Major publications in the critical care pharmacotherapy literature: January–December 2013

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There is a wealth of medical literature published every day, and practicing clinicians have an obligation to keep up with advancements in their specialty field. PubMed, the National Library of Medicine’s literature database, houses over 23 million articles, with over 1 million works published in 2013 alone. A search focusing only on obviously critical care–related publications in 2013 identified 11,376 articles, which equates to an average of over 31 articles daily. This approximation is likely a gross underestimate of all relevant additions to the critical care literature that year because so many areas of medicine and pharmacy are germane to the management of critically ill patients.

The Critical Care Pharmacotherapy Literature Update (CCPLU) group comprises critical care pharmacists across the United States. Each month, group members prospective-ly review each article published in 25 periodicals that have been selected based on their applicability to critical care, pharmacy-related focus, and

Purpose. Ten recently published articles with important implications for critical care pharmacotherapy are summarized. Summary. The Critical Care Pharmacotherapy Literature Update (CCPLU) group is a national assembly of experienced intensive care unit (ICU) pharmacists across the United States. Group members monitor 25 peer-reviewed journals on an ongoing basis to identify literature relevant to pharmacy practice in the critical care setting. After evaluation by CCPLU group members, selected articles are chosen for summarization and distribution to group members nationwide based on (1) applicability to critical care practice, (2) relevance to pharmacy practitioners, and (3) quality of evidence or research methodology. Hundreds of relevant articles were evaluated by the group during the period January–December 2013, of which 98 were summarized and disseminated nationally to CCPLU group members. Among those 98 publications, 10 deemed to be of particularly high utility to critical care practitioners were included in this review. The 10 articles address topics such as rapid lowering of blood pressure in patients with intracranial hemorrhage, adjunctive therapy to prevent renal injury due to acute heart failure, triple-drug therapy to improve neu-rolologic outcomes after cardiac arrest, and continuous versus intermittent infusion of β-lactam antibiotics in severe sepsis. Conclusion. There were many important additions to the critical care pharmacotherapy literature in 2013, including an updated guideline on the management of myocardial infarction and reports on advances in research focused on improving outcomes in patients with stroke or cardiac arrest and preventing the spread of drug-resistant pathogens in the ICU.

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impact factor. All reports on controlled trials, observational studies, or meta-analyses pertaining to both critical care (excluding pediatric and neonatal intensive care) and drug therapy are then summarized in a standardized format that includes an analysis of methodology, results, and the authors’ conclusions, as well as commentary on the applicability of the information to routine practice. Each monthly summary is then disseminated nationally to a national critical care medicine organization in addition to a growing internal mailing list.

The inaugural installment of the CCPLU group’s review of major publications in critical care encompassed articles published from February 2012 through February 2013. As a wealth of critical care literature has been published since, the group endeavored to create a new review covering the period January–December 2013, excluding any publications or guidelines previously summarized; during that period, the CCPLU group wrote synopses of 100 articles, including five consensus guidelines. Members used the Grades of Recommendation Assessment, Development and Evaluation (GRADE) methodology to select the highest-quality works based on methodology and study design. Furthermore, preference was given to publications that were judged to have applicability to the largest potential number of adult intensive care unit (ICU) patients (including those treated in medical, surgical, cardiac, neurology, and trauma ICUs) and most likely to change clinical practice. On this basis, one consensus guideline and nine other articles were selected for inclusion in this review.

O’Gara et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction

The 2013 ST-Elevation Myocardial Infarction (STEMI) guideline is the third edition of this document from the American College of Cardiology Foundation (ACCF) and the American Heart Association (AHA). Using methodology approved by an ACCF–AHA task force, guideline recommendations were formally voted on prior to and after manuscript completion. Pertinent evidence gathered through November 2010 was considered for review and inclusion, with select references added through August 2012. The ACCF–AHA recommendations are ranked in three classes: I (good support for effectiveness), II (conflicting evidence and/or divergence of expert opinion regarding effectiveness), and III (a lack of support and, in some cases, evidence and/or consensus that a procedure or treatment may be harmful). The level of evidence (LOE) for therapeutic recommendations is ranked at three levels: A (multiple randomized clinical trials or meta-analyses), B (a single randomized trial or nonrandomized studies), and C (consensus opinion, case studies, or standard of care).

While the updated guidelines encompass previously described aspects of care of the patient with STEMI, the 2013 version adds new emphasis on the coordination of regional systems of STEMI care, with an increased focus on enhancing community preparedness and adopting quality-improvement measures for providing emergency medical services to help hasten the delivery of care (class I; LOE, B).

