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# CRITICAL CARE PHARMACOTHERAPY LITERATURE UPDATE

November 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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## DURATION OF ANTIBIOTIC THERAPY FOR BACTEREMIA: A SYSTEMATIC REVIEW AND META-ANALYSIS

*Havey TC, Fowler R, Daneman N. Crit Care. 2011;15:R267.*

**Study Question:** What is the optimal duration of antibiotic therapy for patients with non-*Staphylococcus aureus* bacteremia?

**Study Description:** A search through MEDLINE, EMBASE, and COCHRANE databases was conducted to identify trials which randomized patients to shorter (from 5-7 days) versus longer duration (from 7-21 days) of antibiotics for bacteremia or infections that commonly cause bacteremia, including catheter-related blood stream infections (CRBSIs); intra-abdominal infections; pneumonia; pyelonephritis; and skin and soft tissue infections (SSTIs). Eligible trials randomized patients to two durations of the same antibiotic regimen to evaluate clinical cure, microbiologic cure, or survival. Trials were excluded for duration of therapy based on physician discretion, clinical improvement, or biomarker measurements.

**Results:** Twenty-four trials were included in the meta-analysis yielding outcome data for a total of 155 patients with positive blood cultures. One trial focused on patients with bacteremia, and the other 23 evaluated other infections causing bacteremia (0 CRBSI, 3 intra-abdominal infections, 6 pyelonephritis, 1 SSTI, and 13 pneumonia). There were no significant differences overall for clinical cure (87% vs. 96%, risk ratio 0.88, 95% CI 0.77-1.01,  $p = 0.37$ ), microbiologic cure (100% vs 94%, risk ratio 1.05, 95%, CI 0.91-1.21,  $p = 0.78$ ), or survival (88% vs 89.6%, risk ratio 0.97, 95% CI 0.76-1.23,  $p = 0.36$ ). No significant heterogeneity between studies was

detected for clinical cure ( $I^2=5\%$ ), microbiologic cure ( $I^2=0\%$ ), or survival ( $I^2=3\%$ ).

**Conclusion(s):** The authors cautiously concluded there are no significant differences in clinical cure, microbiologic cure, or survival for shorter versus longer antibiotic therapy in the treatment of bacteremia. This indicates shorter duration of therapy *may* be efficacious for treatment of bacteremia, though a larger randomized trial is needed to further support of these findings. The limited number of patients represented in the outcomes suggest future trials should be completed to consider a change in antibiotic duration in bacteremic patients.

**Perspective:** This article emphasizes the lack of evidence that exists for optimal duration of antibiotic treatment of various illnesses. The possibility of shorter antibiotic durations for bacteremia seems promising, but it is important to keep in mind that this meta-analysis only included one trial focused specifically on bacteremic patients.

## TIME COURSE OF ORGAN FAILURE IN PATIENTS WITH SEPTIC SHOCK TREATED WITH HYDROCORTISONE: RESULTS OF THE CORTICUS STUDY

*Moreno R, Sprung CL, Annane D, et al. Int Care Med. 2011;37:1765-72.*

**Study Question:** Does hydrocortisone (HC) therapy in patients with severe sepsis and septic shock lead to faster resolution of organ failure when compared to placebo?

**Study Description:** This is a pre-defined secondary analysis of the previously published CORTICUS trial, a prospective, multicenter, randomized, double-blind placebo-controlled trial comparing HC for 11 days to

placebo. (The primary outcome of the CORTICUS study was 28-day mortality.) The Sequential Organ Failure Assessment (SOFA) score defined organ failure according to each of six organ systems. A score of 3 or 4 points in any one system was defined as failure and achievement of reversal occurred if the patient achieved a score of < 3 after treatment.

