CRITICAL CARE PHARMACOTHERAPY LITERATURE UPDATE

May 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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Abbreviation Key

AKI = acute kidney injury; APACHE = Acute Physiology and Chronic Health Evaluation; ARDS = acute respiratory distress syndrome; BAL = bronchoalveolar lavage; BMI = body mass index; CAP = community-acquired pneumonia; CE = clinically evaluable; CFT = clot formation time; CFU = colony-forming units; CMR = cardiac magnetic resonance; CT = clotting time; DIC = disseminated intravascular coagulation; DVT = deep vein thrombosis; EN = enteral nutrition; EPO = epoetin alfa; ESPEN = European Society for Clinical Nutrition and Metabolism; FiO_2 = fraction of inspired oxygen; Hb = hemoglobin; HCT = hematocrit; HR = hazard ratio; HS = hypertonic saline; ICP = intracranial pressure; ICU = intensive care unit; IQR = interquartile range; IV = intravenously administered; LOS = length of stay; MCF = maximum clot firmness; MIC = minimum inhibitory concentration; MPDN = methylprednisolone; MRSA = methicillin-resistant *Staphylococcus aureus*; MV = mechanical ventilation or mechanically ventilated; NaCl = sodium chloride solution; PCI = percutaneous coronary intervention; PLTs = platelets; PN = parenteral nutrition; pO_2 = oxygen partial pressure; RR = relative risk; Se = selenium; SIRS = systemic inflammatory response syndrome; SOFA = sequential organ failure assessment; STEMI = ST-segment elevation myocardial infarction; TOC = test-of-cure; VAP = ventilator associated pneumonia

Effect of Enteral Versus Parenteral Nutrition on Outcome of Medical Patients Requiring Mechanical Ventilation.

Defne Altintas N, Aydin K, Aybar Turkoglu M, et al. *Nutr Clin Pract*. 2011;26:322-9.

Study Question: Is there a difference between EN and PN in the likelihood of developing of VAP?

Study Description: This study was a single-centered randomized non-blinded trial comparing EN to PN in patients admitted to a medical ICU and requiring MV for at least 72 hours.

Results: Thirty patients received EN and 41 received PN with no statistically significant differences in baseline characteristics between the two groups. VAP was identified in 16.7% in the EN group and 26.8% in the PN group (p = 0.311). There were no statistically significant differences in mortality, catheter infections, sepsis, or LOS between groups. More patients receiving PN attained nutrition targets.

Conclusion(s): There were no differences in outcomes between EN and PN patients receiving MV in a medical ICU.

Perspective: This small trial is the first to randomize MV patients to EN vs PN in a medical ICU. Unfortunately, a power analysis was not reported, making it difficult to draw conclusions given the lack of difference between the two groups in the study's major endpoints. The study's authors admit that the study's impact is limited to hypothesis generation.

When Early Enteral Feeding Is Not Possible in Critically Ill Patients: Results of a Multicenter Observational Study.

Cahill NE, Murch L, Jejeebhoy K, et al. *JPEN J Parenter Enteral Nutr.* 2011;35:160-8.

Study Question: When early *EN* is not possible in critical illness, is early *PN* beneficial?

Study Description: Two identical multicenter, prospective, observational trials were conducted in medical ICU patients in 2007 and 2008. Daily nutrition data were collected for a period of 12 consecutive days from MV adult patients with an expected ICU stay of at least 72 hours. Defining early versus late nutrition initiation at the 48-hour mark, the study's authors looked at three groups: Group 1) early PN + late EN; Group 2) late PN + late EN; and Group 3) no PN + late EN.

Results: A total of 703 medical patients from 193 ICUs were included. The majority of patients (n = 541; 77%) received late EN only (no PN). Of the remaining patients, 83 (11.8%) were given early PN and 79 (11.2%) received late PN. A significant difference in adequacy of calories and protein – defined as the number of times the prescribed nutritional therapy was received within the first 12 ICU days – was observed between Groups 1 and 3 (74% versus 42%, respectively; p < 0.001). This apparent benefit notwithstanding, the proportion of patients who died or remained in the hospital at 60 days was significantly higher in Group 1 compared to Group 3, although the difference disappeared in multivariate analysis. No differences in outcomes between groups were noted in the subgroup of

patients with a low BMI, defined as less than 25 kg/m^2.

Conclusion(s): In medical ICU patients who receive EN starting more than 48 hours after ICU admission, there is no overall benefit to supplementing with PN. Conversely, a trend toward worse outcomes is observed in patients treated with *early* PN.

