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# CRITICAL CARE PHARMACOLOGY LITERATURE UPDATE

**September 2010**

**T**his 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.

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## ANALYSIS OF LINEZOLID-ASSOCIATED HEMATOLOGIC TOXICITIES IN A LARGE VETERANS AFFAIRS MEDICAL CENTER

Minson Q, Gentry CA. *Pharmacotherapy* 2010;30:895-903.

This single-center study sought to characterize the hematologic toxicities in a large patient cohort via retrospective chart review. Included were *all* patients, inpatient or outpatient, who received at least one dose of linezolid in *any* dosage form. A total of 544 linezolid courses were abstracted. Discontinuation due to toxicity occurred in 35 cases (6.4%), with grade 3-4 thrombocytopenia ( $< 50 \times 10^3/\text{mm}^3$ ) developing in 5.2% of patients. A multivariate regression analysis found baseline hemoglobin  $< 10.5 \text{ g/dL}$  (OR 5.37), immunosuppression (OR 8.56), and platelet count  $50\text{-}99.9 \times 10^3/\text{mm}^3$  (OR 229) to be independently associated with grade 3-4 *thrombocytopenia*. Baseline cardiovascular conditions (OR 2.24), urologic conditions (OR 1.59), immunosuppression (OR 1.91), and baseline platelet count  $50\text{-}99.9 \times 10^3/\text{mm}^3$  (OR 5.36) were independently associated with grade 3-4 *anemia*. More adverse events were noted with intravenous versus oral dosage form administrations (34.1% versus 24.5%), although this finding was likely due to uncontrolled differences in severity of illness. All patients had platelet count resolution after discontinuation of linezolid. This is the largest sponsor-independent data set published to date, and the authors conclude that the rate of thrombocytopenia and anemia are higher than those reported in phase III trials (5.2% versus 0-2.5%).

## INSUFFICIENT BETA-LACTAM CONCENTRATIONS IN THE EARLY PHASE OF SEVERE SEPSIS AND SEPTIC SHOCK

Taccone FS, Laterre P-F, Dugernier T, et al. *Crit Care* 2010;14:R126.

Early appropriate antibiotics improve mortality in severe sepsis and septic shock, and the pharmacokinetics of beta-lactams in the critically ill patient population has not been well described previously. Accordingly, researchers set out to conduct this multicenter, prospective, observational study to determine the adequacy of plasma concentrations in critically ill patients following traditional dosing of cefepime, ceftazidime, piperacillin/tazobactam, and meropenem. Inclusion criteria consisted of patients who were: non-pregnant adults; less than 85 years of age; and with severe sepsis or septic shock who received beta-lactam treatment. Patients were *excluded* if they had received the same antimicrobial previously or had end-stage renal disease. The primary outcome of median percentage of time greater than four times the minimum inhibitory concentration ( $T > 4 \times \text{MIC}$ ) was 34% with cefepime, 45% with ceftazidime, 33% with piperacillin/tazobactam, and 57% with meropenem. Prospectively defined target percentages of  $T > 4 \times \text{MIC}$  were achieved most often with meropenem (75%) and least often with cefepime (16%). Critically ill patients demonstrated higher volumes of distribution, lower maximum concentrations, and reduced total clearance compared to previous estimations in normal healthy controls. Clinical variables including age, mechanical ventilation, APACHE II and SOFA scores, presence of shock, fluid balance, and maximal doses of vasopressors were not found to be associated with  $T > 4 \times \text{MIC}$ . The authors note that subtherapeutic antimicrobial concentrations have the potential to negatively influence patient outcomes, increase healthcare costs, and exacerbate already increasing concerns of resistance. Although this is a small study focusing on only the first antimicrobial dose, it is reasonable to conclude that a reappraisal of beta-lactam dosing in critically ill patients is warranted.

## EARLY LACTATE-GUIDED THERAPY IN INTENSIVE CARE UNIT PATIENTS

Jansen TC, van Bommel J, Schoonderbeek FJ, et al. *Am J Resp Crit Care Med* 2010;182:752-61.

