CRITICAL CARE PHARMACOTHERAPY LITERATURE UPDATE

October 2011

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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**Enteral Omega-3 Fatty Acid, γ-Linolenic Acid, and Antioxidant Supplementation in Acute Lung Injury**


**Study Question:** Does supplementation of omega-3 fatty acid, γ-linolenic acid (GLA), and antioxidants increase ventilator-free days in patients with acute lung injury (ALI)?

**Methods:** This study was a randomized, double-blind, placebo-controlled trial was conducted at 44 hospitals of the ARDS Clinical Trials Network between January 2008 and February 2009. Eligible patients were those: receiving mechanical ventilation; who had bilateral pulmonary infiltrates; who had a PaO$_2$-FiO$_2$ ratio < 300; who had no clinical evidence of left atrial hypertension; and in whom the treating physician intended to initiate enteral nutrition. Patients were stratified by whether they had shock at baseline and randomized to twice-daily enteral supplementation of omega-3 fatty acids, GLA, and antioxidants or an isocaloric-isovolemic carbohydrate-rich control until the earliest of 21 days, 48 hours of unassisted breathing, or extubation. All patients were managed using lung-protective ventilation and fluid-conservative hemodynamic management protocols.

**Results:** Two-hundred seventy-two patients were enrolled, with roughly half randomized to the omega-3 supplement group and half to the control group. The study was stopped for futility after the first interim analysis when the observed ventilator-free day (VFD) difference was unfavorable for omega-3 supplementation by -3.2 days. With respect to the primary outcome, the omega-3 supplement group had significantly fewer VFDs (14 vs. 17.2 days; 95% CI -5.8 to -0.7, p = 0.02) compared to patients receiving placebo. In addition, patients receiving omega-3 supplementation had fewer ICU-free days (14 vs. 16.7 days, p = 0.04). The adjusted mortality prior to day 60 or hospital discharge did not differ significantly between the groups (25.1% omega-3 supplement vs. 17.6% control, p = 0.11). Patients receiving omega-3 supplementation experienced more diarrhea compared with controls (28.7% vs. 20.9%, p = 0.001), but other adverse effects and rates of development of new infections did not differ between groups.

**Conclusions:** Twice-daily enteral supplementation of omega-3 fatty acids, GLA, and antioxidants does not improve clinical outcomes and may actually be harmful in patients with ALI.

**Perspective:** The current study was powered to detect differences in clinical outcomes, unlike previous studies. It also addresses several limitations of prior studies, including the lack of intention-to-treat analysis, use of a non-standard “pulmonary” control formula, and lack of control for evidence-based therapeutic interventions known to provide benefit in ALI. Of note, the higher protein provision of the control could potentially account for some benefit compared to the omega-3 supplement.

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**Effect of Pravastatin on the Frequency of Ventilator-Associated Pneumonia and on Intensive Care Unit Mortality: Open-Label, Randomized Study**


**Study Question:** Could the addition of statin therapy reduce the frequency of ventilator-associated pneumonia (VAP) in statin-naïve, critically ill patients?

**Study Description:** This study was an open-label, randomized, controlled trial that enrolled adult patients receiving mechanical ventilation > 48 hours. Exclusion criteria included: previous statin therapy or concomitant medications known to interact with pravastatin; elevated serum creatine kinase; malabsorption; active pneumonia; and pregnancy. Patients were randomized to receive either pravastatin 40 mg daily or placebo. The frequency of VAP was assessed during the 30-day treatment period.

**Results:** A total of 152 patients were randomized. There was no statistically significant difference in VAP frequency found between the pravastatin and placebo group (22.5% vs 34.5%, *p* = 0.11). No differences were detected in regards to VAP frequency at ICU discharge or 30-day mortality. However, the overall ICU mortality was reduced in the pravastatin arm (14.1% vs 29.1%, *p* = 0.03). A subgroup analysis of patients with APACHE scores ≥ 15 had a lower incidence of VAP during their ICU stay (*p* = 0.04) and increased probability of survival during the 30-day treatment period (*p* = 0.04) in the pravastatin group.