Comment: In some nutrition circles, the practice of starting PN early in the ICU is common. While good data are lacking, an oft-cited meta-analysis (Simpson et al., Intensive Care Med 2005) and ESPEN guidelines for nutrition in the ICU (Clinical Nutrition 2009) support early initiation of PN. Although the present is an observational study, the lack of observed benefit and trend toward possible harm calls for a thoughtful reconsideration of starting early PN in ICU patients who do not receive early EN or those in whom titrating to *goal* EN is difficult. Further prospective, randomized trials might yield additional insight.

High-Dose Selenium Substitution in Sepsis: A Prospective Randomized Clinical Trial.

Valenta J, Brodska H, Drabek T, et al. *Intensive Care Med.* 2011;37:808-15.

Study Question: Does the administration of high dose IV selenium (Se) improve mortality, markers of inflammation, and serum Se concentration in critically ill adult patients?

Study Description: A prospective, randomized, open-label study comparing outcomes in 150 ICU patients admitted with SIRS, sepsis, or septic shock who received either high dose Se (1,000 mcg on day one followed by 500 mcg/day for 5-14 days or until discharge) or standard supplementation of < 75 mcg/day.

Results: There was a significant increase in plasma Se levels in patients who received high dose as opposed to standard supplementation. In the high dose supplementation group, there was a significant increase in the selenoenzyme glutathione peroxidase, which protects against reactive oxygen species. There was no difference in overall mortality between groups, and subgroup analysis dividing patients by SOFA or APACHE II scores also indicated no significant difference in mortality.

Conclusion(s): The study's authors conclude that while high dose Se supplementation *did* improve plasma Se levels and increase select antioxidant enzymes, that improvement was *not* associated with any significant effect on mortality.

Comment: This study included patients with a wide range of sepsis severity, and further evaluation of more critically ill patients *may* demonstrate a more profound effect on mortality. However, at this time, there is limited evidence to support high dose Se supplementation in critically ill patients. The study's authors also comment that the initial response to rapid Se administration may cause a pro-oxidant state. As a result, research centering on the optimal dose and time of delivery of Se may provide further insight into whether or not high dose selenium supplementation is beneficial.

Effect of Corticosteroids on the Clinical Course of Community-Acquired Pneumonia: a Randomized Controlled Trial.

Fernández-Serrano S, Dorca J, Garcia-Vidal C, et al. *Critical Care*. 2011;15:R96.

Study Question: Can the administration of steroids to patients admitted to the hospital with CAP-induced respiratory failure lessen the need for MV and improve clinical outcomes?

Study Description: This was a single-center, randomized, double blind study that enrolled patients aged 18 to 74 admitted for CAP with extensive radiographic findings and a pO_2/FiO_2 < 300. Patients were excluded if they had: a clear need for corticosteroid treatment; a recent hospital admission; the presence of shock; a report of *aspiration* pneumonia; or the need for MV prior to study inclusion. All patients received ceftriaxone with levofloxacin and either placebo or methylprednisolone (MPDN) 200 mg IV given 30 min prior to antibiotic administration and followed by 20 mg IV q6h with a 9-day taper.

Results: Fifty-six patients were included in the intent-to-treat analysis, and between the two groups, there were no statistically significant differences in the need for MV, duration of MV, duration of hospital or ICU LOS, or mortality. Time to resolution of morbidity, as determined by a semi-quantitative score incorporating clinical and radiological findings, was significantly improved in the MPDN group. There was an improvement in the inflammatory response, demonstrated by a significant reduction in serum IL-6, IL-8, and C-reactive protein in patients given MPDN. Also, radiographic resolution and pO2/FiO2 measurements were better in patients who received MPDN.

Conclusion(s): The authors conclude that administration of MPDN *may* reduce the inflammatory process in patients with CAP and lead to lower MV requirements.

Comment: This study is limited not only by its small sample size but also its strict exclusion criteria.

Early Corticosteroids in Severe Influenza A/H1N1 Pneumonia and Acute Respiratory Distress Syndrome.

Brun-Buisson C, Richard J-C, Mercat A, et al. *Am J Respir Crit Care Med*. 2011;183:1200-6.

Study Question: Does the addition of a steroid to standard therapy impact outcomes in cases of severe influenza A/H1N1 pneumonia?

Study Description: This study was a retrospective analysis of registry data from critically ill patients hospitalized for severe influenza A/H1N1 infection with a primary outcome of in-hospital mortality.

