CRITICAL CARE PHARMACOTHERAPY
LITERATURE UPDATE

March and April 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 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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**Abbreviation Key**

95% CI = 95% confidence interval; AAN = American Academy of Neurology; ACS = acute coronary syndrome; ADCHF = acute decompensated congestive heart failure; ALI = acute lung injury; ARDS = acute respiratory distress syndrome; ASA = aspirin; ASPEN = American Society for Parenteral and Enteral Nutrition; AUC = area under the curve; BBs = beta-blockers; BMI = body mass index; BP = blood pressure; CAP = community-acquired pneumonia; CFU = colony-forming units; CI = cardiac index; CIRCI = critical illness-related corticosteroid insufficiency; CPC = cerebral performance category; CT = clotting time; DBP = diastolic blood pressure; DIC = disseminated intravascular coagulation; DVT = deep vein thrombosis; EF = ejection fraction; EN = enteral nutrition; EPI = epinephrine; GCS = Glasgow Coma Scale score; GI = gastrointestinal; HAP = hospital-acquired pneumonia; HC = hydrocortisone; HIT = heparin-induced thrombocytopenia; ICU = intensive care unit; IV = intravenously administered; JMHW = Japanese Ministry of Health and Welfare; LOS = length of stay; MAP = mean arterial pressure; MIC = minimum inhibitory concentration; MRSA = methicillin-resistant *Staphylococcus aureus*; MV = mechanical ventilation or mechanically ventilated; NE-DOB = norepinephrine plus dobutamine; NNH = number needed to harm; NNT = number needed to treat; NS = not significant; NSAIDs = nonsteroidal anti-inflammatory drugs; PCP = primary care provider; PE = pulmonary embolism; PN = parenteral nutrition; PO = orally administered; ROSC = return of spontaneous circulation; RR = relative risk; SBP = systolic blood pressure; SCR = serum creatinine; SIRS = systemic inflammatory response syndrome; SOFA = sequential organ failure assessment; SSRIs = selective serotonin reuptake inhibitors; UFH = unfractionated heparin; UGIB = upper gastrointestinal bleeding; UOP = urine output; VTE = venous thromboembolism

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RANDOMIZED, PLACEBO-CONTROLLED TRIAL OF CANDESARTAN IN THE TREATMENT OF ACUTE STROKE: RESULTS FROM THE SCAST STUDY.


**Study Question:** In patients with acute stroke and elevated BP, will antihypertensive treatment with the angiotensin receptor blocker candesartan have beneficial effects on vascular endpoints and functional status during the first six months following a stroke?

**Study Description:** This article described a multi-center, double-blind study in which adult patients were eligible for enrollment if they: had a clinical diagnosis of stroke; presented within 30 hours of symptom onset; and had a SBP of greater than 140 mm Hg. A total of 2,029 patients were randomized in a double-blind fashion to receive either a fixed-dose escalation of candesartan or a matched placebo for a total of seven days. All patients continued to receive standard treatment for stroke, including the possibility of additional antihypertensive agents when clinically warranted. The co-primary endpoints defined were: 1) a composite of vascular death, non-fatal MI, and non-fatal stroke, and 2) functional status; both endpoints were measured at the study’s six-month mark.

**Results:** There was no clinically significant difference in BP between the two groups throughout the treatment period. Mean BP on day 7 was 147/82 mm Hg in the candesartan group and 152/84 mm Hg in the placebo group. Investigators did not find a statistically significant difference between the 3 candesartan and placebo groups in either of the co-primary endpoints at the end of follow-up: the composite vascular endpoint hazard ratio = 1.09 (95% CI 0.84 – 1.41), and the functional status endpoint odds ratio = 1.13 (95% CI 0.97 – 1.32).

**Conclusion(s):** There was no evidence of a beneficial effect associated with the antihypertensive candesartan in acute stroke.

