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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PROCALCITONIN GUIDED INTERVENTIONS AGAINST INFECTIONS TO INCREASE EARLY APPROPRIATE ANTIBIOTICS AND IMPROVE SURVIVAL IN THE INTENSIVE CARE UNIT: A RANDOMIZED TRIAL

Jensen JU, Hein L, Lundgren B, et al. Crit Care. 2011;39:2048-58.

Study Question: Does daily monitoring of procalcitonin (PCT) improve management and outcomes of infections?

Study Description: This study ("PASS") was a multi-center, open-label randomized controlled trial (RCT) conducted in medical/surgical ICUs in Danish academic, tertiary care hospitals. The study intervention consisted of using daily PCT levels to guide escalation of monitoring and antimicrobial coverage in an algorithm/protocol for management of infections in the ICU.

Results: There was no difference in the primary endpoints of 28-day mortality 31.5% (190 of 604) in the PCT arm compared to 32.0% (191 of 596) of patients in the standard-of-care-only arm. Inclusion of PCT levels (vs. standard algorithm) resulted in significantly greater length of MV (65.5% vs. 60.7% of days), median ICU LOS (6 vs. 5 days), median antimicrobial exposure (6 vs. 4 days), and total number of cultures performed (7,874 vs. 6,641), with no apparent advantage in time to appropriate antimicrobial therapy.

Conclusion(s): The authors concluded that real-time, daily knowledge of PCT levels does *not* improve the management or outcomes for protocol-based therapy of infection in ICU patients.

Perspective: This study represents a challenge to the promise of earlier studies suggesting that PCT is an effective biomarker identifying and separating infection and treatment failure from other ICU complications. The negative findings may stem from an emphasis, in study design, on using PCT to unilaterally escalate care, without the apparent balance of using levels to guide de-escalation or cessation of therapy. Finally, the relatively low sensitivity (59%) of PCT for infection was surprising and serves as reminder that the role of PCT in the ICU remains to be elucidated.

CLUE: A RANDOMIZED COMPARATIVE EFFECTIVENESS TRIAL OF IV NICARDIPINE VERSUS LABETALOL USE IN THE EMERGENCY DEPARTMENT

Peacock WF, Varon J, Baumann BM, et al. Crit Care. 2011:15;R157.

Study Question: To determine the safety and efficacy of nicardipine infusion vs. IV bolus labetalol for the management of acute hypertension in the emergency department (ED).

Study Description: Patients were enrolled in this RCT if they were > 18 years old with systolic blood pressure (SBP) > 180 mmHg and able to sign informed consent. There were several exclusion criteria including contraindication to a beta-blocker or calcium channel blocker, or a condition that would preclude randomization to either agent. Medication dosing was at the physician's discretion and physicians were provided with FDA approved dosing recommendations. Use of other

antihypertensive agents was discouraged during the first 30 minutes following study drug administration. The primary endpoint was number of patients within target SBP range (goal SBP ± 20 mmHg; determined by the treating physician) at 30 minutes.

Results: Researchers enrolled 226 patients. Baseline SBP was 212 mmHg and 210 mmHg for the nicardipine and labetalol groups, respectively. There was no significant difference in median initial SBP target (nicardipine 169 mmHg; labetalol 165 mmHg). More patients in the nicardipine group reached their target range at 30 minutes (91.7% vs. 82.5%; p = 0.039). At study completion, median SBP was 163 mmHg for nicardipine and 168 mmHg in the labetalol group (95% CI of the difference = -13.3 to -2.0). The mean number of titrations was 2.2 for nicardipine and 1.3 for labetalol (p < 0.001). There was no difference in the proportion of patients with blood pressure lowered *below* the target range. Patients receiving labetalol had a greater reduction in heart rate.

Conclusion(s): In this clinical trial, patients receiving nicardipine infusion were more likely to reach target SBP range within 30 minutes than patients receiving IV labetalol bolus.

Perspective: The authors note that separation of effect curves was seen at 15 minutes, a time period which allows for re-dosing of labetalol; however, the mean number of labetalol doses was 1.3, indicating that the majority of patients did not receive a second bolus. The decision not to re-dose the patient was left to the discretion of the treating physician and could be a confounding factor. Also, use of other antihypertensive agents was discouraged, but not prohibited, during the first 30 minutes after study drug administration. The authors did not report the nature or extent of additional antihypertensive use.

