CRITICAL CARE PHARMACOTHERAPY LITERATURE UPDATE

September and October2012

This is a monthly review of select articles in the medical literature pertaining to pharmacotherapy used in critically ill patient populations. The content below is for information purposes only and is intended to highlight recent articles that may be of interest to those caring for patients in various intensive care or related settings. Though some core content from the publications is presented, the reader is encouraged to review each article in full for additional detail in order to fully interpret the study, its findings, and its applicability to practice.

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Is Low-Molecular Weight Heparin Safe for Venous Thromboembolism Prophylaxis in Patients with Traumatic Brain Injury? A WesternTraumaAssociationMulti-center Study

Kwiatt ME, Patel MS, Ross SE, et al. J Trauma Acute Care Surg. 2012;73:625-28.

Study Question: Can the safety of low-molecular-weight heparin (LMWH) for venous thromboembolism (VTE) prophylaxisin blunt intracranial injury be demonstrated?

Study Description: The Western Trauma Association (WTA) Multicenter Trials Committee conducted a multi-center, retrospective, cohort study which included patients who presented with intracranial hemorrhage caused by blunt injury. Patients with Abbreviated Injury Scale (AIS) score of ≥3, intracranial hemorrhage, blunt mechanism of injury, age >18 years, head CT at admission, and at least one follow-up CT scan of the head were included. Patients with previous thromboembolic disease, on pre-injury anticoagulation with warfarin or therapeutic LMWH, on heparin for VTE prophylaxis, hospitalized <48 hours, or required emergent thoracic, abdominal, or vascular surgery at admission were excluded. Patients were divided into two groups: those who received LMWH during their hospitalization (LMWH group) and those who did not (control group). The primary outcome measured was progression of intracranial hemorrhage documented by repeated head CT scan. Multivariate logistic regression analysis was performed to identify potential independent risk factors for intracranial hemorrhage progression.

Results: A total of 1,215 patients were included in the study. Of these, 220 patients (18.1%) received LMWH for VTE prophylaxis. The remaining 995 did not receive anticoagulants (81.9%) and served as the control group. Patients who received LMWH had more severe injury and lower GCS score at admission with a longer ICU and hospital length of stay. At presentation, patients in the LMWH group frequently required operation for their intracranial hemorrhages.

Ninety-three (42%) patients in the LMWH group were found to have progressive bleed on follow-up head CT scans. In the control group, 239 (24%)patients were found to have progression on follow-up CT scans ($p<0.001$). There was no difference in the rate of hemorrhage progression after receiving LMWH regardless of timing of LMWH initiation. Factors found to be independent risk factors for hemorrhage progression include age >55 years, male sex, INR >1.3, intra-axial hemorrhage, GCS<9, and LMWH for deep vein thrombosis prophylaxis. LMWH was found to be the strongest risk factor for intracranial hemorrhage progression (OR 2.41; 95% CI 1.65-3.53). The LMWH group had 20 episodes of VTE while the control group had 31 episodes of VTE (9.1% vs. 3.1%, $p<0.001$). However, only 42% LMWH patients and 11% control patients had lower-extremity duplex ultrasounds.

Conclusion(s): Patients receiving LMWH were at higher risk for hemorrhage progression. LMWH was not demonstrated to be safe for VTE prophylaxis in patients with blunt traumatic brain injury. The risk of using LMWH may exceed its benefit.

Perspective: The use of LMWH for VTE prophylaxis in patients with blunt traumatic brain injury was not demonstrated to be safe according to the authors of this study. Nevertheless, the results of this study should be interpreted with caution. There was variability observed among the participating centers

with respect to use of LMWH. Additionally, the baseline characteristics between the LMWH and control groups were significantly different in that the LMWH group was more injured and more likely to require neurosurgical intervention in the first 24 hours. The indications and timing for performing repeated head CT scans for evaluation of progression were variable among the participating centers. The retrospective design of this study precludes making any definitive conclusions regarding the safety of VTE prophylaxis in patients with blunt traumatic brain injury.

Bleeding After Initiation of Multiple Antithrombotic Drugs, Including Triple Therapy, in Atrial Fibrillation Patients Following Myocardial Infarction and Coronary Intervention: A Nationwide Cohort Study

Lamberts M, Olesen JB, Ruwald MH, et al. Circulation. 2012;126:1185-93.

Study Question: What is the risk and time frame of bleeding associated with triple therapy (vitamin K antagonist (VKA) + aspirin + clopidogrel), and is there any thromboembolic benefit to this regimen?