The cornerstone of acute STEMI management is early reperfusion. Primary percutaneous coronary intervention (PCI) remains the reperfusion method of choice (as opposed to fibrinolytic therapy) and should be used when it can be performed in less than 12 hours from STEMI symptom onset (class I; LOE, A). For PCI procedures with stent placement, bare metal stents and drug-eluting stents are equally supported by the guideline (class I; LOE, A); however, bare metal stents are recommended for patients with a high bleeding risk or if there is a concern about nonadherence during the first year of dual antiplatelet therapy, which can pose an increased risk of stent thrombosis (class I; LOE, C). Along with indefinite aspirin therapy, the use of an inhibitor of the platelet receptor $P_2Y_{12}$ (clopidogrel, prasugrel, or ticagrelor) is recommended at the initiation of PCI in patients with stent placement (class I; LOE, B), with continued use for one year (ticagrelor is a newly added option in the 2013 guidelines). The guidelines do not give a formal recommendation regarding concomitant use of clopidogrel and proton pump inhibitor therapy but cite evidence suggesting that the combination does not lead to worse clinical outcomes. Recommendations regarding the use of antithrombotics and anticoagulants given in conjunction with...
PCI remain largely unchanged from the 2009 edition of the ACCF–AHA recommendations.108

Fibrinolytic therapy remains an option for individuals in whom PCI cannot be initiated in a timely manner. Unlike the previous guidelines, the 2013 edition recommends that a fibrin-specific fibrinolytic be administered if a patient cannot receive PCI within 120 minutes of first medical contact (class I; LOE, A); this is a change from the previously recommended 90-minute window.106,107 However, after post-STEMI fibrinolysis, the transfer of the patient to a PCI-capable hospital may be indicated, as doing so leads to improved outcomes in the event of new cardiogenic shock (class I; LOE, B) or failed reperfusion and allows PCI evaluation in high-risk patients (class IIa [the weight of evidence or opinion favors effectiveness]; LOE, B).121-125 At presentation, all patients undergoing fibrinolytic therapy for STEMI should receive aspirin, clopidogrel, and adjunctive anticoagulation therapy (class I; LOE, A). Aspirin should be continued indefinitely, with clopidogrel use continued for at least two weeks (class I; LOE, A). Anticoagulation with heparin (class I; LOE, C), enoxaparin (class I; LOE, A), or fondaparinux (class I; LOE, B) should continue for a minimum of 48 hours or until revascularization is achieved. In addition to reperfusion during STEMI, the prompt initiation of β-blockers (class I; LOE, B) and angiotensin-converting enzyme inhibitors (class I; LOE, A) is highly recommended within the first 24 hours; long-term therapy with a high-intensity statin is also recommended (class I; LOE, B).

A notable addition to the guidelines is the recommendation to promptly initiate therapeutic hypothermia in comatose patients with STEMI or in individuals with out-of-hospital cardiac arrest secondary to ventricular fibrillation or ventricular tachycardia (class I; LOE, B). There are also new recommendations for the management of complications after STEMI; these recommendations are largely supported by low-level evidence or expert opinion.

While the guideline does not present an abundance of new insights or support for basic reperfusion principles or therapies, it is the most thorough and comprehensive set of recommendations on STEMI management to date.

Heyland et al. A randomized trial of glutamine and antioxidants in critically ill patients

The Canadian Critical Care Trials Group conducted a randomized, blinded, 2-by-2 factorial study of mechanically ventilated patients with at least two organ failures related to acute illness within 24 hours of ICU admission. Patients were randomized to glutamine supplementation (0.35 g per kilogram of ideal body weight i.v. plus 30 g enterally daily) or placebo use. As part of the factorial design, patients were also randomized to antioxidant therapy consisting of 500 μg of i.v. selenium plus enteral selenium, zinc, β-carotene, vitamin E, and vitamin C or placebo use. Nutrition therapy was prescribed according to 2003 Canadian critical care nutrition guidelines.126 The primary outcome was 28-day mortality, and secondary outcomes included ICU and hospital length of stay, infectious complications, Sequential Organ Failure Assessment score, duration of mechanical ventilation, antibiotic use, and six-month mortality. Statistical significance was set at p < 0.044.

