CRITICAL CARE PHARMACOTHERAPY LITERATURE UPDATE

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This is a monthly review of select articles in the medical literature pertaining to pharmacotherapy as applied in the critically ill patient population. The content below is for information purposes only and is intended to highlight recent articles that may be of interest those caring for patients in various critical or intensive care 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 and its findings.

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Comparison of bivalirudin and argatroban for the management of heparin-induced thrombocytopenia

Skrupky LP, Smith JR, Deal EN, et al. *Pharmacotherapy*. 2010;3:1229-38.

Study Question: Are there any differences between the direct thrombin inhibitors (DTIs) (argatroban and bivalirudin) in the achievement of therapeutic anticoagulation or in clinical outcomes in patients with heparin-induced thrombocytopenia (HIT).

Study Description: Although DTIs are the drugs of choice for treatment of HIT, only lepirudin and argatroban are FDA-approved for this indication. This study compared the achievement of therapeutic anticoagulation and clinical outcomes in patients who received argatroban or bivalirudin for HIT. Adult patients receiving either argatroban or bivalirudin for at least 24 hours between January 2007 and July 2008 for known or suspected HIT were enrolled in this retrospective, single-center study (N=138; n=46 argatroban; n=92 bivalirudin).

Results: The median initial doses for argatroban and bivalirudin were 1 mcg/kg/min and 0.06 mg/kg/hr, respectively. The achievement and maintenance of therapeutic activated partial thromboplastin times (aPTTs) was similar in both groups, but the argatroban group had a higher number of supratherapeutic aPTTs overall (18% vs 7.9%, p=0.046). Rates of thromboembolic events during or after DTI therapy, clinically significant bleeding, and death were not significantly different between groups.

Conclusions: The dosing information used to achieve therapeutic targets in this study is useful for clinical practice; however, prospective, randomized trials need to be conducted to confirm the safety and efficacy of bivalirudin in HIT management.

Comment: Statistically significant baseline differences between groups as a result of service provider preferences were a major limitation of this study in addition to the retrospective study design.

Fast point-of-care coagulometer guided reversal of oral anticoagulation at the bedside hastens management of acute subdural hemorrhage

Rizos T, Jenetzky E, Herweh C, et al. *Neurocrit Care*. 2010;13:321-5.

Study Question: Is point-of-care (POC), international normalized ratio (INR)-based, stepwise reversal of oral anticoagulants faster than central laboratory (CL) INR-based reversal in patients with nontraumatic subdural hematoma (SDH)?

Study Description: Patients taking phenprocoumon, an oral coumarin anticoagulant with a mechanism similar to warfarin, who were admitted with a nontraumatic SDH were included in this prospective study. Upon arrival to the emergency department, blood samples were sent to the CL for INR testing and an INR was obtained by POC measurement. Stepwise reversal of anticoagulation was performed using prothrombin complex concentrates (PCC) until INR was < 1.4.

Results: Ten patients were treated according to protocol. Agreement between initial POC and CL INR values was excellent, with a mean deviation of paired differences of 0.013 (SD: 0.32); limits of agreement were -0.61 to +0.64. During INR reversal, mean deviation of paired differences between POC and CL INR values was 0.081 (SD: 0.14); limits of agreement were +0.36 to -0.19. Median total time for INR reversal was shorter for POC testing versus CL testing (27 min vs 70 min). An estimated median reduction in PCC dose of 25% could be obtained with POC testing.

Conclusions: POC measurement of INR is a fast and economical way to reverse oral anticoagulants in patients with acute phenprocoumon-associated SDH.

Comment: Given the small sample size, further investigation should be conducted to determine the full extent of possible benefits and consequences of POC testing in this patient population. Additionally, inherent differences in turn-around time for CL INR results and PCC delivery and administration will grossly affect the utility of this regimen at various institutions. Additionally, selection of an appropriate POC device and quality control is critical.

DAPTOMYCIN PHARMACOKINETICS IN CRITICALLY ILL PATIENTS RECEIVING CONTINUOUS VENOVENOUS HEMODIALYSIS

Vilay AM, Grio M, Sowinski KM, et al. *Crit Care Med*. 2011;39:19-25.

