Major publications in the critical care pharmacotherapy literature in 2015

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Purpose. Recently published practice guidelines and research reports on pharmacotherapy in critical care patient populations are summarized.

Summary. The Critical Care Pharmacotherapy Literature Update (CCPLU) Group is composed of over 50 experienced critical care pharmacists who evaluate 31 peer-reviewed journals monthly to identify literature pertaining to pharmacotherapy in critical care populations. Articles are chosen for summarization in a monthly CCPLU Group publication on the basis of applicability and relevance to clinical practice and strength of study design. From January to December 2015, a total of 121 articles were summarized; of these, 3 articles presenting clinical practice guidelines and 12 articles presenting original research findings were objectively selected for inclusion in this review based on their potential to change or reinforce current evidence-based practice. The reviewed guidelines address the management of intracranial hemorrhage (ICH), adult advanced cardiac life support (ACLS) and post–cardiac arrest care, and the management of supraventricular tachycardia (SVT). The reviewed research reports address topics such as nutrition in critically ill adults, administration of β-lactams for severe sepsis, anticoagulant selection in the context of continuous renal replacement therapy, early goal-directed therapy in septic shock, magnesium use for neuroprotection in acute stroke, and progesterone use in patients with traumatic brain injury.

Conclusion. Important recent additions to the critical care pharmacy literature include updated joint clinical practice guidelines on the management of spontaneous ICH, ACLS, and SVT.

Keywords: cardiology, critical care, drug therapy, neurology, nutrition therapy, review

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As precision medicine becomes increasingly important, dissemination of up-to-date evidence is vital to provide such care. A growing volume of literature pertaining to the heterogeneous population of critical care patients becomes available every year. In late 2014, PubMed searches using the terms critical care and intensive care identified 10,927 and 13,866 publications, respectively; conducted in late 2015, the same searches identified 11,857 and 14,367 publications. Advances in evidence-based medicine have resulted in decreased mortality in patients with several common critical care disease states. Staying current with this growing body of literature is crucial to optimize patient outcomes; the challenge to do so increases each year.

The Critical Care Pharmacotherapy Literature Update (CCPLU) Group comprises over 50 critical care pharmacists and was established to provide monthly reviews of published literature focused on pharmacotherapy in critical care. A total of 31 journals are prospectively reviewed monthly, with studies chosen for review based on applicability and relevance to clinical practice as well as strength of study.
design. Over the course of 2015, hundreds of articles were reviewed, with a total of 121 articles summarized for inclusion in a monthly CCPLU Group publication. Articles were selected for this review using objective standards and Grades of Recommendation, Assessment, Development and Evaluation (GRADE) criteria. Additional factors included a general requirement that selected articles pertain to pharmacotherapy in adult patients and have the potential to either change practice or reinforce current evidence-based practice. Based on these criteria, 3 clinical practice guidelines and 12 articles presenting study results were selected for discussion in this review.

**Hemphill et al. 2015 AHA/ASA guidelines for the management of spontaneous intracerebral hemorrhage**

The 2015 guidelines on managing spontaneous intracerebral hemorrhage (ICH) released by the American Heart Association (AHA) and the American Stroke Association (ASA) updated AHA–ASA guidelines published in 2010. Grading of recommendations followed the AHA–ASA classification of recommendation (COR) method of evaluating a procedure or treatment (I, useful and effective; IIa, reasonable to perform; IIb, usefulness/efficacy less well established; and III, not useful/effective and may be harmful) according to level of evidence (LOE) determinations (A, data derived from multiple randomized controlled trials [RCTs]; B, data derived from a single RCT or nonrandomized studies; and C, consensus opinion, case studies, or standard of care) and was based on evaluation of studies published through August 2013. The following summary is focused on updates to the previous AHA–ASA guidelines and new recommendations.

A summary of changes in AHA–ASA recommendations regarding anticoagulation and antiplatelet therapy is provided in Table 1. Key updates pertaining to selection of agents for reversal of anticoagulation were made to reflect the availability of new treatments and a growing body of supporting evidence. A major limitation of current studies in this area is the use of surrogate outcomes (e.g., time to reversal of anticoagulation) instead of clinical outcomes (e.g., mortality), which leads to difficulty in interpretation of clinical benefit. For ICH secondary to use of vitamin K antagonists, prothrombin complex concentrates (PCCs) may be considered as an alternative to fresh frozen plasma (FFP), as PCC therapy is associated with fewer complications (e.g., fluid overload) and more rapid reversal of International Normalized Ratio values. This recommendation is based on an RCT (n = 202) that demonstrated the noninferiority of 4-factor PCC to FFP for reversal of urgent bleeding; however, only 24 patients (11.9% of the study population) had ICH. Use of a PCC may be associated with a risk of thrombotic complications, but the risk appears to be similar to that reported with FFP therapy. Recombinant activated factor VII does not replace all vitamin K agonist–depleted factors, may not restore thrombin generation as well as PCCs, and may increase the risk for thrombosis.

The AHA–ASA guidelines include recommendations regarding the safety of early intensive blood pressure (BP) lowering. For patients with ICH who have a systolic BP of 150–220 mm Hg and no contraindications to acute treatment, lowering of the systolic BP to 140 mm Hg is safe and may improve functional outcomes; this was an updated recommendation (COR, I; LOE, A). This recommendation was based on findings from the INTERACT2 study, which focused on BP lowering within 6 hours of ICH occurrence. Analysis of outcomes in this study were done on an intention-to-treat (ITT) basis. Among patients randomly assigned to receive BP-lowering therapy aimed at achieving a goal systolic BP of <140 mm Hg within 1 hour (intensive treatment), as compared with a control group assigned to a goal systolic BP of <180 mm Hg, there was a trend toward a lower frequency of the primary outcome of death or major disability, defined by a modified Rankin Scale score of 3–6 (0 = no symptoms, 6 = death) at 90 days (hazard ratio [HR], 0.87; 95% confidence interval [CI], 0.75–1.01; p = 0.06). A secondary ordinal analysis of Rankin Scale scores at 90 days found significantly decreased odds of greater disability in the intensive treatment group versus the control group (odds ratio [OR], 0.87; 95% CI, 0.77–1.00; p = 0.04). Additionally, the proportion of patients requiring at least 2 i.v. agents to attain the BP goal was significantly higher in the intensive treatment group (26.6% versus 8.1% in the control group, p < 0.001). At 6 hours after randomization, the mean systolic BP was significantly lower in the intensive treatment group than in the control group (139 mm Hg versus 153 mm Hg, p < 0.0001). Two thirds of the study population was recruited in China; as treatment was based on local availability of medications (e.g., urapidil, an antihypertensive that is not approved by the Food and Drug Administration [FDA] for hypertension treatment, was used in a substantial number of study partici-
pants), the findings may have limited applicability in the United States.