Out of 5633 screened patients, 1223 were enrolled and randomized to receive glutamine (n = 303), antioxidants (n = 308), both (n = 310), or placebo (n = 302). Baseline characteristics were similar among the groups, which primarily consisted of medical patients (79%); notably, only 3.3% were trauma patients. There was a trend toward increased 28-day mortality among patients who received glutamine relative to those who did not (32.4% versus 27.2%, p = 0.05). No significant mortality difference was found between patients who received antioxidants and those who did not (30.8% versus 28.8%, p = 0.48). With regard to the a priori–defined secondary outcomes, patients who received glutamine (irrespective of antioxidant use) had significantly higher six-month mortality than those who did not receive glutamine (43.7% versus 37.2%, p = 0.02) but also an increased duration of mechanical ventilation (11.0 days versus 8.7 days, p = 0.03). Additional outcomes reported in patients who received glutamine included significantly higher inhospital mortality (p = 0.02), increased median times to ICU discharge and hospital discharge (p = 0.03 and p = 0.04, respectively), and an increased risk of surgical wound infections. Antioxidant supplementation did not have a significant effect on any outcome. No significant differences in the rates of serious adverse events were observed. The authors concluded that in critically ill patients with multiorgan failure, early supplementation of glutamine was harmful and antioxidant supplementation offered no therapeutic benefit.

Previous studies reported mixed results with glutamine supplementation in critically ill adults. Compared with the study summarized here, these studies were smaller, had less rigorous designs, and used smaller doses of glutamine, and patients frequently received parenteral nutrition.127-129 In contrast, patients in the study of Heyland et al. received a daily glutamine dose 30 g higher than the maximal dose used in other studies and were enterally fed. Interestingly, patients in the trial had higher severity-of-illness scores than patients in the earlier studies but normal baseline glutamine and selenium concentrations. Whether
glutamine supplementation in the setting of nutritional deficiency might be of value is unclear. A subsequent meta-analysis including the study of Heyland et al. concluded that there is no significant benefit of glutamine on clinical endpoints except for an aggregate reduction in nosocomial infections. Guidelines on nutrition support in critically ill adults issued in 2009 by the Society of Critical Care Medicine and the American Society for Parenteral and Enteral Nutrition recommend enteral glutamine and antioxidants in trauma, burn, and mixed ICU populations (this was a grade B recommendation [i.e., supported by a large randomized trial with clear-cut results]). The results of the study of Heyland et al. challenge the routine use of either glutamine or antioxidant supplementation in critically ill medical patients, as well as the use of glutamine in critically ill surgical patients (due to a potential increase in surgical wound infections). Because trauma and burn populations were not significantly represented in the study, recommendations for glutamine and antioxidant supplementation in those populations cannot be extrapolated.

**Anderson et al. Rapid blood-pressure lowering in patients with acute intracerebral hemorrhage**

The Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage (INTERACT2) study was a multicenter, randomized, open-label trial to investigate whether rapid lowering of elevated blood pressure (BP) improves outcomes in patients with intracerebral hemorrhage (ICH). Patients with ICH were included if their systolic blood pressure (SBP) was 150–220 mm Hg, they had no definite contraindication or indication for BP lowering, and they could be treated within 6 hours of symptom onset. Patients randomized to intensive BP-lowering therapy received primarily i.v. antihypertensive agents, with the goal of achieving a goal SBP of <140 mm Hg within 1 hour of randomization and for up to the first 7 days of hospitalization. A control group received treatment consistent with current guidelines to achieve a goal SBP of <180 mm Hg. Poor outcome, a composite of death and major disability (defined as a score of 3–6 on the modified Rankin scale, on which scores range from 0 for no symptoms to 6 for death) at 90 days, was the primary endpoint. Secondary outcomes included ordinal analysis of physical function across the seven levels of the Rankin scale, death (all-cause and cause-specific mortality), health-related quality of life, days of hospitalization, and requirements for long-term care. The safety endpoints of early neurologic deterioration (defined as an increase of ≥4 points on the National Institutes of Health Stroke Scale [NIHSS] or a decrease of ≥2 points on the Glasgow Coma Scale from baseline to 24 hours), severe hypotension requiring i.v. fluids or vasopressors, and volume of hematoma from baseline to 24 hours in patients who underwent repeat imaging were also assessed.

A total of 2839 patients were included in the study. Baseline characteristics were similar between the intensive-therapy and control groups (mean ± S.D. SBP, 179 ± 17 mm Hg in both groups; mean NIHSS score, 10 versus 11; mean Glasgow Coma Scale score, 14 in both groups). There was no significant between-group difference with regard to the primary endpoint (odds ratio [OR] for poor outcome with intensive therapy, 0.87; 95% confidence interval [CI], 0.75–1.01; p = 0.06). Rankin scale scoring favored the intensive-therapy group (OR for greater disability, 0.87; 95% CI, 0.77–1.00; p = 0.04), but those patients did not have a significantly lower risk of mortality (OR, 0.99). There was a significant benefit favoring intensive treatment with regard to quality of life (p = 0.002) but no significant between-group difference in long-term care requirements, hospital length of stay, or safety outcomes. At one hour after the initiation of treatment, 33% of patients in the intensive-therapy group had achieved the SBP target. The authors concluded that intensive BP reduction in patients with ICH did not have a significant impact on the combined outcome of death and disability but may have benefit when long-term functional outcome and quality of life are considered.

