CRITICAL CARE PHARMACOTHERAPY LITERATURE UPDATE

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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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Dexmedtomidine vs Midazolam or Propofol for Sedation During Prolonged Mechanical Ventilation

Jakob SM, Ruokonen E, Grounds RM, et al. JAMA. 2012;307:1151-1160.

Study Questions: Does dexmedetomidine (DEX) maintain target sedation as well as midazolam (MID) and propofol (PRO)? Is DEX associated with decreased duration of mechanical ventilation?

Study Description: Two parallel, randomized, double-blind multicenter trials were conducted in ICU patients requiring mechanical ventilation and continuous sedation. Exclusion criteria included severe neurological disorder or hemodynamic instability. Patients were randomized to receive DEX 0.2-1.4 mcg/kg/hr or a comparator, MID 0.03-0.2 mg/kg/hr (MIDEX trial) or PRO 5-67 mcg/kg/min (PRODEX trial). Time within the target Richmond Agitation Sedation Scale (RASS) score range of 0 to -3 without rescue medication and duration of mechanical ventilation were the primary outcome parameters.

Results: DEX was noninferior to MID and PRO for time within target RASS range. The median duration of mechanical ventilation was significantly less in the MIDEX trial (DEX: 123 h, MID: 164 h; p = 0.03) but not in the PRODEX trial (DEX: 97 h, PRO: 118 h; p = 0.24). The median time to extubation was reduced with DEX in both MIDEX (DEX: 101 h, MID: 147 h; p = 0.01) and PRODEX (DEX: 69 h, PRO: 93 h; p = 0.04) trials. Hypotension (DEX: 20.6%, MID: 11.6%; p = 0.007) and bradycardia (DEX: 14.2%, MID: 5.2%; p < 0.001) occurred more frequently in the DEX group in the MIDEX trial. First-degree heart block (DEX: 3.7%, PRO: 0.8%; p = 0.04), critical illness polyneuropathy (DEX: 0.8%, PRO: 4%; p = 0.02) and neurocognitive adverse effects (DEX: 18%, PRO: 29%; p = 0.008) including delirium were significantly different in the PRODEX trial.

Conclusion(s): DEX maintained target sedation as well as MID and PRO. DEX was associated with a reduced duration of mechanical ventilation when compared with MID but not PRO.

Perspective: While the authors' conclude that DEX is feasible for long-term sedation, the median DEX exposure in both trials was only 42 h. Sedation interruption was used in approximately 90% of patients in each cohort, while spontaneous breathing trials only occurred in about 50% of cases. The cardiac adverse event profile of DEX was similar to previous studies. Interestingly, DEX and MID had similar rates of delirium while PRO had higher rates of delirium when compared to DEX, although Confusion Assessment Method for the ICU (CAM-ICU) was assessed only once – 48 h after study drug discontinuation – raising questions about the ability to extrapolate to the incidence of delirium overall during patients' stays in the ICU (were CAM-ICU values comparable or different between groups at times other than the 48-h mark?).

Association between Inhaled Nitric Oxide Treatment and Long-Term Pulmonary Function in Survivors of Acute Respiratory Distress Syndrome

Dellinger RP, Trzeciak SW, Criner GJ, et al. Crit Care. 2012;16:R36.

Study Question: Does inhaled nitric oxide (iNO) improve pulmonary function six months post-treatment in acute respiratory distress syndrome (ARDS) survivors compared to placebo?

Study Description: This article was an *a priori*-defined analysis of data from ARDS survivors (n = 92) who took part in a multicenter, randomized, blinded, placebo-controlled study comparing low-dose iNO (5 ppm) and inhaled placebo (nitrogen gas). Patients with a partial-pressure-of-arterial-oxygen-to-fraction-of-inspired-oxygen (PaO_2/FiO_2) ratio ≤ 250 mm Hg due to causes other than severe sepsis were included. Exclusion criteria were: non-pulmonary organ failure at randomization; sepsis-induced ARDS; need for vasopressors; severe head injury; and the presence of severe burns. The study drug was continued until the end of trial (28 days), death, or adequate oxygenation with FiO_2 ≤ 0.40 and PEEP ≤ 5 cm H_20. Pulmonary function tests (PFTs) were performed in survivors six months post-treatment.

