Polymyxin B Hemoperfusion for Septic Shock -- Ready for Primetime?

Early Use of Polymyxin B Hemoperfusion in Abdominal Septic Shock: The EUPHAS Randomized Controlled Trial.

Cruz DN, Antonelli M, et al:

JAMA 2009; 301 (June 17): 2445-2452

In this preliminary trial, adding polymyxin B hemoperfusion filter to conventional therapy for treating patients in septic shock improved hemodynamics and lowered 28-day mortality within 6 hours of abdominal surgery.

Background: Treatments for severe sepsis are limited, and its morbidity and mortality, especially from Gram-negative organisms, continues to be significant. Gram-negative organisms release endotoxin, which initiates inflammatory and coagulation cascades, resulting in end-organ dysfunction in patients. Polymyxin B hemoperfusion filters bind endotoxin.

Objective: To assess the efficacy of polymyxin B hemoperfusion on improving hemodynamics and 28-day mortality in patients with severe sepsis from an abdominal source.

Design: Prospective, randomized, controlled open-label trial conducted in 10 Italian ICUs over 3 years.

Participants: 64 patients with severe sepsis who were within 6 hours of emergency surgery for intra-abdominal infection.

Methods: Primary end points were change in mean arterial pressure (MAP) and vasopressor requirement. Sequential Organ Failure Assessment (SOFA) scores and 28-day mortality were secondary outcomes. The trial was stopped early for efficacy after the first interim analysis. Patients were randomized to receive either conventional medical therapy with (n=34) or without (n=30) 2 polymyxin B hemoperfusion sessions.

Results: Patients treated with polymyxin B hemoperfusion had a significant increase in MAP (76 to 84 mm Hg; \(P = 0.001\)) and reduction in vasopressor requirement (\(P < 0.001\)) at 72 hours, while those treated with only conventional medical therapy saw no change in these parameters (MAP, 74 to 77 mm Hg; \(P = 0.37\)). SOFA scores also improved significantly in the polymyxin B group but not in the conventional medical therapy group. Mortality at 28 days was 53% (16 of 30 patients) in the conventional therapy group compared to 32% (11 of 34 patients) in the polymyxin B group (adjusted hazard ratio, 0.36).

Conclusions: In highly selected, immediately postoperative patients with intra-abdominal infections, polymyxin B hemoperfusion improved MAP, lowered vasopressor requirements, improved SOFA scores, and reduced 28-day mortality.

Reviewer's Comments: At first glance, this is an exciting treatment for patients with severe sepsis. However, closer examination dampens the enthusiasm. This is a small study that enrolled 64 patients immediately postoperative for intra-abdominal infections from 10 ICUs over the course of 3 years (an average of 2 patients per ICU per year). As such, the population is highly selected, limiting the ability to generalize the results to other patients with severe sepsis. Although mortality was statistically improved, early stoppage of the trial after only 64 patients likely exaggerates any mortality difference. Furthermore, physiologic outcomes of MAP, vasopressor requirements, and SOFA scores are compared within groups (instead of change compared across groups), while the 28-day mortality is compared between groups. The overall 28-day mortality in the group treated with standard medical therapy (53%) is on the high range for systematic reports of all patients with abdominal sepsis. Finally, these hemoperfusion filters are currently available only for clinical use in a few countries, further limiting the ability to apply this treatment to patients with severe sepsis. (Reviewer-Todd W. Rice, MD, MSc).

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Keywords: Treatment

Print Tag: Refer to original journal article
Improving Outcomes of Patients With In-Hospital Cardiac Arrest

Vasopressin, Epinephrine, and Corticosteroids for In-Hospital Cardiac Arrest.

Mentzelopoulos SD, Zakynthinos SG, et al:


Adding vasopressin to epinephrine treatment of in-hospital cardiac arrest patients and adding stress-dose steroids to post-resuscitation shock dramatically improves survival to hospital discharge.

Background: Previous studies have found lower plasma vasopressin levels in non-survivors of cardiac arrests and low cortisol levels during and after cardiopulmonary resuscitation (CPR).

Objective: To determine if vasopressin added to epinephrine during CPR, and corticosteroids during and after CPR, increases return of spontaneous circulation (ROSC) and survival.


Participants: 100 consecutive hospitalized patients with either ventricular fibrillation/tachycardia, asystole, or pulseless electrical activity (PEA). Patients resuscitated by defibrillation alone or receiving steroids were excluded.