For patients presenting with a systolic BP of >220 mm Hg, aggressive BP reduction is reasonable (new recommendation: COR, IIb; LOE, C). To prevent recurrent ICH, long-term management of BP at a goal of <130/80 mm Hg may be considered (updated recommendation: COR, IIa; LOE, B); this revised guidance (previously, a BP goal of <140/90 mm Hg was recommended) was based on evidence from a study of patients with recent stroke that found a significantly decreased risk of recurrent ICH with attainment of the lower BP goal.

For management of intracranial pressure, corticosteroids are not recommended due to evidence indicating a lack of benefit and the potential for increased complications such as infections and hypoglycemia (new recommendation: COR, III; LOE, B).

The appropriate timing for resumption of anticoagulation and antiplatelet therapy after ICH remains controversial. An observational study of patients with warfarin-related ICH found that the risk of ischemic or hemorrhagic stroke was minimized when anticoagulation was reinitiated after approximately 10 weeks. An observational study of ICH survivors who received antiplatelet agents did not find an increased risk of ICH recurrence at a median follow-up of 19.5 months in survivors of either lobar hemorrhages (HR, 0.8; 95% CI, 0.3–2.3; p = 0.73) or deep hemorrhages (HR, 1.2; 95% CI, 0.1–14.3; p = 0.88). Stratification of risk for recurrent ICH using known risk factors appears to have the greatest influence on management decisions.

In summary, these guidelines include recommendations for direct oral anticoagulant (DOAC) reversal and targets for early intensive BP lowering. A recently published guideline on reversal of antithrombotics in cases of ICH contained similar recommendations, with greater detail regarding blood factor choice, but is not discussed here because it was not in print at the time of CCPLU Group review (for this publication). Future updates of the AHA–ASA guidelines are expected to address the clinical effectiveness and safety of the DOAC antidotes and the implications of termination of the ATACH II study, the North American component of the INTERACT2 study.

**Table 1.** New and Updated Recommendations on Management of Spontaneous Intracerebral Hemorrhage

<table>
<thead>
<tr>
<th>Therapeutic Issue</th>
<th>Recommendation</th>
<th>CORb</th>
<th>LOEb</th>
<th>Type of Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran reversal</td>
<td>Hemodialysis may be considered</td>
<td>IIb</td>
<td>C</td>
<td>New</td>
</tr>
<tr>
<td>Direct oral anticoagulant reversal</td>
<td>Anti-inhibitor coagulant complex (Feiba, Baxter Healthcare), PCCs, or rFVIIa may be considered along with administration of activated charcoal for recent doses (e.g., within 2 hr)</td>
<td>IIb</td>
<td>C</td>
<td>New</td>
</tr>
<tr>
<td>Heparin reversal</td>
<td>Protamine may be considered</td>
<td>IIb</td>
<td>C</td>
<td>New</td>
</tr>
<tr>
<td>Vitamin K antagonist reversal</td>
<td>PCCs may be considered as alternative to FFP</td>
<td>IIb</td>
<td>B</td>
<td>Update</td>
</tr>
<tr>
<td></td>
<td>rFVIIa not recommended</td>
<td>III</td>
<td>C</td>
<td>Update</td>
</tr>
<tr>
<td>Timing of anticoagulation resumption</td>
<td>Optimal timing unknown; should be avoided for at least 4 wk (unless patient has mechanical heart valve)</td>
<td>IIb</td>
<td>B</td>
<td>New</td>
</tr>
<tr>
<td>Timing of aspirin therapy</td>
<td>Optimal timing uncertain; may be restarted within days</td>
<td>IIa</td>
<td>B</td>
<td>New</td>
</tr>
<tr>
<td>Direct oral anticoagulant therapy for AF</td>
<td>Usefulness uncertain</td>
<td>IIb</td>
<td>C</td>
<td>New</td>
</tr>
</tbody>
</table>

Cor = classification of recommendation, LOE = level of evidence, PCC = prothrombin complex concentrate, rFVIIa = recombinant activated factor VII, FFP = fresh frozen plasma, AF = atrial fibrillation.

Definitions of levels of classification and evidence provided in guideline summary.
benefit or harm) and LOE ratings (A, high-quality evidence; B-R, moderate-quality evidence from randomized studies; B-NR, moderate-quality evidence from nonrandomized studies; and C, lower-quality evidence based on limited data [C-LD] or expert opinion [C-EO]). This summary focuses on AHA recommendations pertaining to advanced cardiac life support (ACLS) and “post-arrest care” for survivors of cardiac arrest.

A summary of changes in the AHA recommendations is detailed in Table 2. The AHA guidelines on ACLS note that in multiple studies, vasopressin administration has not been demonstrated to consistently improve outcomes such as return of spontaneous circulation (ROSC), discharge with a favorable neurologic outcome, attainment of a Cerebral Performance Category score of 1 or 2, and survival to hospital admission or discharge. Epinephrine remains the recommended vasopressor. One study involving patients with out-of-hospital cardiac arrest (OHCA), although halted early and underpowered to detect a significant between-group difference in survival to hospital discharge, showed that relative to placebo use, epinephrine improved rates of ROSC and survival to hospital admission.

Timing of epinephrine administration has been the focus of several recent large observational studies of patients with either in-hospital cardiac arrest (IHCA) or OHCA. For patients with nonshockable rhythms (i.e., asystole or pulseless electrical activity) in both settings, early administration of epinephrine (in IHCA, within 1–3 minutes of CPR initiation; in OHCA, within 10 minutes after emergency medical services-initiated CPR or a 911 call) improved ROSC, survival to hospital discharge, 1-month survival, and neurologically intact survival. For shockable rhythms, the optimal timing of epinephrine administration in the context of early defibrillation in patients with IHCA or OHCA is more difficult to determine; thus, no recommendations were made.

