CRITICAL CARE PHARMACOTHERAPY LITERATURE UPDATE

September 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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Renal Insufficiency After Contrast Media Administration Trial II (REMEDIAL II): RenalGuard System in High-Risk Patients for Contrast-Induced Acute Kidney Injury

Briguori C, Visconti G, Focaccio A, et al. Circulation. 2011;124:1260-9.

Study Question: Does a device that ensures a balance of both high urine output and venous fluid repletion – together with an IV antioxidant – lower the risk of contrast-induced acute kidney injury (CI-AKI)?

Study Description: This REMEDIAL-II study was a multicenter, randomized controlled trial that enrolled 294 non-dialysis patients scheduled to undergo angiography or angioplasty who had baseline chronic kidney disease (a glomerular filtration rate of ≤ 30 mL • min^{-1} • 1.73 m^{-2} as estimated by a Modification of Diet in Renal Disease formula) and a risk of CI-AKI in excess of 26% as determined by a confluence of weighted risk factors, including: hypotension; presence of an intra-aortic balloon pump; heart failure; age > 75 years; diabetes mellitus; anemia; and contrast media (CM) volume. Investigators assigned participants in a 1:1 ratio to one of two groups. The active treatment group patients received IV normal saline, N-acetylcysteine (NAC), and furosemide titrated to a urine output of ≥ 300 mL/h by a closed-loop, fluid-management system known as RenalGuard; patients in the control group received 154 mEq/L of sodium bicarbonate in dextrose and water and PO NAC, both in a manner consistent with standard practice, plus 1,200 mg NAC IV during the procedure.

Results: The incidence of the primary endpoint of CI-AKI (need for dialysis *or* a rise in serum creatinine ≥ 0.3 mg/dL 48 h after CM administration) was nearly halved in the active treatment group (11% vs. 20.5%; odds ratio 0.44; 95% confidence interval 0.24 to 0.92). One of the most important secondary outcomes was the rate of in-hospital dialysis, which trended lower in the active therapy group (0.7% vs. 4.1%; p = 0.056). Increases in levels of serum cystatin C, a kidney function biomarker, were lower in the active treatment group as well (p = 0.001), indicating more favorable renal findings.

Conclusion(s): The study's authors conclude that their active treatment strategy of forced diuresis and repletion with saline and IV NAC is superior to conventional antioxidative CI-AKI prophylactic therapy in high-risk patients undergoing angiography or angioplasty with iodinated CM.

Perspective: The thought behind this strategy is that increasing renal fluid transit while maintaining relative systemic euvolemia ramps up elimination of CM, thereby reducing the net uptake by renal tubular cells. The strategy appears promising and is theoretically sound. As suggested in an accompanying editorial by McCullough et al., desirable future directions include: replication in a larger, independent sample and measurement or estimation of remaining CM in the kidneys and the amount excreted in the urine. In the mean time, it is worth bearing in mind that the decision to employ a strategy of forced diuresis necessitates balancing its accompanying risks of adverse outcomes, including pulmonary edema and electrolyte imbalances.

Acetylcysteine for Prevention of Renal Outcomes in Patients Undergoing Coronary and Peripheral Vascular Angiography (ACT)

ACT Investigators; Circulation 2011, 124:1250-1259:

Study Question: Is acetylcysteine effective in preventing contrast-induced nephropathy (CIN)?

Study Description: This was a multicenter randomized, placebo controlled trial of patients receiving contrast for angiography with at least one risk factor for CIN. Patients were allocated to placebo (including similar smell to study drug) or acetylcysteine 1200mg orally every 12 hours, two doses prior to and two doses after contrast. The primary outcome was a 25% elevation of serum creatinine between 48 and 96 hours after angiography.

Results: A total of 2308 patients were randomized, with no difference found in the primary outcome (12.7% and 12.7%, p=0.97), and no differences detected in all secondary outcomes.

Conclusion(s): Acetylcysteine does not reduce the risk of CIN in at-risk patients undergoing angiography.

Perspective: Being the largest and most methodologically sound study on this subject to date, the controversy may be finally laid to rest. Important limitations include a lack of North American study sites (all Brazilian), use of serum creatinine as the primary outcome marker, and fluid therapy that was not controlled, albeit similar between groups.

