other drugs that are inducers or inhibitors of cytochrome P-450 3A4 may also be problematic. It will be an interesting paradigm shift if warfarin and heparin products are displaced by oral direct thrombin inhibitors and factor Xa inhibitors. (Reviewer-Annette M. Rowden, PharmD).

Keywords: Anticoagulation Pharmacology, Symptomatic DVT, Oral Rivaroxaban

Print Tag: Refer to original journal article
Rivastigmine is not beneficial for the treatment of delirium in critically ill patients and may increase both delirium and mortality in ICU patients.

**Background:** Delirium is associated with increased ICU mortality, but optimal management remains unknown. It is postulated that impaired cholinergic neurotransmission may be a factor in the development of ICU delirium. Rivastigmine is an acetylcholinesterase inhibitor that is approved by the Food and Drug Administration for treatment of dementia from Alzheimer’s or Parkinson’s disease.

**Objective:** To determine if rivastigmine decreases the duration of delirium in critically ill patients.

**Design:** Prospective, randomized, double-blind study.

**Participants:** Adult patients from 6 ICUs in the Netherlands were included.

**Methods:** Patients who screened positive for delirium were eligible for enrollment. The confusion assessment method for the intensive care unit (CAM-ICU) was the routine delirium assessment method used to identify the occurrence of delirium.

**Interventions:** Patients received usual care (haloperidol IV scheduled and titrated when needed, benzodiazepine when needed, propofol when needed) with either placebo or rivastigmine that was titrated upward over a 10-day period. Rivastigmine was tapered off when delirium cleared or the patient was discharged.

**Results:** 6724 patients were screened, and 648 had delirium. A sample size of 440 patients was planned, but the trial was halted after 104 patients (54 on rivastigmine and 50 on placebo) were enrolled due to a recommendation from the data safety and monitoring board. At the time the study was halted, the median duration of delirium was higher in the rivastigmine group compared to the placebo group (5 days vs 3 days), and mortality was higher in the rivastigmine group (22% vs 8%).

**Conclusions:** Rivastigmine should not be used to treat delirium in ICU patients since it does not help and might increase mortality.

**Reviewer’s Comments:** From reading this report, it is difficult to be enthusiastic about the use of acetylcholinesterase inhibitors for the management of delirium in critically ill patients. It is understandable that the study was terminated early given that it was unlikely that outcomes in the remaining patients would be robust enough to demonstrate an overall effect in the opposite direction of what was seen after 25% of the planned enrollment. Notable issues with this study include a low percent of patients screening positive for delirium (<10%), which seems unusual compared to prior delirium studies, and an extensive cocktail of drugs administered as part of usual care. Sedation and delirium studies in the ICU seem to be inherently difficult to interpret due to the many therapeutic strategies used as “standard” management. I am struck by the desire to medicate non-agitated delirium. Until we determine that more good than harm occurs through the administration of anti-delirium agents in patients who are not a danger to themselves or others, I think we should refrain from medicating. Finally, for our own practices and in research trials, we need to think about all of the non-drug strategies we should be utilizing to prevent and treat delirium. These might be the most important tools that can be employed to minimize delirium in our fragile population. (Reviewer-Annette M. Rowden, PharmD).
Initially inappropriate antibiotic treatment is relatively common in patients with sepsis related to Gram-negative organisms and is associated with prolonged hospital length of stay.

**Background:** Mortality from severe sepsis remains high. There is broad consensus that early and appropriate antibiotic therapy is crucial to success. The prevalence and effect of inappropriate antibiotic therapy in Gram-negative sepsis is not well described.

**Objective:** To determine the impact of initial antibiotic treatment on the length of stay (LOS) of patients with confirmed Gram-negative sepsis.

**Design:** Retrospective chart review.

**Methods:** The study cohort was derived from a single academic urban teaching hospital. Adult patients with severe sepsis based on consensus definition AND a Gram-negative pathogen on blood cultures were included. Initially inappropriate antibiotic therapy (IIAT) was defined as occurring if antibiotics prescribed were not active in vitro against the recovered pathogen or if antibiotics were not prescribed within 24 hours (therapy delayed) of the eventually positive culture being drawn. Information on demographics, comorbidities, pathogen identified, and APACHE II score were recorded. For LOS, day 0 was defined as when the first positive cultures were drawn. A Cox proportional hazards model was used to evaluate the role of IIAT on LOS.

**Results:** 760 patients were included in the final analysis; 238 patients (31.3%) received IIAT. Fifty-eight percent of IIAT was because of delayed treatment, with the rest being due to a resistant pathogen. *Escherichia coli* was the most common pathogen followed by *Klebsiella* and *Pseudomonas*. In comparing baseline characteristics, IIAT patients were more likely to have cancer, diabetes, or be undergoing chronic dialysis. Patients with IIAT had a median increase of 2 days in hospital LOS (11 vs 8 days; *P* =0.028). In the Cox model linking IIAT to remaining hospitalized, the adjusted hazard ratio related to IIAT was 1.18 (95% CI, 1.02 to 1.39).

**Conclusions:** IIAT in proven Gram-negative severe sepsis occurred frequently and was independently associated with a 2-day prolongation of hospital stay.

**Reviewer’s Comments:** The authors themselves point out many of the limitations of this study. It is retrospective and from a single center. Furthermore, because there is no consensus definition for IIAT, a comparison of these results to other studies will be difficult. Nevertheless, I was rather surprised how frequently IIAT was started. It reinforces what we already know about early goal-directed therapy for sepsis. Time matters when giving appropriate antibiotics, and an initially very broad coverage strategy is needed. Moreover, perhaps starting several antibiotics with broad Gram-negative coverage for patients with risk factors for increased bacterial resistance (chronic dialysis, cancer, diabetes, living in a nursing home) is prudent. Individual institutions should carefully choose an initial strategy for covering patients suspected of developing sepsis based on local microbiology. If these results are confirmed, the upfront costs of picking broader, more expensive antibiotics may be cost-effective in minimizing morbidity and hospital length of stay. (Reviewer-Timothy Scialla, MD).

