CRITICAL CARE PHARMACOTHERAPY LITERATURE UPDATE

November 2012

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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The Association Between Fluid Balance and Outcomes after Subarachnoid Hemorrhage

Martini RP, Deem S, Brown M, et.al. Neurocrit Care. 2012;17:191-8.

Study Question: Is early fluid balance (as part of triple-H therapy – hypertension, hypervolemia, hemodilution) associated with prognosis following aneurysmal subarachnoid hemorrhage (SAH)?

Study Description: Researchers performed a retrospective review of adult patients (n = 356) with aneurysmal SAH admitted to study center between May 1999 and December 2004. Pregnant patients or those with traumatic, venous or nonaneurysmal SAH were excluded. Patients were grouped as (1) positive fluid balance (group P, ICU day 3 positive cumulative fluid balance) or (2) negative fluid balance (group N, ICU day 3 zero or negative cumulative fluid balance). Patients with SAH were managed based on established guidelines (eg. nimodipine, daily Transcranial Dopplers [TCDs], etc.). Patients with vasospasm had higher BP and CVP targets.

Results: Most baseline characteristics were similar between both groups, though notably, patients in group P had significantly worse GCS and Hunt-Hess scores, but similar Fischer Grades on presentation. On ICU day 3, patients in group P had lower hematocrit, higher SOFA scores, higher serum sodium values, higher percentage of patients with mechanical ventilation, received more blood products, and were less likely to receive fludrocortisone. Patients in group P did not get cumulatively more fluids but that they excreted cumulatively less fluids. The primary outcome, a composite of hospital death or new stroke, was significantly higher in group P (38% vs. 25%, p = 0.02), as was cerebral vasospasm (44% vs. 33%, p = 0.04). Hospital and ICU lengths of stay were also significantly longer in group P.

Conclusion(s): Patients with positive fluid balance had worse neurological presentation and longer ICU and hospital stays, and hypervolemia may be independently associated with vasospasm.

Perspective: SOFA scores and neurologic status may help guide early fluid administration. However, the association of hypervolemia with outcomes is difficult to discern from this study alone because patients in group P had a higher severity of illness on presentation. A standardized protocol of fluid administration may not optimally fit all patients with SAH and should provide the flexibility of deviation and tailoring to an individual patient's response.

Tight Glycemic Control Versus Standard Care After Pediatric Cardiac Surgery

Agus M, Steil G, Wypij D, et.al. N Engl J Med. 2012; 367:1208-19.

Study Question: Does tight glycemic-control reduce peri-operative morbidity, particularly healthcare-associated infections, in children after surgery with cardiopulmonary bypass?

Methods: Investigators conducted a two-center clinical trial that enrolled children up to 36 months old who had been admitted to the cardiac ICU following surgery with cardiopulmonary bypass. Children with diabetes or lack of intravascular access were excluded. Children were randomized to tight glycemic control (blood glucose 80-110 mg/dL) via intravenous insulin infusion or standard care (insulin per physician discretion). The primary outcome was

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number of healthcare-associated infections per 1000 patient-days.

Results: Close to 1,000 patients were randomized: 496 to glycemic-control and 493 to standard care. Baseline characteristics of the groups were similar, and 444 children (91%) in the glycemic-control group received insulin compared to 9 children (2%) in the standard care group ($p < 0.001$). Despite similar admission blood glucose values, the glycemic-control group: achieved normoglycemia earlier than the standard care group (6 hours vs. 16 hours, $p < 0.001$); spent more time within the target glucose range (50% vs. 33%, $p < 0.001$); and had lower time-weighted glucose averages than the standard care group (112 mg/dL vs. 121 mg/dL, $p < 0.001$). Severe hypoglycemia (< 40 mg/dL) was uncommon in both groups (3% glycemic-control vs. 1% standard care, $p = 0.03$), while the rate of *any* hypoglycemia (< 60 mg/dL) was significantly higher with glycemic-control (19% vs. 9%, $p < 0.001$). The study's authors found no difference in 30-days infection rates between the glycemic-control and standard care groups, respectively, in the intention-to-treat (8.9 vs. 9.8, $p = 0.78$) or per-protocol (8.6 vs. 9.9, $p = 0.67$) analysis, nor were there any differences in mortality, length of stay, duration of mechanical ventilation, or rates of organ failure.

