

CRITICAL CARE PHARMACOLOGY LITERATURE UPDATE

MAY 2010

This monthly review of select articles has been compiled and prepared as a service to the members of the Clinical Pharmacy and Pharmacology (CPP) Section of the Society of Critical Care Medicine (SCCM). The content below is for information purposes only and is intended to highlight recent articles that may be of interest to the CPP membership. 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 and its findings.

Contents

iatrogenic gastric acid suppression and the risk of nosocomial <i>Clostridium difficile</i> infection.....	2
Efficacy of corticosteroids in community-acquired pneumonia.....	2
Proton pump inhibitors for prophylaxis of nosocomial upper gastrointestinal tract bleeding: effect of standardized guidelines on prescribing practice.	3
Non-staphylococcal infections of cardiac implantable electronic devices.....	3
Effect of dexmedetomidine versus lorazepam on outcome in patients with sepsis: an a priori-designed analysis of the MENDS randomized controlled trial.....	4
Intensive insulin therapy in severe traumatic brain injury: a randomized trial.....	4
Effectiveness of acetazolamide for reversal of metabolic alkalosis in weaning COPD patients from mechanical ventilation.....	5
Continuous low-dose infusion of human atrial natriuretic peptide in patients with left ventricular dysfunction undergoing coronary artery bypass grafting (NU-HIT for LVD).....	6
Coagulopathy does not protect against venous thromboembolism in hospitalized patients with chronic liver disease.....	6
Contributors.....	7

Iatrogenic gastric acid suppression and the risk of nosocomial *Clostridium difficile* infection.

Howel MD, Novack V, Grgurich, et al. *Arch Intern Med.* 2010;170:784-790

Nosocomial and iatrogenic infections related to *Clostridium difficile* have increased in incidence and severity. *C. difficile* diarrhea has been associated with antibiotic use as well as pharmacologic gastric acid suppression, specifically use of proton pump inhibitors (PPIs). This paper sought to study the relationship between increasing levels of pharmacologic acid suppression and *C. difficile* using a pharmacoepidemiologic cohort approach on 101,796 discharges in a single center over 5 years. Authors performed a secondary analysis of data prospectively collected for other reasons over a four year period and defined *C. difficile* as a newly positive toxin assay on or after the third hospital day. The primary exposure of interest was acid suppressive therapy and patients were categorized into four groups; no acid suppression therapy, histamine-2 receptor antagonist (H2RA) therapy, daily PPI, and > once daily PPI. Antibiotic administration was also documented. Nosocomial *C. difficile* was identified in 665 cases (0.7%) and was strongly associated with exposure to antibiotics. In an unadjusted analysis, as the level of acid suppression increased, the risk of *C. difficile* infection increased. Other important risk factors associated with nosocomial *C. difficile* were age and comorbid conditions. When comparing acid suppressive therapy subgroups, daily PPI was associated with >70% increase in odds of developing *C. difficile* compared to no acid suppressive therapy; patients receiving

>once daily PPI had more than doubling the risk (dose response effect). Limitations of the study include confounding factors, lack of pre-admission antibiotic/acid suppressive therapy, and observational study. Authors conclude that gastric acid suppressive therapy be used judiciously, utilizing the least-intense therapy for the patients clinical condition.



Efficacy of corticosteroids in community-acquired pneumonia.

Snijders D, Daniels JM, de Graaff CS, et al. *Am J Respir Crit Care Med.* 2010;181:975-982.

Community-acquired pneumonia (CAP) is one of the leading causes of mortality in the United States. Due to its anti-inflammatory properties, corticosteroids may have a role in decreasing pulmonary and systemic inflammation caused by this infection. This prospective, double-blinded randomized, single center study evaluated clinical cure of CAP in patients admitted to the hospital who received either prednisolone or placebo for one week (n=213). Patients must have been immunocompetent with signs of pneumonia but without hospital discharge in the previous 8 days to be eligible. The most significant exclusion criterion was the clinical need for corticosteroids, which limited the enrollment of patients with COPD. Antibiotic selection was based on the national guidelines for the treatment of CAP in the Netherlands and did not vary significantly between groups. There was no significant difference between the prednisolone and placebo groups in clinical cure rate at day 7 (80.8 vs. 85.3%, p =0.38). There was also no difference in clinical cure at day 30, mortality, length of stay, time to clinical stability, or early failure. In the intent to treat analysis, the prednisolone group had significantly more late

failures than the placebo group (19.2% vs. 9.2%, $p=0.04$). Furthermore, in patients with *S. pneumoniae* CAP, there was a significant decrease in clinical cure at day 7 and 30 for patients who received prednisolone. There were no significant differences in the subgroup of patients with severe CAP. Overall, results of this study do not support the use of corticosteroids for treatment of CAP in hospitalized patients.