**Keywords:** Sepsis, Mortality, Hospital Length of Stay, Initially Inappropriate Antibiotic Therapy

**Print Tag:** Refer to original journal article
Simple, Non-Technological Interventions Can Meaningfully Impact Delivered Care

The Value of Adding a Verbal Report to Written Handoffs on Early Readmission Following Prolonged Respiratory Failure.
Hess DR, Tokarczyk A, et al:
Chest 2010; 138 (December): 1475-1479

Adding a verbal report to a written summary at the time a patient is discharged from an acute respiratory care unit is associated with significant cost reduction.

Background: ICU patients with chronic respiratory failure are often directly transferred from the ICU to a specialized care facility. Readmission from these centers occurs frequently because of patients’ comorbidities and the complexity of their care.

Objective: To determine if adding a verbal telephone report to a written handoff would reduce readmission within 72 hours of hospital discharge.

Design: Observational study.

Methods: The setting was a 10-bed unit that provided care for patients on mechanical ventilation who were otherwise stable. From November 2003 until October 2005, transfers from the unit to rehabilitation facilities were accompanied by a written discharge summary. From November 2005 till October 2007, in addition to the written report, a telephone discipline-to-discipline report was performed at the time of discharge in a manner similar to transfers from one hospital unit to another. Patient demographics and comorbidities were recorded. The primary end point was readmission to the unit within 72 hours of discharge. A secondary end point was total cost, including readmission cost when applicable. Multivariate analysis was performed using logistic regression analysis.

Results: 362 patients were included in the study (151 before and 211 after the addition of a verbal report). The groups differed in that patients discharged after initiating a verbal report had a shorter LOS in the unit (11 vs 15 days; \( P < 0.001 \)), a lower proportion had a tracheostomy at the time of discharge (46.9% vs 60.9%; \( P = 0.01 \)), and more were discharged on oxygen therapy (28.0% vs 11.3%; \( P < 0.001 \)). There were no differences in readmission rates based on demographics or comorbidities. The odds ratio for readmission if a verbal handoff was included with a written discharge summary was 0.42 (95% CI, 0.17 to 1.04; \( P = 0.06 \)). Median total cost was less in those discharged after initiation of verbal sign out ($111,723 vs $148,574; \( P = 0.002 \)).

Conclusions: The addition of a discipline-to-discipline verbal report to a standard written discharge summary was associated with significant cost reduction, with approximately $184,000 saved for every 100 patients discharged from this acute care facility.

Reviewer's Comments: This is another article that demonstrates that relatively simple, non-technological interventions can have meaningful impact on delivered care. Although the readmission rate of patients with a verbal sign out was not statistically significantly different, the trend is difficult to ignore and probably would reach the sacred \( P < 0.05 \) if the study had more power. I wonder if the results of this study say more about the effectiveness and quality of a telephone call or the lack of quality of written discharge summaries on complicated patients with prolonged hospitalizations and fragmented care. Nevertheless, it appears that simply calling your colleagues at the accepting facility and answering their questions is not only cost-effective but a refreshing step back to the future. (Reviewer-Timothy Scialla, MD).

Keywords: Prolonged Respiratory Failure, Costs, Verbal Reports, Readmission

Print Tag: Refer to original journal article
Large volume saline resuscitation in bacterial meningitis and systemic inflammation may have adverse effects on intracranial hypertension.

**Background:** There are no studies comparing the effects of different resuscitation fluids on intracranial pressure (ICP) in meningitis.

**Objective:** To compare the effects of resuscitation with crystalloid versus colloid solution on ICP following induction of meningitis by intrathecal lipopolysaccharide (LPS) injection in cats.

**Design:** Prospective, randomized animal study.

**Methods:** After injection of LPS into 20 anesthetized cats, the animals were randomized to either albumin (n=7), normal saline (n=7), or no-fluid (n=6). Continuous infusions of 20% albumin or normal saline designed to achieve normovolemia were started 4 hours after injection for 6 hours. ICP, plasma volume, plasma oncotic pressure, and brain metabolism were evaluated.

**Results:** Plasma volume decreased initially after LPS injection in all groups, but recovered in the saline and albumin groups without significant intergroup difference. Plasma oncotic pressure at the end of the experiment was significantly higher in the albumin group compared to the other 2 groups, which were similar. ICP increased during the first 4 hours in all groups from 10 to approximately 20 mm Hg. In the albumin and no-fluid groups, there were no further increases in ICP, while ICP continued to increase in the saline group and reached 25 mm Hg by the end of the experiment. There were no significant differences in brain interstitial glucose, glycerol, and lactate/pyruvate ratio in all groups and remained in the normal range. Mean arterial pressure did not differ among groups. Urine production was significantly higher in the saline group compared with the other 2 groups.

**Conclusions:** In a bacterial meningitis model in which LPS induced intracranial hypertension and hypovolemia, plasma volume was restored with either albumin or saline, but oncotic pressure was lower and ICP higher in the saline group at the end of the experiment.

**Reviewer's Comments:** Although plasma volume was recovered in both the albumin and saline groups, the normal saline group required 18-fold more volume to compensate for interstitial accumulation of fluid and larger urine volume production. Lower ICP in the albumin group was attributed to higher oncotic pressure and less fluid distribution to brain interstitium. Saline may increase ICP by reduction in plasma oncotic pressure or transcapillary filtration through the damaged blood-brain barrier. Current recommendations for management of bacterial meningitis are to avoid negative fluid balance and hypovolemia, which are associated with poor outcome. This study would suggest that in early meningitis, resuscitation with albumin can restore plasma volume without elevation of ICP, which may be observed with saline resuscitation. No conclusions about effect on outcome or about long-term ICP control can be made. Other therapies currently used to control ICP, such as mannitol and hypertonic saline, were also not assessed and may perform equally well or superior to albumin. (Reviewer-Wendy C. Ziai, MD).

Keywords: Meningitis, Brain Edema, Intracranial Pressure, Fluid Therapy, Albumin, Saline

Print Tag: Refer to original journal article
Use of validated intraparenchymal hemorrhage prognostic models alone to evaluate probability for favorable outcome will underestimate this potential in patients without do-not-resuscitate (DNR) orders and may result in a DNR order for patients who may otherwise have had a favorable outcome.

**Background:** Outcome prediction models for spontaneous intraparenchymal hemorrhage (IPH) have typically included patients regardless of "do not resuscitate" (DNR) orders.

**Objective:** To demonstrate how inclusion of DNR patients in the derivation of a prognostic model for IPH would lead to an overly pessimistic prediction of outcome for patients without DNR orders.