Randomized, Placebo-controlled Clinical Trial of an Aerosolized β2-Agonist for Treatment of Acute Lung Injury

Matthay MA, Brower RG, Carson S, et al. The National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network. Am J Respir Crit Care Med 2011;184:561-8.

Study Question: Does β-agonist therapy accelerate the resolution of alveolar edema and improve clinical outcomes in patients with acute lung injury (ALI) and acute respiratory distress syndrome (ARDS)?

Methods: A prospective, randomized, placebo-controlled trial was conducted at 33 hospitals of the ARDS Clinical Trials Network between August 2007 and July 2008. Eligible patients were those receiving mechanical ventilation who had bilateral pulmonary infiltrates, a PaO_2 to FiO_2 ratio ≤ 300, and no clinical evidence of left atrial hypertension. Patients were randomized to 5mg aerosolized albuterol sulfate or saline placebo every 4 hours for 10 days or 24 hours after extubation, whichever was shorter. Dose reduction to 2.5mg or study drug discontinuation occurred in patients experiencing tachycardia beyond pre-specific age-specific limits.

Results: 282 patients were randomized: 152 to the albuterol group and 130 to the saline group. The study was stopped for futility after the second interim analysis when the observed ventilator-free day (VFD) difference was unfavorable for albuterol by -2.2 days. There was no difference between the albuterol and saline groups with respect to the primary outcome of VFDs to Day 28 (14.4 vs. 16.6 days, respectively; 95% CI -4.7-0.3, p=0.087). Patients receiving albuterol had more intensive care

unit-free days compared to saline (13.5 vs. 16.2 days, p=0.023); however, there were no significant difference between the groups with regard to mortality before hospital discharge to Days 60 and 90 and the number of organ failure-free days. Heart rates were higher in patients receiving albuterol, but new onset atrial fibrillation and other dysrhythmias were not significantly different.

Conclusions: Aerosolized β_2-agonist therapy does not improve clinical outcomes in mechanically ventilated patients with ALI or ARDS.

Perspective: Due to the study being stopped early for futility and the fact that no significant differences were demonstrated between the groups with respect to ventilator-free days, organ failure-free days, or mortality, the routine use of aerosolized albuterol therapy for the treatment of ALI cannot be recommended.

TREATMENT OF HYPER-TRIGLYCERIDEMIA IN PATIENTS RECEIVING PARENTERAL NUTRITION

Visschers RGJ, Damink SW, Gehlen JM, Winkens B, Soeters PB, vanGemert WG. JPEN J Parenter Enteral Nutr. 2011;35:610-5.

Study Question: Is there a beneficial effect of short term intravenous lipid (IL) withdrawal from the parenteral nutrition (PN) regimen in patients developing hypertriglyceridemia?

Study Description: The investigators retrospectively studied patients from 2002 to 2006 who required PN and had hypertriglyceridemia defined as a triglyceride (TG) level above 450 g/dL. The primary endpoint of the study was TG concentration following IL withdrawal.

Results: Of 961 patients receiving PN over the study period 73 (7.6%) met the study criteria, of which 16 were excluded for elevated TG levels prior to PN initiation. Following other exclusions only 40 patients remained for the analysis. Patients remained on PN for a median of 30 days and were fully dependant on PN for the duration of the study. Patients had a median (range) of 5 (1-23) days without IL. A statistically significant reduction in TG level (approximately 44%; p<0.001) was observed following IL withdrawal. Patients with a reintroduction of IL had repeat elevations in TG level requiring withdrawal of IL for the remainder of the PN period. Among secondary measures worth noting, following IL discontinuation there was a significant decrease in aspartate aminotransferase and leukocyte count, and an increase in serum albumin.

Conclusion(s): Acutely ill patients receiving PN who develop hypertriglyceridemia exhibit an improvement in laboratory parameters following IL withdrawal.

Perspective: This small retrospective study offers some evidence as to the beneficial effect of IL withdrawal following development of hypertriglyceridemia in patients on short term (ie, not life long) PN. While a reduction in TG level was not unexpected, the observed recurrence of TG rise in patients resuming IL may be of some concern. There was a slight positive effect on a few markers of inflammation with IL withdrawal. Unfortunately, this study did not evaluate other options for managing hypertriglyceridemia in this patient population.