Four recent studies have evaluated the role of corticosteroid administration in both IHCA and OHCA. For IHCA, a corticosteroid bundle consisting of a one-time dose of methylprednisolone 40 mg i.v. followed by i.v. hydrocortisone (300 mg per day) after ROSC plus epinephrine 1 mg per ACLS cycle and vasopressin 20 units per ACLS cycle (for the first 5 CPR

### Table 2. New and Updated Recommendations on Advanced Cardiac Life Support and Postarrest Care

<table>
<thead>
<tr>
<th>Therapeutic Issue</th>
<th>Recommendation</th>
<th>COR&lt;sup&gt;b&lt;/sup&gt;</th>
<th>LOE&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Type of Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Advanced Cardiac Life Support</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Timing of epinephrine</td>
<td>Administer as quickly as feasible for nonshockable rhythms</td>
<td>IIb</td>
<td>C-LD</td>
<td>Update</td>
</tr>
<tr>
<td>Use of epinephrine</td>
<td>Sole vasopressor for shockable and nonshockable rhythms</td>
<td>IIb</td>
<td>B-R</td>
<td>Update</td>
</tr>
<tr>
<td>Use of vasopressin</td>
<td>Removal from algorithm for shockable and nonshockable rhythms</td>
<td>IIb</td>
<td>B-R</td>
<td>Update</td>
</tr>
<tr>
<td><strong>In-Hospital Cardiac Arrest</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use of corticosteroids</td>
<td>Should be considered (in addition to vasopressin and epinephrine)</td>
<td>IIb</td>
<td>C-LD</td>
<td>New</td>
</tr>
<tr>
<td>Use of targeted temperature management for nonshockable rhythm</td>
<td>Recommended for adult comatose patients</td>
<td>I</td>
<td>C-EO</td>
<td>Update</td>
</tr>
<tr>
<td><strong>Out-of-Hospital Cardiac Arrest</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use of corticosteroids</td>
<td>Benefit unknown</td>
<td>IIb</td>
<td>C-LD</td>
<td>New</td>
</tr>
<tr>
<td>Use of targeted temperature management for shockable rhythm</td>
<td>Recommended for adult comatose patients</td>
<td>I</td>
<td>B-R</td>
<td>Update</td>
</tr>
<tr>
<td><strong>Targeted Temperature Management</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration</td>
<td>Minimum of 24 hr</td>
<td>IIa</td>
<td>C-EO</td>
<td>Update</td>
</tr>
<tr>
<td>Goal temperature</td>
<td>Constant at 32–36 °C</td>
<td>I</td>
<td>B-R</td>
<td>New</td>
</tr>
</tbody>
</table>

<sup>a</sup>COR = class of recommendation, LOE = level of evidence.
<br><sup>b</sup>Levels of classification and evidence defined in guideline summary.
cycles) was shown to increase ROSC and survival to discharge relative to epinephrine plus placebo use.\textsuperscript{48,49} For OHCA, the benefit of corticosteroids is unknown due to limited supporting data from studies in which the effects of steroids were evaluated independently of other interventions.\textsuperscript{50-53} In light of the removal of vasopressin from the ACLS algorithms, the widespread implementation of the corticosteroid bundle is unlikely. Subsequent studies should focus on the role of steroids in combination with epinephrine alone.

The term post-arrest care refers to the identification and treatment of the underlying cause of cardiac arrest, as well as the evaluation and management of the ischemic complications caused by interruption of adequate organ perfusion. In this setting, avoidance of hypotension is reasonable (new recommendation: COR, Ib; LOE, C-LD). Targeted temperature management (TTM) is recommended for comatose adult patients with ROSC after cardiac arrest, with the goal of maintaining a constant temperature between 32 and 36 °C. This recommendation updated the previous guideline recommendation of a goal temperature of 32–34 °C. Practitioners are encouraged to individualize the goal temperature for patient-specific factors (e.g., cerebral edema, temperature at presentation, risk of bleeding, seizures). These recommendations were based on observational studies and 1 RCT in patients with OHCA that found that neurologic outcomes and survival at 6 months were not significantly different with the use of a TTM goal of 33 °C versus 36 °C.\textsuperscript{52-54} Although the strength of these recommendations, particularly those pertaining to patients with IHCA and nonshockable rhythms, is controversial, the writing committee maintained that there are essentially no patients for whom TTM with a goal temperature of 32–36 °C is contraindicated.

All future updates and revisions to the AHA guidelines on ACLS and post-arrest care will be done in a continuously updated, Web-based format (www.ECCguidelines.heart.org).

Page et al. 2015 ACC/AHA/HRS guidelines for management of adult patients with supraventricular tachycardia\textsuperscript{6}

The 2015 guidelines on management of supraventricular tachycardia\textsuperscript{6} (SVT) jointly issued by the American College of Cardiology (ACC), AHA, and the Heart Rhythm Society (HRS) updated guidelines issued by the same groups in 2003.\textsuperscript{55} Literature published through April 2014, as well as previously published ACC–AHA–HRS documents related to SVT and select references published through May 2015, were included in the guideline development process. Evidence was ranked according to the same COR and LOE criteria used in the aforementioned guidelines on ACLS.\textsuperscript{4} In the guidelines, SVT is defined as any tachycardia (atrial and/or ventricular rates above 100 beats per minute [bpm] at rest) involving tissue at or above the His bundle; all SVT types are addressed except for atrial fibrillation (AF), which was addressed in ACC–AHA–HRS guidelines issued in 2014.\textsuperscript{56}

Relative to the 2003 guidelines, recommendations for SVT management remain largely unchanged aside from slight COR changes. However, the 2015 guidelines more clearly delineate treatment algorithms for acute and ongoing management for each type of SVT and use a different LOE system (a summary of recommendations is detailed in Table 3). The guidelines also provide long-awaited recommendations regarding management of asymptomatic Wolff–Parkinson–White syndrome (preexcitation) and were published in conjunction with a separate systematic review on the topic.\textsuperscript{57}

Ivabradine is a newly recommended agent in the 2015 guidelines. It selectively blocks the hyperpolarization-activated cyclic nucleotide-gated channel responsible for the cardiac pacemaker current within the sinoatrial node, resulting in heart rate reduction without affecting ventricular repolarization or myocardial contractility.\textsuperscript{58} Ivabradine recently received FDA approval for use in patients in sinus rhythm who have heart failure with reduced ejection fraction (HFREF) and a resting heart rate of ≥70 bpm despite optimal β-blocker therapy; the drug’s approval followed the publication of supportive data from two large randomized trials.\textsuperscript{59,60} Although not FDA approved for use in the setting of inappropriate sinus tachycardia (IST), the guidelines suggest that ivabradine may be a reasonable choice for ongoing management of symptomatic patients based on evidence from a small randomized trial and observational studies.\textsuperscript{61-63} While ivabradine will likely be widely used in the setting of heart failure due to proven benefit and affordable pricing, it remains to be seen whether its use will prove beneficial for IST, since only a small heart rate reduction (6–8 bpm) was observed in the clinical trials leading to ivabradine’s approval.