**Design:** Retrospective, observational cohort study.

**Participants:** 424 consecutive patients with spontaneous IPH were included.

**Methods:** A multivariate logistic regression model based on presenting characteristics was used to generate a prognostic score of favorable outcome, defined as moderate disability or better (modified Rankin scale score ≤3). The observed and predicted proportions of favorable outcome were stratified by DNR status, and the ratio was used to define whether the model was optimistic or pessimistic.

**Results:** Of 424 patients (mean age, 65 years), 43% had a DNR order. The observed proportion of favorable outcome at discharge was 44%, and 38% died in the hospital. Considering all patients together and regardless of DNR status, the observed and predicted proportion of favorable outcome agreed well. In non-DNR patients, the observed probability of favorable outcome was significantly higher than predicted, and in DNR patients, the observed probability was significantly lower than predicted. Using the previously validated IPH score demonstrated similar results. If only non-DNR patients were included to create a prognostic model, predicted probabilities of favorable outcome were no longer pessimistic in the non-DNR patients and the model had a good fit. When applied to the DNR group, the predicted probabilities remained overly optimistic.

**Conclusions:** Using well-calibrated prognostic models for IPH, predictions of favorable outcome were significantly pessimistic in patients without DNR orders and significantly optimistic in patients with DNR orders.

**Reviewer's Comments:** This study suggests that some IPH patients have potential for a favorable outcome, but perhaps, due to the use of an overly pessimistic model, may be assigned a DNR order, which may have led to a decision not to attempt aggressive treatment. IPH prognostic models might be more useful if derived from large cohorts limited to IPH patients without DNR orders who therefore have aggressive care pursued. Although results suggest caution in being overly pessimistic about the potential for recovery in IPH patients, prognostication is usually based on clinician experience and judgment rather than a derived probability score. There are several patient factors that could not be included in a retrospective analysis that would influence why DNR orders were written, including development of medical complications later in the hospital course and prior DNR orders. However, this study raises the warning that dire prognoses can become self-fulfilling prophesies. Note that this was a single center study that has not been externally validated, and the outcome measure was not assessed at a typical interval post-event point for this condition. (Reviewer-Wendy C. Ziai, MD).
Radial Artery Grafts No Better Than SVGs in CABG Patients

Radial Artery Grafts vs Saphenous Vein Grafts in Coronary Artery Bypass Surgery: A Randomized Trial.

Goldman S, Sethi GK, et al:

JAMA 2011; 305 (January 12): 167-174

Beyond the left internal mammary graft, little else improves conduits in coronary artery bypass grafting patients.

**Background:** Coronary artery bypass graft (CABG) surgery is a common revascularization modality in patients with coronary disease. For the last 25 years, the left internal mammary artery (LIMA) has been the superior conduit to the left anterior descending (LAD), reducing risk of mortality and myocardial infarction compared to using all saphenous vein graft (SVG) conduits. This benefit has resulted in enthusiasm for other arterial grafts, such as the radial artery, for CABG. Whether this improves outcomes is uncertain.

**Objective:** To compare the 1-year patency of a radial artery versus an SVG in a randomized, prospective trial in first-time CABG patients.

**Participants/Methods:** 757 patients from 11 Veterans Affairs medical centers (99% male) who needed first-time CABG surgery were enrolled. Patients were randomized 1:1 to receive either radial artery or SVG graft. Prior to surgery and randomization, the surgeons specified which vessel was to receive the study graft. The majority of patients with LAD stenoses received a LIMA graft to that vessel. All patients received aspirin therapy. Patients underwent graft angiography 1 week and 1 year postoperatively. The main outcome of the study was the 1-year graft occlusion rate.

**Results:** The 757 randomized patients were well balanced by demographics, severity of coronary disease, and postoperative medications. The 30-day mortality rate was not different between the 2 groups (0.7%). At the 1-week angiography, 99% of radial grafts compared to 97% of SVG were patent. At 1 year, 89% of radial artery grafts and 89% of SVGs were patent by angiography. On prespecified subgroup analysis, diabetics fared better with SVG, and nondiabetics fared better with a radial artery graft. High-grade graft stenoses were more common at 1 year in patients with radial grafts compared to SVGs. Clinical events were similar in both groups.

**Conclusions:** The 1-year patency of radial artery grafts and SVGs are high and not different.

**Reviewer’s Comments:** This study adds to our knowledge and recommendations for our patients undergoing CABG surgery. The randomized nature of this study contributes to its importance. These data suggest there is no 1-year difference between a radial artery conduit and SVG conduit for CABG surgery. There are more high-grade stenoses, called the string sign, with radial artery conduits than has previously been described when this graft is not anastomosed to a vessel with a high-grade stenosis. Importantly, it would be difficult to apply this knowledge to women requiring CABG, which is a major short coming of this study. Furthermore, longer term angiographic follow-up would be interesting to know whether the radial artery and SVG have similar rates of atherosclerosis development. Based on this study, beyond the LIMA to LAD anastomosis, it appears the conduits used for other anastomoses do not affect outcome. (Reviewer-Steve P. Schulman, MD).

Keywords: Coronary Artery Bypass Grafting, Radial Artery Grafts, Saphenous Vein Grafts

Print Tag: Refer to original journal article
In large diameter conduits and low-risk patients, aspirin alone is all that is needed.

**Background:** Coronary artery bypass grafting (CABG) is used frequently for symptomatic coronary disease. Typically, surgeons place the internal mammary graft to the left anterior descending and separate saphenous vein grafts (SVGs) anastomosed to other diseased coronary arteries or branches. The achilles heel of CABG surgery is the long-term patency of SVGs. Prior angiographic studies suggest that within the first several months following CABG, varying degrees of thrombosis and intimal hyperplasia occur resulting in a 1-year SVG patency of 75% to 80%. The early process of intimal hyperplasia in SVG is thought to be mediated by platelet activation. Aspirin therapy is standard care in CABG patients. In animal studies, adding clopidogrel to aspirin reduces intimal hyperplasia and subsequent SVG occlusion.

**Objective:** To assess whether the addition of clopidogrel to aspirin therapy in first-time CABG patients who have received >2 SVGs reduces 1-year severity of SVG intimal hyperplasia determined by intravascular ultrasound (IVUS).