Results: Thirty percent of those who survived the trial completed the 6-month assessment. The remainder of patients died prior to follow-up (7%), were lost to follow-up (16%), or did not have PFT results available (47%). Baseline characteristics, oxygenation, and respiratory parameters were clinically similar between groups. The mean PaO_2/FiO_2 ratio at baseline was 140.5 vs 136.1 mm Hg. At 6 months, patients treated with iNO had improved: total lung capacity (TLC; 5.54 L vs 4.81 L; p = 0.026); % predicted TLC (93.3% vs 76.1%; p < 0.001); FEV_1 (80.2% vs 69.5%, p = 0.042); forced vital capacity (FVC; 83.8% vs 69.8%; p = 0.019); and FEV_1/FVC (96.1% vs 87.9%; p = 0.033). There were no significant differences in FEV_1, FEV_1/FVC, functional residual capacity or carbon monoxide diffusion.

Conclusion(s): ARDS survivors who receive iNO have improved PFTs at 6 months post-treatment.

Perspective: Because pre-morbid pulmonary function was unknown, six-month data was unavailable for the majority of ARDS survivors and exclusion criteria were restrictive, the findings in this analysis are very challenging to interpret and generalize. iNO has not been shown to improve ARDS mortality, thus utilizing this medication outside of salvage therapy for severe ARDS likely remains unwarranted at the present time.

What is the Efficacy and Safety of Colistin for the Treatment of Ventilator-Associated Pneumonia? A Systematic Review and Meta-Regression

Florescu DF, Qiu F, McCartan MA, et al. Clin Infect Dis. 2012;54:670-80.

Study Question: What is the safety and efficacy of intravenous and aerosolized colistin for the treatment of ventilator-associated pneumonia (VAP)?

Study Description: This article was a quantitative amalgamation of studies that reported safety and efficacy of IV and/or aerosolized colistin for treatment of VAP.

Results: Six two-arm (colistin vs. control therapy) and 13 single-arm were included in the meta-regression, although the two types of studies were analyzed separately. No difference was found in the 2-arm studies with respect to clinical outcome, microbiologic outcome, mortality, length of stay, or safety (e.g., rates of nephrotoxicity). The results from the single-arm studies mirrored that of the 2-arm studies.

Conclusion(s): Colistin may be as safe and as efficacious as standard antibiotics for the treatment of VAP.

Perspective: A power analysis found that the meta-regression was underpowered to detect a difference

in clinical outcome. Moreover, a third of the studies in the 2-arm group used *inhaled* formulations of colistin, which has a safety profile different from that of intravenous colistin; lumping the studies together makes it difficult to draw conclusions about each formulation's safety profiles and may or may not have been appropriate with respect to efficacy. While this analysis provides an excellent aggregation of the sparse data on the use of inhaled colistin in VAP, the critical care community is still left with too few data to draw practice-changing conclusions with regard to safety and efficacy at this time.

Replacement of Fentanyl Infusion by Enteral Methadone Decreases the Weaning Time from Mechanical Ventilation: A Randomized Controlled Trial

Wanzuita R, Pli-de-Figueiredo LF, Pfuetzenreiter F, et al. Crit Care. 2012;16:R49.

Study Question: Can a regimen of enteral methadone decrease mechanical ventilation (MV) weaning time in adult critically patients?

Study Description: This article described a randomized, double-blind, multi-centered trial conducted in adult ICUs in Brazil. Adult, MV patients (n = 68) who received five or more consecutive days of fentanyl and met defined MV weaning criteria were randomized to receive either enteral methadone (10 mg every 6 h) or matching placebo. After 24 hours of enrollment, patients in the methadone group were taken off fentanyl and given an IV infusion of saline in its place while the placebo group was maintained on a fentanyl infusion. In both groups, the infusions were reduced by 20% every 24 hours to prevent withdrawal syndrome. Daily interruptions of sedation, sedation scales, and delirium diagnoses were not standardized. Patients were assessed for spontaneous breathing trial eligibility daily and were followed until death or hospital discharge. Outcomes included weaning time, duration of MV, and ICU and hospital lengths of stay (LOSs).