The trial was conducted after results from the 404-patient INTERACT pilot study showed a decrease in hematoma size at 24 hours and a lack of adverse effects in the group receiving intensive BP-lowering therapy. A similar pilot study, the Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH) study, investigated three tiers of SBP goals and found sufficient evidence of the feasibility and safety of intensive BP lowering to proceed to the main phase trial; ATACH II is expected to conclude in 2016. Largely because of the ATACH pilot study results, current guidelines jointly issued by AHA and the American Stroke Association state that acute BP lowering to achieve an SBP of ≤140 mm Hg in patients presenting with an SBP of 150–220 mm Hg is probably safe (class IIa; LOE, B per the recommendation grading scheme used in the aforementioned ACCF–AHA guidelines on STEMI management). Future guidelines will likely incorporate the results of these two trials.

The INTERACT2 trial was a large, international, multicenter study conducted on the basis of a pilot trial. While the open-label, assessor-blinded endpoint was not optimal, a double-blind trial would have been impractical due to the nature of the intervention; moreover, the INTERACT2 trial design has been used in other influential studies of interventions for ICH.
Chen et al. Low-dose dopamine or low-dose nesiritide in acute heart failure with renal dysfunction: the ROSE Acute Heart Failure randomized trial25

The ROSE Acute Heart Failure trial was a randomized, placebo-controlled trial that was designed to compare the efficacy and safety of low-dose i.v. dopamine hydrochloride (2 μg/kg/min) and nesiritide (0.005 μg/kg/min without bolus) when added to conventional diuretic regimens to prevent renal injury in the treatment of acute heart failure. Adults with a prior diagnosis of heart failure or at least one sign and one symptom of heart failure, as well as renal dysfunction (defined as a glomerular filtration rate of 15–60 mL/min per 1.73 m² of body surface area, as estimated by the Modification of Diet in Renal Disease study equation), were enrolled in the study within 24 hours of admission. Patients were excluded from study participation if they had received vasoactive medications or ultrafiltration during the hospitalization or were hemodynamically unstable.

A total of 360 patients were randomized to the nesiritide and dopamine groups in a 1:1 ratio; patients in both groups were then assigned to receive the active drug or a placebo in a 2:1 ratio. Study drugs were administered for 72 hours. Baseline characteristics were similar between the active treatment and placebo groups in each arm of the study and between both placebo groups.

There was no difference in the primary efficacy endpoint of 72-hour cumulative urine volume with dopamine therapy relative to placebo use (8296 mL versus 8524 mL, p = 0.59); there was also no significant between-group difference in the primary safety endpoint of the mean change in cystatin C concentration from baseline to 72 hours (0.12 mg/L versus 0.11 mg/L, p = 0.72). Patients who received dopamine were more likely than placebo users to experience treatment failure due to tachycardia (7.2% versus 0.9%, p < 0.001) but were less likely to experience treatment failure due to hypotension (0.9% versus 10.4%, p < 0.001). The overall rates of treatment failure were similar in the dopamine and placebo groups.

In the nesiritide arm, there was no difference between the comparator groups with respect to 72-hour cumulative urine volume (8574 mL with nesiritide versus 8296 mL with placebo use, p = 0.49) or the mean change from baseline in the cystatin C concentration at 72 hours (0.07 mg/L with nesiritide versus 0.11 mg/L with placebo use, p = 0.36). There was no difference in the rate of treatment failure for any cause between the nesiritide and placebo groups. There was also no difference between nesiritide or dopamine versus placebo in any of the secondary endpoints (death, serious adverse events, and days alive or free from heart failure hospitalization at 60 days).

This trial did not support the addition of either dopamine or nesiritide to standard diuretic therapy in the setting of acute heart failure and moderate-to-severe renal dysfunction. Current ACCF–AHA recommendations for acute heart failure management state that low-dose dopamine, as an adjunct to loop diuretic therapy, may be considered to improve diuresis and preserve renal function and blood flow (class IIb; LOE, B).137 Additionally, previous studies have indicated positive outcomes associated with dopamine use in acute heart failure.38-141 However, the ROSE Acute Heart Failure study differed from those studies in that it enrolled only patients with preexisting renal dysfunction and used a lower dose of dopamine for a standardized duration. It has been speculated that low-dose dopamine can potentially reduce the incidence of renal injury in heart failure by selectively stimulating dopamine receptors to cause renal vasodilation while also increasing cardiac output through β1-agonist activity without causing vasoconstriction through activation of α receptors.139 While increased cardiac output was evident in the ROSE Acute Heart Failure study from the increased rate of study drug discontinuation due to tachycardia, a beneficial effect on renal function was not observed, which confirmed the findings of published randomized placebo-controlled trials that have not shown a benefit.142-144