Proton pump inhibitors for prophylaxis of nosocomial upper gastrointestinal tract bleeding: effect of standardized guidelines on prescribing practice.

Yachimski PS, Farrell EA, Hunt DP, et al. *Arch Intern Med.* 2010;170:779-783.

Nosocomial Upper Gastrointestinal Tract Bleeding or gastric mucosal “stress ulcers” is quickly recognized as an easily preventable event, yet many patients receive gastric acid suppressing agents such as proton pump inhibitors (PPIs) despite not having risk factors. The study authors implemented a guideline on PPI use and determined its effect on PPI prescribing practice on a non-ICU general medicine patient population. Included were 458 patients in the one month before implementation group and 484 in the one month after group. No difference in PPI prescribing was found overall before and after (52% vs. 46% of patients, $p = 0.36$). In patients without outpatient use of PPIs, fewer were prescribed PPIs while inpatient (27% vs. 16%, $p = 0.001$) and at discharge (16% vs. 10%, $p = 0.03$) after guideline implementation. It is difficult to determine the impact of this guideline since it was only presented once to the medical staff, was not enforced, was

somewhat strict, and did not include patients transferred from the ICU. Nonetheless, this study demonstrated a tangible effect of such a guideline in a very restricted population and may lead to wider future applications.

Non-staphylococcal infections of cardiac implantable electronic devices.

Viola GM, Awan LL, Darouiche RO. *Circulation.* 2010;121:2085-2091.

Although a majority of cardiac implantable electronic device (CIED)-related infections are caused by *Staphylococcus* species, about 10% to 30% of these infections result from other organisms. This retrospective analysis aimed to determine the most common non-staphylococcal pathogens causing CIED-related infections to better understand the risk factors and outcomes associated with them. All patients admitted with CIED-related infections at 1 of 4 tertiary care centers in Houston, TX between 2002 and 2009 were included in the study. Eighty patients were identified with clinical symptoms (intraoperative purulence, 80%; external purulent discharge, 73%; erythema, 70%; pain, 51%; warmth, 36%) and microbiological confirmation of non-staphylococcal infections (16% of CIED-related infections) from available culture data. The 87 offending organisms included gram-negative bacteria ($n=52$), most commonly *Pseudomonas aeruginosa*, *Serratia marcescens*, *Enterobacter cloacae* and *Acinetobacter baumannii*; gram-positive (excluding *Staphylococcus*) bacteria ($n=24$), most commonly Vancomycin-sensitive *Enterococcus faecalis*, *Streptococcus viridans* and *Corynebacteria*; fungi ($n=10$), most commonly *Candida albicans* and *Candida tropicalis*; and one case of *Mycobacterium*

fortuitum. Non-staphylococcal infections were characterized as being caused by a diverse group of organisms (examples listed above), presenting 109±27 weeks after device implantation, and 44% of patients had a history of device manipulation. Greater than 91% of devices required removal for treatment. Limitations include the retrospective study design, referral bias that may be present due to the inclusion from tertiary care centers only, and missing data from those patients lost to follow-up. When treating CIED-related infections, it is important to consider other non-staphylococcal pathogens if clinical symptoms persist.

Effect of dexmedetomidine versus lorazepam on outcome in patients with sepsis: an *a priori*-designed analysis of the MENDS randomized controlled trial.

Pandharipande P, Sanders R, Girard T, et al. *Critical Care*. 2010;14:R38.

Delirium and coma are highly prevalent manifestations of organ failure that can potentially worsen outcomes in septic patients. The Maximizing Efficacy of Targeted Sedation and Reducing Neurological Dysfunction (MENDS) trial demonstrated dexmedetomidine (DEX), an alpha₂ (α₂) adrenoceptor agonist, to be a safe and effective sedative in critically ill patients, and to significantly improve brain organ dysfunction when compared to sedation with lorazepam (LZ). To assess an effect on clinical outcomes in septic and non-septic patients receiving DEX-based sedation versus LZ-based sedation, an *a priori* subgroup analysis among patients from the MENDS trial was conducted. Septic patients treated with DEX

had a mean of 3.2 more delirium/coma free days ($p=0.005$); and a mean of 6 more ventilator-free days ($p=0.03$) when compared to septic LZ-treated patients. Also, septic patients receiving DEX for sedation had a lower risk of death at 28 days compared to patients receiving LZ (Hazard Ratio=0.3; 95% CI, 0.1 to 0.9). Although a significant difference was not seen in these outcomes in non-septic patients, there were more ventilator-free days, fewer days in the intensive care unit, and a lower risk of death at 28 days for non-septic patients receiving LZ when compared to non-septic DEX-treated patients. For adverse events associated with DEX, there was a significantly higher percent ($p=0.02$) of bradycardia seen in non-septic DEX-treated patients and no observed difference was seen for hypotension in either subgroup. The results of this study signal a favorable treatment effect of DEX in septic patients; however, it is difficult to make a definitive conclusions or treatment recommendations due to the limited populations in each of the subgroups.