**Conclusion(s):** Although statins were not beneficial in reducing VAP rates in the overall patient sample, they may have a beneficial effect on ICU mortality in patients who have more severe illness on admission.

**Perspective:** The pleiotropic effects of statins, including potential anti-inflammatory and immunomodulatory characteristics, make this drug class theoretically appealing in the prevention or treatment of infectious and inflammatory processes. Larger, blinded studies with a better-defined patient population are necessary to determine if adjunctive statin therapy can affect VAP rates in the critically ill.

**Premorbid Statin Use Is Associated with Improved Survival and Functional Outcomes in Older Head-Injured Individuals**


**Study Question:** Is pre-injury statin use associated with improved survival and functional outcome in adults ≥ 65 years of age who experience moderate or severe head trauma?

**Study Description:** This multicenter, retrospective study of patients with traumatic brain injury (TBI) and Abbreviated Injury Score of ≥ 3 and age > 65 years of age were included. Exclusion criteria included presentation of fixed dilated pupils and patients who died within 24 hours of admission.

**Results:** A total of 523 met inclusion criteria. Statin users (22%) were more likely to: have a cardiovascular comorbidity or risk equivalent such as hypertension, heart failure, or diabetes; taking more medications pre-injury; and receiving beta-blocker

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therapy. Statin users were had a 76% lower adjusted risk (RR 0.24; 95% CI 0.08-0.69) of hospital mortality. There was no difference in Extended Glasgow Outcome Scale scores at 3 months. However at 12 months, statin users had a 13% higher likelihood of good recovery (RR 1.13; 95% CI 1.01-.26). The presence of cardiovascular comorbidity obviated the protective effect.

Conclusion(s): The study’s authors conclude that premorbid statin use in older adults and TBI is associated with reduced risk of hospital death and improved functional recovery at 12 months. Statin users with cardiovascular comorbidity did not derive benefit.

Perspective: The benefits of premorbid statin use have been suggested in ischemic stroke, sepsis, and trauma. However, the benefit of statin use post-subarachnoid hemorrhage has not been conclusively demonstrated. Continuation of statin use seems reasonable post injury. It would be desirable to see a larger randomized study examining the benefit of continuing or initiating statin use post-TBI.

**IMPACT OF QUETIAPINE ON RESOLUTION OF INDIVIDUAL DELIRIUM SYMPTOMS IN CRITICALLY ILL PATIENTS WITH DELIRIUM: A POST-HOC ANALYSIS OF A DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED STUDY**


**Study Question:** Does antipsychotic therapy with quetiapine affect the duration and time to first resolution of individual delirium symptoms?

**Study Description:** In this post-hoc analysis, delirium symptoms evaluated by the Intensive Care Delirium Screening Checklist (ICDSC) were compared between groups randomized to receive either 50 to 200 mg q12h quetiapine or placebo. Eighteen patients with delirium (ICDSC ≥ 4) were enrolled in each group and delirium assessments were conducted every eight to 12 hours. Both groups received as-needed intravenous haloperidol. Baseline symptoms, symptom resolution, and time to first symptom resolution were compared between groups. P-values of ≤ 0.010 was considered statistically significant.

**Results:** Data was available for 29 of 36 patients. There were no differences between individual symptoms at baseline between the quetiapine and placebo group. There were a higher proportion of patients with resolution of symptom fluctuation in the quetiapine group (p = 0.009) and these patients had shorter time to first resolution of symptom fluctuation (4 h vs. 14 h; p = 0.004) and disorientation (48 h vs. 204 h; p = 0.10). Patients in the quetiapine group had longer time to first resolution of agitation (84 h vs. 36 h; p = 0.07) and hyperactivity (120 h vs. 24 h; p = 0.04). Quetiapine-treated patients tended to spend a smaller percentage of time with inattention (47% vs. 78%; p = 0.03), hallucinations (0% vs. 28%; p = 0.10), and symptom fluctuation (47% vs. 89%; p = 0.04).