Methods: The study group (n=48) received 20 IU vasopressin plus 1 mg epinephrine per resuscitation cycle for up to the first 5 cycles, plus 40 mg methylprednisolone followed by post-resuscitation hydrocortisone (300 mg daily) for new or worsened shock 4 hours after ROSC. The control group (n=52) received 1 mg epinephrine per resuscitation cycle plus placebos. Primary end points were ROSC for >15 minutes and survival to hospital discharge or up to 60 days.

Results: Groups were similar in baseline characteristics. The length of pre-randomization hospital stay was 3.5 days with admitting diagnoses of cardiovascular (45%), respiratory (15%), and trauma (15%) diseases. About half the patients arrested on the ward, and one third in the ICU. The initial rhythm was asystole in 60% and PEA in 25%, with time to advanced cardiac life support (ACLS) initiation being about 1 minute in both groups. The study group had a significantly higher percentage of patients achieve ROSC for at least 15 minutes (81% vs 52%; P =0.003) and, more importantly, a much higher percentage of patients who survived to hospital discharge (19% vs 4%; P =0.02). About 80% of patients who survived 4 hours after ROSC experienced post-resuscitation shock. However, none of the control patients with post-resuscitation shock survived to hospital discharge compared to 30% (8 of 27) of study patients.

Conclusions: The combination of vasopressin added to epinephrine and methylprednisolone during CPR, along with steroids for post-resuscitation shock, resulted in higher rates of ROSC and improved survival to hospital discharge for patients with in-hospital cardiac arrest.

Reviewer's Comments: This study, unlike many evaluating interventions for CPR that report only ROSC, also looked at the effect on survival to hospital discharge. A relatively simple change in ACLS, namely the addition of 20 IU of vasopressin to epinephrine for the first 5 cycles of CPR combined with treatment of post-resuscitation shock with stress-dose hydrocortisone, dramatically improved survival to hospital discharge. In fact, survival was 5-fold better in the study group (19% vs 4%). Although this was only a single-center study, the relative ease of implementation of this regimen has resulted in me using it in my patients, but I have limited it to patients with either asystole or PEA since these patients represented the majority of the study population. (Reviewer-Todd W. Rice, MD, MSc).

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Keywords: Cardiopulmonary Resuscitation, In-Hospital Cardiac Arrest, Vasopressin

Print Tag: Refer to original journal article
Should Physicians Offer Recommendations About Limiting Life Support?

Are Physicians’ Recommendations to Limit Life Support Beneficial or Burdensome? Bringing Empirical Data to the Debate.

White DB, Evans LR, et al:

Am J Respir Crit Care Med 2009; 180 (August 15): 320-325

This study confirms that surrogate decision-makers have heterogeneous preferences and rationale for the desire of physician input about withholding end-of-life care.

Background: Surrogate decision-making regarding limitations of care in the ICU is frequent, complicated, and lacks evidence-based guidelines. A controversial aspect of surrogate decision-making is whether physicians should provide recommendations during discussions regarding limitation of life support. Little is known about surrogates’ attitudes toward receiving physicians’ recommendations.

Objective: To understand the attitudes of surrogate decision-makers toward receiving a physician’s recommendation during deliberation about whether to limit life support.

Design: Prospective, mixed methods single-center study.

Participants: Eligible subjects were surrogates of any critically ill patient who was hospitalized in 1 of 4 ICUs at a single center.

Methods: Surrogates sequentially viewed 2 videos of simulated discussions between a surrogate and physician about limitations of life support. The 2 videos differed only by the presence or absence of a recommendation by the physician. The main outcomes were whether the surrogate preferred to receive the physician’s recommendation and the reasons for that preference.

Results: 169 surrogate decision-makers were included in this study. Of incapacitated patients, 50% were male, 69% were white, and 39% were admitted for neurological failure. Overall, 56% of surrogates preferred to receive a recommendation from the physician regarding limitation of care, while 42% preferred to not receive a recommendation. The remaining 2% felt both approaches were acceptable. Four main themes explained these preferences: (1) surrogates’ beliefs on the appropriate role of the physician, (2) perception of consequences of a recommendation on the physician-surrogate relationship, (3) surrogates’ beliefs about the decision-making process, and (4) surrogates’ beliefs about long-term regret for the family.

Conclusions: Surrogate decision-makers demonstrate varied beliefs about whether physicians should routinely provide recommendations regarding end-of-life decisions. Physicians should ask surrogates whether they wish to receive a recommendation regarding life-support decisions, and they should be prepared to have different approaches for different surrogate interactions.