**Design:** Double-blind, phase II, randomized study.

**Participants/Methods:** All subjects received 162 mg aspirin daily and were randomized to placebo or 75 mg clopidogrel daily. Antiplatelet therapy was initiated when postoperative chest tube drainage was <50 mL/h for 2 hours. Patients were followed clinically and underwent a research coronary angiogram at 1 year with IVUS of the SVG to measure the degree of intimal hyperplasia, which was the primary end point of this study.

**Results:** 113 patients were randomized to aspirin or dual antiplatelet therapy. Both groups were well matched in terms of number of grafts, severity of disease, and other therapies received. Ninety two patients underwent 1-year coronary angiography. The primary outcome, SVG intimal hyperplasia, was similar in both treatment groups. Overall internal mammary artery patency was 96.6% in the aspirin-clopidogrel arm and 100% in the aspirin-placebo arm. SVG patency was 94.3% in the aspirin-clopidogrel arm compared to 93.2% in the aspirin-placebo arm. Clinical events were low and not different in the 2 arms. Chest tube drainage was greater with dual antiplatelet therapy, but the need for blood products and major bleeding at 1 year were similar in the 2 groups.

**Conclusions:** This randomized, placebo-controlled study showed no benefit on SVG disease at 1 year with adding clopidogrel to aspirin therapy compared to aspirin therapy alone.

**Reviewer's Comments:** This study adds to our knowledge regarding dual antiplatelet therapy. Despite these data, including other negative trials in chronic coronary artery disease, many practitioners continue to use dual antiplatelet therapy in these patients, which only increases bleeding risk. The limitations of this study include a small sample size. Furthermore, the SVG patency at 1 year was quite high, suggesting a very low-risk population. SVGs will continue to be an important CABG conduit; we need more studies to assess how to optimize their long-term patency. (Reviewer-Steven P. Schulman, MD).

Keywords: Coronary Artery Bypass Surgery, Saphenous Vein Grafts, Dual Antiplatelet Therapy

Print Tag: Refer to original journal article
Severe Premorbid Functional Limitation Predicts Mortality in Critically Ill Pneumonia Patients

Only Severely Limited, Premorbid Functional Status Is Associated With Short- and Long-Term Mortality in Patients With Pneumonia Who Are Critically Ill: A Prospective Observational Study.

Sligl WI, Eurich DT, et al:

Chest 2011; 139 (January): 88-94

Severe limitation in premorbid functional status predicts poor short- and long-term outcomes in critically ill patients with pneumonia.

**Objectives:** To describe short- and long-term mortality in critically ill patients with pneumonia and evaluate whether premorbid functional status is an independent predictor of mortality.

**Design/Participants:** Prospective cohort study of adults with pneumonia who required ICU admission within 24 hours of presentation at 2 academic medical centers and 1 community-based hospital in Alberta, Canada.

**Methods:** Pneumonia was defined by radiographic findings and the presence of at least 2 of the following signs or symptoms: cough; pleuritic pain; dyspnea; temperature >38°C, and crackles or bronchial breath sounds. The patient or a proxy provided information about premorbid functional status, which was categorized as independent, limited mobility (ie, requiring a walking aid), or completely dependent (ie, bedridden).

**Results:** Among 351 patients admitted to the ICU with pneumonia, 80 (23%) were excluded from this analysis because functional status was not known. The final cohort included 271 patients (mean age, 61 ± 18 years; 59% male; 16% from nursing homes). Most patients required mechanical ventilation (82%), and the mean APACHE II score at presentation was 17 ±7, with a mean Pneumonia Severity Index (PSI) score 113 ± 36. In regard to premorbid functional status, 121 patients (45%) were independent, 115 (42%) had limited mobility, and 35 (13%) were completely dependent. Overall, 30-day mortality was 11%, and 1-year mortality was 27%. Stratified by functional status, mortality rates at 30 days and at 1 year were 6% and 17% for independent patients, 10% and 31% for those with limited mobility, and 39% and 48% for those who were completely dependent. After adjusting for potential confounders including age, gender, and disease severity, the hazard ratio (HR) for death at 30 days for completely dependent patients was 5.3 (95% CI, 2.0 to 14.1) compared to independent patients and 4.8 (95% CI, 1.5 to 6.1) compared to patients with limited mobility. The adjusted HR for death at 1 year for completely dependent patients was 3.0 (95% CI, 1.5 to 6.1) relative to independent patients and 2.3 (95% CI, 1.3 to 4.4) compared to patients with limited mobility. Patients with limited mobility did not have a significantly increased risk of mortality compared with independent patients.

**Conclusions:** In this study, a severe limitation in functional status was an independent risk factor for short- and long-term mortality in critically ill patients with pneumonia. However, patients with moderately limited mobility were not at increased risk of death compared to completely independent patients.

**Reviewer's Comments:** Many scoring systems used to predict outcomes in critical illness do not account for premorbid functional status, but physicians often consider functional status when providing a prognosis to patients and their families. This study supports the practice that a simple assessment of functional status may be useful in predicting mortality in critically ill patients with pneumonia. (Reviewer-Cristine E. Berry, MD).

**Keywords:** Functional Status, Pneumonia, Mortality

**Print Tag:** Refer to original journal article
Empiric antimicrobial therapy for nosocomial pneumonia is appropriate in the same proportion of patients with ventilator-associated pneumonia compared to nonventilated ICU patients.

**Objectives:** To compare hospital-acquired pneumonia (HAP) etiology and outcomes in mechanically ventilated (MV) and nonventilated ICU patients.

**Design/Participants:** This prospective study included adults with HAP in 6 medical and surgical ICUs in a university hospital in Spain.

**Methods:** HAP was defined by a simplified Clinical Pulmonary Infectious Score (CPIS) of at least 6 points or by a new radiologic infiltrate with at least 2 other criteria: temperature >38°C or <36°C, WBC count >12,000 mm3 or <4,000 mm3, or purulent respiratory secretions. Ventilator-associated pneumonia (VAP) was diagnosed in MV patients ventilated for at least 48 hours. Microbiological evaluation included culture of at least 1 lower respiratory sample (sputum, tracheobronchial aspirate, protected specimen brush, or bronchoalveolar lavage). Blood and pleural fluid samples were also cultured as indicated. Etiology confirmation of pneumonia was defined by growth of at least 1 potentially pathogenic microorganism with predefined colony count thresholds. Empiric antimicrobial therapy was determined by American Thoracic Society/Infectious Disease Society of America (ATS/IDSA) guidelines and hospital data.