Results: Fourteen patients died before ventilation weaning could take place. Among the survivors, weaning time was significantly lower in the methadone group ($p < 0.004$), with a median time of 4 days vs. 7 days in the placebo group. However, there was no significant difference in *total* MV duration or ICU or hospital LOSs. In the methadone group, 10 patients experienced signs of opioid withdrawal intolerance compared to 12 in the placebo group ($p = 0.30$).

Conclusion(s): The study's authors conclude that results show that introducing enteral methadone during MV weaning may shorten weaning time. Larger trials needed to confirm these results and apply to clinical practice setting.

Perspective: MV patients often require prolonged or high dose opioids that may contribute to a withdrawal syndrome and difficulty in weaning. Patients in either group who experienced symptoms of opioid withdrawal were allowed intermittent doses of fentanyl and dose of methadone was increased by 50%. This trial suggests that methadone may be one possible adjunctive therapy in the weaning of fentanyl by continuous infusion. However, there are several alternative strategies that may be employed (intermittent opioids doses, switching to short acting analgesia/sedative regimens, etc.) to achieve the same goals.

LINEZOLID IN METHICILLIN-RESISTANT STAPHYLOCOCCUS AUREUS NOSOCOMIAL PNEUMONIA: A RANDOMIZED, CONTROLLED STUDY

Wunderink RG, Niederman MS, Kollef MH, et al. Clin Infect Dis. 2012;54:621-629.

Study Question: Compared to dose-optimized vancomycin, is linezolid superior in treating methicillin-resistant *Staphylococcus aureus* (MRSA) nosocomial pneumonia?

Study Description: This article described a multicenter, double-blind trial evaluating clinical outcome at the end of the study (EOS) in 348 adult patients with MRSA pneumonia. Patients received either vancomycin (dose-adjusted for trough concentrations, goal trough not specified) or linezolid (600 mg IV every 12 h).

Results: At the EOS, there was a significant improvement in clinical cure for patients treated with linezolid compared to vancomycin (57.6% and 46.6%, respectively; p= 0.042), with similar results for microbiologic cure. Vancomycin trough levels were reported as medians of 12.3, 14.7, and 16.1 mcg/mL on days 3, 6, and 9, respectively. There was an increase incidence of nephrotoxicity in the vancomycin treated group (7.3% vs 3.7% with linezolid; p-value not reported), but overall no difference in the number of adverse drug events between groups and no difference in 60-day mortality.

Conclusion(s): Clinical response in patients treated with linezolid was significantly better at the EOS compared to vancomycin for the treatment of nosocomial MRSA pneumonia.

Perspective: This study had a number of notable limitations. A target vancomycin trough was never specified, and the median levels suggest that a significant number of patients had not achieved troughs that are acceptable by current standards (15-20 mcg/mL) even by day 6. Accordingly, the reader is left to wonder what the results would have been had patients randomized to vancomycin been treated more optimally. Although 1,225 patients were randomized, only 348 patients were evaluated for the primary outcome of clinical outcome at the EOS, and the results of an intention-to-treat evaluation of the primary outcome were not presented. While not apparently statistically significant, more patients who received vancomycin were receiving mechanical ventilation (73.9% vs. 66.9%) and had MRSA bacteremia (10.8% vs. 5.2%) at baseline.

FLUID MANAGEMENT AND RISK FACTORS FOR RENAL DYSFUNCTION IN PATIENTS WITH SEVERE SEPSIS AND/OR SEPTIC SHOCK

Muller L, Jaber S, Molinari N, et al. Crit Care. 2012;16:R34.

Study Question: Is the use of low molecular weight hydroxyethylstarch (HES 130/0.4) in sepsis or septic shock associated with the development of renal dysfunction?

Study Description: This article describes a retrospective review of a French, multicenter study pre- and post-implementation of ten recommendations from the Surviving Sepsis Campaign guidelines. The purpose was to determine factors associated with renal dysfunction. Prescribers were able to choose fluids, antibiotics, and vasoactive medication at their discretion.