Reviewer’s Comments: End-of-life decisions in the ICU are complex, unique experiences for both the surrogate decision-maker and the physician. This study quantitatively and qualitatively measures preferences of a group of surrogate decision-makers. The results of this study confirm that heterogeneous preferences and rationale for decision-making exist. These findings highlight the need of critical care physicians to determine preferences of surrogate decision-makers and to recognize that one approach will not fit all situations. (Reviewer-M. Bradley Drummond, MD).

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Keywords: Surrogate Decision-Making, Physician Recommendations, Empirical Ethics

Print Tag: Refer to original journal article
Early mobilization in critically ill patients holds promise as a measure to prevent critical illness polyneuropathy.

**Background:** Critical illness polyneuropathy (CIPN) is the most common peripheral neuromuscular disorder in the ICU. Characterized by symmetric proximal muscle weakness, CIPN is associated with prolonged mechanical ventilation and need for rehabilitation. Early activity in immobilized patients may curb or minimize development of CIPN.

**Objective:** To determine whether a daily exercise session with bedside cycle ergometer prevents or attenuates the decrease in functional exercise capacity, functional status, and quadriceps force in ICU patients with prolonged lengths of stay.

**Design:** Single-center, randomized controlled trial.

**Participants:** 90 patients admitted to surgical and medical ICUs for at least 5 days who had an expected stay of at least 7 more days were eligible for inclusion. Patients were included as soon as their cardiopulmonary condition allowed bedside cycling exercise.

**Methods:** Both groups underwent standard respiratory physiotherapy and daily passive or active motion sessions in upper and lower limbs. The treatment group also performed 20 minutes of passive or active bedside cycling per day. The primary outcome was 6-minute walk distance (6MWD) at hospital discharge. Secondary outcomes included quadriceps force and functional status. Data on weaning time, length of stay, and 1-year mortality were also collected.

**Results:** Of 90 patients randomized, 32 control patients and 26 treatment patients had full data collection. The majority of patients (n=71) were recruited from surgical ICUs. Both groups were well matched for baseline characteristics and ICU therapies, although the treatment group had a longer period of IV sedation (11 vs 8 days; *P* <0.05). 6MWD was higher in the treatment group than in the control group (196 vs 143 minutes; *P* <0.05). Short Form 36 Health Survey questionnaire results and quadriceps force were also higher at hospital discharge in the treatment group. Weaning time, ICU and hospital lengths of stay, and 1-year mortality did not differ between groups.

**Conclusions:** Early exercise training with bedside cycle ergometer in critically ill ICU patients with a prolonged length of stay improved functional exercise capacity, self-perceived functional status, and quadriceps strength at hospital discharge.

**Reviewer's Comments:** This study demonstrates that early activity in ICU patients may minimize development of CIPN, and it represents the first randomized trial to address this hypothesis in an ICU population. Although limited by the lack of objective measures of exercise intensity, standardized post-ICU rehabilitation, and formal electrophysiologic diagnosis of CIPN, the authors have provided the framework for larger studies to investigate preventive measures for minimizing development of CIPN. (Reviewer-M. Bradley Drummond, MD).

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**Keywords:** Exercise Therapy, Physiotherapy, Critical Illness, Muscle Weakness, Functional Recovery

**Print Tag:** Refer to original journal article
When treatment of methicillin-resistant Staphylococcus aureus bacteremia has failed with use of vancomycin, linezolid is a viable alternative.

**Background:** Vancomycin remains the preferred first-line treatment for methicillin-resistant Staphylococcus aureus (MRSA) bacteremia. Unfortunately, treatment failure is a major clinical problem, and optimal alternative therapy has not yet been defined. There is no consensus on management of vancomycin treatment failure. Carbapenems have been shown to enhance killing of MRSA by linezolid in vitro.

**Objective:** To estimate the efficacy of linezolid with or without carbapenem in salvage treatment of MRSA bacteremia.

**Design:** Retrospective case review over 2 years at Seoul National University Hospital.

**Participants:** Patients with persistent MRSA bacteremia for at least 7 consecutive days while on appropriate therapy for at least 5 days.

**Methods:** Treatments were divided into 2 major categories: vancomycin-continue and linezolid salvage (ie, at least 72 hours of linezolid therapy). Salvage was successful if the agent was not subsequently changed due to ineffectiveness and if S aureus-related death did not occur.