Conclusions: Tight glycemic-control did not change the rate of healthcare-associated infections, mortality, or ICU length of stay compared to standard care; however, generalization of these results to other institutions and pediatric populations should be made cautiously.

Perspective: Another in pediatric critical illness of comparable design (Vlasselaers D et al. Lancet. 2009;373:547-56) demonstrated decreased mortality and secondary infections with tight glycemic-control. However, because the mortality in the earlier study was mostly related to factors indirectly related, at best, to metabolic circumstances (e.g., surgical or anatomical complications), it is difficult to attribute the early study's mortality benefit to tight glycemic control. Taken together, the two studies do not appear to suggest significant clinical benefit from tight glycemic control outside, perhaps, of the setting of metabolic derangement.

Etomidate Increases Susceptibility to Pneumonia in Trauma Patients

Asehnoune K, Pierre JM, Philippe S, et.al. Intensive Care Med. 2012;38:1673-82.

Study Question: In trauma patients, does etomidate increase the rate of critical illness-related corticosteroid insufficiency (CIRCI) and 28-day hospital-acquired pneumonia (HAP) rate, and does subsequent hydrocortisone treatment curtail the rate of HAP in patients receiving etomidate?

Methods: This article is a *post hoc* analysis of the HYPOLYTE trial: a multi-center, randomized, double-blind trial of 149 trauma patients age > 15.25 years old with expectation of mechanical ventilation (MV) > 48 hours. The exclusion criteria included previous adrenal insufficiency, immunosuppression, pregnancy, and treatment with corticosteroids within last 6 months, and patients with CIRCI (basal cortisol < 15 mcg/dL or Δ < 9 mcg/dL from 0.25 mg corticotropin injection) were assigned to receive either hydrocortisone (continuous infusion 200 mg/day x 5 days, 100 mg on day 6 and 50 mg day 7) or placebo.

Results: Ninety five patients (64%) received etomidate, and more of these patients developed CIRCI (83% vs. 63%, $p = 0.006$) and HAP (51.6% vs. 29.6%; $p = 0.009$) than those who had not although

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there was no difference in basal cortisol levels between patients who had and had not received etomidate. Of the patients who received etomidate, 52.6% received hydrocortisone and 47.4% placebo. The incidence of HAP was lower in those receiving hydrocortisone (40% vs. 62%, p = 0.032), as well as duration of MV (9 vs. 18 days, p < 0.001) and ICU LOS (13 vs. 21 days, p < 0.001), but not mortality (6.7% vs. 6%, p = NS). Independent risk factors for HAP were etomidate use (OR 2.48, 95% CI 1.19-5.18) and TBI (OR 3.05, 95% CI 1.5-6).

Conclusions: Etomidate use should be limited in severe trauma patients unless hydrocortisone is used to counteract its effects.

Perspective: This study provides further support for avoiding etomidate in critically ill trauma patients. ICU teams should consider testing for CIRCI post-etomidate administration in this patient population and treating with low-dose hydrocortisone if CIRCI is detected.

Diurnal Sedative Changes During Intensive Care: Impact on Liberation from Mechanical Ventilation and Delirium

Seymour CW, Pandharipande PP, Koestner T, et al. Crit Care Med. 2012;40:2788-96.

Study Question: Are benzodiazepine and propofol doses increased at night (as past anecdotal evidence suggests), and is the magnitude of daytime and nighttime sedative dosing associated with delirium, coma, and delayed liberation from mechanical ventilation (MV)?