Intensive insulin therapy in severe traumatic brain injury: a randomized trial

Coester A, Neumann CR, Schmidt MI. *J Trauma*. 2010 Apr;68:904-11.

Hyperglycemia has been shown to exacerbate secondary brain injury and independently predicts poor neurologic outcomes in patients with severe traumatic brain injury (STBI). Previous studies comparing conventional glycemic therapy (CGT) with intensive insulin therapy (IIT) have resulted in conflicting results. The purpose of this prospective randomized controlled study was to evaluate the effect of IIT on mortality and neurologic outcomes in

patients with STBI at 6 months. 42 patients received continuous infusion IIT (glucose maintained between 80 mg/dL and 110 mg/dL) adjusted hourly and 46 patients received sliding-scale CGT (glucose maintained < 180 mg/dL) adjusted every four hours. There was no statistically significant difference in the primary endpoints of mortality (IIT 28.2% vs CGT 27.5% $p = 1.0$) or good neurologic outcomes as assessed by having a Glasgow Outcome Scale equal to 5 (IIT 10.5% vs CGT 15.0% $p = 0.27$). Although the study was underpowered to detect such a difference, there was no trend indicating a favorable outcome with IIT. There was also no benefit in the secondary endpoints of infection rate, duration of ICU stay, renal failure, and need for transfusions. There was a statistically significantly higher percentage of patients who experienced hypoglycemia (IIT 82.1% vs CGT 17.5% $p = 0.0001$) and severe hypoglycemia (IIT 15.4% vs CGT 0% $p = 0.012$) in the IIT group but none of these episodes were associated with seizures or hemodynamic instability. The authors concluded that IIT significantly increases the risk of hypoglycemia, but does not improve mortality or neurologic outcomes in patients with STBI. Until further studies clarify how IIT affects clinical outcomes after STBI, CGT should remain the better option.



Effectiveness of acetazolamide for reversal of metabolic alkalosis in weaning COPD patients from mechanical ventilation.

Faisy C, Mokline A, Sanchez O, et al. *Intensive Care Med.* 2010;36:859-63.

Noting that past studies have established that acetazolamide (ACET) effectively reverses

metabolic alkalosis in patients with chronic obstructive pulmonary disease (COPD), researchers decided to take the idea one step further to determine if the drug might be associated with improved outcomes – namely faster weaning from the ventilator. The theory is that ACET, a carbonic anhydrase inhibitor, might measurably hasten the weaning process by lowering the risk of central respiratory drive and cardiac depression associated with metabolic alkalosis. The study's authors conducted a retrospective case-control study of 52 critically ill patients with COPD exacerbations – half of whom were treated with ACET 500 mg IV once a day, half of whom received no ACET. Patients were matched on the basis of age, severity of illness at admission, and the degree of metabolic alkalosis at the time they became eligible to wean from the vent. The authors designed their study to assess to two primary outcomes: variations in serum bicarbonate and blood arterial pH values between the time of readiness to wean and successful weaning. The only significant differences between groups was ACET being associated with a significant difference in serum bicarbonate. The ACET group had an eighteen-point increase in PaO₂/FiO₂, while the control group had a five-point drop. Otherwise, there were no differences in changes in PaCO₂, in extubation success rates, or duration of weaning, although the small sample size may have limited the study's ability to detect such differences.



Continuous low-dose infusion of human atrial natriuretic peptide in patients with left ventricular dysfunction undergoing coronary artery bypass grafting (NU-HIT for LVD)

Sezai A, et.al. *J Am Coll Cardiol* 2010; 55: 1844-51.

Patients with left ventricular dysfunction (LVD) undergoing CABG experience significant perioperative morbidity and mortality. Human atrial natriuretic peptide (hANP), a hormone released in response to atrial stretch, is a coronary artery vasodilator and RAAS inhibitor with potent natriuretic effects. This single-center, randomized, double blind, placebo-controlled trial (n=133) examined the short and long-term cardiac and renal effects of hANP in patients undergoing CABG with LVD, defined as a pre-operative EF of $\leq 35\%$. Patients with cardiogenic shock, hemodialysis or who received off-pump CABG were excluded. A continuous infusion of hANP 0.02 mcg/kg/min was started with bypass initiation, with the dose-reduced to 0.01 mcg/kg/min when oral medications commenced, and discontinued 12 hours after. The mean duration of infusion was shorter in the treatment arm (2.8 vs 3.4 days, $p=0.027$). Baseline characteristics and intra-operative management were not different. The primary endpoints were early post-operative and long-term outcomes. No difference in 30-day or 180-day mortality was observed, though patients in the hANP group had shorter ICU and hospital length of stay (3.6 vs 4.4, $p=0.04$; 13.7 vs 19.3, $p=0.04$, respectively). Fewer post-operative complications, including arrhythmia and heart failure requiring intervention, were observed in the hANP group. Although

furosemide was utilized less in the hANP group, post-operative fluid balance was not reported. This study also lacks discrete endpoint variables, a powering analysis and adjustments for multiple comparisons. hANP is likely safe in this patient population, but it remains unknown if the claimed cardio- and renal-protective effects of the drug are independent of post-operative fluid balance.