Results: During the first 24 hours of severe sepsis or septic shock, 379/388 (98%) of patients received either HES 130/0.4 (10%), crystalloids (17%), or both (73%). The mean total amount of fluid during the first 24 hours was 3,780 ± 2,487 mL. The mean volume of HES 130/0.4 in 0-6 hours was 938 ± 529 mL and 830 ± 731 mL in 6-24 hours. On regression analysis, the following patient characteristics were independently associated with renal dysfunction: male gender, increase in Simplified Acute Physiology II (SAPS II) score, surgical admission, no Sequential Organ Failure Assessment (SOFA) score improvement during first 24 hours. The need for vasopressors and baseline creatinine were independently associated with renal replacement therapy.

Conclusion(s): HES 130/0.4 was widely used and not associated with renal dysfunction.

Perspective: At best, this observational study provides hypothesis-generating information. However, due to multiple limitations (e.g., prescriber able to choose therapies, how quickly fluid given, variability in compliance with recommendations), it does not provide strongly applicable clinical guidance.

Association of Body Temperature and Antipyretic Treatments with Mortality of Critically Ill Patients with and without Sepsis: Multi-centered Prospective Observational Study

Egi M, Kim JY, Suh GY, et al. Crit Care. 2012;16:R33.

Study Question: Is there an independent association between fever, antipyretic treatment, and mortality in critically ill patients with and without sepsis?

Study Description: This prospective, observational study included adult patients requiring ≥ 48 hours of intensive care at 25 hospitals in Korea and Japan from September through November 2009. Patients were stratified based on the presence or absence of sepsis during the first 24 hours of ICU admission. Body temperatures were recorded every four hours for 28 days or until ICU discharge. No protocols were utilized for prevention or treatment of fever, but all antipyretics administered for fever (not pain) were recorded. The primary outcome was 28-day mortality and its association with maximum body temperature (MAX_{ICU}) and antipyretic treatment.

Results: Over 1,400 patients were included: 606 (42.5%) with and 819 (57.5%) without sepsis. Septic patients were older and more severely ill, less likely to be post-operative or require mechanical ventilation, and had significantly higher 28-day mortality and MAX_{ICU} compared to non-septic patients. On multivariate analysis, MAX_{ICU} 37.5°C-38.4°C was associated with decreased mortality in septic patients compared to the reference range (36.5°C-37.4C°), while MAX_{ICU} ≥ 38.5°C was not. For non-septic patients, risk of death increased with MAX_{ICU}, and MAX_{ICU} ≥39.5°C was associated with mortality (odds ratio [OR] 8.14; p = 0.01). Over half of patients received antipyretic treatment with non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen, or physical cooling. Pharmacologic antipyretic treatment was significantly associated with increased mortality in septic patients (NSAIDs : OR 2.32, p = 0.02; acetaminophen OR 2.3 and p = 0.002); no similar relationship was observed in non-septic patients.

Conclusion(s): The association of fever and antipyretic treatment with mortality differed

between critically ill patients with and without sepsis. MAX_{ICU} ≥39.5°C was associated with 28-day mortality in non-septic patients, while the administration of NSAIDs and acetaminophen was independently associated with mortality in septic patients.

Perspective: These findings support the hypothesis that fever as a host response is protective against infectious diseases and its suppression with antipyretics may worsen outcomes. However, given the observational nature of this trial, it would be a mistake to assume causality.

Evaluating Contemporary Antibiotics as a Risk Factor for *Clostridium difficile* Infection in Surgical Trauma Patients

Shah K, Pass LA, Cox M, et al. J Trauma. 2012;72:691-5.

Study Question: To identify whether specific antibiotics are associated with an increased risk of *Clostridium difficile* infection in hospitalized patients.

Study Description: This article describes a retrospective study where the case group had a positive *C. difficile* toxin assay at least 48 hours after admission and the control group did not. Patients between groups were matched for age and length of stay. If > 5% of case patients had been exposed to a particular antibiotic, then it was chosen for comparison.

Results: Sixty-seven patients had a positive *C. difficile* toxin assay, with trauma patients representing over half of both groups. Patients with prolonged exposure (defined as > 7 days) to cefepime, imipenem/cilastatin, and piperacillin/tazobactam were significantly more likely to develop CDI. Case patients more commonly received regimens consisting of 3 of more antibiotics and were exposed to 3 or more antibiotic classes.

Conclusion(s): Authors conclude these results may be used to help guide antimicrobial selection.