Study Question: To determine the pharmacokinetics (PK) of daptomycin in patients receiving continuous venovenous hemodialysis (CVVHD)

Study description: Daptomycin, a concentration-dependent antimicrobial for non-pulmonary resistant gram-positive infections, is increasingly being used in critically ill patients. Researchers conducted a prospective, open-label study of eight adults with a known or suspected gram-positive infection and were receiving CVVHD. Patients were excluded if: their treatment was intended for osteomyelitis, meningitis, or pneumonia; they were pregnant; or they were receiving additional extracorporeal therapies.

Results: Daptomycin was infused at a dose of 8 mg/kg q48h to attain a goal C_{max} of 100 mcg/mL and an AUC_{0-24} of 500 mcg*hr/mL to approximate the estimated target goals for patients with bacteremias. Patients in this analysis had mean ± SD BMI of 28.3 ± 6.6 kg/m^2, received an average dose of 7.7 ± 0.6 mg/kg, and underwent a mean dialysate flow rate of 26 ± 4 mL/kg/h. The observed C_{max} was 81.2 ± 19 mcg/mL and calculated PK parameters included a median apparent steady-state Vd 0.17 L/kg, with a fraction unbound of 17.5 ± 5% (both higher than in healthy individuals), and a median $T_{1/2}$ 15.9 hours. A simulation comparing 4 mg/kg q24h to 8 mg/kg q48h demonstrated a higher C_{max} at steady-state with the 8 mg/kg dose, with comparable AUC_{96-144}.

Conclusion: This study demonstrates that 8 mg/kg q48h achieves approximate therapeutic goals for bacteremic CVVHD patients and is well tolerated and safe.

Comment: Intra-patient variability within the context of a small sample size may have had an affect on PK modeling, and the results should not be extrapolated to patients at extremes of weight.

TELAVANCIN VERSUS VANCOMYCIN FOR HOSPITAL-ACQUIRED PNEUMONIA DUE TO GRAM-POSITIVE PATHOGENS

Rubinstein E, Lalani T, Corey GR, et al. *Clin Inf Dis.* 2011;52:31-40.

Study Question: Is telavancin noninferior to vancomycin for the treatment of hospital-acquired pneumonia (HAP) due to Gram-positive pathogens?

Study Description: Two identical multicenter, randomized, double-blinded, comparator-controlled phase III trials, termed ATTAIN (Assessment of Telavancin for Treatment of Hospital-Acquired Pneumonia) were conducted from January 2005 to June 2007. Adult patients with a diagnosis of HAP were randomized to receive either telavancin (10 mg/kg IV q24h) or vancomycin (1 g IV q12h) for

seven to 21 days. Site-specific vancomycin monitoring and dose adjustments and concomitant therapy for Gram-negative coverage with aztreonam or piperacillin-tazobactam were permitted.

Results: Just over 1,500 patients received at least one dose of study medication. Of these, a total of 480 patients were considered microbiologically evaluable, defined as having a Gram-positive respiratory pathogen cultured from baseline respiratory or blood cultures. *S. aureus* was the most common pathogen cultured, with MRSA making up 56% of *S. aureus* isolates in the telavancin group and 65% of isolates in the vancomycin group. Cure rates were similar between groups for all patients treated and for the microbiologically evaluable subgroup. The incidences of serious adverse events (AEs) and treatment-emergent AEs resulting in discontinuation of study medication were both higher in the telavancin group, although specific types of AEs were not clearly stated. The telavancin group had a higher rate of renal impairment (10% vs 8%) and serum creatinine increase (16% vs 10%) than the vancomycin group.

Conclusions: The authors conclude that telavancin is as effective as vancomycin in the treatment of HAP caused by Gram-positive bacteria and possesses an acceptable safety profile.