Study Description: This study used data from nationwide registries in Denmark to identify patients with atrial fibrillation who had been hospitalized for myocardial infarction (MI) or percutaneous coronary intervention (PCI). Patients were included 7 days after discharge if they met 3 criteria: ongoing antithrombotic treatment, age ≥ 30 years, and no record of bleeding, MI, or ischemic stroke during the 7-day waiting period. Based on prescription claims, patients were classified into 5 categories of antithrombotic regimens: triple therapy; VKA + single antiplatelet; dual antiplatelet; VKA monotherapy; or single antiplatelet. The primary outcome was fatal or nonfatal bleeding. For each antithrombotic regimen, bleeding risk was determined for early (0-89 days from inclusion) and delayed (90-360 days from inclusion) time periods. The secondary outcome was occurrence of thromboembolic events: cardiovascular death, death from ischemic stroke, nonfatal MI, or nonfatal ischemic stroke.

Results:A total of 11,480 patients were included in the study; 13% received triple therapy, 16% VKA + single antiplatelet, 27% dual antiplatelet, 7% VKA monotherapy, and 36% single antiplatelet therapy. Approximately 24% of study patients met inclusion criteria following PCI with no preceding MI. Of the 76% who had an MI, 17.3% of those patients had undergone PCI within one week. Nearly 10% of patients had a history of bleeding prior to study inclusion. The average HAS-BLED score was 2.1 and the average $CHADS_2$ score was 1.5.

Within the first 30 days of antithrombotic therapy, there were 22.6 major bleeding events/100 person-years for triple therapy, 20.3 events/100 person-years for VKA + single antiplatelet, and 14.3 events/100 person-years for dual antiplatelet therapy. Nine of the 10 fatal bleeding events were intracranial or gastrointestinal. Bleeding rates for patients on triple therapy remained higher than rates for any other regimen throughout the 360-day study period. For all regimens except VKA monotherapy, bleeding risk was highest in the first 90 days of therapy.

The secondary endpoint of cardiovascular death, MI, and ischemic stroke was observed in 2,534 (22.1%) events during the study period. The rate of this

endpoint was similar among patients on triple therapy and VKA + single antiplatelet therapy.

Conclusions: Triple antithrombotic therapy with a VKA, aspirin, and clopidogel creates a high risk of bleeding after MI or PCI in patients with atrial fibrillation.

Perspective: Triple antithrombotic therapy, limited to as short a time as possible, is currently recommended for patients with atrial fibrillation who present with an MI or undergo PCI. This study suggests that the bleeding risk with triple therapy is evident even within the first 30 days of treatment. Although the risk decreases over time, it is still greater than that seen with less intense antithrombotic regimens. In addition to the bleeding risk, this study found that a triple therapy regimen does not provide thromboembolic benefit over a VKA + single antiplatelet regimen. The results of this study suggest that triple antithrombotic therapy be prescribed only after careful evaluation of bleeding risk.

Influence of Parenteral Nutrition Delivery System on the Development of Bloodstream Infections in Critically Ill Patients – EPICOS Study

Pontes-Arruda A, Cesarino dos Santos MCF, Martins LF, et al. J Parenter Enteral Nutr. 2012;36:574-86.

Study Question: Do commercially available terminally sterile total nutrient admixtures (TNA) influence the risk of blood stream infections (BSI) in critically ill patients receiving parenteral nutrition (PN)?

Study Description: This was a multicenter, prospective, open-label, controlled trial that compared the rates of BSI among patients randomized to commercially available terminally sterile multichamber bags (MCB) compared to locally compounded PN (COM). COM were further randomized to either olive oil-based fat emulsion (COM1) compared to medium-chain triglyceride/ long-chain triglyceride-based fat emulsion (COM2). BSI was defined as any positive blood culture within 28 days of PN initiation. All patients had blood cultures sampled 72 hours after the start of PN and additional cultures were collected at the physician's discretion. Patients received PN through either a subclavian or jugular single lumen catheter exclusive for PN (periperhally inserted central lines were not used).

Results: A total of 406 patients were included; 202 in MCB, 103 in COM1, 101 in COM2. Baseline characteristics, including severity of illness and rates of malnourishment, were comparable between treatment groups. Ileus was the most common reason to start PN.