Perspective: This study's results reaffirm the association between antibiotic exposure and the risk of developing CDI. Risk lies with broad-spectrum antibiotics in particular and the use of multiple antibiotic classes, reinforcing the importance of streamlining antimicrobial therapy outside of select indications such as polymicrobial infections and empiric therapy in patients with risk factors for infection with multi-drug resistant organisms.

Ventilator-Associated Pneumonia: Bacteremia and Death after Traumatic Injury

O'Keefe GE, Caldwell E, Cuschieri J, et al. J Trauma. 2012;72:713-9.

Study Question: What is the incidence of bacteremia with ventilator-associated pneumonia (VAP) and impact on patient outcomes in critically ill, trauma patients?

Study Description: This article describes a retrospective, single-center study of critically ill patients with culture-positive VAP. Secondary bacteremias were considered associated with VAP if the same organism from respiratory cultures was isolated in the blood within 24 hours of VAP diagnosis. A VAP treatment algorithm favored cephalosporins ± vancomycin, and the duration of therapy depended on the pathogen identified and the presence or absence of a secondary bacteremia.

Results: The study included 554 patients with VAP, 14% of whom had secondary bacteremias. The

majority of patients had a monomicrobial infection, with the most common organisms being *Staphylococcus aureus* and *Acinetobacter* spp. Patients with VAP and an associated bacteremia experienced higher rates of morbidity and mortality (26% and 12%, respectively; $p < 0.001$ for the latter) than patients with isolated VAP. VAP with bacteremia was associated with an approximate 2.5-fold increase in the risk for death.

Conclusion(s): Traumatically injured patients who experience a secondary bacteremia associated with VAP have worse outcomes than those without a bacteremia.

Perspective: In general, trauma populations are often younger and otherwise healthy at the time of injury (in contrast to medical ICU patients and others) and are therefore likely to represent the lower end of the range of bacteremic incidence associated with episodes of VAP.

OTHER RECENT PUBLICATIONS OF INTEREST

Angiolillo D, Firstenberg MS, Price MJ, et al. **Bridging Antiplatelet Therapy with Cangrelor in Patients Undergoing Cardiac Surgery. A Randomized Controlled Trial.** *JAMA*. 2012;307:265-74.

Cline JM, Woods CR, Ervin SE, et al. **Surveillance tracheal aspirate cultures do not reliably predict bacteria cultured at the time of an Acute Respiratory Infections in Children with Tracheostomy Tubes.** *Chest*. 2012;141:625-31.

Domingo A, Al-Yahya AA, Asiri Y, et al. **A Systematic Review of the Effects of Pharmacological Agents on Walking Function in People with Spinal Cord Injury.** *J Neurotrauma*. 2012;29:865-79.

Jakoby MG, Nannapaneni. **An Insulin Protocol for Management of Hyperglycemia in Patients Receiving Parenteral Nutrition Is Superior to Ad Hoc Management.** *JPEN J Parenter Enteral Nutr*. 2012;36:183-8.

Jensen LO, Thayssen P, Hansen HS, et al. **Randomized Comparison of Everolimus-Eluting and Sirolimus-Eluting Stents in Patients Treated with Percutaneous Coronary Intervention (The SORT OUT IV Trial).** *Circulation*. 2012;125:1246-55.

Leung S, Pokharel R, Gong MN. **Statins and outcomes in patients with bloodstream infection: a Propensity-Matched Analysis.** *Crit Care Med*. 2012;40:1064-71.

Li G, Gu R, Wen X, et al. **The Effect of Early Enteral Nutrition on Hyperthermic Intraoperative Intraperitoneal Chemotherapy-Induced Mucosal Permeability Following Gastrectomy.** *JPEN J Parenter Enteral Nutr*. 2012;36:213-8.

Stewart GC, Givertz MM. **Mechanical Circulatory Support for Advanced Heart Failure: Patients and Technology in Evolution.** *Circulation*. 2012;125:1304-15.

Turpin RS, Canada T, Rosenthal V, et al. **Bloodstream Infections Associated with Parenteral Nutrition Preparation Methods in the United States: a Retrospective, Large Database Analysis.** *JPEN J Parenter Enteral Nutr*. 2012;36:169-76.