**Results:** There were 211 cases of MRSA bacteremia, with 35 (17%) meeting the definition of persistence. In 3 cases, the minimum inhibitory concentration (MIC) of vancomycin was 2 μg/mL. All other cases had MICs of ≤1 μg/mL. Nineteen patients were continued on vancomycin-based regimens, and 16 were switched to linezolid-based regimens. Patients switched to linezolid were older (mean, 70 vs 59 years). Many patients had complicated or metastatic infections. In patients who remained on vancomycin with the addition of aminoglycoside or rifampin, salvage was never successful. Salvage with linezolid-based regimens was successful in 88% of cases. Thirty-day mortality was 53% in the vancomycin-continue group and 25% in the linezolid group, with all deaths in the vancomycin group and half the deaths in the linezolid group attributed to S aureus. Of evaluable patients, 57% developed linezolid-associated thrombocytopenia.

**Conclusions:** Linezolid-based therapy was effective in eradicating S aureus from the blood within 72 hours in patients with persistent MRSA bacteremia who are failing vancomycin therapy. Thrombocytopenia from prolonged use of linezolid prompted switches back to vancomycin-based regimens but allowed for ultimately successful treatment. Usage was too low to evaluate any benefit from carbapenem use in combination with linezolid.

**Reviewer’s Comments:** Although this study suffers from inherent limitations of a retrospective observational study design, it does help inform the dialogue regarding appropriate treatment options for MRSA bacteremia that is not responsive to vancomycin. Study results should not be construed to mean that linezolid is the best first-line treatment option. Prolonged use of linezolid often causes unacceptable toxicity. Also, cases of linezolid-resistant MRSA have been reported. Linezolid does not have FDA approval for MRSA bacteremia. Vancomycin remains the preferred first-line therapy. When first-line therapy fails, however, switching to linezolid might be more effective than just sticking with vancomycin. (Reviewer-Annette M. Rowden, PharmD).
IV N-acetylcysteine may be beneficial in early stage non-acetaminophen-induced liver failure.

**Background:** N-acetylcysteine (NAC) prevents toxicity when administered shortly after acetaminophen overdose, and it appears to improve survival in acetaminophen-induced acute liver failure. Aside from transplantation, no treatment improves survival in acute liver failure not caused by acetaminophen.

**Objective:** To determine if NAC improves 3-week survival in liver failure not caused by acetaminophen. Transplant-free 3-week survival was a secondary outcome.

**Design:** Prospective, randomized double-blinded trial, stratified by coma category and site.

**Participants:** Patients were identified through the NIH-funded Acute Liver Failure Study Group at 22 sites in the United States over 8 years, ending in 2006.

**Methods:** Inclusion criteria were age ≥18 years, encephalopathy, and international normalized ratio of at least 1.5 caused by illness <24 weeks. Exclusion criteria included pregnancy, cancer, refractory hypotension, septic shock, expected liver transplant in <8 hours, and age >70 years. Patients received 5% dextrose alone (placebo) or with IV NAC, administered over 72 hours. Other care was determined by study site.

**Results:** 92 patients received placebo, and 81 received NAC. Most patients fell into 4 etiologic categories: drug-induced (n=45), autoimmune hepatitis (n=26), hepatitis B virus (n=37), and indeterminate (n=41). Time from jaundice to liver failure was longer, and female sex was more common in the placebo group. Other baseline characteristics were similar. A total of 63% of placebo patients and 59% of NAC patients completed 72 hours of therapy. Premature discontinuation was mostly from death or transplantation. Three-week survival was not different in the 2 groups (70% for NAC vs 66% for placebo), but transplant-free survival was higher in the NAC group (40% vs 27%). Benefit of NAC appeared confined to patients with coma grades I to II. Overall transplantation rates were 32% for NAC and 45% for placebo (P=0.093).

**Conclusions:** NAC improves transplant-free survival in patients with early stage non-acetaminophen acute liver failure.

**Reviewer's Comments:** Making firm conclusions from these findings is difficult. The intervention did not improve overall mortality. The improvement seen in transplant-free survival is from subgroup analysis of patients who had less severe encephalopathy at enrollment. In addition to these limitations, there are other difficulties with data interpretation. The standard of care for acute liver failure is transplantation. This appropriate intervention does not allow the natural history outcome of recovery or death to occur. But because transplantation rates are also dependent on organ availability and local decisions, care cannot be assumed to be equal across study sites. Finally, there is a potential effect of time over the 8-year study period. Despite these limitations, there probably won't be another trial of NAC for this indication. Due to its safety, low cost, and lack of alternatives, administration of IV NAC may become the standard of care in acute liver failure from any cause and perhaps with any coma grade. (Reviewer-Annette M. Rowden, PharmD).