Comment: While telavancin was found to be noninferior to vancomycin, the use of vancomycin trough monitoring was inconsistent among sites. When used, the majority of vancomycin troughs were in the range of 5–15 µg/mL, which is inadequate for HAP and not surprising given the low, flat-dosing strategy. Consistent with past literature, this study strongly supports the close monitoring of renal function during telavancin therapy.

Intensive Insulin Therapy in the Neurocritical Care Setting is Associated with Poor Clinical Outcome

Graffagnino C, Gurram AR, Kolls B, et al. *Neurocrit Care.* 2010;13:307-12.

Study Question: Is there any benefit from Intensive Insulin Therapy (ITT; blood glucose [BG] goal 80 – 120 mg/dL) on morbidity and mortality in neurologically injured patients compared to Standard Infusion Therapy (SIT; BG goal < 150 mg/dL)?

Study Description: Retrospective, before-(Feb 2005 to Aug 2006, SIT)-and-after (Sept 2006 – Mar 2008, IIT), single center study of 3709 patients in a neuro ICU. Endpoints included hospital mortality, length of stay (LOS), and hypoglycemia.

Results: Hospital mortality was higher in the IIT group (11% vs 7.9%, p = 0.0013). Hypoglycemia in any group was associated with increased mortality (BG < 70 mg/dL: OR 3.26, 95% CI 2.52-4.22; BG < 40 mg/dL: OR 3.65, 95% CI 2.21-6.02; BG < 20 mg/dL: OR 6.25, 95% CI 2.41-16.23). The use of IIT was associated with more hypoglycemia (BG < 70 mg/dL, OR 1.8, 95% CI 1.5-2.3). LOS was longer in the IIT group (mean of 9.5 vs 8.7 days, p=0.046). Hyperglycemia was also associated with an increased mortality (OR 1.99, 95% CI 1.46-2.71).

Conclusions: Both hyperglycemia and hypoglycemia results in increased mortality. The IIT protocol in this study resulted in more hypoglycemia and hyperglycemia.

Comment: Although limited by being a single center study, assessing outcomes during different time periods, and not assessing metrics for neurological and critical illness, it does underscore the importance of avoiding both *hypo*- and

*hyper*glycemia in any glycemic protocol used to treat patients in the neuro ICU population.

Intensive versus Conventional Insulin Therapy in Critically Ill Neurologic patients

Green DM, O'Phelan KH, Bassin SL, et al. *Neurocrit Care.* 2010;13:299-306.

Study Question: Is there any benefit from Intensive Insulin Therapy (ITT; BG goal 80 – 110 mg/dL) on mortality and neurological function in neurologically injured patients compared to Conventional Therapy (CT; BG goal < 151 mg/dL)?

Study Description: Prospective, randomized, single center study of 81 patients expected to have an ICU stay of at least 3 days in a neuro ICU from September 2004 to July 2008. An insulin infusion guided by the Glucommander software was used to achieve BG goal for the IIT. For the CT protocol, BG was measured q6h and an algorithm for SQ regular insulin was used to achieve BG goal. If SQ insulin therapy did not adequately result in in-range glucose values, patients could be switched to an IV insulin infusion. Endpoints included 90-day death from any cause, a 90-day modified Rankin score, ICU LOS, hospital LOS, number of days of mechanical ventilation, number of hypoglycemia episodes, bloodstream infections, pneumonia, and PRBC transfusions.

Results: Investigators were not able to meet enrollment necessary (540 patients) to meet power. There were no differences in any of the endpoints except that there were more hypoglycemic events (BG < 60 mg/dL) in IIT (47% vs 11%, p = 0.0006).

Conclusions: There was no benefit of IIT in this small study.

Comment: Although a well designed study, and the first to assess neurologic outcome, there is still a need for a well-powered study to draw any conclusions. Hopefully, continuous monitoring of BG will provide more optimal BG control while avoiding hypoglycemia.

Early jejunal feeding initiation and clinical outcomes in patients with severe acute pancreatitis

Hegazi R, Raina A, Graham T, et al. JPEN 2011;35:91-6.

Study Question: In patients with severe acute pancreatitis (SAP), is there an association between the time to initiation of enteral tube feedings and achievement of goal rates and clinical outcomes?