The ACC–AHA–HRS guidelines include several other minor changes to recommendations on pharmacologic therapy (detailed in Table 3). There are no longer recommendations regarding administration of calcium channel blockers for management of IST, and dofetilide was incorporated into the management recommendations (based on limited supportive data).\textsuperscript{44,65} Overall, the 2015 SVT guidelines are similar to the 2003 guidelines with regard to pharmacologic treatment options but provide significantly more guidance on specific agent selection for acute and ongoing management (including management of patients with asymptomatic preexcitation, which previously was not well defined). However, high-quality evidence to support the use of pharmacologic agents in SVT management is still lacking. Recommendations for antiarrhythmic therapy are often extrapolated from outcomes data documented in the setting of AF and the recommendations for ivabradine are largely based on evidence from trials.
performed in HFrEF populations. Additional trials are warranted to better define the role of the various antiarrhythmics and ivabradine in the management of specific types of SVT.

**Arabi et al. Permissive underfeeding or standard enteral feeding in critically ill adults**

The PermiT study was a multicenter RCT that evaluated outcomes of moderate restriction of nonprotein calories versus standard enteral feedings in critically ill adults in Saudi Arabia and Canada. The primary outcome was 90-day mortality, and patients were included in the study if they were able to receive enteral nutrition within 48 hours of intensive care unit (ICU) admission and were expected to remain in the ICU for at least 72 hours. The permissive-underfeeding group (PUG) received a goal of 40–60% of caloric requirements, while the standard-feeding group (SFG) goal was 70–100%. Both groups received full protein requirements (1.2–1.5 g per kilogram of body weight per day). Dosing of nutrition support therapy was based on clinical guidelines using total body weight, with the enteral nutrition formula determined by the clinical team. In addition, patients in the PUG received 0.9% sodium chloride injection to minimize differences in volume delivery between groups. Interventions were continued for up to 14 days or until ICU discharge, oral feeding initiation, death, or withholding of nutrition as part of palliation. Secondary outcomes included ICU mortality, 28-day mortality, in-hospital mortality, and ICU and hospital length of stay (LOS).

A total of 894 patients were randomly assigned to the SFG (n = 446) or the PUG (n = 448). The SFG achieved a mean ± S.D. intake of 71% ± 22% of the daily caloric goal, as compared with a mean ± S.D. intake of 46% ± 14% of the daily goal in the PUG (p < 0.001). No significant difference was seen in the primary outcome or any secondary outcome. The PUG had a lower mean ± S.D. blood glucose level than the SFG (9.1 ± 5.3 mmol/L versus 9.4 ± 5.0 mmol/L, p = 0.04) and a lower mean ± S.D. insulin requirement (15 ± 27 units/day versus 27 ± 22 units/day, p = 0.02) at 14 days, as well as a lower daily fluid balance (490 mL/day versus 688 mL/day, p < 0.001). The investigators concluded that permissive underfeeding is not associated with improved mortality.

In guidelines on nutritional support in critically ill adults jointly issued by the American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) and the Society of Critical Care Medicine (SCCM) in 2016, expert consensus recommendations call for permissive underfeeding or hypocaloric feeding (intake of 65–70% of estimated energy needs) within the first week of hospitalization for patients with a body mass index (BMI) greater than 30 kg/m² (no LOE provided). However, the expert consensus recommendations stipulate that nonobese, high-risk patients should receive more than 80% of goal calories, as attainment of caloric intake above that threshold is

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Recommendation</th>
<th>CORb</th>
<th>LOEb</th>
<th>Type of Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class Ia antiarrhythmics</td>
<td>No longer recommended for management of focal atrial tachycardia or atrial flutter</td>
<td>. . .</td>
<td>. . .</td>
<td>Update</td>
</tr>
<tr>
<td>Digoxin</td>
<td>No longer recommended for acute focal atrial tachycardia</td>
<td>. . .</td>
<td>. . .</td>
<td>Update</td>
</tr>
<tr>
<td>Dofetilide</td>
<td>May be reasonable for patients with acute atrial flutter</td>
<td>I</td>
<td>A</td>
<td>New</td>
</tr>
<tr>
<td></td>
<td>May be reasonable for supraventricular tachycardia of unknown origin</td>
<td>Ilb</td>
<td>B-R</td>
<td>New</td>
</tr>
<tr>
<td>Ibutilide</td>
<td>May be reasonable for sinus rhythm restoration for acute focal atrial tachycardia</td>
<td>Ilb</td>
<td>C-LD</td>
<td>New</td>
</tr>
<tr>
<td>Ivabradine</td>
<td>May be reasonable as monotherapy for symptomatic patients</td>
<td>Ila</td>
<td>B-R</td>
<td>New</td>
</tr>
<tr>
<td></td>
<td>May be reasonable in conjunction with β-blockers for symptomatic patients</td>
<td>Ilb</td>
<td>C-LD</td>
<td>New</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>Option for acute and ongoing management of multifocal atrial tachycardia</td>
<td>Ila</td>
<td>C-LD</td>
<td>New</td>
</tr>
</tbody>
</table>

**Table 3. New and Updated Recommendations on Management of Supraventricular Tachycardia**

*COR = class of recommendation, LOE = level of evidence.
*Definitions of levels of classification and evidence provided in guideline summary.
*Not applicable.
associated with reduced mortality; a similar correlation of higher caloric intake with lower mortality has not been demonstrated in low-risk patients. In the PermiT study, average caloric intake in the SFG was only about 71% of the goal intake, which may have affected the ability to detect a meaningful between-group difference in outcomes. Also, only 14.1% of the patients initially screened were included in the study, and a majority of included patients (75.1%) were admitted for medical indications, limiting the broad application of these data. Most patients (68.5%) were recruited from 1 site in the study. This was particularly concerning because each site used an institution-specific protocol, which likely differed from those of other sites. With 1 institution accounting for two thirds of the study population, generalizability is likely limited. Finally, the mean BMI in both groups approached the definition of obesity. The protocol used predictive equations for calculating caloric goals, a practice discouraged in the A.S.P.E.N.–SCCM guidelines, which instead favor indirect calorimetry, particularly in the obese patient population.