**Comment:** This study was underpowered to detect a difference, leading the authors to conduct a post hoc meta-analysis that corroborated the study’s findings. The findings presented here are unlikely to have any effect on clinical practices within the emergency or critical care setting; current AAN guidelines recommend against the acute treatment of hypertension unless it is elevated to a SBP of > 220 mm Hg or DBP > 120 mm Hg or if the patient has a SBP > 180 mm Hg and is otherwise a candidate for thrombolysis. This trial provides further evidence to support AAN’s recommendation.

DALTEPARIN VERSUS UNFRACTIONATED HEPARIN IN CRITICALLY ILL PATIENTS.


**Study Question:** Is dalteparin superior to unfractionated heparin (UFH) for the prevention of proximal leg deep vein thrombosis (DVT) in critically ill patients?

**Study Description:** ICU patients are at high risk of VTE as a result of a confluence of risk factors. Adult patients who were expected to stay in the ICU for at least 3 days were randomized to receive dalteparin (5,000 units SQ daily; n = 1,873) or UFH (5,000 units twice daily; n = 1,873 UFH) in this prospective, multicenter study. Outcomes included the incidence of VTE and mortality.

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of: proximal DVT (primary); PE; VTE; bleeding; heparin-induced thrombocytopenia (HIT); and death.

**Results:** Proximal DVT occurred at an incidence of 5.1% and 5.8% in the dalteparin and UFH groups, respectively (p = 0.57), but PE developed in significantly fewer patients receiving dalteparin (p = 0.01). Rates of other VTE, death, catheter-related thrombosis, major bleeding, and HIT did not differ significantly between the two groups.

**Conclusion(s):** The authors concluded that dalteparin is not superior to UFH in decreasing the incidence of proximal DVT, but they note that the results might have been different if the study enrollment had been larger or if they had used different drugs or doses.

**Comment:** To a limited extent, one may extrapolate these findings to medically ill patients, as 76% of the admissions in the study were medical, with the reminder being surgical admissions excluding major trauma, neurosurgery, and orthopedic surgery patients. Patients in the dalteparin group did have significantly fewer PEs. However, this study’s generalizeable is limited by the fact that much of it took place before October 2009 when there was an update in United States Pharmacopeia standards resulting in up to a 10% reduction in UFH potency. Even more importantly, many institutions dose UFH q8h in the majority of their medical patients, preventing these health systems from applying the study’s findings to their own populations.

**Cardiogenic Shock. A Prospective, Randomized Pilot Study.**


**Study Question:** In non-ACS cardiogenic shock, which vasopressors are most suitable in optimizing systemic and regional hemodynamics?

**Study Description:** Patients were enrolled in this open-label trial if they met all of the following inclusion criteria: EF < 30%; CI < 2.2 L/min/m²; absence of hypovolemia; SBP < 90 mmHg or MAP < 60 mmHg; UOP < 0.5 mL/kg/h and resistant to diuretics; lactate > 2 mmol/L; signs of hypoperfusion; and no evidence of acute cardiac ischemia. Prior to randomization, patients were started on dobutamine for hypotension associated with low cardiac output and signs of hypoperfusion, with dopamine added for persistent hypotension. For patients who remained hypotensive, dopamine was stopped and patients were then randomized to either norepinephrine plus dobutamine (NE-DOB) or epinephrine (EPI) alone.

**Results:** Thirty patients were treated according to protocol, with fifteen in each treatment arm. There were no differences in baseline values between the two groups. Patients in both treatment arms saw significant elevation in MAP, CI, and mixed venous oxygen saturation when compared to baseline; HR was significantly higher in the *EPI* group (p < 0.05). EPI was associated with new supraventricular arrhythmia in two patients and with sustained ventricular tachycardia in one patient. Oliguria was reversed in ten patients in the EPI group and thirteen patients in the NE-DOB group. Arterial lactate concentrations increased in the EPI group and decreased in the NE-DOB group, but the lactic

**Comparison of Norepinephrine-Dobutamine to Epinephrine for Hemodynamics, Lactate Metabolism, and Organ Function Variables In**

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acidosis observed in the EPI group was transient and resolved within twelve hours.