Study Description: This study was a single-center, prospective, cohort study (n = 140) that was conducted within the Awaking and Breathing Controlled randomized trial evaluating paired sedation and ventilator weaning protocols for MV ICU patients. (Of note, the trial protocol did not include explicit instruction for nighttime sedation.) Adult patients receiving MV for > 12 hours were excluded if they were admitted after cardiopulmonary arrest, had neurologic deficits that prevented independent living, were of moribund status, received MV for > 2 weeks, or were enrolled in a separate trial. Average hourly sedative doses for benzodiazepine and propofol during daytime (7 AM to 11 PM) and nighttime (11 PM to 7 AM) hours were evaluated.

Results: Overall, the average hourly dose of benzodiazepines and propofol among those receiving the drugs remained relatively constant. The change in nighttime hourly sedative dosing was small: nighttime doses were increased in 33-45% of patients receiving benzodiazepines and 30-59% of patients receiving propofol. On logistic regression analysis, both higher daily doses and increases in nighttime benzodiazepine doses were associated with reduced odds of successful SBT the following day (p < 0.01). Higher daytime benzodiazepine doses were associated with unsuccessful extubation the following day (p = 0.02), although nighttime benzodiazepines dose changes haad no association with successful extubation the following day. Neither the average hourly daytime nor changes in nighttime propofol rates were associated with delay in successful SBT or delayed extubation. The average hourly daytime dose and nighttime increases of benzodiazepines were associated with delirium (p < 0.01 and p = 0.05, respectively), although propofol use was not associated with the incidence of delirium. The average hourly daytime doses of benzodiazepines and propofol were associated with coma the following day (p < 0.01 and p < 0.02, respectively).

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Conclusion: Benzodiazepine and propofol doses remained relatively constant day and night. High daytime benzodiazepine use and nighttime dosing increases were associated with reduced odds of successful SBT and extubation, and higher incidence of delirium and coma.

Perspective: Reduction in sedative exposure remains an important goal in MV, critically ill patients. Because of delays in extubation and increased risk of delirium, benzodiazepines should be employed as a second-line sedatives except in cases of demonstrated need and where they are the unequivocal standard of care (e.g., dependence, alcohol withdrawal, etc.).

Hydroxyethyl Starch or Saline for Fluid Resuscitation in Intensive Care

Myburgh JA, Finfer S, Bellomo R, et.al. N Engl J Med. 2012; Oct 17. Epub ahead of print.

Study Question: Is it safe and effective to use 6% hydroxyethyl starch (HES) (130kD/0.4) versus normal saline (NS) for fluid resuscitation in the intensive care unit (ICU)?

Study Description: This multicenter, blinded, randomized, controlled trial compared HES and NS for fluid resuscitation in ICU patients (n = 7,000). Adult participants were included if they required resuscitation with an IV fluid bolus in addition to maintenance fluids as determined by the treating clinician. Notable exclusion criteria were receipt of >1 L of HES prior to screening, current or impending need for dialysis, burn, cardiac surgery, or evidence of intracranial hemorrhage. Volume administration was guided by clinician preference with protocol-suggested objective markers (e.g., HR > 90, CVP < 10, etc.). The maximum daily dose of HES was 50 mL/kg, beyond which patients were given open-labeled NS for the remainder of the 24-hour period.

Results: There was no difference in the primary outcome of 90-day mortality was observed in patients receiving HES compared to NS (18% vs. 17%, p = NS). HES patients required the use of renal-replacement therapy more frequently (7% vs. 5.8%, p = 0.04) and experienced more adverse events (5.3% vs. 2.8%, p < 0.001; primarily pruritus). No difference in coagulopathy was noted between groups. Patients in the NS arm developed new cardiovascular failure more frequently than those who received HES [RR 0.91 (0.84 to 0.99)]. The HES arm showed statistically, but not clinically significant less volume of total daily fluid administration during the first 4 days after randomization (daily average of 526 ml vs. 616 ml, p < 0.001).

Conclusion(s): For ICU patients requiring fluid resuscitation, 90-day mortality was not different for those patients receiving HES vs. NS, although patients who received HES required renal-replacement therapy more frequently.