In contrast to a previous pilot study that showed preservation of renal function with the administration of low-dose nesiritide during and after cardiopulmonary bypass surgery,145 nesiritide did not produce any significant changes in renal function or clinical outcomes. A post hoc analysis of data from the Acute Study of Clinical Effectiveness of Nesiritide and Decompensated Heart Failure (ASCEND-HF) trial found that nesiritide had no effect on urine output.146

The lack of a clear benefit of low-dose dopamine or nesiritide in terms of surrogate markers of renal function, urine output, or clinical outcomes should limit the use of either therapy in patients with concomitant acute heart failure and renal dysfunction and challenge current guideline recommendations on dopamine use in acute heart failure.

Mentzelopoulos et al. Vasopressin, steroids, and epinephrine and neurologically favorable survival after inhospital cardiac arrest: a randomized clinical trial72

This was a randomized, double-blind, placebo-controlled, parallel-group trial conducted in three tertiary care hospitals in Greece from 2008–10. The purpose of the trial was to investigate whether the combination of vasopressin, steroids, and epinephrine (VSE) during cardiopulmonary resuscitation (CPR)
for inhospital cardiac arrest led to improved outcomes relative to the standard of care (epinephrine alone).

Patients were randomly assigned to receive either vasopressin (20 units per CPR cycle) plus epinephrine (1 mg per CPR cycle) or epinephrine plus a saline placebo for the first five CPR cycles after randomization. Each CPR cycle was three minutes. Patients receiving vasopressin also received methylprednisolone (40 mg i.v.) during the first CPR cycle. All surviving patients who were in postresuscitation shock after four hours (as evidenced by a SBP of <70 mm Hg or a greater than 50% increase in any prearrest vasopressor/inotropic support) were started on a continuous infusion of hydrocortisone (300 mg/day for up to seven days, with the dosage tapered thereafter). Patients with acute myocardial infarction received stress-dose hydrocortisone for three days or less to avoid hindering infarct healing.

Patients included in the trial had experienced inhospital, vasopressor-requiring cardiac arrest. Resuscitation was performed according to 2005 European Resuscitation Council guidelines. The exclusion criteria included patient age of less than 18 years, terminal illness (i.e., life expectancy of less than six weeks) or do-not-resuscitate status, cardiac arrest due to exsanguination (i.e., a ruptured aortic aneurysm), cardiac arrest before hospital admission, and treatment with i.v. corticosteroids before cardiac arrest. Advanced life support was conducted according to European guidelines. The primary study endpoints were the return of spontaneous circulation (ROSC) for 20 minutes or longer and survival to discharge with a favorable neurologic recovery, defined as Glasgow-Pittsburgh cerebral performance category 1 or 2 (good or moderate recovery). Secondary endpoints were as follows: mean arterial pressure during and approximately 20 minutes after CPR, mean arterial pressure and central venous oxygen saturation during days 1–10 after randomization, number of organ failure-free days during days 1–60, and rates of potentially corticosteroid-associated complications such as hyperglycemia, infections, bleeding, peptic ulcers, and paresis.

A total of 364 patients were assessed for study eligibility, with 268 patients included in the final analysis (VSE group, n = 130; control group, n = 138). Baseline characteristics were similar in the two groups. Hypotension was the primary cause of cardiac arrest in both groups. Patients in the VSE group had a higher probability of ROSC for 20 minutes or longer than patients in the control group (83.9% versus 65.9%; OR, 2.98; p = 0.005). On average, VSE-treated patients also had a shorter duration of life support than the controls (13 minutes versus 19 minutes, p = 0.01), fewer CPR cycles (four versus five, p = 0.001), and a lower median dose of epinephrine administered (4 mg versus 5 mg, p = 0.002). The rates of postarrest therapeutic hypothermia in the two groups did not differ (24.6% in both groups, p > 0.99).