**Results:** Over 3 years, 315 ICU patients were identified with HAP, including 164 patients with VAP and 151 nonventilated patients with HAP (NV-ICUAP). Patients with VAP had higher APACHE-II scores and shorter hospital stays prior to ICU admission, while patients with NV-ICUAP had more comorbid conditions, including solid cancer. Among those with NV-ICUAP, 79 (52%) eventually required MV. Patients with VAP had more samples processed for microbiological testing. Overall, an etiologic diagnosis was obtained in 181 patients. A greater proportion of patients with VAP received an etiologic diagnosis compared to those with NV-ICUAP (71% vs 42%; P <0.001). Among those with an etiologic diagnosis, the distribution of etiologic pathogens was similar between patients with VAP and NV-ICUAP, except for *Streptococcus pneumoniae*, which was more common in patients with NV-ICUAP (2% vs 9%; P =0.045). Nonfermenting Gram-negative rods (GNR) were the most prevalent etiologic diagnosis in each group (39% in VAP vs 36% in NV-ICUAP; P =0.78), followed by enteric GNR (36% vs 30%; P =0.50) and *Staphylococcus aureus* (methicillin-resistant S. aureus, 12% vs 19%; P =0.32; methicillin-sensitive S. aureus, 20% vs 14%; P =0.46). Among those with an etiologic diagnosis, empiric antimicrobial therapy was appropriate in 72% of patients (n=137), with similar proportions between VAP and NV-ICUAP groups. Length of ICU stay was longer in the VAP group, but there was no significant difference in hospital length of stay or in-hospital mortality between groups.

**Conclusions:** Among ICU patients who received an etiologic diagnosis, the pathogens were similar in patients with VAP compared to nonventilated patients with HAP.

**Reviewer’s Comments:** Patients with severe immunosuppression were excluded from this study, so the results may not apply to this population. Also, this study was conducted in a single hospital in Spain, and given regional and institutional variability in pathogens responsible for hospital-acquired infections, these results may not be generalizable. (Reviewer-Cristine E. Berry, MD).

**Keywords:** Hospital-Acquired Pneumonia, Mechanical Ventilation, Nonventilation

**Print Tag:** Refer to original journal article
Simulator-Based Training Superior to Video-Based Training for Central Line Placement

Performance of Medical Residents in Sterile Techniques During Central Vein Catheterization: Randomized Trial of Efficacy of Simulation-Based Training.
Khouli H, Jahnes K, et al:

Chest 2011; 139 (January): 80-87

Simulator-based training programs in sterile techniques for central vein catheter insertion reduce the rate of catheter-related bloodstream infections compared to traditional apprenticeship models.

Background: Catheter-related bloodstream infection (CRBSI) is a preventable cause of a potentially lethal ICU infection. The optimal method to teach health care providers correct sterile techniques for central line placement is unclear.

Design: Randomized trial.

Methods: This was a 2-phase trial. In phase 1, second and third year internal medicine residents, who had already completed 5 central line procedures, were randomly assigned to either a simulation-based training plus video training or to video training alone over a 1-year period (24 residents in the simulation plus video training and 23 to video alone). The primary outcome measures were median residents' scores in sterile techniques. In the second phase, internal medicine residents rotating through the MICU were trained in sterile technique by simulation-based training plus video training and compared to SICU residents trained in a traditional apprenticeship model. In this second phase, the rates of CRBSI per 1000 catheter-days were examined.

Results: In phase 1, the median baseline score for all groups was 12.5 to 13 out of a maximum score of 24. After training, the simulation group had a median score of 22 versus a median score of 18 in the video alone group (P <0.001). During the follow-up period, there was a significantly lower rates of CRBSI in the MICU (1 per 1000 catheter-days) compared to the SICU (3.4 per 1000 catheter-days) (P =0.03). By Poisson regression, there was a 70% reduction in the incidence of CRBSI in the postintervention MICU compared with the preintervention MICU and the postintervention SICU (0.30; 95% CI, 0.10 to 0.91).

Conclusions: Simulation-based training in sterile techniques during central vein catheterization is superior to traditional training or video training alone and is associated with a decreased rate of CRBSI.

Reviewer's Comments: This study provided an element of randomization that was lacking in prior studies of simulator-based training. The authors also utilized another method of instruction as a comparison group. This study strengthens the argument for simulator-based training systems, but there was still a significant improvement from baseline in the video only group suggesting standardized training in sterile technique can reduce rates of CRBSI. One major limitation of the study is that the element of training promoted a more conscientious approach to sterility, which truly accounted for the difference in rates of CRBSI in the MICU versus the SICU. However, this still speaks to the benefit of a formalized training protocol in sterile technique, and simulator-based training appears to be superior to a video-based training protocol. (Reviewer-Mark J. Hamblin, MD).

Keywords: Central Vein Catheterization; Sterile Techniques, Simulation Based Training

Print Tag: Refer to original journal article
Normal albumin and transferrin levels have a high negative predictive value for patients with acute respiratory distress syndrome.

Background: Acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) are characterized by inflammation of the alveolar-capillary barrier with vascular hyperpermeability and protein-rich pulmonary edema, potentially lowering plasma proteins. Methods to assess permeability edema of the lungs (such as 67Gallium transferrin pulmonary leak index) are obtainable but laborious. It is hypothesized that low plasma protein levels relate to increased pulmonary edema and provide a simple biomarker to predict ARDS.

Objective: To assess the predictive values of plasma albumin, transferrin, and total protein levels together with fluid balance for pulmonary vascular permeability and lung injury.

Design: Prospective, observational study.

Participants/Methods: 83 mechanically ventilated patients (18 septic and 65 nonseptic) with or at risk for ALI/ARDS. Patients with an elevated central venous pressure or wedge pressure were excluded.

Results: Plasma albumin and transferrin levels were 30% lower in ARDS than ALI ($P < 0.01$) patients and in patients without lung injury ($P < 0.05$). Protein levels were inversely related to the pulmonary leak index and the lung injury score, independent of sepsis, severity of disease, and fluid loading. Albumin and transferrin had a sensitivity range of 77% to 93% and a negative predictive value of 80% to 98% for elevated pulmonary vascular permeability and ARDS.