Randomized Controlled Trial Comparing The Effect Of 8.4% Sodium Bicarbonate And 5% Sodium Chloride On Raised Intracranial Pressure After Traumatic Brain Injury

Bourdeaux CP, Brown JM. Neurocrit Care. 2011;15:42-5.

Study Question: What are the effects of equi-osmolar (EO) doses of 8.4% sodium bicarbonate and 5% NaCl on elevated intracranial pressure (ICP) after a traumatic brain injury (TBI)?

Study Design: This study was a single-center RCT of adult patients requiring sedation, ventilation, and ICP monitoring following TBI. For each episode of unprovoked ICP > 20 mmHg for > 5 min, patients were randomized to receive EO doses of either hypertonic NaCl (100 ml, 5%) or sodium bicarbonate (85 ml, 8.4%) over 30 minutes.

Results: Twenty episodes of elevated ICP were identified in 11 patients. Both treatments reduced ICP effectively, causing a decrease from baseline at all time points (P < 0.001). ICP fell below 20 mmHg after 30 minutes in all treatment episodes. There were no significant differences in ICP over time between patients receiving NaCl vs. sodium bicarbonate.

Conclusion(s): Both 8.4% sodium bicarbonate and 5% NaCl were effective in decreasing ICP in patients with TBI, and there were no significant differences in measures between either of the agents. The study's authors suggest that hypertonic sodium bicarbonate may be a desirable therapeutic option in patients with or at risk of developing hyperchloremic acidosis.

Perspective: While the agents appear equally as effective in decreasing ICP, it is worth bearing in mind that this study was not designed to detect differences in *clinical* outcomes. Nonetheless, both agents may be viable options in lowering ICP following TBI, with NaCl retaining its first-line status in patients who do not have or are not at risk of hyperchloremia.

Safety And Efficacy Of Heparin Or Enoxaparin Prophylaxis In Blunt Trauma Patients With A Head Abbreviated Injury Severity Score >2

Minshall CT, Eriksson EA, Leon SM, et al. J Trauma. 2011;71:396-400.

Study Question: What is the optimal timing and type of chemical prophylaxis, UFH vs. LMWH, in patients with TBI?

Study Description: This was a 42 month retrospective review of adult trauma patients admitted to the ICU with a Head Abbreviated Injury Severity score (HAIS) > 2 and ICU LOS > 48 hours. Patients were excluded if they had isolated neck injury. All included patients were treated with sequential compression devices initially and throughout hospital stay; chemical prophylaxis was initiated once a patient's ICH was considered stable. The prescribing physician determined the type of prophylaxis: enoxaparin 30 mg SC BID or UFH 5,000 units SC TID. Data collected included worsening ICH, clinical finding of DVT confirmed with duplex ultrasound, and clinical finding of PE confirmed by 128-slice helical CT pulmonary angiogram.

Results: A total of 386 patients were included in the review. Most patients received chemical prophylaxis at some point during their stay: 40.9% received LMWH; 44.3% received UFH; and 14.8% received only SCDs. HAIS and ISS scores were significantly higher in patients who received UFH compared to LMWH, although patients who *did not* receive chemical prophylaxis had the *highest* HAIS. There were no significant differences between ICU and hospital LOS in the LMWH (eight and nineteen days) compared to UFH group (eleven and seventeen days) (patients in the SCD only group had much shorter LOSs of two and four days). The UFH group had a significantly higher rate of DVT (1%) and PE (3.7%) than those treated with LMWH (1% and 0; $p < 0.05$). There were no hemorrhagic complications requiring transfusion in either chemical prophylaxis group.

Conclusion(s): The authors conclude that early administration of chemical prophylaxis in patients with severe TBI had a low rate of hemorrhagic complications requiring surgical intervention and that LMWH is more effective than UFH in preventing thrombotic complications. Further prospective studies are needed for comparison and determination of optimal chemical prophylaxis in this high risk population.