A higher proportion of patients in the VSE group than in the control group were alive at hospital discharge with a favorable neurologic recovery (13.9% versus 5.1%; OR, 3.28; p = 0.02). On multivariate analysis, the following variables were associated with an increased hazard for poor outcome during follow-up, a lower probability of being alive with favorable neurologic recovery at hospital discharge, or both: increasing epinephrine, atropine, and bicarbonate doses during CPR; no use of therapeutic hypothermia; cardiac arrest rhythm (i.e., nonventricular fibrillation or ventricular tachycardia) and cause (noncardiac); and cardiac arrest on a weekend or holiday or during the night (from 11:00 p.m. to 7:00 a.m.). Among patients with postresuscitation shock, those in the VSE group were also more likely than those in the control group to be alive at discharge with a favorable neurologic recovery (21.1% versus 8.2%; OR, 3.74; p = 0.02). Among survivors (patients alive for four or more hours after CPR initiation), postarrest morbidity and rates of inhospital complications were similar between the study groups.

The investigators concluded that VSE therapy in patients with inhospital cardiac arrest was associated with improved survival to hospital discharge with favorable neurologic function. This study was a well-designed trial with evenly matched study groups. Currently, clinical practice guidelines recommend the use of vasopressin in patients with cardiac arrest only during a narrow time frame early in the performance of life support. A previous study suggested that the combination of vasopressin–epinephrine therapy and corticosteroid supplementation during CPR was associated with an improved rate of ROSC and decreased systemic inflammatory response, but it did not assess postevent neurologic function.

The study of Mentzelopoulos et al. suggests a potential favorable neurologic outcome with the use of multiple doses of vasopressin and epinephrine combined with a single dose of methylprednisolone. However, the study should be interpreted with caution. The use of sodium bicarbonate and atropine during CPR was high in both groups, which may have had a confounding influence on patient outcomes. Moreover, prearrest hemodynamic variables were not assessed, and it is difficult to fully determine whether the beneficial effects noted were due to VSE therapy or, perhaps, to the combination of vasopressin and methylprednisolone.

Overall, the study has the potential to influence clinical practice. Future studies should investigate whether the observed benefits were mainly due to the addition of vasopressin to standard epinephrine therapy, the
addition of methylprednisolone, or the additive benefit of both agents.

Dulhunty et al. Continuous infusion of beta-lactam antibiotics in severe sepsis: a multicenter double-blind, randomized controlled trial

This was a multicenter, prospective, double-blind, randomized controlled trial to determine clinical and pharmacokinetic differences with the use of continuous versus intermittent dosing of ticarcillin–clavulanate, piperacillin–tazobactam, and meropenem in critically ill patients with severe sepsis. Participants were randomly assigned to receive either an active infusion and placebo boluses (the intervention group) or a placebo infusion and active boluses (the control group). The 24-hour antibiotic doses were clinician determined and unaffected by randomization. Patients included in the study had severe sepsis within the previous 48 hours, received one of the study medications, and had an expected or actual ICU stay greater than 48 hours.

A total of 60 patients were enrolled, meeting the sample size required to achieve a power of 80% to detect a 15% absolute difference in the primary outcome of plasma antibiotic concentrations above the minimum inhibitory concentration (MIC) on days 3 and 4. Despite adequate enrollment, only 43 of the 60 patients underwent plasma sampling due to discontinuation of their assigned treatment within 3 days; therefore, 17 patients were excluded from the primary outcome analysis. Despite the small sample size, there was a significant between-group difference in the primary outcome, with antibiotic concentrations exceeding the MIC documented in 82% of patients (18 of 22) in the continuous-infusion group and only 29% of patients (6 of 21) in the intermittent-infusion group (p = 0.001); this outcome was most prominently seen in those who received meropenem, as 100% of patients (8 of 8) receiving continuous-infusion therapy had plasma concentrations above the MIC, compared with 22% of the controls (2 of 9 patients). Among patients receiving piperacillin–tazobactam and ticarcillin–clavulanate, there were less pronounced differences in the respective rates of attainment of above-MIC concentrations in the intervention and control groups: 75% (9 of 12 patients) versus 36% (4 of 11 patients) and 50% (1 of 2 patients) versus 0% (1 patient treated).

Secondary outcomes included clinical response (assessed 7–14 days after study medication cessation), time to clinical resolution, ICU-free days at day 28, and inhospital survival. A higher rate of clinical cure was observed with the use of continuous versus intermittent infusion (76.7% versus 50.0%, p = 0.032), while there were no significant differences in terms of time to clinical resolution (6 days versus 5 days, p = 0.14), ICU-free days (19.5 days versus 17.0 days, p = 0.14), and inhospital survival (90% versus 80%, p = 0.47).