Perspective: Although a protocolized resuscitation strategy was not used in this heterogenous group of critically ill patients, this study does add to existing literature reinforcing the concerns about starches, even a low-molecular weight alternative, as they appear to be associated with an increased risk of adverse renal function. The increased risk and cost does not justify the use of HES over crystalloids in all ICU patients.

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Treatment with Neuraminidase Inhibitors for Critically Ill Patients with Influenza A (H1N1) pdm09

Louie JK, Yang S, Acosta M, et.al. Clin Infect Dis. 2012;55: 1198-204.

Study Question: Does treatment with neuraminidase inhibitors (NAIs), including timing of treatment, affect survival of critically ill patients with Influenza A H1N1 PDM09 (pH1N1)?

Study Description: In this retrospective observational database study, patients with pH1N1 treated with NAIs were compared to those not treated with regard to survival. A California state database of all patients who were hospitalized or died from pH1N1 from Apr 3, 2009 and Aug 10, 2010 was used for data extraction. Included patients were polymerase chain reaction-positive for pH1N1, admitted to an ICU, and had signs and symptoms of respiratory failure.

Results: During the study period, 2,144 cases were identified of which 1,950 (91%) were hospitalized in the ICU and 194 (9%) died outside of the hospital; 1,859 ICU patients had information available on treatment of which 1676 (90%) were treated with NAIs and 183 (10%) were not. NAI-treated patients were younger, had a lower prevalence of metabolic disease, and a higher prevalence of pregnancy. Among the NAI-treated patients, 99.7% received oseltamivir. Treatment regimens varied greatly by dosing and duration. The median time from symptom onset to NAI treatment was 4 days, and survival was higher in patients treated with NAIs (75% vs. 58%, $p < 0.0001$). Patients treated with NAIs up to 5 days after symptom onset were more likely to survive compared with all untreated patients ($p < 0.05$). There were no significant differences between NAI-treated and not-treated cases with regard to development of complications such as pneumonia or other secondary bacterial infection, sepsis, acute kidney injury, or the need for mechanical ventilation.

Conclusion: Critically ill patients with pH1N1 are more likely to survive when treated with NAIs, with earlier initiation of NAI treatment conveying the most benefit. Treatment ≤ 5 days after symptom onset is associated with improved survival compared with non-treatment.

Perspective: This study offers some evidence of a mortality benefit of initiating NAI treatment in critically ill hospitalized pH1N1 patients up to 5 days after symptom onset. This study does not address outpatient NAI treatment. Optimal dose and duration of treatment is unknown as dosing varied widely in this study.

Other Recent Publications of Interest

Desmettre T, Dehours E, Samama CM, et al. **Reversal of vitamin K antagonist (VKA) effect in patients with severe bleeding: a French multicenter observational study (OPTIPLEX) assessing the use of prothrombin complex concentrate (PCC) in current clinical practice**. *Crit Care*. 2012;16:R185. doi: 10.1186/cc11669.

Fuster V, Bhatt DL, Califf RM, et.al. **Guided antithrombotic therapy: current status and future research direction. Report on a National Heart, Lung and Blood Institute Working Group.** *Circulation*. 2012;126:1645-62.

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Hurt RT, Frazier TH, McClave SA, et.al. **Stress prophylaxis in intensive care unit patients and the role of enteral nutrition**. *JPEN*. 2012;36:721

Paredes-Andrade E, Solid CA, Rockswold SB, et al. **Hypertonic saline reduces intracranial hypertension in the presence of high serum and cerebral osmolalities**. *Neurocrit Care*. 2012;17:204-10.

Shah SJ. **Pulmonary hypertension.** *JAMA*. 2012; 308:1366-74.

Sheth KN, Shah N, Morovati T, et.al. **Intravenous rt-PA is not associated with increased risk of hemorrhage in patients with intracranial aneurysms.** *Neurocrit Care*. 2012;17:199-203.

Siegal D, Yudin J, Kaatz S, et al. **Periprocedural heparin bridging in patients receiving vitamin K antagonists: systematic review and meta-analysis of bleed and thrombotic rates**. *Circulation*. 2012;126: 1630-9.

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