Study Description: This was a retrospective chart review of patients with SAP receiving jejunal feeding. Patients were included if they had one or more major local complications such as pseudocysts, necrosis, or abscesses. Exclusion criteria were: chronic liver, renal, or respiratory failure; HIV/AIDS; and acute-on-chronic pancreatitis. Caloric needs were calculated using a range of 20-25 kcal/kg of ideal body weight (IBW). A semi-elemental formula was started at a rate of 20-25 mL/hr and advanced based on tolerance and bowel function q12-24h until the target rate was reached.

Results: Seventeen patients total were included in the study. Patients who never reached their goal enteral feeding rate had a significantly longer ICU stay than those patients who did. Patients in whom it took >12 days from the onset of abdominal pain to reach their goal enteral feeding rate *also* had a significantly longer ICU stay (19 vs. 9 days, p<0.001). Patients who did not survive were significantly more likely to experience a delay in tube feeding initiation as compared to survivors (17 vs. 8 days, p<0.05).

Comment: This study indicates that earlier initiation of jejunal feeding in SAP and more rapid

achievement of goal enteral feeding rates are associated with shorter ICU lengths of stay and lower mortality rates. The small number of patients and retrospective nature of the study, however, make it difficult to establish a causal link between the intervention and clinical outcomes.

Lactobacillus GG as Treatment for Diarrhea During Enteral Feeding in Critical Illness: Randomized Controlled Trial

Ferrie S, Daley M. *J Parent Enteral Nutr*. 2011;35:43-9.

Study Question: In critically ill patients experiencing diarrhea during enteral tube feeds, does the administration of the probiotic Lactobacillus GG (LGG) reduce duration and severity of loose stools?

Study Description: A randomized, double-blind, placebo-controlled trial that enrolled 36 consecutive ICU patients who were receiving tube feeds and had persistent diarrhea > 48 hours after discontinuation of laxatives. Diarrhea was defined as 3 or more loose stools or >200 mL of liquid stool in a 24 hr period with no suspected/known malabsorption. Patients received either LGG 1 capsule via feeding tube q12h for seven days or a matched placebo.

Results: There were no differences in baseline characteristics between groups. Investigators found no significant differences between groups in duration or severity of diarrhea, adverse effects, or six-month mortality. In the fourteen-day study period, there were also no differences in mean number of loose stools per day (1.58 [SD 0.88] in LGG group versus 1.10 [SD 0.79] in placebo; P=0.15) or duration of diarrhea from day 1 of study (3.83 d [SD 2.39] in LGG group versus 2.56 [SD 1.85]; P=0.096). Results were similar in the per-protocol and intent-to-treat analysis.

Conclusion: Results of this study do not demonstrate a benefit in treatment of diarrhea in critically ill patients with LGG.

Comment: Although there was no difference in duration of diarrhea, the study was only powered to demonstrate a decrease in duration of at least 2.7 days, warranting a larger study to evaluate a more conservative decrease in duration

Interrupted Pharmacologic Thromboprophylaxis Increases Venous Thromboembolism in Traumatic Brain Injury

Salottolo K, Offner P, Levy AS, et al. *J Trauma*. 2011;70:19-26.

Study Question: What is the optimal administration of pharmacologic thromboprophylaxis (PTP) in patients with stable traumatic intracranial hemorrhage (tICH)?

Study Description: This was a retrospective cohort study of adult (age ≥ 18 years) trauma patients consecutively admitted to two Level I trauma centers in Denver, Colorado. Patients enrolled (n = 480) were admitted with blunt traumatic brain injury (TBI) to Swedish Medical Center from September 1, 2007 to August 31, 2009 and to St. Anthony Central Hospital from May 1, 2007 to November 30, 2008. TBI was identified based on International Classification of Diseases-9th Revision diagnosis. The primary outcome was the development of a VTE during hospitalization, while secondary outcomes included in-hospital mortality and hemorrhage progression. Data on time to initiation of PTP and interruption of PTP were also captured.