**Results:** The study included 499 participants who were enrolled within 72 hours of septic shock diagnosis. The groups did not differ in baseline total SOFA scores (HC  $10.8 \pm 3.2$  vs placebo  $10.8 \pm 3.1$ ;  $p = 0.55$ ) nor in any of *individual* components of the score. Serial SOFA assessments from day 0 to day 7 demonstrated a faster decrease in the cardiovascular ( $p < 0.0001$ ) and hepatic ( $p < 0.0001$ ) organ failure scores favoring the hydrocortisone group. Significant deviation between treatment groups appeared to begin at approximately day 3. There were no other significant differences between groups for other organ systems in the first seven days. Over the course of *28 days, however*, cardiovascular failure resolution ( $p = 0.043$ ) and renal failure resolution ( $p = 0.039$ ) both favored hydrocortisone, whereas liver failure resolution proved no different ( $p = 0.42$ ).

**Conclusion(s):** Despite an inability to demonstrate improvements in 28-day *mortality*, the study suggests *morbidity improvements* in the hydrocortisone group, particularly with respect to cardiovascular failure.

**Perspective:** Selection of the most optimal endpoint for critical care studies is challenging, but these findings suggest some value in continuing the approach of conducting post hoc analyses. Unfortunately, the practical applications of the approach are less clear. To what extent can the findings be applied in care and to what extent should they be relegated to hypothesis generation? Critical

care practitioners are unfortunately left to determine where priority should be placed.

## EARLY USE OF SUPPLEMENTAL PARENTERAL NUTRITION IN CRITICALLY ILL PATIENTS: RESULTS OF AN INTERNATIONAL MULTICENTER OBSERVATIONAL STUDY

*Kutsogiannis J, Alberda C, Gramlich L, et al. Crit Care Med. 2011;39:2691-9.*

**Study Question:** Does the early use of supplemental parenteral nutrition (PN) have any impact on clinical outcomes in critically ill patients?

**Methods:** Data from two international, prospective, observational studies conducted in 2007 and 2008 were combined to provide a robust sample. Over 225 intensive care units (ICUs) from 29 countries were included, and eligible patients were those who: were receiving mechanical ventilation (MV); remained in the ICU for greater than 72 hours; and received early enteral nutrition (EN), which was defined as being initiated within 48 hours of admission.

**Results:** Two thousand nine hundred twenty patients were included: 2,562 (87.7%) received early EN alone, 188 (6.4%) received early supplemental PN, and 170 (5.8%) received late supplemental PN. Patients receiving PN were more likely to be surgical patients, to have acute respiratory distress syndrome, and to have been in the hospital greater than 1 day prior to ICU admission when compared to patients receiving early EN alone. Among patients receiving PN, those receiving *early* therapy were significantly older and had lower BMIs, while those receiving *late* therapy were more likely to have

experienced GI dysfunction for 2 or more days. Adequacy of calories and protein was highest in the early PN group (81.2% and 80.1%, respectively) and lowest in the early EN group (63.4% and 59.3%,  $p < 0.001$ ). Sixty-day mortality was significantly lower in patients receiving early EN (27.8%) compared to those receiving early PN (34.6%) or late PN (35.3%,  $p = 0.02$ ). Additionally, patients receiving early EN had significantly fewer days on MV and shorter ICU and hospital lengths of stay. The rate of discharge alive from the hospital was lower among patients receiving early PN and late PN compared to those receiving early EN. No change in outcomes was demonstrated by adjusting for confounders.

**Conclusions:** Supplemental PN was associated with improved protein and calorie provisions but did not demonstrate a clinical benefit.

**Perspective:** These findings are consistent with five randomized, controlled trials comparing EN alone to EN with supplemental PN, as well as additional observation and retrospective studies. Given this data and known complications of PN, the routine use of supplemental PN in critically ill patients cannot be recommended at this time.

## EVALUATION OF DEXMEDETOMIDINE: SAFETY AND CLINICAL OUTCOMES IN CRITICALLY ILL TRAUMA PATIENTS

*Devabhakthuni S, Pajoumand M, Williams C, et al. J Trauma. 2011;71:1164-1171.*

**Study Question:** What is the comparative safety and outcomes of prolonged infusion of standard dose dexmedetomidine (SDD,  $\leq 0.7$  mcg/kg/hr), high dose dexmedetomidine (HDD,  $> 0.7$  mcg/kg/hr), and propofol in trauma patients receiving MV?