Results: Data from 208 patients with ARDS and confirmed influenza infection were analyzed. Eighty-three patients received steroids at a median dose of 270 mg (IQR 200-400) hydrocortisone equivalents and a median duration of 11 (IQR 6-20) days. Unadjusted results showed a higher incidence of mortality in the steroid (33.7%) comopared to the no-steroid (16.8%) group, with a HR 2.39 (95% CI 1.32-4.31; p = 0.004) that remained significant following adjustment for propensity score. The steroid treated group also had significantly higher rates of ICU acquired infections and pneumonia.

Conclusion(s): Routine early use of corticosteroids in the treatment of ARDS associated with viral pneumonia should be discouraged. There may be a benefit with *delayed* administration of steroids; however, this use should be limited to experimental settings.

Comment: Use of corticosteroids in the treatment of ARDS has been associated with detrimental outcomes, and this finding appears to hold for the subset of patients with confirmed influenza infection. The authors of the present study suggest that early administration of steroids may aid viral replication.

Clinical and Microbiologic Outcomes in Trauma Patients Treated for *Stenotrophomonas maltophilia* Ventilator-Associated Pneumonia.

Czosnowski QA, Wood GC, Magnotti LJ, et al. *Pharmacotherapy*. 2011;31:388-45.

Study Question: What are clinical success rates in the antimicrobial treatment of trauma ICU patients with *Stenotrophomonas maltophilia* VAP?

Study Description: This was a retrospective, single center, medical record review of 101 patients with *S. maltophilia* VAP from 1997 through 2007. The study population was predominately male (76%) with a median age of 40 years old, and patients were included if they had documented VAP with *S. maltophilia* after at least 48 hours of MV. Diagnosis of VAP required bacterial growth of at least 105 CFU/mL from a BAL and new or changing infiltrate on chest radiograph plus at least two of the following: abnormal temperature (> 38°C or < 36°C); abnormal white blood cell count (> 10 x 10^3 cells/mm3 or < 4 x 10^3 cells/mm3, or > 10% immature neutrophils); and macroscopically purulent sputum. Once culture results returned, alteration of therapy in accordance with susceptibilities was considered the standard of care. As all included patients had *S. maltophilia* isolated, 86% of the population was transitioned to monotherapy with trimethoprim/sulfamethoxazole, with the most common dose being 12 mg/kg/day.

Results: The primary outcome measured was clinical success rate, defined as an improvement in signs and symptoms of VAP that allowed for the discontinuation of antimicrobial therapy without relapse. This outcome was met by 88/101 (87%) of patients. The mortality rate in the patient sample was 13%, and the average LOS was 62 days.

Conclusion(s): Patients with *S. maltophilia* VAP appeared to have similar rates of clinical success and mortality when compared with previous reports of patients with other Gram-negative bacilli from this study site.

Comment: These data suggest that patients who have *S. maltophilia* VAP *do not* experience lower clinical success rates despite a delay in initiating the treatment of choice, trimethoprim/sulfamethoxazole, while cultures and sensitivities are pending.

LINEZOLID VS GLYCOPEPTIDE ANTIBIOTICS FOR THE TREATMENT OF SUSPECTED METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS* NOSOCOMIAL PNEUMONIA.

Walkey AJ, O'Donnell MR, Wiener RS.
***Chest*. 2011;135:1148-55.**

Study Question: Is linezolid as efficacious as glycopeptides antibiotics (vancomycin, teicoplanin) for the treatment of nosocomial pneumonia with suspected MRSA?

Study Description: Eight randomized, controlled trials of patients age > 12 with nosocomial pneumonia were included in this meta-analysis (n = 1,641). Studies were excluded if: they were non-English; did not provide study details; or clinical success was not an endpoint. The primary endpoint, clinical success, was defined as resolution of signs and symptoms of pneumonia compared to baseline at the test-of-cure (TOC) visit in the clinically evaluable (CE) population. Secondary endpoints were: clinical success at the TOC in the ITT population; clinical success at end-of-therapy in the CE population; microbiologic success; all-cause mortality; and adverse drug events. Two studies compared linezolid to teicoplanin, while the remainder compared it to vancomycin.