Multiple studies have compared permissive underfeeding with feeding to attain standard caloric goals and have shown mixed clinical outcomes, though the weight of evidence supports providing full goal protein requirements. A recent pilot study of surgical and trauma ICU patients found no difference in infection rates, LOS, or mortality between eucaloric- and hypocaloric-feeding groups. In contrast, a large retrospective analysis of the Glucontrol trial database found a J-shaped relationship between caloric intake and survival. In that study, the second quartile of patients (i.e., those receiving 25–50% of caloric requirements) had the lowest mortality and LOS; data on protein administration were lacking, and baseline severity of illness was lower in the second quartile (the final analysis adjusted for this factor). The PermiT study investigators attempted to show benefit from permissive underfeeding in a critically ill population for a longer duration than in the 2 aforementioned studies, but the study did not provide strong enough evidence (or have broad enough inclusion criteria) to warrant recommending a change to standard practice or current guidelines.

**Braunschweig et al. Intensive nutrition in acute lung injury: a clinical trial (INTACT)**

The INTACT study was a single-center RCT evaluating the influence of intensive medical nutrition therapy (IMNT) versus standard nutrition support care (SNSC) in patients with acute lung injury (ALI). The primary outcome was the rate of nosocomial infection from the time of ALI to hospital discharge. Adult patients with ALI in medical or surgical ICUs were included. Patients were randomly assigned within 24 hours of ALI diagnosis to receive either IMNT (more than 75% of energy and protein needs provided via enteral nutrition and oral diet) or SNSC (standard enteral nutrition and ad-lib feeding). Daily energy requirements were calculated as 30 kcal per kilogram of admission weight or obesity-adjusted ideal body weight (IBW). Protein requirements were estimated as 1.5 g protein per kilogram of IBW in nonobese patients (per kilogram of obesity-adjusted IBW in obese patients). Secondary outcomes were days of mechanical ventilation, ICU and hospital LOS, and mortality.

Seventy-eight patients were randomly assigned to receive IMNT (n = 40) or SNSC (n = 38). The patients were mostly obese, with 35.9% classified as moderately or severely malnourished. The mean Acute Physiology and Chronic Health Evaluation II (APACHE II) score at ICU admission was significantly lower in the IMNT group (23.4 versus 27.7 in the SNSC group, p = 0.03). Although calculated energy and protein requirements were similar in the IMNT and SNSC groups, on average patients in the IMNT group received a significantly higher percentage of calculated energy needs (mean, 84.7% versus 55.4%; p < 0.0001) and protein needs (mean, 76.1% versus 54.4%; p < 0.0001). Parenteral nutrition use was similar in the 2 groups. There were no significant between-group differences in rates of nosocomial infection, duration of mechanical ventilation, and ICU or hospital LOS. An interim review found a significantly higher mortality rate in the IMNT group (40.0% versus 15.8% in the SNSC group, p = 0.017), resulting in early study discontinuation. The researchers concluded that IMNT in patients with ALI increases mortality, although mortality was not the primary outcome of interest. Potential hypotheses put forth by the investigators to explain the observed increased mortality associated with IMNT included the effect of feedings on gut microbiota and impairment of the immune response.

The INTACT study results contrasted with national guidelines, which recommend early enteral nutrition with either trophic or full enteral nutrition for patients who have ALI or acute respiratory distress syndrome and are expected to be mechanically ventilated for at least 72 hours (high LOE, strong recommendation). However, the INTACT study data were not considered during development of that guideline. Several other recent pertinent studies have yielded conflicting results, including the PermiT study described above (the percentage of patients with ALI in that study is unknown). The EDEN trial was a multicenter RCT that compared the effects of 6 days of trophic versus full feeding on the primary outcome of ventilator-free days at 28 days in patients evaluated within 48 hours of developing ALI. There was no significant between-group difference in the primary outcome or 60-day mortality; relative to the trophic-feeding group, the full-feeding group had a higher frequency of gastrointestinal intolerance despite greater use of prokinetic agents. A systematic review and meta-analysis that evaluated data from RCTs comparing ICU outcomes
with hypocaloric versus normocaloric feeding found no significant differences in outcomes such as mortality and ICU LOS. The question of the optimal regimen and timing of feeding in ICU patients with ALI requires further investigation given the conflicting results reported thus far, especially considering the heterogeneity of ICU populations.

Dulhunty et al. A multicenter randomized trial of continuous versus intermittent β-lactam infusion in severe sepsis

The BLING-II study was a multicenter, double-blind RCT designed to compare the effects of continuous versus intermittent infusion of β-lactam antibiotics. The primary outcome was the number of “alive ICU-free days” at 28 days. Adults with severe sepsis who were initiated on meropenem, piperacillin–tazobactam, or ticarcillin–clavulanate within the previous 24 hours were included. Treatment was continued until ICU discharge or completion of therapy. Blood culture testing was performed prior to study drug administration and repeated until there was no growth of the initially identified organism. Secondary outcomes included alive organ failure–free days at 14 days, duration of bacteremia, and mortality at 90 days.

A total of 432 patients were randomly assigned to receive continuous infusions (n = 212) or intermittent 30-minute infusions (n = 220) of β-lactam therapy. There was no significant difference between the continuous- and intermittent-infusion groups in the median number of alive ICU-free days: 18 days (interquartile range [IQR], 2–24 days) versus 20 days (IQR, 3–24 days); p = 0.38. The continuous- and intermittent-infusion groups also did not differ significantly in terms of 90-day survival (HR, 0.91; 95% CI, 0.63–1.31; p = 0.61) and the likelihood of clinical cure (OR, 1.12; 95% CI, 0.77–1.63; p = 0.56). In patients with a pathogenic organism identified, there was no difference in the duration of bacteremia between groups. Thirty-nine organisms (97.5%) in the continuous-infusion group and 37 (86.0%) in the intermittent-infusion group were susceptible to the study drug (no p values reported). There was a significant (p = 0.042) difference in ICU LOS: 7 days (IQR, 3–13 days) with continuous infusion versus 6 days (IQR, 3–11 days) with intermittent infusion. There were no significant differences in rates of adverse events and hospital LOS.