Conclusions: In critically ill patients, decreased plasma albumin and transferrin levels parallel increased pulmonary vascular permeability regardless of the underlying disease and fluid status. Normal levels help exclude ARDS.

Reviewer’s Comments: In this study, ARDS, low albumin, and transferrin levels were most derived from the 18 patients with sepsis. Given the small patient sample size and that most of the data supporting the hypothesis are derived from a small subgroup of patients with sepsis, the results and clinical utility are open to speculation. Additionally, protein permeability does not necessarily imply pulmonary edema. It would be interesting to see if the negative predictive value remains when cardiogenic failure or hypervolemia is superimposed on ALI. This would seem to be the necessary standard to consider albumin and transferrin as clinically useful biomarkers in the assessment of ARDS. Still, this study suggests that, in septic patients, albumin and transferrin may prove to be useful biomarkers to predict the development of ARDS, but more investigation is necessary before this practice is implemented. (Reviewer—Mark J. Hamblin, MD).

Keywords: Plasma Protein Markers, ARDS, Acute Lung Injury

Print Tag: Refer to original journal article
Extracorporeal cardiopulmonary resuscitation may improve survival for patients with prolonged in hospital cardiac arrest.

**Objective:** To determine if survival from in hospital cardiac arrest can be improved by the use of extracorporeal cardiopulmonary resuscitation (E-CPR) and extracorporeal membrane oxygenation (ECMO).

**Design/Methods:** This retrospective, single-center observational study examined the outcomes of patients who had received >10 minutes of CPR after a witnessed in hospital cardiac arrest between 2003 and 2009. Patients who received conventional CPR (C-CPR) were compared to patients who received E-CPR. E-CPR was defined as support with ECMO during CPR until return of spontaneous circulation, as determined by echocardiography. Contraindications to E-CPR included age >80 years, severe neurologic impairment, sepsis, uncontrolled bleeding, and irreversible organ failure. The primary outcome measure was survival to discharge, with minimal neurologic impairment as defined by a score of ≤2 on the Glasgow-Pittsburgh cerebral performance scale. Results were analyzed using propensity scores to adjust for selection bias and potential confounders.

**Results:** 1108 patients underwent CPR during the study. Of the 406 patients enrolled, 85 received E-CPR and 321 received C-CPR. ECMO was successfully initiated in 80 of 85 patients who were selected to undergo E-CPR. After matching using propensity scores, patients who underwent E-CPR had a significantly higher rate of survival with minimal neurologic impairment at hospital discharge and 6 months. Patients whose arrest was determined to be cardiac in origin had a higher rate of survival with minimal neurologic impairment after E-CPR as well. In patients with arrests lasting >30 minutes, E-CPR led to a survival rate of 19.2% versus 1.3% with C-CPR.

**Conclusions:** ECMO improves survival after extended in hospital cardiac arrest.

**Reviewer's Comments:** This observational study provides a number of important insights into the use of ECMO in patients with witnessed in hospital arrests. Perhaps most important, this study shows that it is feasible to place patients with prolonged arrest times on ECMO, as >94% of patients assigned to the E-CPR group ultimately received the intervention. Patients in the E-CPR group were more likely to survive to discharge with minimal neurologic impairment, suggesting that, in the right population, E-CPR may be an appropriate and valuable intervention in the case of witnessed in hospital arrests. However, a number of factors limit the applicability of these results to general practice. First, the study was conducted at a center with extensive experience in both ECMO as well as E-CPR. Second, the decision to initiate E-CPR was attending-dependent and, despite the use of propensity scores, may have resulted in unknown confounders and bias. E-CPR holds promise as a treatment for in hospital arrest, but its indications and applications need to be better defined. (Reviewer-Brian T. Garibaldi, MD.)

**Keywords:** Cardiac Arrest, Extracorporeal Cardiopulmonary Resuscitation, Conventional CPR

**Print Tag:** Refer to original journal article
The duration of delirium is an independent predictor of poor outcome in mechanically ventilated patients.

**Objective:** To determine the relationship between duration of delirium and mortality, ICU length of stay, and time on mechanical ventilation.

**Design/Methods:** This was a prospective cohort analysis of patients enrolled in the Safety and Efficacy of Dexmedetomidine Compared with Midazolam trial. Ventilated patients in 68 medical centers across 5 countries were randomized to continuous infusion of midazolam or dexmedetomidine to maintain a Richmond Agitation-Sedation Scale (RASS) score of $-2$ to $+1$. Of those initially enrolled in the trial, patients who received at least 1 initial delirium assessment were eligible for further study. Exclusion criteria included burns, dialysis, liver disease, general anesthesia, cardiovascular instability, or central nervous system disease. The presence of delirium was assessed daily using the Confusion Assessment Method for the ICU. The duration of delirium was defined as the cumulative number of days that patients were found to have delirium during study drug treatment and for 48 hours after study drug discontinuation. The primary outcomes were 30-day mortality, time to first successful extubation, and time to ICU discharge. The effect of delirium duration on the primary outcomes was assessed using Cox proportional hazards regression analysis.

**Results:** 354 patients were included in the final analysis, and the majority of patients were in medical ICUs. Sixty percent of patients had evidence of delirium at enrollment; the prevalence of delirium over the course of the study was 64%. Patients with at least 1 episode of delirium had a higher mortality, longer length of stay, and longer times on mechanical ventilation than patients without delirium. There was a dose-response between the duration of delirium and these primary outcomes. The effect of delirium duration on mortality was nonlinear, with the greatest effect observed in the early days of delirium.

**Conclusions:** The duration of delirium increases the duration of ventilation, length of stay, and mortality.

**Reviewer’s Comments:** It has been recognized for some time that delirium is an independent predictor of poor outcomes in hospitalized patients. This realization has been part of the motivation for attempting to minimize sedation in the ICU. It is interesting that the prevalence of delirium remained relatively high despite the lighter RASS targets used in the trial. It is important to note that the choice of study drug did not appear to affect the primary outcomes (ie, regardless of the cause of delirium, its effects on mortality were the same). It is also interesting that the effects of delirium on mortality were most apparent in the early days of delirium. These results suggest that minimizing sedation alone will not eliminate ICU delirium and confirm that delirium is an independent predictor of poor outcome in the ICU. They also suggest that identifying delirium and attempting to treat it early may be the most effective way to mitigate its negative effects. (Reviewer-Brian T. Garibaldi, MD).