Results: There were 255 patients (53.1%) who received PTP during hospitalization. Those who *did* receive PTP had multiple baseline characteristics that were significantly different than those patients who did not received PTP. Similarly, those patients who received continuous PTP (73.7%) differed significantly from those whose PTP was interrupted. Roughly 95% of all patients enrolled received mechanical prophylaxis with sequential compression devices (SCD). A total of 15 patients (3.13%) developed VTE. Neither administration of PTP nor timing of PTP was an independent predictor of

developing VTE (PTP vs. none: odds ratio [OR] = 0.36, $p = 0.18$; early PTP vs. late PTP: OR = 2.00, $p = 0.41$). Patients with interrupted PTP had significantly increased odds of developing VTE compared with patients with continuous PTP (OR = 7.07, $p = 0.04$). Walking before discharge significantly decreased the odds of developing a VTE (OR = 0.19, $p = 0.02$).

Conclusions: Interrupted administration of PTP in patients with TBI is associated with significantly increased risk of VTE. These findings underscore the importance of continuous PTP administration, and every effort should be made to avoid interruption if possible.

Comment: This article discussed the possibility of a statistical type 2 error in the detection of differences in the primary outcome due to the relatively small number of patients. Also, potentially confounding the results is the fact that many patients had therapy interrupted due to the need for surgical intervention, which could independently lead to increased rates of VTE.

THROMBOEMBOLIC PROPHYLAXIS WITH LOW-MOLECULAR-WEIGHT HEPARIN IN PATIENT WITH BLUNT SOLID ABDOMINAL ORGAN INJURIES UNDERGOING NON-OPERATIVE MANAGEMENT: CURRENT PRACTICE AND OUTCOMES

Eberle BM, Schnüriger B, Inaba K, et al. *J Trauma*. 2011;70:141-7.

Study Question: At a Level I trauma center, does the current practice of utilizing low-molecular-weight heparin (LMWH) for prophylaxis of venous thromboembolic complications (VTE) in patients with blunt splenic, liver, and/or kidney injuries impact the failure rate of nonoperative management and packed red blood cell (PRBC) transfusions?

Study Description: This was a 4 year retrospective study including all adult patients (≥15 years) who had an available abdominal CT scan and "an initial attempt" at nonoperative management. Those who underwent an exploratory laparotomy *within* six hours of admission were defined as cases undergoing operative management, while exploratory laparotomies *after* six hours signaled *failure* of non-operative management. Patients were further divided into three groups: (1) use of LMWH within three days of admission ("early"), (2) use of LMWH three days after admission ("late"), or (3) no LMWH during entire hospital stay. Endpoints included failure of nonoperative management, amount of PRBC transfusions and rates of VTE.

Results: Of the 565 patient who were admitted with blunt abdominal organ injuries, 312 patients underwent an initial attempt at nonoperative management. Overall, 35.6% of patients received LMWH during their hospital stay: 13.2% early and 22.4% late. The severity of solid organ injuries at baseline was similar. However, severe pelvic and lower extremity fractures were significantly more common in the early and late groups as compared to those who *did not* receive LMWH. Differences in transfusion requirements within the first 24 hours were not statistically significant between the early and late groups, but *were* statistically different when compared to those not receiving LMWH (p=0.005). The overall transfusion requirements were lower in the *early* LMWH group compared to the late group (p=0.027), while the adjusted failure rate of non-operative management was no different between LMWH groups. The overall rate of VTE was 1.3%, and all events occurred prior to LMWH administration.

Conclusions: There were no differences between either early, late, or no LMWH administration with respect to failure rates of non-operative management or rates of VTE.

Comment: In addition to the finding that early use of LMWH did not appear to increase non-operative

failure rates or blood transfusion requirements, it is important to recognize *other* risk factors for failure rates of non-operative management (contrast extravasation, pseudoaneurysm, AV-fistulas, large hemoperitoneum volume) that were not described by authors. As expected, the study showed that current practice of LMWH administration was guided by injury type and VTE risk factors.

Contributors

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