**Conclusion[s]:** Both EPI and NE-DOB improved arterial pressure, oxygen delivery, and renal perfusion in patients with cardiogenic shock after failure of dopamine.

**Comment:** In light of the recent norepinephrine shortage, this trial demonstrates that EPI may be an alternative in non-ACS cardiogenic shock.

**CONTINUATION OF STATIN THERAPY IN PATIENTS WITH PRESUMED INFECTION: A RANDOMIZED CONTROLLED TRIAL.**


**Study Question:** Does administration of a statin (atorvastatin) influence organ dysfunction or inflammation in patients previously on statins admitted to the hospital with presumed infection?

**Study Description:** This study was a randomized, double-blind clinical trial. Patients who: had a proven or suspected infection; were receiving antibiotics; met two SIRS criteria; and were receiving a statin prior to admission were included. Atorvastatin 20 mg or matched placebo was given at the earliest possible opportunity and continued for 28 days or until discharge or death. The primary endpoint was proportion of patients in each group with severe sepsis at prespecified time points.

**Results:** Baseline characteristics and need for intravenous antibiotics were similar in the 75 patients receiving placebo and 75 patients receiving atorvastatin. Severe sepsis was present at baseline in 32% of patients in both treatment arms, and there proved to be no significant difference between groups at any time during follow-up. Likewise, SOFA scores were similar at baseline and decreased over time with no significant difference between the groups.

**Conclusion[s]:** This study does not suggest any beneficial immunological effects when continuing statin therapy in the setting of acute infection.

**Comment:** Statins have been shown to have beneficial effects beyond lipid lowering within several subgroups, including: those with ACS; acute stroke; and major non-cardiac surgery. While this study failed to measure a benefit in the short term treatment of an infectious episode in medically ill patients previously taking a statin, it does not rule out the possibility of a beneficial effect in more seriously ill patients or those not previously taking a statin.

**RELATIONSHIP BETWEEN TIME TO TARGET TEMPERATURE AND OUTCOME IN PATIENTS TREATED WITH THERAPEUTIC HYPOTHERMIA AFTER CARDIAC ARREST.**


**Study Question:** In therapeutic hypothermia after cardiac arrest, does time to target temperature correlate with neurologic outcome?

**Study Description:** This article describes a single center, retrospective chart review of cardiac arrest patients who had received therapeutic hypothermia. Time between the return of spontaneous circulation (ROSC) and the attainment of a target temperature of < 34°C by esophageal probe was compared to

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Pittsburgh cerebral performance category (CPC) data. Because the study was meant to assess long term neurological outcome, patients who died during the study's acute phase were excluded.

**Results:** A total of 588 patients were studied. Time from ROSC to target temperature was divided into groups: < 120 minutes, 120-220 minutes, > 220 minutes. Thirty-seven, 50, and 56% of patients had favorable neurologic outcomes (CPC 1-2) in the < 120 min, 120-220 min, > 220 min groups, respectively (p = 0.01). The median time to reach target temperature was 209 minutes in patients with favorable neurologic outcomes versus 158 minutes in patients with unfavorable neurologic outcomes. Logistic regression showed longer time to target temperature and lower age to be associated with a favorable neurologic outcome.

**Conclusion(s):** The study’s authors concluded that a faster decline in body temperature predicts a less favorable neurologic outcome, although they acknowledge that finding may be indicative of more severe injuries and a resultant greater loss of thermoregulation.

**Comment:** The exact mechanism behind the difference in neurologic outcomes remains unclear, as there were multiple potential confounders (e.g., the difference in time between first attempt at resuscitation and ROSC, time to attainment of target temperature, age, and severity of neurologic injury). Nonetheless, the study does suggest a need for more research to determine the optimal rate of cooling in the hypothermic treatment of cardiac arrest patients.

**Randomized Trial of Initial Trophic Versus Full-Energy Enteral Nutrition in Mechanically Ventilated Patients with Acute Respiratory Failure.**


**Study Question:** Do MV patients initially receiving trophic EN have improved clinical outcomes compared to those who receive full-energy nutrition?