**Keywords:** Delirium, ICU Sedation, Outcome

**Print Tag:** Refer to original journal article
In critically ill adult patients, the IV administration of colistin methanesulfonate at commonly used doses results in suboptimal plasma concentrations of colistin. Also, colistin is undetectable in bronchoalveolar lavage.

**Background:** Options for the treatment multidrug-resistant gram-negative bacterial infections are limited. These infections have become common and have sparked a renewed interest in colistin. The pharmacokinetics of colistin have not been well described in critically ill patients, and lung penetration as evaluated by concentration in bronchoalveolar lavage (BAL) has not been previously studied.

**Objective:** To evaluate the pharmacokinetics and BAL concentrations after IV administration of colistin in critically ill patients.

**Design:** Prospective, open-label study.

**Participants:** 13 adult patients with ventilator-associated pneumonia caused by gram-negative bacteria.

**Methods:** Subjects were treated for at least 2 days with colistin methanesulfonate (CMS) IV, 2 million International Units (174 mg) every 8 hours. Blood samples were collected at time intervals after the end of infusion. BAL was performed 2 hours after infusion. The liquid chromatography-based method used for colistin levels was highly sensitive and selective, allowing differentiation between CMS and active colistin.

**Results:** Patients received between 1.58 and 3.16 mg/kg of CMS per dose, which was well tolerated without associated nephrotoxicity observed. Colistin maximum (Cmax) and trough (Ctrough) concentrations were 2.21 ± 1.08 and 1.03 ± 0.69 µg/mL, respectively. Elimination half-life was 11.5 ± 6.2 µg x h/mL. Cmax/minimum inhibitory concentration (MIC) ratio was 1.1 ± 0.5. Colistin was undetectable in BAL.

**Conclusions:** In critically ill adult patients, the IV administration of CMS at commonly utilized doses results in suboptimal plasma concentrations of colistin. Also, colistin is undetectable in BAL. The authors suggest that further studies are needed to better characterize the relationship between pharmacokinetics-pharmacodynamics and treatment efficacy in order to help determine optimal dosing regimens.

**Reviewer’s Comments:** This study is limited in that patient-oriented outcomes such as infection response and mortality were not assessed, but this probably should not dissuade practicing clinicians from using IV colistin in the treatment of highly resistant infections. While it is possible that the plasma concentrations are suboptimal, the authors mention that concentration efficacies have been based on other assays, which are unable to differentiate CMS from the active antimicrobial, colistin, and have also been performed largely in vitro. The lack of colistin in BAL samples does not clearly prove lack of efficacy in the treatment of pulmonary infections. Colistin binds to tissues, which may prevent entrance into alveolar space. However, IV CMS has clearly been successful in the treatment of multidrug-resistant gram-negative infections. It is somewhat reassuring that the conversion from CMS to colistin clearly occurred in a control patient given inhaled CMS. This observation coupled with the lack of colistin in BAL could be taken as reason for simultaneous administration of IV and inhaled CMS. (Reviewer-Robert Reed, MD).

**Keywords:** Colistin, Critical Illness

**Print Tag:** Refer to original journal article
Intensivist DVT Ultrasound Assessment Is Fast and Accurate

Accuracy of Ultrasonography Performed by Critical Care Physicians for the Diagnosis of Deep Venous Thrombosis.
Kory PD, Pellechcia CM, et al:
Chest 2010; October 28 (): epub ahead of print

Intensivist-performed compression ultrasonography yields accurate assessments for deep venous thrombosis and prevents a median delay to diagnosis of approximately 14 hours, according to this study.

Background: Deep venous thrombosis (DVT) is a significant complication that is common in critically ill patients. A rapid and accurate diagnosis is essential for optimal patient care.

Objective: To assess intensivist-performed compression ultrasound studies (IP-CUS) for proximal lower-extremity DVT (PLEDVT) in terms of accuracy and time to diagnosis compared to a formal vascular study (FVS), performed by ultrasonography technicians and interpreted by radiologists.

Design: Multi-center, retrospective review.

Participants: Patients in intensive care units suspected of having DVT.

Methods: IP-CUS exams were performed in an intensive care unit by pulmonary and critical care fellows and attending physicians who had 4 hours of training in the technique. Patients suspected of having DVT underwent IP-CUS, using a standard 2-dimensional compression ultrasound protocol for the diagnosis of PLEDVT, after which a formal vascular study was ordered. The IP-CUS results were recorded and timed at the end of the exam on a standardized report form. Time delays between the IP-CUS and FVS were subsequently recorded.

Results: 128 IP-CUS exams were performed compared with FVS. IP-CUS took an average of 12.5 minutes to complete. DVT prevalence in the sample was 20%. The sensitivity and specificity of IP-CUS was 86% and 96%, respectively. Ninety-five percent of results obtained by each method were in agreement. The median time delay between the ordering of FVS and the FVS result was 13.8 hours.

Conclusions: Rapid and accurate diagnosis of proximal lower-extremity DVT can be achieved by intensivists performing compression ultrasound at the bedside.

Reviewer's Comments: This study provides evidence that intensivists with brief training can rapidly perform and interpret compression ultrasound evaluations for proximal DVTs. While the results may be favorably biased by lack of blinding by the radiologists reading the formal vascular studies, the results are still compelling. Practicing clinicians contemplating the possibility of venous thromboembolism are often faced with the decision to subject their patients to the risks of travel outside the unit for a CT scan with exposure to IV contrast, the risk of potentially unnecessary anticoagulation, and the risk of delay in initiating necessary anticoagulation. While the median delay for the FVS was 13.8 hours, one institution’s delay was 29.3 hours. The importance of prompt diagnosis is highlighted by a recent study (Chest 2010; 137 [6]: 1382-1390) showing considerably higher 30-day mortality (5.6% vs 14.8%; \( P =0.037 \)) associated with a 24-hour delay in achieving therapeutic aPTT levels after diagnosis of PE. (Reviewer-Robert Reed, MD).