Effect of Antibiotic Diversity on Ventilator-Associated Pneumonia Caused by ESKAPE Organisms

Sandiumenge A, et al. CHEST 2011; 140(3):643-651.

Study Question: Does antimicrobial diversity affect resistance of *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella* species, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* species (ESKAPE) pathogens in ventilator-associated pneumonia (VAP).

Study Description: Single center, prospective, interventional study of adult patients admitted to a medical-surgical ICU. Excluded patients were those admitted for less than 48 hours, immunocompromised, or less than 18 years of age. Only documented microbiological VAPs were included. Included patients then received three different antimicrobial strategies for empirical treatment of VAP; a 10 month patient-specific period, a 24 month scheduling period composed of prioritization (12 months) & restriction (12 months) periods, and a 10 month mixing period. Antibiotic prescription patterns were then determined to be homogeneous or diverse according to the antibiotic heterogeneity index (AHI) for each period.

Results: 127 documented microbiological VAPs occurred in 119 patients. Patient-specific (AHI, 0.88) and mixing (AHI, 0.87) periods were significantly more antimicrobial diverse than the scheduling (AHI, 0.65) period ($p<0.01$). No difference was observed in the incidence of ESKAPE organisms between the three periods but resistant ESKAPE strains significantly increased in the scheduling period compared to the patient-specific period (RR, 2.67; 95% CI, 1.01-7.08) and the mixing period (RR, 3.84; 95% CI, 1.55-12.9). Mortality of patients with resistant ESKAPE VAP was significantly higher compared to patients without ESKAPE VAP (RR, 2.25; 95% CI, 1.67-9.48).

Conclusion(s): Implementation of antimicrobial diversity for empiric VAP treatment may help prevent emergence of resistant ESKAPE organisms.

Perspective: This study suggests using antimicrobial strategies that are more homogeneous than heterogeneous as defined by AHI promote the rise of VAP caused by resistance ESKAPE. The rise in resistance may be due to the selective antimicrobial pressure caused by homogeneous strategies. Practitioners should remain cognizant of patient specific co-morbidities and previous antibiotic use when determining appropriate empirical therapy.

Levosimendan Reduces Heart Failure After Cardiac Surgery: A Prospective, Randomized, Placebo-Controlled Trial

Lahtinen P, Pitkanen O, Polonen P, Turpeinen A, Kiviniemi V, Uusaro A. Crit Care Med. 2011;39:2263-2270.

Study Question: Does levosimendan decrease the incidence of heart failure after cardiopulmonary bypass (CPB) in postoperative cardiac surgery patients?

Methods: A prospective, single-center study was performed in adult patients undergoing elective heart valve or combined heart valve/coronary artery bypass graft (CABG) surgery requiring CPB. Patients were randomized to receive either levosimendan (bolus: 24 mcg/kg IV over 30 minutes, infusion: 0.2

mcg/kg/min x 24 hours) or placebo. The primary outcome was incidence of heart failure. Secondary outcomes included in-hospital and 6-month mortality in addition to major organ failure.

Results: The incidence of heart failure, defined as CI < 2 L/min/m2 or inotrope administration within 2 hours postoperatively after CPB, was statistically significant in favor of the levosimendan group (levosimendan: 15% vs placebo: 58%, p<0.001). There were no significant differences in secondary outcomes between cohorts. Levosimendan-induced hypotension occurred frequently in the study with 82% of patients requiring norepinephrine postoperatively compared to 51% in the placebo group (p<0.001).

Conclusions: Levosimendan may be a useful option for patients undergoing high-risk cardiac surgery if trouble weaning from CPB is anticipated.

Perspective: Levosimendan is a unique agent with calcium sensitizing properties and inotropic/vasodilatory effects. Although theoretical advantages may exist with levosimendan based on its mechanism of action, this study was not powered to show a difference in patient outcome data between groups. The use of an arbitrary definition of heart failure, a small sample size and single center design are limitations of the current study.