**Conclusion(s):** The authors conclude that quetiapine use may be associated with more rapid resolution of many common ICU delirium symptoms compared to placebo; however, agitation and hyperactivity took longer to resolve with quetiapine.

**Perspective:** This analysis is perhaps the first to measure the response of individual delirium symptoms to antipsychotic therapy in this setting. The authors did find that quetiapine is associated with a shorter time to resolution of symptom

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fluctuation and disorientation. Nonetheless, patients taking quetiapine had longer time to resolution of hyperactive delirium symptoms. In the trial’s initial publication, patients in the placebo group trended toward receiving more haloperidol than in the quetiapine group; the extent to which that trend impacts this post-hoc analysis’ findings is unclear.

**STEADY-STATE PHARMACOKINETICS OF INTRAVENOUS LEVETIRACETAM IN NEUROCritical CARE PATIENTS**


**Study Question:** What is the optimal dosing regimen, maintaining a serum concentration within 6 and 20 mcg/mL, of levetiracetam for seizure prophylaxis following subarachnoid hemorrhage, subdural hematoma, or traumatic brain injury?

**Study Description:** This was a single center, prospective, open-label, steady-state pharmacokinetic study. Patients admitted to adult neurocritical care unit received intravenous levetiracetam therapy for seizure prophylaxis following hemorrhagic stroke, subarachnoid hemorrhage, or traumatic brain injury. Doses were initiated at 500 mg every 12 hours and serum levels were measured at specified times after at least 4 doses had been administered. Analysis of samples and pharmacokinetics parameters were described in detail. Monte Carlo simulations were used for multiple dosing regimens including 500, 1000, 1500, and 2000 mg IV every 12 hours as well as 500, 1000, and 1500 mg IV every 8 hours.

**Results:** A total of 12 patients were included in the study. Indications for IV levetiracetam included subarachnoid hemorrhage (n=10), subdural hematoma (n=1), and traumatic brain injury (n=1). None of the patients experienced a seizure during the study. The probabilities of the dosing regimens achieving trough concentrations within the suggested range were as follows: the highest probability was 1000 mg IV every 8 hours (57.1%), followed by 2000 mg every 12 hours (51.2%), 1500 mg every 12 hours (51.1%), and 500 mg every 8 hours (48.1%).

**Conclusion(s):** The investigators concluded that the pharmacokinetics of levetiracetam are altered in neurocritically ill patients compared to healthy volunteers. These changes suggest that higher and/or more frequent dosing may be needed to achieve a goal serum concentration between 6 and 20 mcg/mL.

**Perspective:** The relationship of serum concentrations and clinical efficacy has not been established, although a goal concentration of 6 – 20 mcg/mL has been suggested. It is important to note that none of the patients in the study seized while receiving a dose of 500 mg IV q 12 hours.

**TIMING OF OSELTAMIVIR ADMINISTRATION AND OUTCOMES IN HOSPITALIZED ADULTS WITH PANDEMIC 2009 INFLUENZA A (H1N1) VIRUS INFECTION**


**Study Question:** Does the timing of oseltamivir administration affect outcomes of patients hospitalized with confirmed influenza A (H1N1) viral infection?

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Study Description: This was a multi-center, prospective observational trial of patients with confirmed H1N1 infection receiving oseltamivir at any time following hospital admission. Patients were divided into four groups based on timing of administration. Outcomes of interest included: duration of fever, hospital length of stay (LOS), need for mechanical ventilation, and hospital mortality. Neither ICU admission criteria nor treatment decisions were standardized.

Results: The study included 538 patients who were: mostly male; a median of 39 years old; and had no previous H1N1 vaccination or exposure to oseltamivir. Concomitant steroids were used in 28.3% of the population. The median duration of oseltamivir therapy was 5 days, and the study’s authors found that each one-day delay in initiating oseltamivir was associated with: increased duration of fever (OR 1.10; 95% CI, 1.02-1.19) and LOS (OR 1.07; 95% CI, 1.00-1.15) beyond the sample medians; a need for mechanical ventilation (statistical significance not maintained on multivariate analysis); and hospital mortality (OR, 1.2; 95% CI, 1.06-1.35). Similar results were found on the aforementioned subgroup analysis.