Keywords: Venous Thromboembolism, Ultrasonography

Print Tag: Refer to original journal article
Holding PTP Increases Risk of VTE in TBI Patients

Interrupted Pharmacologic Thromboprophylaxis Increases Venous Thromboembolism in Traumatic Brain Injury.

Salottolo K, Offner P, et al:

J Trauma 2011; 70 (January): 19-26

The interruption of pharmacologic thromboprophylaxis and walking before discharge are independently associated with the development of venous thromboembolism in patients with traumatic brain injury.

Background: In critically ill patients, pharmacologic and mechanical methods to prevent venous thromboembolism (VTE) significantly reduce morbidity and mortality. Patients with traumatic brain injury (TBI) are at particularly high risk for the development of VTE; however, concern for extension of intracranial bleeding as well as frequent invasive procedures often limit pharmacologic thromboprophylaxis (PTP).

Objective: To determine if the timing of initiation or interruption of PTP increases the risk of VTE in patients with TBI.

Design: Retrospective, observational study.

Participants: Consecutive blunt TBI patients with stable head CTs admitted to 2 Level I trauma centers in Denver, Colorado, over a 2-year period were included. Exclusions were patients with <3 day length of stay, progression of hemorrhage on CT within 24 hours, or VTE development within 24 hours of admission.

Methods: The primary outcome was the development of VTE during hospitalization. Secondary outcomes were hospital mortality and hemorrhage progression on follow-up CT. Demographic data, injury severity score (ISS), Glasgow coma scale (GCS) score, comorbid injuries, and walking before discharge were recorded. Dichotomized variables included the use of PTP (yes/no), time to PTP initiation (early, <72 hours; late, ≥72 hours), and interruption of PTP (yes/no). Logistic regression analysis was performed to compare these groups.

Results: 480 patients were included (mean age, 53 years); Of these subjects, 61% were male. The mean GCS was 12.2, and 30.6% of subjects had concomitant severe extracranial injury; 53.1% received PTP (42.4% early vs 57.6% late) compared to 46.9% who did not (92% received mechanical VTE prophylaxis). Those not receiving PTP were younger, were more often on pre-injury anticoagulation, had higher GCS scores, and had more significant extracranial injuries. Continuous PTP was administered in 73.1% of subjects compared to interrupted PTP in 26.9%. By logistic regression analysis, there were no significant risk factors for the development of VTE based on receiving PTP or based on the timing of initiation of PTP in this cohort. The interruption of PTP significantly increased the risk of VTE (OR, 7.07; 95% CI, 1.08 to 46.36; P =0.04). Walking before discharge significantly reduced the risk of VTE (OR, 0.19; P =0.02), although mortality was not different based on the presence or absence of VTE in this cohort.

Conclusions: Interruption of PTP and walking before discharge were independently associated with the development of VTE in patients with TBI.

Reviewer’s Comments: Although this study does not aid in defining risks for the development of VTE in patients with TBI in relation to the timing of initiation of pharmacologic prophylaxis, the significant risk of VTE in patients who had interruptions of PTP identified by the investigators is intriguing. The presence of confounders cannot be excluded; patients having PTP interrupted may have had a complication leading to that decision, and patients walking before discharge are likely less ill and certainly less bed-bound. (Reviewer-Jeffrey B. Hoag, MD, MS).

Keywords: Thromboprophylaxis, Traumatic Brain Injury

Print Tag: Refer to original journal article
Lung Protective Ventilation Improves Lung Donor Eligibility

Effect of a Lung Protective Strategy for Organ Donors on Eligibility and Availability of Lungs for Transplantation: A Randomized Controlled Trial.

Mascia L, Pasero D, et al:

JAMA 2010; 304 (December 15): 2620-2627

Lung protective ventilation compared to conventional ventilation results in twice as many lungs harvested for transplantation.

**Background:** Intensivists must frequently deal with issues of organ donation. Organ supply remains a major limitation in lung transplantation. Strategies to improve recovery of organs from potential donors without sacrificing the quality of the harvested organs present an opportunity to address this issue. Deterioration in the measures used to assess suitability for harvest is often observed in potential donors. Whether a lung-protective ventilator strategy can attenuate this deterioration has not previously been prospectively evaluated.

**Objective:** To assess the effects of a low-tidal volume, high positive end-expiratory pressure (PEEP) lung ventilation strategy on organ harvest in potential lung donors.

**Design:** Multicenter, randomized, controlled trial.

**Methods:** 118 potential lung donors from 12 intensive care units in Italy and Spain were evaluated. Potential donors were randomized between 2 ventilatory strategies. The conventional ventilatory strategy consisted of tidal volumes of 10 to 12 mL/kg of predicted body weight and a PEEP of 3 to 5 cm H₂O, which is consistent with current expert panel recommendations and consensus guidelines for the management of potential lung donors. The protective ventilatory strategy consisted of tidal volumes of 6 to 8 mL/kg of predicted body weight with a PEEP of 8 to 10 cm H₂O. Primary outcomes evaluated included the number of organ donors meeting eligibility criteria for harvesting, the number of lungs harvested, and the 6-month survival of lung transplant recipients.

**Results:** Lung donor eligibility criteria were met in 54% of the conventional strategy group versus 95% of the protective strategy group, with a 95% confidence interval (CI) for the difference of 26.5% to 54.8% (P <0.001). Lungs were successfully harvested in 27% of the conventional strategy group versus 54% of the protective strategy group, with a 95% CI for the difference of 10.0% to 44.5% (P =0.004). Post-transplant survival rates at 6 months did not differ by ventilatory strategy used.

**Conclusions:** The lung protective strategy resulted in an increase in the number of eligible and harvested lungs in potential organ donors.

**Reviewer’s Comments:** This well-designed trial provides compelling evidence that should affect practice. The system by which lungs are allocated to recipients was changed in 2005, in part, to prioritize patients at greatest risk for death while on the waiting list. Despite the improvements, waiting list mortality remains a significant problem. Between 2005 and 2010, 1590 patients died while waiting for a lung transplant. The magnitude of improvement in organ availability attributable to lung-protective ventilator strategy observed in this study is remarkable and offers great hope for those waiting for lungs. Intensivists should be aware of the results of this study and should manage potential organ donors accordingly. (Reviewer-Robert Reed, MD).

Keywords: Organ Donors, Lung Transplantation, Vent Management

Print Tag: Refer to original journal article