Despite similar duration of catheter days, the incidence of BSI was lower in the MCB PN group compared to COM PN (16.8% vs. 22.5%, p=0.03). The observed raw BSI rate was 35.3% higher in patients who received COM PN compared to patients who received MCB PN. *A. baumannii* and *S. aureus* were more commonly isolated in the COM group. There were no significant differences between groups for 28 day all-cause mortality, development of severe sepsis or septic shock, or ICU/hospital length of stay. Although patients provided MCB PN received nutrition therapy faster (4 hrs vs. 12 hrs, p<0.001), patients who received COM PN reached goal energy requirement quicker (2 days vs. 3 days, p<0.001) and received more calories from protein (87 g vs. 80 g, p<0.001). The type of fat emulsion didn't appear to influence rates of BSI.

Conclusion(s): COM was associated with a higher incidence of BSI suggesting that the use of MCB PN may play a role in reducing the incidence of BSI in patients who receive PN.

Perspective: PN-associated BSI are estimated to cost $22,383 per infection in the US. If MCB PN is associated with a 5.7% absolute reduction in rates of BSI compared to COM, it can be estimated that 12,500 cases of PN-associated BSI could be avoided with an overall savings of more than $279 million per year in the United States alone. Still, the difference in rates of BSI was not associated with worse outcomes and must be balanced with the ability of COM to provide individualized nutrition support therapy.

Patterns of Use of Perioperative Angiotensin-Converting Enzyme Inhibitors in Coronary Artery Bypass Graft Surgery with Cardiopulmonary Bypass: Effects on In-Hospital Morbidity and Mortality

Drenger B, Fontes ML, Miao Y, et al. Circulation. 2012;126:261-69.

Study Question: Is there an association of ACE inhibitor (ACEI) administration and on-pump coronary artery bypass graft (CABG) surgery with clinical outcomes?

Study Description: This study was a prospective multinational observational study of 4,224 patients undergoing CABG surgery (nonvalvular) treated with any dose ACEI (ARBs not included). Patients were divided into the following groups: continuation (on an ACEI pre-op and post-op), withdrawal (on an ACEIpre-op but stopped post-op), addition (not on ACEI pre-op but started post-op), and no ACEI (ACEI never started). The primary outcome was a composite of cardiac, cerebral, and renal events and in-hospital mortality.

Results: Patients in the no ACEI group had fewer comorbidities, while patients treated with ACEI prior to surgery had longer on-pump times. The continuation group had a 31% lower odds of the composite outcome (p=0.009) versus no ACEI, however the continuation group required more non-routine inotropes (28.1% vs 13.8%, p<0.001) despite having similar cardiac indices. The continuation group had a 50% lower odds of the composite outcome (p<0.001) versus the withdrawal group as well as significantly lower use of transfusion and cardiac assist devices (p<0.001). The addition group had a 44% lower odds of the composite outcome (p=0.004) versus the no ACEI group.

Conclusion: Discontinuation of ACEIfollowingCABG is associated with nonfatal in-hospital ischemic events.

Perspective: The results of this study should serve as a launching point for a large randomized controlled trial to definitively dictate appropriate ACEI (or even RAAS blocking) therapy in these patients. We can see parallels to the benefits seen with beta-blockers in this population, yet must give pause with non-protocolized postoperative management. At minimum the results should require us to analyze the current practice of discontinuation of preoperative ACEI.

INTRAPLEURALFIBRINOLYTIC THERAPY FOR TREATMENT OF ADULT PARAPNEUMONIC EFFUSIONS ANDEMPYEMAS

Janda S, Swiston J.CHEST.2012;142:401-11.

Study Question: What is the role of fibrinolytic therapy in the management of parapneumonic effusions and empyemas?

Study Description: This systematic review and meta-analysis utilized multiple databases to identify randomized controlled trials comparing fibrinolytic therapy to placebo in the treatment of parapneumonic effusions and empyemas. Only studies involving adults (> 19 years of age) were included. Data included: study publication year, country of origin, study design, number of patients in each arm, chest tube size, type, dose, and duration of fibrinolytic given, need for thoracic surgery, death, and treatment failure.