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Keywords: Acute Liver Failure, Early Stage, IV-N-Acetylcysteine, Transplant-Free Survival

Print Tag: Refer to original journal article
Troponin Predicts ECG, Echo Abnormalities After SAH

Elevated Cardiac Troponin I and Relationship to Persistence of Electrocardiographic and Echocardiographic Abnormalities After Aneurysmal Subarachnoid Hemorrhage.

Hravnak M, Frangiskakis JM, et al:

Stroke 2009; August 27 (epub ahead of print):

Persistence of cardiac injury beyond the acute phase of aneurysmal subarachnoid hemorrhage suggests ongoing vigilance and follow-up transthoracic echocardiogram are clinically indicated.

Background: Elevations in cardiac troponin I (cTnI) after aneurysmal subarachnoid hemorrhage (SAH) are not infrequent, although their relationship to ECG or echocardiographic abnormalities and persistence over time are not well described.

Objective: To determine relationships between cTnI with early and late ECG, transthoracic echocardiogram (TTE), and Holter monitoring during the acute and subacute phases of SAH.

Participants: 204 patients with aneurysmal SAH with Fisher grade ≥2 and/or Hunt/Hess grade ≥3.

Methods: Data for analysis included cTnI collected on days 1 to 5; 12-lead ECG at ≤4 days and ≥7 days; Holter monitoring on days 1 to 5; TTE at days 0 to 5 (early) and days 5 to 12 (late). cTnI was dichotomized at a threshold of ≥3 ng/mL (elevated). QTc (corrected) interval, left ventricular ejection fraction (EF), stroke volume, cardiac output (CO), and wall motion scores were calculated.

Results: Elevated cTnI occurred in 31% of patients and was significantly associated with older age, higher Hunt/Hess grade, Fisher score, lower admission Glasgow Coma Scale score, coil embolization (vs surgical clipping), and early use of IV vaspressors/inotropes. Elevated troponin was an independent predictor of poor outcome at 3 months. Mean QTc interval was longer for patients with elevated troponin on both early and late ECGs. Ventricular tachycardia/ventricular fibrillation (VT/VF) was more common in the elevated troponin group (22% vs 9%), although only 2 patients had sustained VT/VF. On early TTE, mean EF was significantly lower in patients with elevated troponins (52% vs 63%). On late TTE, EF was almost identical to earlier values in both groups, and one third of patients with troponin elevation still had an EF <50%. Regional wall motion abnormalities (RWMAs) occurred in 15% of early studies and were significantly more frequent in the high troponin group (44% vs 4%). On late TTE, RWMAs occurred in 41% in the high troponin group and in 3% of the normal group.

Conclusions: Cardiac injury is common after aneurysmal SAH and increases with severity of SAH. Over the acute/subacute phase, persistent QTc prolongation, ventricular arrhythmias, depressed EF, and RWMAs are observed and are significantly more prevalent with elevated baseline cTnI.

Reviewer’s Comments: This study indicates that cardiac injury may take longer to resolve after SAH than previously thought. The late echo study occurred during the peak of vasospasm, when induced hypertension treatment for vasospasm may be deleterious to cardiac function. A CO-driven therapeutic approach may be preferable. Limitations to this study include lack of follow-up echocardiograms on all patients, and variable time windows between SAH onset and initial echo and between early and late studies. It was not clear how use of vasopressors/inotropes affected cardiac function. Long-term follow-up TTE would have been important to determine whether all patients experience full recovery of cardiac function. (Reviewer-Wendy C. Ziai, MD).

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Keywords: Aneurysmal Subarachnoid Hemorrhage, Cardiac Troponin I, Echocardiography, ECG, Wall Motion Abnormality

Print Tag: Refer to original journal article
New Antiplatelet Therapies Promising in ACS

Ticagrelor Versus Clopidogrel in Patients With Acute Coronary Syndromes.

Wallentin L, Becker RC, et al:


Ticagrelor, a new ADP platelet receptor antagonist, is promising as treatment in acute coronary syndrome.

**Background:** Randomized trials have established dual antiplatelet therapy with aspirin and clopidogrel as standard of care for acute coronary syndrome (ACS). Recent clinical trials have evaluated new platelet ADP antagonists in ACS patients. Clopidogrel, a prodrug, is extensively metabolized by the hepatic P450 system. Genetically slow metabolizers make a less-active drug and have a greater risk for recurrent ischemic events and stent thrombosis. Onset of action for clopidogrel is several hours, which may be an issue in ACS. Lastly, clopidogrel permanently inhibits the platelet ADP P2Y12 receptor, thereby increasing bleeding risk if patients require urgent coronary artery bypass surgery. Ticagrelor is a reversible, oral antagonist of the platelet P2Y12 ADP receptor with a faster onset of action and more consistent platelet inhibition compared to clopidogrel.