This study did not find a significant difference in a variety of outcomes between patients with severe sepsis with the use of continuous versus intermittent antimicrobial therapy. Current guidelines for the management of severe sepsis do not make a recommendation regarding the method of β-lactam administration. Previous RCTs have shown an improvement in clinical outcomes such as clinical cure and ventilator-free days with continuous versus intermittent β-lactam infusion, though they were not powered to demonstrate a significant difference in LOS or mortality. This study was the largest to date and differed from previous studies in that it included patients receiving continuous renal replacement therapy (CRRT). Continuous-infusion antimicrobial therapy is thought to be superior to intermittent-infusion therapy on the basis of pharmacodynamic simulations demonstrating a higher likelihood of maintaining drug concentrations above the pathogen’s minimum inhibitory concentration (MIC). Several factors may have influenced the BLING-II study results. Only blood cultures were collected, although more than 50% of the patients involved in the study were treated for suspected pulmonary infections; among the 19.2% of patients with positive cultures, the most common organisms identified were *Escherichia coli* and *Klebsiella pneumoniae*, which have been found to have low rates of resistance (0–4.5%) where the study took place (Australia). Low MICs may have decreased the importance of optimizing antibiotic pharmacodynamics and accounted for the similarity in outcomes. Future studies in this area should focus on patients with organisms that commonly harbor resistance mechanisms in order to truly evaluate the hypothesized advantage of continuous-infusion antibiotics.

Gattas et al. A randomized controlled trial of regional citrate versus regional heparin anticoagulation for continuous renal replacement therapy in critically ill adults

Gattas and colleagues performed a multicenter open-label RCT comparing regional anticoagulation with citrate plus calcium versus heparin plus protamine for CRRT in adult ICU patients in Australia and New Zealand. The primary outcome was median functional CRRT circuit life. Patients with chronic kidney disease requiring dialysis prior to ICU admission, liver failure or hepatitis, or suspected or confirmed heparin-induced thrombocytopenia (HIT) were excluded. CRRT as prescribed and the study medications were given per institution protocol. Secondary outcomes included changes in interleukin (IL)-6, IL-8, and IL-10 levels within 48–72 hours of CRRT initiation, duration of CRRT, hospital mortality, ICU LOS, and need for red blood cell transfusion.

A total of 212 patients were randomly assigned to receive regional citrate and calcium (n = 105) or heparin and protamine (n = 107), with 857 circuits analyzed (390 in the citrate group and 467 in the heparin group). With regard to the primary outcome, median functional circuit life was significantly longer in the citrate group (39.2 hours [95% CI, 32.1–48.0 hours] versus 22.8 hours [95% CI, 13.3–34.0 hours] in the heparin group, p = 0.0037). Patients in the heparin group were more likely to experience circuit clotting than those in the citrate group (HR, 2.03; 95% CI, 1.36–3.03; p < 0.0005). There were no significant differences in secondary outcomes. The researchers concluded that relative to...
regional heparin, regional citrate is associated with prolonged CRRT circuit life and fewer adverse events.

This study was the largest evaluation of regional citrate anticoagulation for CRRT to date. The study results are concordant with those of other recent studies that found citrate to be as safe and effective as heparin. 78-80 The study protocol reflected modern CRRT practice patterns in regard to citrate use. The practice of heparin reversal with protamine, as described in the study, is not universal, particularly in the United States; however, a recent single-center RCT 81 found that outcomes of citrate-based versus heparin anticoagulation without protamine use were similar to those reported by Gattas et al. 10

Common concerns cited with the use of citrate anticoagulation in CRRT include concerns about safety and adverse events in patients with hepatic dysfunction. In the study of Gattas et al., adverse events occurred more frequently in the heparin group, with two confirmed and three possible occurrences of HIT. In the citrate group, there was one case of acidosis with hypotension and two administration errors (hypercalcemia and skin necrosis with peripheral administration) attributed to protocol violations. Strict adherence to citrate protocols can allow for the safe implementation of this method. 78 Although patients with hepatic failure were excluded from the study, recent observational studies suggest that citrate can be used safely in the context of hepatic failure, likely due to increased extrahepatic citrate metabolism. 81,82 Outside that population, the findings of Gattas and colleagues indicate, regional citrate should potentially serve as a first-line agent for regional anticoagulation for adults requiring CRRT.

**Jerath et al. Volatile-based short-term sedation in cardiac surgical patients: a prospective randomized controlled trial**

Jerath and colleagues 11 performed an a priori subgroup analysis of data from a single-center, open-label RCT involving cardiac surgery patients. The primary outcome was time to extubation in patients undergoing elective coronary artery bypass graft (CABG) surgery who had preserved systolic function (an ejection fraction of >40%) and were randomly assigned to i.v. propofol or volatile anesthetic-based anesthesia and sedation. Volatile anesthetics (i.e., isoflurane or sevoflurane) were administered using the Anesthetic Conserving Device, or AnaConDa (Sedana Medical, Naas, Ireland), a vaporizer that can be connected to a mechanical ventilation circuit for drug administration. Secondary outcomes included analgesia requirements, hospital LOS, rates of postoperative nausea and vomiting, sedation and pain scores, and rate of shivering.

A total of 141 patients were assigned to the volatile-anesthetic (n = 67) and i.v. propofol (n = 74) groups. Patients in the volatile-anesthetic group had a significantly shorter median time to extubation readiness than those treated with propofol (135 minutes [range, 95–200 minutes] versus 215 minutes [range, 150–280 minutes], p = 0.001) and also a shorter time to extubation (182 minutes [range, 140–255 minutes] versus 292 minutes [range, 210–420 minutes], p < 0.001). Relative to propofol-treated patients, those in the volatile-anesthetic group had a higher mean cardiac index value at ICU admission (mean difference, 0.43 L/min/m² [95% CI, 0.38–0.63 L/min/m²]; p < 0.001) and were significantly more likely to require intraoperative use of norepinephrine (OR, 3.7; 95% CI, 1.8–7.6; p < 0.001). There was also a trend of higher use of vasopressin in the ICU in the volatile-anesthetic group (OR, 3.4; 95% CI, 1.0–11.4; p = 0.05). There were no significant between-group differences in secondary outcomes. There were no serious adverse events or technical difficulties with use of the AnaConDa device. The investigators concluded that compared with propofol, inhaled volatile-agent anesthesia facilitated faster extubation in patients undergoing CABG surgery.

This trial demonstrated that the novel use of perioperative sedation with volatile anesthetics was associated with a shorter time to extubation in patients with preserved systolic function undergoing CABG surgery. Decreased use of mechanical ventilation in the volatile-anesthetic group was an important finding; however, it did not result in shortened ICU or hospital LOS. The observed decrease in time to extubation might have been due to the lack of dependence on end-organ extraction of volatile anesthetics with use of the AnaConDa device, which might have led to low systemic anesthetic accumulation. 83 This study excluded patients needing more than 14 hours of mechanical ventilation, limiting its generalizability. Additionally, it is yet to be determined if the observed benefit of volatile-anesthetic use in terms of decreased time to extubation may be offset by increased vasopressor usage both intraoperatively and postoperatively, especially because hypotension is a very common adverse effect of inhaled anesthetics. 84 With sedation practices continuing to shift away from the use of benzodiazepines, this study provided evidence that volatile anesthetics given via the AnaConDa device are a safe and effective alternative. However, issues such as cost (data not provided), feasibility of implementation into institutional protocols, and credentialing of personnel responsible for monitoring patients who receive this form of anesthesia will need to be considered.