Results: A total of 682 citations were identified. Based on title and abstract alone, 669 were excluded and 13 were retrieved for full review. One study was then excluded based on lack of a placebo arm and five because the study population was made up of mainly tuberculous pleural effusions. Seven studies were included in the final analysis yielding a total of 801 patients (384 in fibrolytic group; 417 in placebo group). The overall quality of the studies was determined to be good using the Jadad Scale and Cochrane allocation approach. Doses of fibrinolytics utilized in the studies include: streptokinase 250,000 IU daily or BID x 3 or 7 days, urokinase 100,000 IU daily x 3 days, and alteplase 10 mg BID x 3 days +/- DNase 5mg BID x 3 days. Fibrinolytic therapy was found to be beneficial for the outcome of treatment failure (need for surgical intervention or death) (RR 0.50; 95% CI 0.28-0.87) as well as to decrease the need for surgical intervention alone (RR 0.61; 95% CI 0.45-0.82). There was no difference in mean duration of hospital stay with fibrinolytic therapy compared to placebo (standard mean difference0.69; 95% CI -1.54-0.16) or a reduction in death (RR 1.14; 95% CI 0.74-1.74). A subgroup analysis of loculated pleural effusions showed a statistically significant decrease in surgical interventions with fibrinolytics (RR 0.41; 95% CI 0.26-0.65) but did not decrease overall treatment failure (RR 0.55; 95% CI 0.30-1.01). A sensitivity analysis was performed, which did not change the statistical outcomes.

Conclusion(s): Fibrinolytic therapy may be beneficial in the management of parapneumonic effusions and empyemas in the adult population, but evidence is insufficient to support routine use. There may be a role for fibrinolytics in patients with loculated pleural effusions to decrease surgical interventions.

Perspective: Despite no definitive recommendations regarding treatment, fibrinolytics have been utilized in the setting of pleural infection since the 1950s. This meta-analysis attempts to identify their place in therapy, but ultimately bases its conclusions on only 7 trials. Of note, the two most recent trials (MIST1 and MIST2) showed no benefit in terms of surgical intervention, mortality, duration of hospitalization, or radiographic improvement with fibrinolytic therapy. However, the adverse effect profile of fibrinolytics in this setting has been shown to be favorable and the subgroup analysis demonstrating benefit in the setting of loculated pleural effusions suggests they may be an option in elderly patients or non-surgical candidates. Unfortunately, further studies are still required to definitively address the impact of fibrinolytic therapy on clinical outcomes as well as the role of DNase in this setting.

Pharmacologically Dosed Oral Glutamine Reduces Myocardial Injury in Patients Undergoing Cardiac Surgery: A Randomized Pilot Feasibility Trial

Sufit A, Weitzel LB, Hamiel C, et al. J Parenter Enteral Nutr 2012;36:556-61.

Study Question: Is the administration of pharmacologically dosed preoperative oral glutamine (GLN) safe and feasible as an option to attenuate myocardial injury in cardiac surgery patients?

Study Description: This study was designed as a randomized pilot feasibility study at U.S. hospitals to determine if the use of pharmacologically dosed GLN was both safe and feasible to administer. Study inclusion criteria included undergoing elective cardiac surgery (CABG, valvular surgery, or pulmonary vein repair) in which cardiopulmonary bypass (CPB) was utilized. Notable study exclusion criteria included patients with preexisting kidney or liver dysfunction, history of HIV, hepatitis B or C or ongoing signs of myocardial ischemia. Subjects were randomized to either GLN or maltodextrincontrol (CONT) taken at home starting 3 days prior to surgery. GLN was dosed at 25 grams orally twice daily, with a final dose 2 hours prior to induction of anesthesia. Patients in the CONT group received a corresponding dose of maltodextrin. Patient compliance was assessed using daily reminder calls from the study nurse and required empty package returns. Investigators and clinical caregivers were blinded to study assignment. Myocardial injury markers (Troponin I and CKMB), plasma glutamine and heat shock protein (HSP) levels were assessed at baseline (time of consent), 6, 24, 48 and 72-hours postoperatively. Blood was also collected for HSP and plasma glutamine levels prior to anesthesia.

Results: A total of 14 patients met study inclusion criteria and were enrolled. Four patients were not included in the analysis (3 withdrawn consent [GLN] and 1 intraoperative death [CONT]) leaving a total of ten patients included in the study analysis (GLN-4, CONT-6).

Plasma troponin I levels peaked in both groups 6-hours postoperatively. Patients in the GLN group had significantly decreased troponin I levels at 24, 48 and 72-hours postoperatively, compared to patients in the control group. The GLN group also had decreased CK-MB levels at 24 and 48-hours. There were no differences noted in HSP levels throughout the study period. Plasma glutamine levels were similar between the 2 groups prior to anesthesia. Additionally, both groups demonstrated a statistically significant decrease in plasma glutamine levels postoperatively compared to prior to anesthesia.