**Objective:** To compare ticagrelor with clopidogrel in preventing recurrent ischemic events.

**Design:** Randomized double-blind study.

**Participants:** 18,624 ACS patients with high-risk ST-segment elevation myocardial infarction (STEMI) or non-STEMI.

**Methods:** Patients received ticagrelor, 180-mg load followed by 90 mg twice daily, or clopidogrel, 300-mg load followed by 75 mg daily. All patients received aspirin and standard ACS therapies. The primary end point was time to vascular death, myocardial infarction, or stroke at 12 months. Major life-threatening bleeding was also prospectively evaluated.

**Results:** In this large trial, the ticagrelor and clopidogrel groups were well matched. Approximately 38% of patients had STEMI. The primary end point at 12 months occurred significantly less often in the ticagrelor group (9.8%) compared to the clopidogrel group (11.7%). This difference was apparent within 30 days and persisted throughout 1 year of follow-up. Secondary individual end points of myocardial infarction, vascular death, death from any cause, and stent thrombosis were significantly less in ticagrelor patients. Hemorrhagic stroke tended to be greater in patients randomized to ticagrelor (0.3%) compared to those receiving clopidogrel (0.2%; P = 0.06). Overall, rates of major hemorrhage were similar.

**Conclusions:** Ticagrelor is superior to clopidogrel in preventing vascular death, myocardial infarction, and death over 12 months, without an increase in major bleeding.

**Reviewer’s Comments:** Dual antiplatelet therapy with aspirin plus clopidogrel is superior to aspirin alone in ACS patients. New ADP antagonists may replace clopidogrel in certain situations. Prasugrel offers greater platelet inhibition than does clopidogrel, with greater prevention of ischemic events but more bleeding than clopidogrel in ACS patients. Ticagrelor has certain favorable pharmacologic features. First, it gives more complete platelet inhibition and more rapid onset of action compared to clopidogrel. This may explain the superiority of ticagrelor in the PLATO trial. It is completely reversible, making its use attractive prior to knowledge of the coronary anatomy and in those who require non-cardiac surgery with a stent already in place. (Reviewer-Stephen P. Schulman, MD).

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Keywords: Acute Coronary Syndromes, Antiplatelet Therapy, Ticagrelor, Clopidogrel

Print Tag: Refer to original journal article
Renal insufficiency is a powerful predictor of death in patients with non-ST-segment elevation myocardial infarction.

**Background:** Early coronary revascularization in non-ST-segment elevation myocardial infarction (STEMI) decreases recurrent ischemic events and mortality. Observational studies demonstrate that as estimated glomerular filtration rate (eGFR) falls, short-term mortality in non-STEMI rises. Patients with renal insufficiency are rarely enrolled into cardiovascular trials, making clinical decisions challenging.

**Objective:** To evaluate the influence of baseline eGFR on 1-year mortality in non-STEMI patients, as well as the interaction of eGFR and coronary revascularization.

**Methods:** The SWEDEHEART registry prospectively enrolled all non-STEMI patients aged ≤80 years in Sweden between 2003 and 2006. Of subjects, 99.4% were followed up for 1 year. Patients were classified by admission eGFR from normal through renal failure. Demographics, treatments, revascularization procedures, and outcomes were recorded. A propensity score was created to express the likelihood for early revascularization. A Cox proportional hazards model assessed the association between revascularization strategy and mortality.

**Results:** 23,262 non-STEMI patients were enrolled; 48% were treated conservatively, and 52% received coronary revascularization. Following adjustment for the propensity for revascularization, the 2 groups were similar. Nearly one fourth of the cohort had eGFRs <60. Those with lower eGFRs were less likely to undergo coronary angiography or revascularization, and they had a higher incidence of left main and 3-vessel disease. Coronary angiography was performed in 82% of patients with an eGFR ≥90 and in 24% with an eGFR 15 to 29 and <15. Overall 1-year survival was 90.3%. Mortality climbed as eGFR fell, from 7% to 8% with an eGFR >60, up to 55% with an eGFR <15. In the multivariate Cox regression model, there was a significant interaction between early revascularization, mortality benefit, and eGFR. As eGFR fell, the mortality benefit for early revascularization declined such that there was no significant benefit for an eGFR 15 to 29 and a trend toward harm with an eGFR <15.

**Conclusions:** Renal insufficiency is a powerful predictor of death in patients with non-STEMI. Although early revascularization improves overall 1-year survival, there was an important interaction of this benefit by eGFR. As kidney function declines, the benefit for early revascularization is less, with potential harm in patients with renal failure.