**Study Description:** This study was a single-center, open-label trial of medical ICU patients (n = 200) expected to be MV ≥ 72 hours. Exclusion criteria were: history of chronic lung disease; > 48 hours since inclusion criteria had been met; refractory shock; moribund state; end-stage liver disease; PN use; malnutrition; and refusal of consent. Patients were randomized to initially receive either trophic EN (10 mL/hr) for 6 days and were then advanced to goal caloric intake or to full-energy nutrition (25-30 non-protein kcal/kg based on IBW and 1.2-1.6 g/kg protein). MV management and weaning were standardized.

**Results:** The primary outcome of days alive and free of MV in 28 days was similar between groups (23 versus 23 days; p = 0.9). Similarly, there were no differences in secondary outcomes, including: all-cause hospital mortality; 28-day all-cause mortality, organ-failure free days; ICU-free days; hospital-free days; new infections; need for prokinetic agents; or GI intolerance (e.g., diarrhea or gastric residuals > 300 mL).

**Conclusion(s):** Patients receiving initial trophic EN have similar clinical outcomes as those who receive full-energy EN with trend toward improved GI tolerance.

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Comment: Support for the SCCM and ASPEN consensus guideline recommendation to advance to goal caloric intake within 48-72 hours in critically ill patients is limited. This study does suggest that initial, short term trophic feeding leads to similar outcomes as rapid advancement to dietary goals in medical ICU patients. Practitioners should treat the initiation of EN within 24-48 hours as a priority of care. However, extrapolation of these results to surgical or trauma patients is not appropriate on the basis of this trial.

**HYDROCORTISONE THERAPY FOR PATIENTS WITH MULTIPLE TRAUMA.**


Study Question: Does stress-dose hydrocortisone (HC) decrease the prevalence of HAP in trauma patients?

Study Description: This study was a multicenter, double-blind trial that enrolled multi-trauma patients expected to require MV for more than 48 hours. Patients were randomized to receive either an intravenous continuous infusion of HC or placebo. The treatment was discontinued if patients were not deemed to have critical illness-related corticosteroid insufficiency (CIRCI) based on a corticotropin test. The rate of HAP within 28 days of study inclusion was the primary endpoint. Secondary outcomes included: MV-free days; ICU LOS; vasopressor support; non-HAP infections; organ failure; mortality; and adverse drug events.

Results: Of the 149 randomized patients included in the analysis, 76% had CIRCI (HC, n = 56; placebo, n = 57). There was a significantly different rates of HAP at day 28 with placebo in patients overall (HC 35.6% versus placebo 51.3%; p = 0.007) and in those with CIRCI (HC 35.7% versus placebo 54.4%; p = 0.01).

When comparing patients overall, those treated with HC experienced significantly: more MV-free days (16 versus 12 with placebo; p = 0.001); fewer ICU days (18 versus 24 with placebo; p = 0.03); less ARDS or ALI (4.3% versus 14.5% with placebo; p = 0.04); and less hyponatremia (0% versus 9.2% with placebo; p = 0.01) in the intervention arm. In the subset of patients with CIRCI, those treated with HC experienced significantly: more ventilator-free days (16 versus 10 with placebo; p < 0.001); fewer ICU days (17 versus 25 with placebo; p = 0.002); fewer days on vasoactive drugs (2.5 versus 3 with placebo; p = 0.04); and less hyponatremia (0% versus 12.3% with placebo; p = 0.008).

Conclusion(s): The authors conclude that early stress-dose steroid treatment in multi-trauma patients reduces the rate of HAP at 28 days, time on MV, and ICU LOS.

Comment: Although early steroids were shown to be beneficial in this study, it would be reassuring to see the results replicated in other trials before application in practice.

**DIURETIC STRATEGIES IN PATIENTS WITH ACUTE DECOMPENSATED HEART FAILURE.**


Study Question: What is the optimal diuretic strategy for patients with acute decompensated heart failure (ADCHF)?