Although an increased lactate level is an important *prognostic* indicator of poor outcome, it is unknown whether active and successful reduction of lactate levels during resuscitation leads to improved clinical outcomes. The goal of this multicenter, open-label randomized controlled study was to determine if serial lactate monitoring with therapy aimed at decreasing lactate by 20% every 2 hours for 8 hours would result in a reduction of in-hospital mortality when compared to standard therapy. Adult patients treated at one of four Dutch ICUs over a two-year period with a lactate level  $\geq 3$  mEq/L on ICU admission were included in the study, with *excluded* patients characterized by any of the following: liver failure; recent liver surgery; epileptic seizures; or those with hyperlactatemia secondary to an *aerobic* etiology. Therapy in the *control group* was aimed at previously established parameters for heart rate, mean arterial pressure, central venous pressure, urine output, arterial oxygen saturations, and hemoglobin levels. In addition to those measures, the study's authors added the aforementioned decreases in lactate to the treatment goals of patients in the *intervention group*. The primary outcome, in-hospital mortality, was significantly different in the lactate-targeted group ( $n = 171$ ) when adjusted for age, sex, APACHE II/SOFA scores, and stratified by institution and sepsis group ( $p = 0.006$ ), compared to a control group ( $n = 177$ ); hazard ratio (HR) 0.61, 95% confidence interval (CI): 0.43-0.87. An adjusted ICU mortality rate (HR 0.66, 95% CI: 0.45-0.98), mechanical ventilation duration (HR 0.72, 95% CI: 0.54-0.98), and ICU length-of-stay (LOS; HR 0.65, 95% CI: 0.50-0.85) were also decreased in the lactate-targeted cohort. Interestingly, the lactate levels between the two groups were not significantly different throughout the 8-hour active treatment period. However, patients with lactate goals were given significantly more fluids and vasodilators. This study's findings suggest that a therapeutic plan aimed at reducing initial lactate levels may lead to improved clinical outcomes.

## PROBIOTICS IN THE CRITICALLY ILL PATIENT: A DOUBLE BLIND, RANDOMIZED, PLACEBO-CONTROLLED TRIAL

Barraud D, Blard C, Hein F, et al. *Intensive Care Med* 2010;36:1540-7.

The objective of this clinical trial was to evaluate the effect of probiotic administration on outcomes in mechanically ventilated patients. All intubated patients with a predicted need for mechanical ventilation  $> 2$  days were assigned to receive either probiotics (a combination of predominantly *Lactobacillus rhamnosus* GG, but that also *Lactobacillus casei*, *Lactobacillus acidophilus*, and *Bifidobacterium bifidum*) or placebo. Patients were excluded if they were:  $< 18$  years old; pregnant; immunosuppressed; had short bowel disease; or were enrolled in another clinical trial. Treatment was discontinued once patients remained successfully extubated for at least 2 days (maximum duration of treatment was 28 days). All patients received enteral nutrition within 24 hours of admission. There proved to be *no* difference in the primary outcome of 28-day mortality overall between the probiotic and placebo groups (25.3% vs 23.7%;  $p = 0.80$ ); however, a significant mortality reduction *was noted* in a subgroup of patients with *severe sepsis* who were treated with probiotics (OR for death 0.38; 95% CI 0.16–0.93). There was no effect of probiotic administration on the 90-day mortality rate (31% vs 30%;  $p = 0.90$ ), ICU LOS, hospital LOS, or organ dysfunction resolution. While there *was* a decline in catheter-related bloodstream infections in the probiotic group (1.84 vs 6.78 catheter days;  $p = 0.005$ ), there were no differences in a number of other measures, including: ventilator-associated pneumonia; urinary tract infections; antibiotic consumption; and nasal or rectal colonization of multidrug resistant bacteria. With 167 patients in the intention-to-treat analysis, the study fell well short of the 740 patients originally calculated to provide 90% to detect a five-percent difference in mortality. In the end, the study was halted early at the recommendation of its data safety and monitoring committee, which concluded futility of treatment. In addition to being underpowered, the sample may have been drawn

from too heterogenous a study population, and the subgroup finding of efficacy in septic patients highlights a potential direction for future trials. What's more, it is worth noting that the bacterial species studied represent only a fraction of those commercially available.