This study was the second to find an increase in the rate of clinical cure with continuous versus intermittent administration of β-lactam antibiotics and the first to link this outcome with the use of meropenem, piperacillin–tazobactam, and ticarcillin–clavulanate. The lack of an identified causative organism and susceptibility data in 53% of cases was a major study limitation, as it prohibited assessment of a more appropriate pharmacokinetic parameter, the time above MIC, which is a key determinant of the effectiveness of β-lactam antibiotics. Furthermore, little detail was provided about the dosing regimens for the bolus group; for example, data on infusion duration and frequency of administration—either of which could impact pharmacokinetic parameters such as maximum concentration and time above MIC, as well as clinical outcomes—were not reported. The significant findings of this study may be related to the relatively high acuity of the patient population and the use of 24-hour dosing that was comparable between treatment groups (i.e., piperacillin–tazobactam versus meropenem versus ticarcillin–clavulanate).

The potential benefits of continuous-infusion β-lactam therapy are numerous, including optimization of pharmacokinetic parameters, minimization of drug resistance, improved clinical outcomes, and increased cost-effectiveness with regard to clinician workload and labor. In light of these potential benefits, these study results showing improved cure rates support the need for larger, adequately powered studies to detect differences in clinical outcomes such as mortality, ICU length of stay, and antimicrobial resistance.

Huang et al. Targeted versus universal decolonization to prevent ICU infection

The Randomized Evaluation of Decolonization versus Universal Clearance to Eliminate MRSA (REDUCE MRSA) trial was a multicenter, pragmatic, three-group, cluster-randomized trial designed to evaluate three strategies for the prevention of methicillin-resistant Staphylococcus aureus (MRSA) infection. Patients were recruited from 45 Hospital Corporation of America hospitals in 16 states, with a total of 43 hospitals and 74 ICUs implementing the assigned interventions. Patients in group 1 (screening and isolation) had bilateral nares screening on ICU admission and were placed under contact precautions if they had a history of MRSA or any positive MRSA test. Patients in group 2 (targeted decolonization) were subject to the same screening and isolation process as those in group 1 and, if found to be colonized with MRSA, underwent a five-day decolonization protocol consisting of twice-daily
intrasanal mupirocin and daily baths with chlorhexidine-impregnated cloths. Group 3 (universal decolonization) had no MRSA screening upon ICU admission, but contact precautions were implemented, and the patients received twice-daily intranasal mupirocin for five days and daily chlorhexidine baths for the entire ICU stay. The study consisted of a 12-month baseline period \((n = 48,390)\) divided among groups, a phase-in period, and an 18-month intervention period \((n = 74,256)\) divided among groups. The primary study outcome was ICU-attributable, MRSA-positive clinical cultures; secondary outcomes included ICU-attributable bloodstream infections caused by MRSA and any other pathogen. All clinical cultures were obtained at clinicians' discretion.

With regard to the primary outcome, hazard ratios (HRs) for MRSA-positive clinical cultures in the intervention versus baseline period indicated significant \((p = 0.01)\) differences between groups: the HR values were 0.92 (95% CI, 0.77–1.10) in group 1, 0.75 (95% CI, 0.63–0.89) in group 2, and 0.63 (95% CI, 0.52–0.75) in group 3, with greater reductions observed in groups 2 and 3. The absolute frequency of MRSA-positive clinical cultures decreased the most in group 3 (from 240 events [3.4 per 1000 patient-days] at baseline to 217 events [2.1 per 1000 patient-days] during the intervention period). This benefit, however, did not translate to the secondary outcome of ICU-attributable MRSA bloodstream infections: the HR values were 1.23 (95% CI, 0.82–1.85) in group 1, 1.23 (95% CI, 0.80–1.90) in group 2, and 0.72 (95% CI, 0.48–1.08) in group 3 \((p = 0.11\) for all comparisons). There were significant differences in HR values for ICU-attributable bloodstream infections from any pathogen (group 1, 0.99 [95% CI, 0.84–1.16]; group 2, 0.78 [95% CI, 0.66–0.91]; and group 3, 0.56 [95% CI, 0.49–0.65]; \(p < 0.001\)). Overall, universal decolonization was the most effective strategy, reducing MRSA-positive clinical cultures by 37% and bloodstream infections from any pathogen by 44% from baseline levels. The study results indicated that 181 patients would need to undergo decolonization to prevent one MRSA-positive clinical culture, and 99 patients would need to undergo decolonization to prevent one bloodstream infection from any pathogen.

The findings of this study support decolonization in ICU patients to decrease infections caused by multidrug-resistant pathogens, including MRSA. Theoretically, a decrease in MRSA infections should confer decreased mortality. However, further studies are needed to evaluate this approach in terms of patient outcomes. Interestingly, the reduction in MRSA-positive cultures in this study did not translate to a significant reduction in MRSA bloodstream infections. Detailed data regarding MRSA-positive clinical cultures might have been helpful in determining the types of MRSA infections that benefit most from this intervention.