**Klinger et al. Intraoperative magnesium administration does not reduce postoperative atrial fibrillation after cardiac surgery**

Klinger and colleagues 12 performed a secondary analysis of a completed single-center, double-blind RCT that evaluated neurocognitive outcomes with the use of i.v. magnesium after cardiac surgery. 84 The primary outcome was the frequency of new-onset postoperative atrial fibrillation (POAF). Patients scheduled to undergo...
CABG or valve surgery (or both) with cardiopulmonary bypass were included; patients with chronic alcohol use, planned circulatory arrest, or renal or hepatic failure were excluded.

The patients were randomly assigned to receive either a bolus of i.v. magnesium 50 mg/kg over 20 minutes after anesthesia induction, with an additional infusion of 50 mg/kg over 3 hours \((n = 186)\), or 0.9% sodium chloride injection \((n = 177)\). Postoperative care for patients included i.v. magnesium supplementation for serum magnesium concentrations less than 2.0 mg/dL (no details provided on frequency of monitoring or replacement). Patients were subject to continuous telemetry monitoring after surgery until hospital discharge. Risk factors for POAF were taken into account using the internationally validated Multicenter Study of Perioperative Ischemia (McSPI) risk index, a tool for predicting the likelihood of POAF in patients undergoing cardiac surgery.\(^{85}\)

After the infusions, there were significant \((p < 0.001)\) increases in mean serum magnesium levels in the magnesium group relative to the control group at all evaluated time points, but there was no significant difference in rates of new-onset POAF \((42.5% \text{ versus } 37.9%, p = 0.40)\), mean times to POAF onset \((2 \text{ days in both groups, } p = 0.71)\), or rates of AF at discharge \((7.2% \text{ versus } 10.7%, p = 0.54)\) even with adjustment for McSPI risk index scores. The researchers concluded that high-dose intraoperative magnesium does not decrease the rate of POAF after cardiac surgery.

Hypomagnesemia is a known risk factor for the development of AF after cardiac surgery, with the peak incidence occurring approximately 2–3 days after CABG procedures.\(^{86-88}\) RCTs have shown mixed results regarding the benefits of supplemental magnesium for AF prevention. A larger RCT, involving 202 patients, did not show an overall reduction in POAF with prophylactic magnesium use\(^{86}\); a meta-analysis of data from 7 RCTs indicated a benefit.\(^{88}\) The study by Klinger and colleagues was the largest evaluation of the effects of supplemental magnesium on POAF to date; as it was a secondary analysis of data from a completed RCT, the researchers were unable to evaluate if the RCT was appropriately powered. Also, when comparing magnesium levels between groups, significant differences in serum magnesium levels were observed at all time points but were considered to be of minimal clinical relevance. The potential benefit of a higher serum magnesium level after treatment remains in question. While it is essential to maintain magnesium levels within normal limits after cardiac surgery, the use of prophylactic magnesium supplementation does not appear to be beneficial for the prevention of POAF.

**Mouncey et al. Trial of early, goal-directed resuscitation for septic shock\(^{13}\)**

The ProMISE trial was a multicenter open-label, parallel-group RCT. The primary outcome was the difference in 90-day mortality with use of an early goal-directed therapy (EGDT) resuscitation bundle \((n = 630)\) versus usual care \((n = 630)\) in patients with early septic shock in England.\(^{13}\) The ProMISE trial was the most recent of 3 multicenter RCTs—the earlier ones being the ARISE\(^{11}\) and ProCESS\(^{90}\) trials—comparing mortality rates with EGDT versus usual care in early septic shock. EGDT was coordinated by trained individuals at each site and mandated; systolic BP, rather than solely mean arterial pressure (MAP), as the BP goal was allowable; and minimum goals, as opposed to targeted ranges of values, were set for central venous pressure (CVP) and MAP. Secondary outcomes included ICU LOS and cost-effectiveness measures at 90 days and 1 year. Resuscitative efforts were supported by continuous central venous oxygen saturation \((\text{ScvO}_2)\) monitoring in 87.3% of patients in the EGDT group and 0.3% of those receiving usual care. With regard to baseline characteristics, the EGDT and usual-care groups differed significantly only in terms of mean age \((66.4 \text{ and } 64.3 \text{ years, respectively; } p = 0.01)\). Protocol adherence was greater than 80% in the EGDT group, with the majority of nonadherence resulting from nonperformance of ScvO\(_2\) monitoring. On average, in the first 6 hours of treatment, patients in the EGDT group received larger volumes of fluids and were more frequently administered vasopressors and dobutamine, transfused with red blood cells, and admitted to an ICU than usual-care patients \((p \text{ values provided})\).

With regard to the primary outcome of all-cause mortality at 90 days, results were similar in the 2 groups before and after adjustment for baseline characteristics (postadjustment mortality was 29.5% with EGDT versus 29.2% with usual care; OR, 0.95; 95% CI, 0.74–1.24; \(p = 0.73\)). Results were similar across all subgroup analyses. Patients in the EGDT group had a higher mean Sequential Organ Function Assessment score at hour 6 \((6.4 \text{ versus } 5.6 \text{ with usual care, } p < 0.001)\) and a longer mean ICU LOS \((2.6 \text{ days versus } 2.2 \text{ days, } p = 0.005)\). In the cost-effectiveness analysis, quality-adjusted life-years (QALYs) were estimated by combining quality-of-life scores at 90 days with survival data. The incremental net benefit was estimated by valuing incremental QALYs at a willingness-to-pay threshold of $28,430 after subtracting incremental costs. Average costs at 90 days were similar in the EGDT and usual-care groups \((\text{cost differential favoring usual care, }$1,406; 95% CI, $1,032 \text{ to } $3,845; p = 0.26)\). The probability that EGDT was cost-effective was less than 20%. The authors concluded that the addition of strict protocolization for management of early septic shock did not improve patient outcomes and was likely not cost-effective.