Results: The average Jadad score, which is taken from a six-point (0 - 5) scale that evaluates methodological quality, was 3 ± 0.93. No differences were noted between linezolid and glycopeptide antibiotics for the primary and any of the secondary endpoints. For all endpoints, the I^2 was < 0.25, indicating that the included studies engendered a relatively *low* degree of heterogeneity. Thrombocytopenia occurred more frequently in the linezolid arm, though it was not significantly different from comparators. Clinical success in the subgroup of patients with *confirmed* MRSA pneumonia (RR 1.23, 95% CI 0.97-1.53; p = 0.09) was not different from those patients who *did not* have confirmed MRSA pneumonia (RR 0.95, 95% CI 0.83-1.09; p = 0.48).

Conclusion(s): Linezolid is not superior to glycopeptide antibiotics for the treatment of nosocomial pneumonia *with or without* confirmed MRSA.

Comment: The meta-analysis and the studies it included had a number of limitations. Vancomycin was dosed at 1 g IV q12h in five of the six vancomycin trials and no drug levels were reported, raising the question of whether vancomycin might have *outperformed* linezolid if dosed pharmacokinetically. For patients with *confirmed* MRSA pneumonia, vancomycin MICs were not reported in the meta-analysis. While awaiting *detailed* results from the ZEPHYR study in a peer-reviewed publication, local resistance patterns, availability, and cost should continue to drive empiric antibiotic selection.

PREDICTING HIGH VANCOMYCIN MINIMUM INHIBITORY CONCENTRATION IN METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS* BLOODSTREAM INFECTIONS.

Lubin AS, Snydman DR, Ruthazer R, et al. *Clin Infect Dis*. 2011;52:997-1002.

Study Question: Which factors are associated with elevated vancomycin MICs in patients with MRSA bacteremia?

Study Description: This is a prospective cohort study of adults with MRSA bacteremia at a single medical center. A high MIC for vancomycin was defined as ≥ 2 mcg/mL. Factors associated with high vancomycin MICs were compiled into a scoring system to predict which patients have a higher likelihood of infection with organisms with high vancomycin MICs.

Results: Out of 296 separate MRSA bacteremic events from 272 patients, there were 57 cases (19%) with high vancomycin MICs. Variables associated with high MICs in the final predictive model were: age > 50 years (3 points); vancomycin administered for > 48 hours in the previous week (2 points); chronic liver disease (2 points); history of MRSA bacteremia (2 points); and nontunneled central line (2 points). A score cutoff of ≥ 4 had a sensitivity of 75% and specificity of 59%.

Conclusion(s): A simple predictive tool can help identify which patients are likely to have high-vancomycin-MIC MRSA isolates.

Comment: This study suggests that using this tool will enhance the ability to predict high MIC isolates, despite its modest performance in positive prediction. The tool is limited by the relatively small sample size and the elimination of other significant variables from the tool such as: prior daptomycin use; presence of septic shock; and recent surgery or ICU exposure. These factors, among others, were associated with high MICs found both in this study and previous ones. This tool may be useful in concert with other variables found to be associated with high vancomycin MICs.

Comparison of Hypertonic Saline and Mannitol on Whole Blood Coagulation *in vitro* Assessed by Thromboelastometry.

Luostarinen T, Niiya T, Schramko A, et al. Neurocrit Care. 2011;14:238-43.

Study Question: Is blood coagulation affected by differing strengths of hypertonic saline (HS) versus mannitol and how do they compare?

Study Description: Hyperosmolar therapy with mannitol and, more recently, HS has been used for the treatment of elevated ICP in neurosurgical patients with traumatic brain injury as well as in those with brain tumors or subarachnoid hemorrhage. Previous studies suggest that both agents interfere with coagulation, so this study sought to compare the anticoagulation effects of the two therapies when equiosmolar and equivolemic solutions of each were used. Healthy volunteers (n = 10) donated venous blood that was diluted in citrated solution in 0, 10, and 20 volume % concentrations. The solutions studied included 0.9% NaCl, 2.5% NaCl, 3.5% NaCl, and 15% mannitol (which is equiosmolar with 2.5% NaCl). Thromboelastometry devices were used to make coagulation analyses, and parameters measured included clotting time (CT), clot formation time (CFT), maximum clot firmness (MCF), alpha angle, PLTs, Hb, and HCT.

Results: Notable results include: a prolonged CT and weaker MCF for mannitol when compared to control ($p < 0.05$); a delay in CFT with mannitol when compared to all strengths of NaCl ($p < 0.05$); and a decreased alpha angle, which measures the rate of formation of a solid clot, in the mannitol group ($p <$

0.05). No other parameter was significantly different between solutions.