## EARLY COMBINATION ANTIBIOTIC THERAPY YIELDS IMPROVED SURVIVAL COMPARED WITH MONOTHERAPY IN SEPTIC SHOCK

**Kumar A, Zarychanski R, Light B, et al. *Crit Care Med* 2010;38:1773-85.**

For treatment of septic shock, *appropriate* initial antimicrobial therapy has been shown to be better than antibiotic regimens that *do not* adequately cover the identified organism and, in theory, the use of combination therapy *should* increase the likelihood of appropriate initial coverage. Accordingly, influential guidelines recommend double coverage of Gram negative organisms with empiric antibacterial agents in patients with septic shock. The current analysis is a retrospective, propensity-matched study involving septic shock patients that compares adequate *monotherapy* with patients who received *two* appropriate antimicrobials. The matched groups each contained 1,223 patients in whom cultures eventually yielded Gram negative organisms. Mortality was significantly lower in the combination therapy group (20% vs. 36.3%;  $p = 0.0002$ ) although, consistent with other literature, the benefit was reduced when there was a delay in the addition of the second antibiotic by several hours. Patients on combination therapy also had significantly lower ICU (28.8% vs. 35.7%) and hospital mortality (37.4% vs. 47.8%) and significantly increased vasopressor- (17 vs. 10) and ventilator-free (25 vs. 23) days. The study suggests a benefit of two antibiotics over one adequate antibiotic, although prospective analysis will be needed to validate the suggested benefit.

## UPDATING THE EVIDENCE FOR THE ROLE OF CORTICOSTEROIDS IN SEVERE SEPSIS AND SEPTIC SHOCK: A BAYESIAN META-ANALYTIC PERSPECTIVE

**Moran JL, Graham PL, Rockliff S, Bersten AD. *Crit Care* 2010;14:R134.**

Corticosteroid use in severe sepsis and septic shock (SS/SS) remains a controversial practice. This meta-analysis was designed to evaluate the effect of high-versus low-dose (> 1000 mg of hydrocortisone or its equivalent vs. < 1000 mg) corticosteroid use on clinical outcomes. Only randomized-controlled trials that reported mortality data were included, and descriptive, retrospective, and pediatric studies were excluded. Fourteen studies (n=1991 patients) were evaluated for the primary outcome of hospital mortality and secondary outcomes of shock resolution (free from vasopressor support for 24 hours), adrenocorticotropin hormone (ACTH) responsiveness, secondary infection, and non-infectious complications (e.g., gastrointestinal bleed and hyperglycemia). A mortality benefit was observed in neither the low- nor high-dose corticosteroid arms (odds ratio [OR]: 0.912, 95% CI 0.313-1.253 and 0.796 (0.396-1.386), respectively]. There were also no significant complications associated with corticosteroids, regardless of dosage, and ACTH response did not appear to be associated with mortality or successful shock reversal. Limitations of this publication are common to those of meta-analyses: variability in the primary outcome measures between trials and a lack of standardized definitions – in this case for SS/SS. Despite the often-cited limitations of CORTICUS, the findings of this meta-analysis do mirror those found in CORTICUS, including: the lack of demonstrated mortality benefit and the limited utility of ACTH stimulation tests in guiding therapy for SS/SS. The authors note that their predictive estimates do not suggest efficacy in future, larger trials.

## RESULTS OF THE CONTROL TRIAL: EFFICACY AND SAFETY OF RECOMBINANT ACTIVATED FACTOR VII IN THE MANAGEMENT OF REFRACTORY TRAUMATIC HEMORRHAGE

Hauser CJ, Boffard K, Dutton R, et al. *J Trauma* 2010;69:489-500.

Traumatic coagulopathy contributes to patient outcomes and requires intervention. Recombinant factor VIIa has been used frequently as an adjunct to treat traumatic coagulopathy, although it is only currently indicated for the use in patients with hemophilia. This trial was designed to evaluate the efficacy and safety of rFVIIa in patients with active bleeding caused by trauma who had already received 4 units of packed red blood cells (PRBCs) but who had *not* yet received *eight* units. The CONTROL trial was a prospective, randomized, double-blind multicenter trial that included patient 18 – 70 years old with blunt and/or penetrating trauma with continuing bleeding despite PRBCs and standard hemostatic interventions. There was a tiered primary efficacy endpoint defined *a priori*: first, researchers looked at 28-day mortality. If noninferiority between treatment groups was determined for that endpoint, then researchers looked at differences in pulmonary and renal dysfunction by day 30. Secondary endpoints included amount of product administered at 24 and 48 hours, multiple organ failure, ICU, hospital, and ventilator days. The trial was terminated with only 573 of 1502 planned subjects enrolled. Mortality in the blunt trauma (11% rFVIIa vs. 10.5% placebo) and penetrating trauma (18.2% rFVIIa vs. 13.2% placebo) groups were not statistically significantly different ( $p>0.05$ ). Patients in the blunt trauma arm demonstrated no difference in morbidity, including: ventilator free days, safety profiles, or the need for renal replacement therapy. The rFVIIa group *did* show significant reductions in PRBC, FFP, and *total* units of allogenic transfusions but not in platelet, fibrinogen, or cryoprecipitate transfusions. Patients in the *penetrating* trauma population showed no difference in mortality, morbidity, or safety profiles. With the lone exception of FFP ( $p=0.04$ ), transfusion