**Reviewer's Comments:** Although this registry has all the caveats of an observational study, its nearly complete follow-up and inclusion of the entire non-STEMI population from a single country are strengths. The failure of revascularization to benefit non-STEMI patients with severe renal insufficiency is likely multifactorial. The high morbidity in this group may predict poor survival, no matter what the intervention. The biology of non-STEMI in advanced renal disease may be different, perhaps relating to diffuse calcification of the coronary tree. Lastly, standard non-STEMI therapies have not been studied in patients with end-stage renal disease and may not work in this group. This important hypothesis would need confirmation with prospective testing.

(Reviewer-Steven P. Schulman, MD).

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Keywords: Acute Coronary Syndromes, Renal Insufficiency, Revascularization

Print Tag: Refer to original journal article
RBC Transfusion Improves Cerebral DO$_2$ in Anemic SAH Patients

Red Blood Cell Transfusion Increases Cerebral Oxygen Delivery in Anemic Patients With Subarachnoid Hemorrhage.

Dhar R, Zazulia AR, et al:

Stroke 2009; 40 (September): 3039-3044

Transfusion in anemic patients after subarachnoid hemorrhage may minimize cerebral ischemia, although this strategy cannot be recommended without further clinical studies.

Background: A critical reduction in oxygen delivery (DO$_2$) underlies cerebral ischemia. After subarachnoid hemorrhage (SAH), anemia is common, may worsen DO$_2$, and may place vulnerable brain regions at greater risk for ischemia.

Objective: To test the hypothesis that transfusion increases oxygen delivery to regions at risk for ischemia.

Participants: 8 patients with spontaneous SAH who had a secured aneurysm, had a hemoglobin level <10 g/dL, and were at risk for delayed cerebral ischemia (DCI).

Methods: $^{15}$O-labeled PET was performed to measure cerebral blood flow (CBF), DO$_2$, oxygen extraction fraction (OEF), and cerebral metabolic rate of oxygen (CMRO$_2$) before and after transfusion of 1 unit of packed red blood cells (RBCs). Regional analysis focused on regions with vasospasm and with baseline oligemia (reduced DO$_2$ and elevated OEF).

Results: RBC transfusion caused a 15% rise in both hemoglobin (8.7 to 10.0 g/dL) and oxygen content. Mean global CBF did not change after transfusion. Oxygen delivery increased by almost 20% and was associated with a fall in OEF from 48.7% to 41.0% with stable CMRO$_2$. Mean cerebral blood volume was unchanged. In regions with oligemia, oxygen delivery improved to a greater extent than in non-oligemic regions, and the decrease in OEF was larger. No rise in CMRO$_2$ was seen. Regions with vasospasm had an attenuated response to transfusion. The increase in delivery after transfusion was smaller (10% vs 24%), although reduction in OEF was similar, corresponding to a 7% decrease in CBF. Only 57% of vasospastic regions resolved after transfusion, compared to 85% of such regions without vasospasm.

Conclusions: RBC transfusion in anemic patients with SAH significantly increases cerebral DO$_2$ while reducing OEF and without lowering global CBF.

Reviewer's Comments: This small study suggests that, in the acute phase, raising hemoglobin in patients with SAH may have similar benefits to augmenting CBF through other measures. Transfusion increased arterial oxygen content, but not at the expense of CBF. This indicates that cerebral blood vessels did not vasoconstrict in response to higher arterial oxygen content. In regions with vasospasm, oxygen delivery still rose, but it was attenuated and associated with a decrease in CBF. This suggests that higher viscosity may impair flow when flow is already reduced and compensatory vasodilation is not possible. The main limitation of the study is that only the immediate response to transfusion was measured and not longer-term effects. The effect of RBC storage time also needs further study. At this time, the optimal hemoglobin level in patients with SAH is uncertain. (Reviewer-Wendy C. Ziai, MD).

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Keywords: Anemia, Blood Transfusion, PET, Subarachnoid Hemorrhage, Vasospasm

Print Tag: Refer to original journal article
Antiplatelet agents may be equal to anticoagulation for stroke prevention after closed head trauma.

**Background:** Systemic heparin has been the treatment of choice after blunt cerebrovascular injuries (BCVIs) to prevent devastating injury-related strokes. Recent studies suggest that antiplatelet agents may be more efficacious.