**Study Description:** This retrospective, single-center cohort study ( $n = 127$ ) included adult trauma patients admitted to the ICU who received the study drug(s). Patients were excluded if they received the study drug(s) for less than 24 hours, received dexmedetomidine with propofol for greater than 6 hours, or were not receiving MV. The primary endpoints were the occurrence of hypotension, hypertension, bradycardia, and tachycardia using SEDCOM criteria. Secondary endpoints were overall mortality, ICU or hospital LOS, duration of MV, and concomitant administration of analgesics, sedatives, and antipsychotics.

**Results:** Baseline characteristics were matched overall with a few notable differences: more patients who received dexmedetomidine had thoracic injury, spinal cord injury and/or hepatic impairment. Duration of therapy was longer in the HDD arm (6 vs 2 vs 3 days,  $p < 0.001$ ). Injury severity score was similar across groups. Patients who received HDD experienced more hypotension than those who received SDD or propofol (98% vs 86% vs 78%, respectively,  $p = 0.02$ ). There was no difference in the incidences hypertension, bradycardia, or tachycardia. Both the HDD and SDD groups had longer ICU and hospital LOS, though no mortality difference was observed. Oxycodone, midazolam, and haloperidol administration was greatest in the HDD arm.

**Conclusion(s):** HDD may be associated with a higher incidence of hypotension, longer LOS, and concomitant sedative, analgesic and antipsychotic use in critically ill trauma patients receiving MV.

**Perspective:** Limitations include a heterogeneous trauma population, lack of standardized sedation goals or a routine assessment of sedation, and the inability to control for provider preference with concomitant medication prescribing. Regardless,

HDD likely increases risk of hypotension, particularly in the hypovolemic trauma patient.

## OTHER RECENT PUBLICATIONS OF INTEREST

Castellanos-Ortega I, Suberviola B, García-Astudillo LA, et al. **Late Compliance with the Sepsis Resuscitation Bundle: Impact on Mortality.** *Shock*. 2011;36:542-7.

Faisy C, Llerena MC, Savalle M, et al. **Early ICU Energy Deficit is a Risk Factor for *Staphylococcus aureus* Ventilator-Associated Pneumonia.** *Chest*. 2011;140:1254-60.

Irola T, Aantaa R, Laitio R, et al. **Pharmacokinetics of Prolonged Infusion of High-dose Dexmedetomidine in Critically Ill Patients.** 2011;15:R257.

Levine M, Ruha A-M, Graeme K, et al. **Toxicology in the ICU Part 3: Natural Toxins.** *Chest*. 2011;140:1357-70.

Lilly CM, Zuckerman IH, Badawi O, Riker RR. **Benchmark Data from more than 240,000 Adults that Reflect the Current Practice of Critical Care in the United States.** *Chest*. 2011;140:1232-42.

Martino JL, Stapleton RD, Wang M, et al. **Extreme Obesity and Outcomes in Critically Ill Patients.** *Chest*. 2011;140:1198-1206.

Naidech AM. **Intracranial Hemorrhage.** *Am J Resp Crit Care Med*. 2011; 184: 998-1006.

Parodi G, Marcucci R, Valenti R, et al. **High Residual Platelet Reactivity After Clopidogrel Loading and Long-term Cardiovascular Events Among Patients with Acute Coronary Syndromes Undergoing PCI.** *JAMA*. 2011;306:1215-23.

Wahidi MM, Jain P, Jantz M, et al. **American College of Chest Physicians Consensus Statement on the Use of Topical Anesthesia, Analgesia, and Sedation During Flexible Bronchoscopy in Adult Patients.** *Chest*. 2011;140:1342-50.