Study Description: This study was a randomized, double-blind trial that enrolled patients within 24 hours of initial presentation with: ≥ one symptom and ≥ one sign of heart failure; a history of chronic heart failure; and prior receipt of diuretics for ≥ 1 month. Patients were excluded for: renal

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between insufficiency; hypotension; or need for vasopressors or inotropes. Patients were randomized to one of four treatment arms: low dose (total daily IV furosemide equal to total daily PO loop diuretic dose at home in furosemide equivalents) by IV bolus; low dose by continuous infusion; high dose (total daily IV furosemide 2.5 times the total daily PO furosemide dose) by IV bolus; or high dose by continuous infusion. Patients were maintained on their assigned dosage regimen for 48 h, at which time the dose could be increased by 50% if necessary.

**Results:** *Bolus versus continuous infusion:* There was no significant difference in the primary efficacy endpoint (patient-reported global assessment of symptoms) or the primary safety endpoint (change in SCR from baseline to 72 hours). *Low dose versus high dose:* There was a trend toward greater improvement in patient-reported global assessment in the *high dose* group (NS). There was no difference between groups of the change in SCR at 72 hours; however, more patients in the high dose group met the prespecified secondary safety endpoint of worsening renal function, which was defined as a rise in SCR of at least 0.3 mg/dL. Patients in the high-dose group had greater fluid loss, weight loss, and relief from dyspnea. More patients in the *low dose* group had a serious adverse event (38% versus 50%, *p* = 0.03), including renal failure (based on investigator report).

**Conclusion(s):** There were no *significant* differences in patients’ global assessment of symptoms or in changes from baseline renal function with either bolus versus continuous infusion, or low versus high dose IV furosemide.

**Comment:** These results may not be applicable to patients with low outpatient loop diuretic requirements or those with *newly diagnosed* heart failure.

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**Beneficial Association of Beta-Blocker Therapy on Recovery from Severe Acute Heart Failure Treatment: Data from the Survival of Patients with Acute Heart Failure in Need of Intravenous Inotropic Support Trial.**


**Study Question:** Does maintaining or initiating beta-blockers (BBs) during hospitalization affect post-discharge survival in the short or long term?

**Study Description:** This is a *post hoc* analysis of the SURVIVE trial, which examined 180 day survival in patients receiving dobutamine or levosimendan for ADCHF. The present analysis evaluated survival at 31 and 181 days and divided patients into groups on the basis of whether they were taking BBs at admission and at discharge, making it possible for them to fall into one of four groups: Yes/Yes, Yes/No, No/No, and No/Yes.

**Results:** There were 1,104 patients included, distributed as follows: Yes/Yes (*n* = 549), Yes/No (*n* = 40), No/No (*n* = 259), No/Yes (*n* = 256). Significant baseline differences, including age and reason for hospitalization, were taken into account in regression analyses. Kaplan-Meier survival curves demonstrated a significant increase in survival between the Yes/Yes and No/No groups (*p* < 0.001), and between the Yes/Yes and Yes/No groups (*p* = 0.028).

**Conclusion(s):** For patients with ADCHF, BB use at hospital admission and discharge was associated with a.

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with improvement in both short and long term outcomes. Data suggested cessation of BB therapy at discharge in those admitted on a BB is detrimental.

Comment: These results appear to confirm the beneficial effects of BB therapy on survival in patients with ADCHF. In the context of controversy over continuation of BB therapy during hospitalization for ADCHF, this study suggests that judicious use of these agents may be favorable.

THE IMPORTANCE OF EARLY TREATMENT WITH TRANEXAMIC ACID IN BLEEDING TRAUMA PATIENTS: AN EXPLORATORY ANALYSIS OF THE CRASH-2 RANDOMIZED CONTROLLED TRIAL.


Study Question: In trauma patients, what is the impact of tranexamic acid on mortality associated with bleeding?