Coagulopathy does not protect against venous thromboembolism in hospitalized patients with chronic liver disease

Dabbagh O, Oza A, Prakach S, Sunna R, Sletteie T. *Chest* 2010;137:1145-1149

It is uncertain whether pathologically prolonged international normalized ratio (INR) seen in chronic liver disease (CLD) protects against venous thromboembolism (VTE).

This retrospective cohort study sought to evaluate the relationship between the level of pathologic INR elevation and VTE. The primary outcome of this study was the development of symptomatic deep vein thrombosis (DVT) or pulmonary embolism (PE) as confirmed by extremity VD-US, spiral CT scan of the chest, high probability ventilation-perfusion (VQ) scan, or pulmonary angiography. Secondary outcomes were hospital length of stay and in-hospital mortality. Patients were divided into quartiles based on INR (INR < 1.4; $1.4 \leq$ INR < 1.7; $1.7 \leq$ INR < 2.2; INR \geq 2.2). The overall incidence of VTE was 6.3% (12 of 190). The rate of VTE in this study was higher than previously reported studies involving patients with cirrhosis, although this study was not limited strictly to cirrhotic patients. There was no

difference in the incidence of VTE between INR quartiles. Higher in-hospital mortality was seen with patients in the highest INR quartile (32% vs. 4%, $p < 0.001$). Approximately 25% of the patients received DVT prophylaxis, and the study lacked adequate power to draw conclusions of the success or failure of DVT prophylaxis in this patient population. Future studies are needed to determine the benefit of DVT prophylaxis in this patient population. In conclusion, this study finds the notion that auto-anticoagulation protects against VTE is unfounded. In fact, patients in higher INR quartiles had equal incidence of VTE to those in lower quartiles, and patients with Child Pugh stage C had the highest incidence of VTE.



Prospective, randomized, single-blinded comparative trial of intravenous levetiracetam versus phenytoin for seizure prophylaxis.

Szafarski JP, Sangha KS, Lindsell CJ, Shutter LA. *Neurocritical Care* 2010; 12: 165-172.

Phenytoin has been considered the standard for seizure prophylaxis in patients with traumatic brain injury (TBI), but because of the complicated dosing and significant adverse effects, many neurocritical care units are turning to levetiracetam for prophylaxis. This is a controlled randomized study in 52 patients with subarachnoid hemorrhage (SAH) or TBI comparing the two agents. They were randomized in a 2:1 ratio, putting 18 patients in the phenytoin group and 34 patients in the levetiracetam group. Patients were treated for an average of 7 days in both groups, although the duration was not pre-specified by the study protocol. The primary outcome was incidence of clinical adverse effects. Levetiracetam was

less likely to cause deterioration in mental status ($p = 0.024$) and gastrointestinal problems ($p = 0.043$). Secondary outcomes included incidence of seizures and mortality for which there was no significant difference between the groups. Outcomes measures were also reported. Among the many outcomes evaluated with statistical analysis, patients treated with levetiracetam had significantly lower disability rating scores at 3 and 6 months ($p = 0.006$ and 0.037) and higher extended Glasgow outcomes scales at 6 months ($p = 0.016$). This study was limited by the number of patients in the phenytoin group which make it difficult to detect differences in efficacy.



Contributors

Regina Arellano, PharmD ((Midwestern-Chicago); Marcus Costner, PharmD, BCPS (VA); Erin Frazee, PharmD (Mayo); Haley Goodwin, PharmD (Johns Hopkins); Deanna McMahon Horner, PharmD, BCPS (UCSF); Emily Hutchinson, PharmD, BCPS (Methodist); Erin Koopman, PharmD, BCNSP (Mayo); Shawn Kram, PharmD, BCPS (Via Christi); Jessica Mercer, PharmD (MUSC); Heather Personett, PharmD (Mayo); Angela Plewa, PharmD, BCPS (Stroger); David Pokrywiecki, PharmD Candidate (Midwestern- Chicago); Bridgette Therriault, PharmD (Mayo); Charles J Turck, PharmD, BCPS (UMass); Peter Herout, PharmD, BCPS (EPI-Q, Inc.). Reviewed by: Deepali Dixit, PharmD Jane Janik, PharmD Candidate (UIC); Christine Lesch, PharmD, BCPS (New York Pres).