Perspective: To date, this is the largest comparison of LMWH and UFH chemical prophylaxis in patients with severe blunt head trauma. Limitations of this study include those inherent to a retrospective review, including potential selection bias. Of note, the small number of patients included in this review who *did not* receive chemical prophylaxis *included* those who were discharged or died within 96 hours of admission. The results suggest that patients with *less severe* injuries were more likely to get LMWH, while those with *more severe* injuries were treated with UFH or no agent. The low rates of DVT are likely due to a lack of a routine screening protocol.

Dosing Frequency of Unfractionated Heparin Thromboprophylaxis: A Meta-analysis

Phung OJ, Kahn SR, Cook DJ, et al. Chest. 2011;140:374-81.

Study Question: Is there a difference between BID and TID dosing of unfractionated heparin (UFH) in thrombosis and major bleeding rates for hospitalized medical patients?

Study Description: This was a pooled analysis of sixteen RCTs and 27,667 non-surgical patients. Eligible studies compared UFH BID, UFH TID, or LMWH to one another or an inactive group.

Results: There was a significant reduction in *DVT* rates in patients who received thromboprophylaxis as compared to the inactive therapy but *no* significant difference between active therapy groups. However, there were no statistically significant differences in rates of PE, death, or major bleeding between any of the thromboprophylaxis groups and the inactive groups.

Conclusion(s): The authors conclude that there is no difference in thrombosis or bleeding rates between BID and TID dosing of UFH for medical patients admitted to the hospital.

Perspective: This analysis included non-surgical patients with a variety of indications for thromboprophylaxis. As no head-to-head RCTs between different UFH prophylactic dosing regimens exist, the authors noted that this was likely the best comparison possible utilizing existing studies. However, results of this study may not be completely applicable to patients admitted to the medical ICU, given that floor patients were included in the analysis.

Quetiapine In Refractory Hyperactive And Mixed Intensive Care Delirium: A Case Series

Ruth YY Wan, Moneesha Kasliwal, Catherine A McKenzie, et.al. Crit Care. 2011;15:R159.

Study Question: Is quetiapine safe and effective when administered to patients with hyperactive or mixed delirium refractory to other management strategies?

Study Description: This is a retrospective, single-center case series of quetiapine-naïve ICU patients. Refractory hyperactive or mixed delirium was defined as a RASS > 1 for longer than 48 hours, electronic medical record (EMR) documentation of an acute confusional state, and use of two or more agents prior to introduction of quetiapine.

Results: Seventeen patients were included in this series, the majority of which were male (88%) and on mechanical ventilation (MV) (94%). Both medical (59%) and surgical patients (41%) were included, and median (range) ICU length of stay (LOS) was protracted at 41 days (16-235). Quetiapine was initiate 15 (3-48) days into the course of delirium and a combination of several agents including haloperidol, lorazepam, propofol, opioids, and clonidine were used prior to and during quetiapine therapy. Patients experienced a resolution of delirium within 4 (2-29) days after starting quetiapine. Adverse effects included QTc prolongation (n = 1), excessive somnolence (n = 1), and transient hypotension (n = 2).

Conclusion: There is a temporal association between the commencement of quetiapine therapy and the resolution of refractory hyperactive or mixed delirium.

Perspective: Despite carrying limited weight as a small case series, this study yields some insights into treatment of a patient population (those with treatment refractory delirium in the ICU) from who there are limited data published. Proactive identification of delirious patients using validated tools such as the CAM-ICU or ICDSC is important to ensure that deliriogenic medications such as benzodiazepines, which were used for early delirium management in many of the patients in this series, do not contribute to or exacerbate this dangerous condition. Patients with hypoactive delirium remain challenging to identify and treat, and this case series unfortunately does not provide any information about that subpopulation of delirious patients.

Safety of Intravenous Thrombolysis within 4.5 h of Symptom Onset in Patients with Negative Post-Treatment Stroke Imaging for Cerebral Infarction

Giraldo E, Khalid A, Zand R. Neurocrit Care. 2011;15:76-9.

Study question: To determine the safety of IV thrombolysis within the first 4.5 hours of stroke symptom onset in patients later determined not to have had a cerebral infarction.