Study Description: This article describes a post hoc analysis of the CRASH-2 trial, which was a prospective, multinational, randomized, double-blind trial of adult trauma patients at risk of significant bleeding who were treated with the antifibrinolytic tranexamic acid or placebo within 8 hours of injury. The primary endpoint of mortality attributable to bleeding was stratified according to time from and type of injury, severity of hemorrhage, and Glasgow Coma Scale score (GCS).

Results: The study included 20,118 trauma patients approximately 35 years of age, the majority of whom were hemodynamically stable, had GCS 13-15, and a third of whom each presented: ≤1 hour, >1-3 hours, and ≥3 hours from injury. Tranexamic acid reduced the risk of bleeding death (RR 0.85, 95% CI 0.76-0.96; p = 0.0077) but not non-bleeding death (RR 0.94, 95% CI 0.86-1.02; p = 0.13). Time to treatment with tranexamic acid was significantly associated with the risk of bleeding-related death, with therapy in the first 3 hours protective (NNT 42 for ≤1 hour from injury, p < 0.0001; 77 for >1-3 hours; p < 0.03). In contrast, in patients who were >3 hours from injury, tranexamic acid was associated with an increased risk of bleeding-related (NNH 77; p = 0.004) but not overall mortality (RR 1, 95% CI 0.9-1.13).

Conclusion(s): Early tranexamic acid administered to bleeding trauma patients may improve bleeding-related mortality, whereas late administration may increase death from bleeding.

Comment: Cautions about the merits of post hoc analyses aside, selection of appropriate patients who would benefit from this therapy remains challenging. However, but time from injury may be a reasonable exclusion for late presentation traumas.

THROMBOMODULIN ALFA IN THE TREATMENT OF INFECTIOUS PATIENTS COMPLICATED BY DISSEMINATED INTRAVASCULAR COAGULATION (DIC): SUBANALYSIS FROM THE PHASE 3 TRIAL.


Study Question: Is thrombomodulin α (TM-α) effective for the treatment of infection-induced DIC?

Study Description: This article describes a retrospective analysis from a phase 3 multicenter,
double-blind, randomized trial in patients with DIC caused by hematologic malignancy or infection. Results suggested that TM-α was more effective than heparin in DIC resolution and resulted in less bleeding-related adverse events. The present analysis excluded patients with non-infection induced DIC. TM-α 0.06 mg/kg IV over 30 min daily was compared to heparin 8 units/kg/hour for six consecutive days. Outcomes included DIC resolution, defined by JMHW criteria, at 7 days and 28-day all-cause mortality.

**Results:** Of the 227 patients in the original study, 80 patients were identified with infection-induced DIC. The only difference in baseline demographics was age, which trended higher in the TM-α group. Comparing TM-α to heparin, respectively, the 28-day mortality rates were 21.4% and 31.6% (p = NS), and the DIC resolution rate was 73.2% versus 63.2% (p = NS). Two patients in the heparin group and none in the TM-α group died due to bleeding.

**Conclusions:** The authors were unable to confirm the effectiveness of either group secondary to limitations in study design, although a prospective, randomized trial of 750 patients with sepsis-induced DIC is presently in progress.

**Comment:** It is uncertain as to whether TM-α will be a viable option in the treatment of sepsis-induced DIC in future. The results of the aforementioned, larger trial are anticipated.

**IMPACT OF VANCOMYCIN EXPOSURE ON OUTCOMES IN PATIENTS WITH METHICILLIN-RESISTANT STAPHYLOCOCCUS AUREUS BACTEREMIA: SUPPORT FOR**

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**CONSENSUS GUIDELINES SUGGESTED TARGETS.**


**Study Question:** How is the extent of exposure to vancomycin associated with outcomes in patients with MRSA bacteremia?