**Design:** Retrospective review of a prospective database at a Level I regional trauma center.

**Participants:** Patients with BCVIs from 1997 to 2007.

**Methods:** The main outcome measure was the incidence of cerebrovascular accidents (CVAs) in each treatment arm.

**Results:** 422 BCVIs were identified in 301 patients during this 10-year study period. Of patients, 64.8% were men, average age was 37.0 years, and mean injury severity score was 27.0. Twenty-two patients presented with neurologic ischemia, and 5 sustained CVAs after embolization and/or stenting of an injury. In 282 asymptomatic BCVIs, treatment was started with heparin in 192, aspirin in 67, and aspirin and/or clopidogrel in 23. One patient had a stroke (0.5%). Of 107 patients with untreated, asymptomatic BCVIs, 23 (21.5%) had a stroke. Mean time to diagnosis was 58 hours in untreated patients sustaining BCVI-related CVAs. In patients who did not show signs of symptoms within 2 hours of injury, mean time to CVA diagnosis was 75 hours. Injury healing rates (heparin, 39%; aspirin, 43%; aspirin/clopidogrel, 46%) and injury progression rates (12%, 10%, 15%, respectively) were equivalent between regimens.

**Conclusions:** With an overall stroke risk of 21% and a documented latent period, comprehensive screening, early diagnosis, and institution of antithrombotic therapy for BCVI are clearly justified. Type of treatment (heparin vs antiplatelet agents) does not appear to affect stroke risk or injury healing rates.

**Reviewer's Comments:** While the subset of patients in whom anticoagulation is contraindicated might benefit from antiplatelet agents, such a patient would be rare as most patients with such contraindications would not allow either therapy. Measuring and documenting adequate antiplatelet therapy causes additional challenges. The downside of antiplatelet agents and possible resultant intracranial hemorrhage may outweigh any benefit for those patients at greatest risk. While it might be more practical to use heparin in the acute phase of the early hospital course, there may be some benefit in prescribing antiplatelet agents as patients are prepared for discharge. (Reviewer-I. Michael Leitman, MD).

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**Keywords:** Closed-Head Injury, Anticoagulation, Antiplatelet Agents, Stroke Risk

**Print Tag:** Refer to original journal article
Use and monitoring of compliance with a ventilator protocol reduces the incidence of ventilator-associated pneumonia.

**Background:** Ventilator-associated pneumonia (VAP) causes significant morbidity, increases costs, and increases the risk of death in critically ill surgical patients. Recent studies suggest that the success of measures to prevent VAP is dependent on compliance with ventilator bundle protocols. Implementation of an electronic dashboard may improve this compliance and reduce rates of nosocomial pneumonia in patients on mechanical ventilators in the surgical ICU (SICU).

**Design:** Time series analysis of VAP rates.

**Participants:** Patients admitted to a multidisciplinary SICU at a tertiary care referral center between 2005 and 2008.

**Interventions:** Protocol and dashboard implementation in July 2007.

**Methods:** Rates of VAP and total ventilator days were determined using infection control data. For the time series analysis, VAP rates were calculated as quarterly VAP events per 1000 ventilator-days. Analysis of ventilator bundle compliance was done after the protocol and dashboard implementation. Differences between expected and observed VAP rates were based on time series analysis and were used to estimate the effect of this intervention.

**Results:** Average Ventilator bundle compliance improved, on average, from 39% in August 2007 to 89% in July 2008 ($P<0.001$). VAP rates decreased from a mean of 15.2 to 9.3 events per 1000 ventilator days after introduction of the protocol dashboard ($P=0.01$). Quarterly VAP rates were significantly reduced in the November 2007 through January 2008 period and in the February through April 2008 period ($P<0.05$). However, the observed rate reduction was not statistically significant for the August through October 2007 and May through July 2008 periods.

**Conclusions:** Implementation of an electronic protocol dashboard appears to improve compliance with ventilator bundle measures and is associated with reduced rates of VAP in the SICU.

**Reviewer’s Comments:** Emergency surgical patients have a high rate of VAP. The “bundle” is not going to reduce rates to zero. The rates in this study, even after the intervention, were still twice the national benchmark rate. However, patients in trauma ICUs have historically had higher-than-expected rates of VAP. Use of bronchoalveolar lavage to document diagnosis of VAP would appear to be more objective than a diagnosis of VAP made on clinical criteria alone. Additional novel interventions, such as use of silver-coated endotracheal tubes or selective gastrointestinal decontamination in specific patient groups may also further reduce the incidence and morbidity of VAP. (Reviewer—I. Michael Leitman, MD).

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**Keywords:** Ventilator-Associated Pneumonia, Nosocomial, Protocol, Mechanical Ventilation

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