Conclusion(s): The study’s authors conclude that delays in oseltamivir administration following symptoms of influenza are associated with increased duration of fever, LOS, and hospital mortality.

Perspective: While the idea that timing of therapy is directly related to outcomes is not new in infectious diseases, this study provides further support for and underscores the necessity of timely administration of antiviral drugs in H1N1 influenza infection.

Presence of Tobramycin in Blood and Urine During Selective Decontamination of

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THE DIGESTIVE TRACT (SDD) IN CRITICALLY ILL PATIENTS, A PROSPECTIVE COHORT STUDY


Study Question: Is enterally administered tobramycin for selective decontamination of the gut significantly absorbed systemically and, if so, is there a clinically significant effect on the kidneys?

Study Description: This prospective, observational cohort study was conducted in a 20-bed general ICU in the Netherlands where, per hospital standard, all patients with an expected ICU length of stay > 2 days receive SDD with an enteral solution q6h and an oral paste, each containing polymyxin E, tobramycin, and amphotericin B. Patients had blood and urine tobramycin measured during the first day of ICU admission only (day 1). The primary endpoint of the study was the proportion of patients with tobramycin leakage to systemic circulation (at least one serum tobramycin concentration ≥ 0.050 mg/L) vs. no tobramycin leakage. Secondary endpoints included the concentration of tobramycin in serum and urine, and the relation between tobramycin leakage and markers of circulation, renal, and other organ function.

Results: A total of 105 patients were included, 83% had at least one detectable tobramycin concentration. The median highest serum concentration per patient was 0.120 (IQR 0.063-0.232) mg/L. Ninety-nine percent of patients had at least one urine sample with detectable tobramycin, and 49% had a urine concentration that was above the therapeutic trough level (> 1mg/L). The highest tobramycin concentration correlated positively with CRP, urea, and bilirubin on admission; and to highest dopamine dose, noradrenalin dose, urinary output

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on day 1, and RIFLE based on creatinine during the study period (p = 0.03). The highest tobramycin concentration was significantly higher in patients without AKI compared to those with any degree of AKI according to RIFLE and was not significantly related to total SOFA or APACHE scores. The differences in markers of organ failure were most pronounced on day of ICU admission.

**Conclusion(s):** The study authors concluded that the high percentage of patients with detectable serum tobramycin suggests gut barrier failure. At risk patients should have serum concentrations monitored during prolonged SDD use to prevent possible toxicity.

**Perspective:** While the direct clinical utility of this study is limited in geographical areas where SDD is not a widespread standard of care, it does provide further evidence that gut permeability is altered during the course of critical illness.

**Reversal of Clopidogrel-Induced Bleeding with rFVIIa in Healthy Subjects: A Randomized, Placebo-Controlled, Double-Blind, Exploratory Study**


**Study Question:** Can recombinant factor VIIa (rFVIIa) be used to mitigate spontaneous or traumatic bleeding in clopidogrel-treated patients?

**Study Description:** This study was a single-center, placebo-controlled, double-blind, dose escalating trial that randomized 40 healthy participants to receive IV placebo or one of five rFVIIa doses (5, 10, 20, 40, or 80 mcg/kg). Participants were given clopidogrel 300 mg PO x 1 then 75 mg PO Daily for 2 days prior to rFVIIa administration. The study’s authors employed a method called the punch biopsy that is meant to measure bleeding duration (BD) and blood volume (BV) in healthy participants. Researchers performed the biopsy at 4 different time periods: prior to clopidogrel administration; four days after initiating clopidogrel; two and a quarter hours after study drug (rFVIIa or placebo) administration; and five hours after study drug administration. A platelet inhibition assay measured response to clopidogrel, and clot dynamics were assessed using thromboelastography (TEG).