Conclusion(s): The use of GLN is both feasible and safe when given in pharmacologic doses to preoperative cardiac surgery patients. These data support the need for a larger, definitive, randomized controlled trial of GLN therapy to reduce myocardial injury and improve clinical outcome in cardiac surgery.

Perspective: The use of pharmacologically dosed GLN preoperatively in cardiac surgery appears to be safe and feasible, perhaps paving the way for larger, randomized studies. While not designed to deliver definitive answers on the topic, the study did offer insight about the potential benefits of a pharmacologically dosed regimen of GLN in cardiac surgery patients.

The Cardiopulmonary Effects ofVasopressin Compared WithNorepinephrine in Septic Shock

Gordon AC, Wang N, KR Walley, et al. CHEST 2012; 142:593–605.

Study Question: Is there a difference in cardiac output and other measures of hemodynamics between vasopressin- and norepinephrine-treated patients with septic shock?

Study Description: This study analyzed data from the VASST trial, a multi-center, double-blind, randomized controlled trial of vasopressin vs. norepinephrine in addition to standard vasopressors for the treatment of septic shock. Between July 2001 to April 2006, patients >16 years old with septic shock (≥2 SIRS criteria with proven or suspected infection, new dysfunction of at least one organ, and hypotension despite adequate fluid resuscitation requiring vasopressor support) were randomized to receive vasopressin (0.01-0.03 units/min) or norepinephrine (5-15 mg/min). Exclusion criteria included patients with unstable coronary syndromes, severe chronic heart disease (NYHA class III and IV), and vasospastic diathesis.

Results: 779 patients were randomized and infused with the blinded study drugs. Cardiac output monitoring was used 241 (31%) patients (vasopressin, 123 patients; norepinephrine, 118 patients; P=0 .97). Patients who had a PA catheter had several markers of more severe organ dysfunction than patients who did not have a PA catheter. Vasopressin use resulted in a significant reduction in norepinephrine requirements (p<0.001). There was a rapid and significant drop in heart rate after starting the vasopressin infusion (p<0.001), which was more pronounced in the less severe shock stratum. There was also a significantly greater use of inotropic drugs in the vasopressin group compared to norepinephrine. There was no difference in cardiac index, stroke volume index, markers of oxygen delivery or left ventricular stroke work index associated with vasopressin in the whole population or in either the more or the less severe shock strata.

Conclusion(s): Vasopressin treatment in septic shock is associated with a significant reduction in heart rate but no change in cardiac output or other measures of perfusion.

Perspective: This study used data from the VASST trial to study the hemodynamic effects of vasopressin and norepinephrine therapy, but PA catheters were only used in 31% of VASST patients. Vasopressin use was not associated with a significant decrease in cardiac output compared with norepinephrine. However, there was greater use of inotropic drugs that augment cardiac output in the vasopressin group than in the norepinephrine group.

Other Recent Publications of Interest

Al-Qadheeb NS, Roberts RJ, Griffin R, et al. **Impact of Enteral Methadone on the Ability to Wean Off Continuously Infused Opioids in Critically Ill, Mechanically-Ventilated Adults: A Case-Control Study.** *Ann Pharmacother***.** 2012; 46:1160-66.

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Dysglycemia andIn-hospital Mortality. *Crit Care Med.* 2012; doi: 10.1097/CCM.0b013e3182656ae5.

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Brophy GM, Bell R, Claassen J, et al. **Guidelines for the Evaluation and Management of Status Epilepticus.** *Neurocrit Care*. 2012;17: 3-23.

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John BK, Khan MA, Speerhas R, et al. **Ethanol Lock Therapy in Reducing Catheter-Related Bloodstream Infections in Adult Home Parenteral Nutrition Patients: Results of a Retrospective Study.** *J Parenter Enteral Nutr.* 2012;36:603-10.

Kowalski RG, Ziai WC, Rees RN, et al. **Third-line Antiepileptic Therapy and Outcome in Status Epilepticus: The Impact of Vasopressor Use and Prolonged Mechanical Ventilation.** *Crit Care Med*. 2012;40:2677-84.

Larabee TM, LiuKY, Campbell JA, Little CM. **Vasopressors in Cardiac Arrest: A Systematic Review.** *Resuscitation*. 2012;83:932-39.

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Zelenitsky SA,Ariano RE, McCrae ML, Vercaigne LM. **Initial Vancomycin Dosing Protocol to Achieve Therapeutic Serum Concentrations in Patients Undergoing Hemodialysis.** *Clin Infect Dis*. 2012; 55:527-33.