Conclusions: Based on the results, authors conclude that 15% mannitol leads to a slower coagulation process when compared to various saline concentrations and that clot formation may be weaker with mannitol therapy. When comparing results between different *NaCl* solutions, higher concentrations were associated with weaker coagulation processes, although no *significant* difference was observed in such a small sample.

Comment: Although a handful of results were *statistically* significant, the *clinical* significance may be questionable (i.e., difference in clotting time of mannitol compared to control reported to be ~30 seconds). As unimpaired coagulation is often necessary in an interventional neurosurgical setting, this study may make HS look more favorable than mannitol to treat elevated ICPs. However, the decision to do so should continue to be driven, in part, by the risks posed by the serious side effects of each therapy (e.g., AKI, hypernatremia, metabolic acidosis, etc.) when considering using one form of therapy over another.

Intravenous Erythropoietin in Patients with ST-Segment Elevation Myocardial Infarction (REVEAL: A Randomized Controlled Trial).

Najjar SS, Rao SV, Melloni C, et al. *JAMA*. 2011;305:1863-72.

Study Question: Does erythropoietin have a cardioprotective effect in STEMI patients?

Study Description: Investigators conducted a randomized, double-blind, placebo-controlled trial involving an initial dose-escalation safety phase (15,000-, 30,000-, or 60,000-unit epoetin alfa [EPO] doses) followed by a single-dose efficacy phase at 28 American study sites. In the efficacy phase, patients with STEMI were randomized to receive either a single dose of IV EPO 60,000 units or placebo within four hours of successful PCI. To assess outcomes, patients underwent cardiac magnetic resonance (CMR) imaging between 2 and 6 days post-intervention and then again at 12 weeks. Safety endpoints included patients enrolled in both dose-escalation and efficacy phases.

Results: A total of 138 patients were evaluated for the efficacy phase. There was no difference between EPO and placebo groups in the primary end point of infarct size at the region of the culprit artery based on first CMR. In subgroup analysis, the mean infarct size was 41.2% *larger* in the EPO group in patients aged 70 years and older (n = 21). Safety outcomes were assessed using both cohorts (n = 223), and the EPO group had a higher risk of death, MI, stroke, or stent thrombosis compared to placebo (4% vs. 0%; p = 0.04).

Conclusion(s): EPO, administered in STEMI patients following successful PCI, does not reduce cardiac infarct size. In fact, in *older* patients, treatment with EPO is associated with *increased* infarct size. The incidence of severe adverse effects, primarily thromboembolic, was higher in EPO-treated patients.

Comment: Despite its theorized physiologic benefits and recent *animal* trials suggesting a cardioprotective role, EPO currently has *no place* in post-ischemic injury care given the lack of benefit and association with adverse outcomes demonstrated in this trial.

OTHER ARTICLES OF INTEREST

Bogard KN, Peterson NT, Plumb TJ, et al. **Antibiotic Dosing During Sustained Low-Efficiency Dialysis: Special Considerations in Adult Critically Ill Patients**. *Crit Care Med*. 2011;39:560-70.

Frontera JA, Kalb T. **Neurological Management of Fulminant Hepatic Failure**. *Neurocrit Care*. 2011;14:318-27.

Green SM, Robacki MG, Kennedy RM, et al. **Clinical Practice Guideline for Emergency Department Ketamine Dissociative Sedation: 2011 Update.** *Ann Emerg Med*. 2011;57:449-61.

Hays AN, Lazaridis C, Neyens R, et al. **Osmotherapy: Use Among Neurointensivists**. *Neurocrit Care*. 2011;14:222-8.

Juffermans NP, Prins DJ, Vlaar APJ, et al. **Transfusion-Related Risk of Secondary Bacterial Infections in Sepsis Patients: A Retrospective Cohort Study**. *Shock*. 356;35:355-9.

Martin-Loeches I, Sanchez-Corral A, Diaz E, et al. **Community-Acquired Respiratory Coinfection in Critically Ill Patients with Pandemic 2009 Influenza A(H1N1) Virus**. *Chest*. 2011;139:555-62.

Ulldemolins M, Roberts JA, Lipman J, Rello J. **Antibiotic Dosing in Multiple Organ Dysfunction Syndrome.** Chest. 2011;139:1210-20.

Hsin-Yun S, Fujitani S, Quintilliani R, Yu VL. **Pneumonia Due to *Pseudomonas aeruginosa*: Part II: Antimicrobial Resistance, Pharmacodynamic Concepts, and Antibiotic Therapy.** Chest. 2011;139:1172-85.

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