**Study Description:** This was a retrospective cohort study of 320 adult patients who received vancomycin as initial therapy for a documented MRSA bloodstream infection for at least 72 h. Only first episodes of bacteremia were included in the analysis, and patients were excluded if they received < 3 days of vancomycin therapy. Vancomycin treatment failure was defined as: 1) mortality within 30 days; 2) persistent signs and symptoms of infection at the end of vancomycin therapy; or 3) persistent bacteremia, defined as ≥ 7 days. Post-infection hospital LOS was calculated from the first blood culture positive for S. aureus until discharge or death.

**Results:** A total of 168 patients (52.5%) experienced treatment failure with vancomycin. Several patients had treatment failure for more than one reason, and the results are as follows: 21% due to 30-day mortality; 55.7% due to persistent signs or symptoms of infection at the end of therapy; and 76% due to ≥ 7 days of bacteremia. Of the deaths that occurred, 74.3% were attributed to MRSA bacteremia (infective endocarditis and pneumonia were the most common sites), although eight of the nine other patients also had persistent infection or prolonged bacteremia. Patients in whom a first vancomycin trough returned at 15 to 20 mg/L saw significantly lower failure rates. Patients more likely to experience therapeutic failure had lower AUC₂₄₀;MIC ratios and higher MIC values.

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Unsurprisingly, nephrotoxicity was most common in patients with trough levels > 20 mg/L.

Conclusions: Vancomycin has been the empiric antimicrobial of choice for MRSA infections in the recent past, but resistance is increasingly limiting its utility. This study showed a > 50% failure rate of vancomycin in patients treated for MRSA bacteremia. Its results support current guidelines in that: 1) lower failure rates were seen with AUC:MIC ratios > 400; 2) lower failure rates were seen with vancomycin trough levels of 15 to 20 mg/L; and 3) higher MICs result in increasing vancomycin failure rates.

Comment: Current guidelines recommend trough concentrations of 15 to 20 mg/L in patients with complicated infections (e.g., meningitis, osteomyelitis, and pneumonia). Based on this study, those patients with complicated bacteremia may also benefit from empiric target troughs of 15 to 20 mg/L.

RISK OF UPPER GASTROINTESTINAL BLEEDING WITH LOW-DOSE ACETYLSALICYLIC ACID ALONE AND IN COMBINATION WITH CLOPIDOGREL AND OTHER MEDICATIONS.


Study Question: Is the risk of upper gastrointestinal bleeding (UGIB) higher with low dose ASA (75 to 300 mg/d) or clopidogrel alone, in combination, or in co-administration with select other gastrototoxic medications (e.g., NSAIDs, oral anticoagulants, oral corticosteroids, SSRIs, and statins)?

Study Description: This study was a nested case-control analysis of information from a UK primary care database where 2,049 patients with a UGIB diagnosis were compared to a control group of 20,000. For inclusion, patients had to be aged 40 to 84 years and have an on-file prescription history of at least one year. The study end points were: diagnosis of UGIB; reaching 85 years of age; death; or the study’s end at the close of 2007.

Results: Of the confirmed UGIB cases, 30.8% involved low dose ASA, 3.3% involved clopidogrel, and 1.6% involved both agents. The risk of UGIB was higher in current users of low dose ASA (RR 1.80) or clopidogrel (RR 1.67) compared with nonusers, regardless of length of therapy. Compared with low dose ASA monotherapy, the risk of UGIB was significantly increased when coadministered with clopidogrel (RR 2.08), oral anticoagulants (RR 2.00), NSAIDs (RR 2.63 or 2.66, depending on dose range), or high-dose oral corticosteroids (> 10 mg/day of prednisone equivalents; RR 4.43). An increased risk was not apparent when ASA was coadministered with statins, low dose corticosteroids, or SSRIs.

Conclusions: The use of low dose ASA is associated with an almost 2-fold increase in the risk of UGIB compared with nonuse, and that risk may be increased when it is coadministered with other, select drugs. Neither ASA nor clopidogrel monotherapy appears to be associated with a significantly higher risk of UGIB than the other.

Comment: Because the database only captured recorded prescription medications, over-the-counter NSAID could not be taken into account.

OTHER ARTICLES OF INTEREST


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