requirements were not statistically significantly different in this study population. Of note, thrombotic events *were not* different between any of the groups and populations. The one exception was venous thrombosis was significantly higher *with placebo* in *penetrating* trauma patients. Also worth noting is that because the CONTROL trial ended early, it was underpowered to detect differences in its primary endpoints.

## DOSE COMPARISONS OF CLOPIDOGREL AND ASPIRIN IN ACUTE CORONARY SYNDROMES

The CURRENT-OASIS 7 Investigators. *N Engl J Med* 2010;363:930-42.

Studies using higher doses of antiplatelet agents have demonstrated greater inhibition of platelet aggregation, potentially leading to improved clinical outcomes in patients with acute coronary syndromes (ACS). Additionally, the optimal dose of aspirin as part of combination regimen varies between 100 mg and 162-325 mg daily, as recommended by European and American guidelines, respectively. CURRENT-OASIS 7 was a randomized, active control, multinational trial ( $n=25,086$ ) evaluating rates of primary outcome: cardiovascular death, myocardial infarction, or stroke within 30 days while treating NSTEMI/STEMI patients. *One part* of the 2 x 2 factorial design involved double-dose clopidogrel, where patients received a loading dose of 600 mg on day 1, followed by 150 mg on days 2 through 7, and 75 mg daily for the remaining 23 days. Patients in the *standard-dose* group received a 300-mg loading dose followed by 75 mg daily for the remainder of 29 days. All patients received an initial, 300-mg dose of aspirin and then were randomized to either 75-100 mg or 300- 325 mg daily on days 2 through 30. No differences in primary outcomes were observed in high and standard-dose clopidogrel (4.2% vs. 4.4%;  $p=0.30$ ) and aspirin (4.2% vs. 4.4%;  $p=0.61$ ) groups. However, higher dose clopidogrel group *did* lead to an increased rate of major bleeding (2.5% vs. 2.0%;  $p=0.01$ ), although it also reduced the secondary outcome of stent thrombosis in patients who underwent PCI (1.6% vs. 2.3%;  $p=0.0001$ ). Higher doses of aspirin led to a greater incidence of *minor* bleeding (0.3% vs. 0.5%;  $p=0.02$ ) but not of *major* bleeding.

## OTHER ARTICLES OF INTEREST

### Pediatric and neonatal:

**Protein C concentrate as adjuvant treatment in neonates with sepsis-induced coagulopathy: a pilot study.** Decembrino L, D'Angelo A, Manzato F, et al. *Shock* 2010;34:341-5.

### Observational literature:

**Factors associated with nonadherence to early goal-directed therapy in the ED.** Mikkelsen ME, Gaiski DF, Goyal M, et al. *Chest* 2010;138:551-8.

**End-of-life treatment and bacterial antibiotic resistance: a potential association.** Levin PD, Simor AE, Moses AE, Sprung CL. *Chest* 2010;138:588-94.

### Review articles:

**International recommendations for glucose control in adult non diabetic critically ill patients.** Ichai C, Preiser J-C, Société Française d'Anesthésie-Réanimation, Société de Réanimation de langue Française. *Crit Care* 2010;14:R166. DOI:10.1186/cc9258

**Management of submassive pulmonary embolism.** Piazza G, Goldhaber SZ. *Circulation* 2010;122:1124-9.

**PROWESS-SHOCK trial: a protocol overview and perspectives.** Silva E, Poli de Figueiredo, LF, Colombari F. *Shock* 2010;34(Suppl.1):48-53.

### Case reports:

**An interaction between levodopa and enteral nutrition resulting in neuroleptic-like syndrome and prolonged ICU stay.** Bonnici A, Ruiner C-E, St-Laurent L, Hornstein D. *Ann Pharmacother* 2010;44:1504-7.

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