Study description: This article described a retrospective study of patients treated with IV recombinant tissue plasminogen activator (rt-PA) within 4.5 h of stroke symptom onset. Patients had pre-thrombolytic head CT as well as post-thrombolytic multi-modal brain MRI with diffusion-weighted imaging (DWI) and head and neck MRA. Patients who did not have a cerebral infarction were diagnosed retrospectively with a TIA or stroke mimic based on the clinical presentation, hospital course, and negative post-thrombolytic DWI for cerebral infarction.

Results: Eighty-nine patients were treated with rt-PA within 4.5 h of stroke symptom onset. One patient expired shortly after rt-TPA infusion due to ruptured aortic aneurysm and was excluded from the study. Twenty-six percent of patients had negative DWI for cerebral infarction within 24 h of admission. Of those, 15.7% had a TIA and 10.1% had a stroke mimic (complicated migraine, seizure with Todd's paralysis, or somatoform disorder). The patients with negative DWI were significantly younger (52 vs. 62 years old; $p < 0.01$) and had: a lower rate of arterial hypertension (52% vs. 80%; p = NR); a higher rate of psychiatric disease (17% vs. 3%; $p < 0.05$); a lower median NIHSS score (6 vs. 11; $p < 0.001$); and a shorter hospital LOS (4 vs. 9 days; $p < 0.01$). Twenty-six percent of both the DWI-negative and -positive patients were treated within 3-4.5 h after stroke symptom onset. Among the patients who had a confirmed diagnosis of ischemic stroke (n = 66), 4 (6.1%) had symptomatic ICH (and one received rt-PA within the 3-4.5 h timeframe). None of the DWI-negative patients had symptomatic or asymptomatic ICH on follow-up imaging.

Conclusion: The study authors suggest that administration of rt-PA within 4.5 hours of stroke symptom onset is safe in patients with suspected stroke even if post-thrombosis stroke imaging *does not* demonstrate cerebral infarction.

Perspective: This study suggests that delaying rt-PA to rule out TIA or stroke mimic is not warranted in terms of safety. Although the application of this

study is limited by its retrospective nature and small sample size, it adds to the literature supporting the current practice of allowing rt-PA administration up to 4.5 hours after stroke symptom onset.

Mild Hypoglycemia Is Independently Associated With Increased Mortality In The Critically Ill

Krinsley JS, Schultz MJ, Spronk PE, et al. Crit Care. 2011;15:R173.

Study Question: Is *mild* hypoglycemia, defined as blood glucose (BG) < 70 mg/dl, associated with an increased mortality risk?

Study Description: Data from two observational cohorts, one in Stamford, CT (ST; 1 hospital), and one in the Netherlands (NL; 3 hospitals), and from the prospective GLUCONTROL trial (GL; 19 European hospitals, 7 countries) were analyzed. Patients were included if they had at least 3 BG values during their ICU stay. A total of 3,263 patients were included in the ST cohort, with a glycemic target of 80-125 mg/dl. The NL cohort included 2,063 patients who were treated with either loose (BG < 150 mg/dl) or intensive insulin therapy (IIT; BG 80-110 mg/dl). The GL cohort included 914 patients treated with either IIT targets (BG 80-110 mg/dl) or loose targets (140-180 mg/dl).

Results: A total of 6,240 patients were included. Overall, the RR of death for patients with minimum BG < 40, 40-54, 55-69, and 70-79 mg/dl compared to those patients with a minimum BG 80-110 mg/dl was 3.55, 2.70, 2.18, and 1.43, respectively, with all differences being statistically significant. This association was independent of medical or surgical diagnosis, presence of diabetes, ICU LOS, and frequency of BG checks. Even patients with only a *single* incident of mild hypoglycemia (OR 1.31; p=0.01) had a higher risk of mortality.

Conclusion(s): A BG < 70 mg/dl was associated with an increased risk of mortality in ICU patients, even in patients with a single hypoglycemic episode, and this risk increased with worsening degree of hypoglycemia.

Perspective: Earlier observed associations have demonstrated an increased risk of mortality with *severe* hypoglycemia (BG < 40 mg/dl). This study confirms the association is also present with milder degrees of hypoglycemia. It is interesting that this association was present in a large, diverse patient population, exposed to different insulin protocols. Providers and institutions should strive to prevent hypoglycemia in ICU patients.