The use of the decolonization protocol occurred in a variety of ICU and hospital settings, suggesting that this approach is feasible for a broad ICU population, including community hospitals. However, previously published evidence suggests that the cost of this approach may be prohibitive. A cost analysis in a Canadian academic hospital study found that two years of MRSA screening, which identified 99 patients infected or colonized with MRSA, cost $109,813. The estimated hospital cost for a patient with a MRSA bloodstream infection is $10,000–$20,000, therefore, decolonizing 99 patients to prevent one bloodstream infection may cost more than treating one case of bacteremia. Further cost analyses are necessary to determine if the product and labor costs are offset by the reductions in infection before widespread adoption of universal decolonization protocols can ensue. Moreover, the development of resistance is concerning and would need to be evaluated. All of these factors—outcomes, cost, and resistance—must be weighed and analyzed when deciding to implement such strategies. If implemented, follow-up and continued surveillance would be necessary for continual evaluation of benefit and monitoring.

Broderick et al. Endovascular therapy after intravenous t-PA versus t-PA alone for stroke

Ciccone et al. Endovascular treatment for acute ischemic stroke
The standard dose of i.v. alteplase (0.9 mg/kg, with 10% given as a bolus and the remainder infused over 1 hour for a maximum dose of 90 mg) was utilized in both trials. In the IMS III study, patient randomization occurred within 40 minutes after the start of the alteplase infusion; those in the alteplase group received the remainder of the standard dose while those in the endovascular treatment group were sent for urgent angiography. In the SYNTHESIS Expansion study, patients assigned to the endovascular treatment group did not receive any i.v. alteplase. In both trials, decisions regarding specific endovascular intervention after angiography were made at the discretion of the treating neurointerventionalist. I.V. heparin infusions were used throughout all angiography procedures.

The primary outcome measures in the IMS III and SYNTHESIS Expansion studies were functional independence (defined as a modified Rankin scale score of ≤2) and disability-free survival (a modified Rankin scale score of ≤1) at 90 days, respectively. Primary safety measures included 90-day mortality and symptomatic ICH within 24 hours of randomization (in the IMS III study), as well as fatal and nonfatal symptomatic ICH, infarction, and recurrent ischemic stroke and death at 7 days after thrombolysis (in the SYNTHESIS Expansion trial).

A total of 656 patients underwent randomization in the IMS III trial (434 were assigned to endovascular treatment and 222 to alteplase alone). Baseline patient characteristics were similar in the two groups, with the exception of a higher rate of coronary artery disease in the group treated with alteplase alone. Based on a prespecified criterion, the study was stopped early due to demonstration of futility. The proportion of patients with a modified Rankin scale score of ≤2 did not differ significantly with the use of endovascular treatment versus alteplase alone in the entire patient sample (40.8% versus 38.7%; absolute difference, 1.5 percentage points; CI, –6.1 to 9.1 percentage points) or in the prespecified subgroups of patients with severe or moderate stroke. Of note, the likelihood of achieving the primary outcome increased with greater reperfusion in the endovascular treatment group. Primary safety outcomes were similar in the two groups, with the exception of a higher rate of symptomatic ICH in the endovascular treatment group (p = 0.01).

Overall, 362 patients underwent randomization in the SYNTHESIS Expansion trial (181 were assigned to endovascular treatment and 181 to i.v. alteplase). Baseline characteristics were similar in the two groups, with two exceptions: patients in the endovascular treatment group had a lower incidence of atrial fibrillation, and they were more likely to have a diagnosis of dissection (probably angiography related) as the cause of stroke. With regard to outcomes, the proportion of patients with a modified Rankin score of ≤1 did not differ significantly between the groups (30.4% with endovascular treatment versus 34.8% with i.v. alteplase; absolute difference, –4.4 percentage points; CI, –14.1 to 5.2 percentage points). Safety outcomes were similar in the two groups.

Despite the promising results reported in previous trials, the IMS III and SYNTHESIS Expansion trials failed to demonstrate a benefit with endovascular intervention as compared with standard i.v. alteplase therapy. Given the lack of clear evidence of clinical benefits with the use of endovascular intervention, in addition to the invasive and expensive nature of this form of therapy, it should be used for the treatment of acute ischemic stroke (either in place of or in combination with i.v. alteplase) only after careful consideration.

Conclusion

There were many important additions to the critical care pharmacotherapy literature in 2013, including an updated guideline on the management of myocardial infarction and reports on advances in research focused on improving outcomes in patients with stroke or cardiac arrest and preventing the spread of drug-resistant pathogens in the ICU.

References


+Hemorrhage+%28TACH%29&ra=nk1 (accessed 14 April 10).