**Results:** The study was halted when, midway through, the sponsor (NovoNordisk A/S) decided to allocate resources to studies evaluating rFVIIa use only for FDA-approved indications. Data was collected for patients who received placebo or 5, 10, or 20 mcg/kg of rFVIIa. Treatment with rFVIIa had no effect on the primary endpoint of a reduction in BD. Compared to placebo, rFVIIa 10 and 20 mcg/kg doses significantly reduced BV. TEG evaluation showed a significant reduction in time to clot onset and an increase in clot angle for all patients who received rFVIIa compared to placebo. No other TEG assessments were different between groups. There were no thromboembolic complications and all side effects were considered mild or moderate.

**Conclusion(s):** The study’s authors conclude that 10 and 20 mcg/kg rFVIIa may improve BD and BV in patients treated with clopidogrel.

**Perspective:** There important limitations – both shortfalls in the study’s internal validity and barriers to its generalizability. First, the authors noted larger variation in BV and BD in patients who received punch biopsies by one of the two physicians, suggesting problems in methods standardization. They also did attempt to account

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for this difference statistically and any additional detail (e.g., values) beyond a single statement. The study excluded patients who were on additional antiplatelet therapy, limiting its widespread applicability; as the authors themselves note, it is not uncommon for patients to receive dual antiplatelet therapy with aspirin and clopidogrel. Overall, the utilization of rFVIIa for a reduction in BD was not very convincing at the doses studied. The results might have been significantly different if investigators had evaluated the effect of the 40 or 80 mcg/kg doses of rFVIIa, but the trial was halted before those doses were evaluated.

**INCIDENCE OF DEEP VEIN THROMBOSIS AFTER SPINAL CORD INJURY: A PROSPECTIVE STUDY IN 37 CONSECUTIVE PATIENTS WITH TRAUMATIC OR NONTRAUMATIC SPINAL CORD INJURY TREATED BY MECHANICAL PROPHYLAXIS**


**Study Question:** What is the incidence of deep vein thrombosis (DVT) and the effect of mechanical prophylaxis in patients with spinal cord injury (SCI)?

**Study Description:** This was a single-center, observational study of consecutive SCI patients admitted over a one-year period for either acute (within 1 week of injury) traumatic or non-traumatic SCI. Patients were included if they had no contraindications to mechanical prophylaxis and were excluded if they had: multi-organ injury; known abnormality of the coagulation system; or a history of anticoagulation management. In all patients, mechanical prophylaxis for thromboembolic events entailed a combination of: gradient elastic stockings; external, sequential pneumatic compression applied to lower limbs; and early mobilization within 30 days. Pharmacologic prophylaxis was not used. Patients were routinely checked for DVT with color Doppler ultrasonography.

**Results:** Sixteen (43%) of the total sample of 37 were found to have a DVT between two and 49 days’ (mean 17.2 days’) follow up: ten patients showed new thrombosis within 7 days; 3 patients after 2-3 weeks; 3 patients more than 1 month after injury. Two patients had symptomatic pulmonary embolism. A total of 10 of 17 (59%) patients with complete motor palsy (American Spinal Injury Association Impairment Classification [ASIA] A or B) and 6 of 20 (30%) with incomplete motor palsy (ASIA C or D) had DVT (p = 0.078). There were eight DVTs each in the traumatic and non-traumatic groups (p = 0.886).

**Conclusion(s):** These findings are different than some past studies showing lower rates of DVT in SCI patients in a similar geographic region of Southeast Asia. This study supports the western literature regarding the high rate of DVT in SCI patients. Mechanical prophylaxis for DVT without medical treatment may be inadequate for preventing DVT. The authors recommend using anticoagulant prophylaxis for DVT prophylaxis in SCI unless there is a contraindication.

**Perspective:** Although this is a small study, it does provide important data. Patients with SCI without anticoagulant prophylaxis had a very high rate of DVT, and most DVTs in this study were found early after injury. Patients with more severe ASIA grades trended toward a higher rate of DVT. The results from this study provide further support that mechanical prophylaxis alone, regardless of whether multiple types are used in combination, is

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inadequate in this patient population and that early pharmacologic prophylaxis is warranted.

OTHER RECENT PUBLICATIONS OF INTEREST