Alongside the ARISE and ProCESS trials, the ProMISE trial challenged some components of the EGDT pro-
tocol established by Rivers and colleagues.\textsuperscript{35} Advances in care and early recognition of sepsis may help to explain the differences in mortality between patients treated today and those treated 15 years ago.\textsuperscript{94} After publication of the ProMISe trial findings, a 2012 Surviving Sepsis Campaign recommendation to achieve an ScvO\textsubscript{2} of 70% or a mixed venous oxygen saturation of 65% and a CVP of 8–12 mm Hg\textsuperscript{72} was revised to de-emphasize the placement and use of a central line for invasive monitoring.\textsuperscript{85} Although mixed, research results suggest that serial lactate measurements may be just as effective and more cost-effective than invasive monitoring.\textsuperscript{96,97} However, it could be argued that patients in the usual-care group of the ProMISe trial received some EGDT components (e.g., 50.9% underwent central venous catheter placement).

Patients in the ProMISe trial were more likely to experience refractory hypotension and hyperlactatemia than those in the ARISE or ProCESS trials, indicating a population with a higher severity of sepsis\textsuperscript{91,92}; the 90-day mortality rate in the usual-care group (29.5%) was greater than the 18.6% mortality rate in the ARISE trial but less than the 31.9% mortality rate in the ProCESS trial. The authors of a recent meta-analysis, which included data from all 3 trials, concluded there was no significant difference in 90-day mortality with EGDT and usual-care treatment strategies.\textsuperscript{98} When early antibiotics and aggressive, guideline-based fluid resuscitation efforts are initiated in patients experiencing early septic shock, use of an individualized approach appears to be just as effective and less costly than more invasive methods.

**Noto et al. Chlorhexidine bathing and healthcare-associated infections: a randomized clinical trial\textsuperscript{14}**

Noto and colleagues\textsuperscript{14} performed a single-center, crossover RCT evaluating the effect of chlorhexidine bathing in 5 adult ICUs in the United States. The primary outcome was the frequency of a composite of central line–associated bloodstream infection (CLABSI), catheter-associated urinary tract infection, ventilator-associated pneumonia (VAP), and *Clostridium difficile* infection. Patients received once-daily bathing with chlorhexidine or disposable nonantimicrobial cloths. Infection-control personnel used standardized definitions to determine infection outcomes and were blinded to treatment assignments. Bathing treatments were performed for a 10-week period followed by a 2-week washout period (nonantimicrobial disposable cloths were used in both groups) and then use of the alternative bathing treatment for 10 weeks. Secondary outcomes included the rates of culture results positive for multidrug-resistant organisms (MDROs) and healthcare-associated bloodstream infections.

A total of 9,340 patients were assigned, via cluster randomization by ICU, to the chlorhexidine (\(n = 4,488\)) and control (\(n = 4,852\)) groups. Overall, 55 infections occurred during the chlorhexidine bathing period, and 60 infections occurred during the control bathing period (\(p = 0.95\)). There were no significant between-group differences in individual components of the primary outcome or any secondary outcomes, although there was a trend of a decreased rate of VAP in the chlorhexidine group versus the control group (difference in number of events per 1,000 patient-days, 0.5 day; 95% CI, 0.0013–0.999 day; \(p = 0.05\)). The researchers concluded that daily bathing of patients with chlorhexidine did not reduce the incidence of healthcare-associated infection.

A multicenter study of 7,727 patients indicated a significant reduction in methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant enterococci, healthcare-associated bloodstream infections, and CLABSI with chlorhexidine bathing\textsuperscript{99}; however, the duration of chlorhexidine bathing was 24 weeks, and bone marrow transplant patients were included. Chlorhexidine bathing is widely practiced to reduce healthcare-associated infections, but the costs incurred and the potential for exposure to chlorhexidine to create microbial resistance should be considered. Further studies of ICU patients and chlorhexidine bathing that include evaluation of adherence to treatment protocols may be beneficial.

**Saver et al. Prehospital use of magnesium sulfate as neuroprotection in acute stroke\textsuperscript{15}**

The FAST-MAG study was a multicenter, double-blind, placebo-controlled RCT that investigated the effects of magnesium therapy, administered by emergency medical services personnel within 2 hours of stroke symptom onset based on the Los Angeles Prehospital Stroke Screen, to patients 40–95 years of age.\textsuperscript{15} The primary outcome was the degree of disability, as assessed by the modified Rankin Scale, 90 days after the event. Randomization was stratified according to the enrolling ambulance. The use of concomitant therapies followed national practice guidelines.\textsuperscript{19,100} Patients with preexisting conditions that can confound neurologic or functional outcome evaluations, with rapidly improving neurologic deficits, or with a documented stroke within the past 30 days were excluded. Secondary outcomes included degree of neurologic deficit, level of activities of daily living, and overall functional outcomes, as determined using validated tools.

A total of 1,700 patients were randomly assigned to receive a magnesium 4-g i.v. bolus given over 15 minutes followed by 16 g of magnesium administered as an infusion over 24 hours (\(n = 857\)) or 0.9% sodium chloride injection (\(n = 843\)). The median time to administration of the study drug was 45 minutes (IQR, 35–62 minutes), with 74.3% of patients receiving their infusion within the first hour of symptoms. There was no significant between-group difference in 90-day modified Rankin Scale scores (\(p = 0.28\)) or any secondary outcomes. The frequency of serious adverse events
was high in both the magnesium and placebo groups (51.2% and 50.1%, respectively; \( p = 0.67 \)); no clarification was given as to what qualified as a serious event. Evaluation of subgroups based on type of stroke and thrombolytic management did not indicate any significant differences in the primary outcome. The researchers concluded that prehospital administration of magnesium in acute stroke was safe but did not improve disability outcomes at 90 days.

Current treatment modalities for ischemic stroke consist of reperfusion-based therapies and are only moderately effective.\(^{101}\) Neuroprotective therapies can be used to complement reperfusion strategies in the hope of improving the functional status of patients in the months to years after ischemic stroke. Magnesium acts as a competitor of calcium, decreasing excessive cellular calcium entry into neurons and thereby reducing cellular death.\(^{102,103}\) It has been shown to be of benefit when given within 2 hours after neurologic insult in rodent models, though no human studies have enrolled patients treated with magnesium within 2 hours of symptom onset. To date, over 70 neuroprotective agents have been tested in RCTs, with little benefit demonstrated. Laboratory data suggest that early administration of neuroprotective therapies is crucial.\(^{104}\) A key confounding factor in prior investigations of neuroprotective therapies in humans was delayed treatment. The study of Saver et al. was the first to show that earlier and safe administration of a prehospital neuroprotective agent is achievable.

**Saunders et al. Trial of short-course antimicrobial therapy for intraabdominal infection\(^ {106} \)**

The STOP-IT study was a multicenter open-label RCT that compared a short course of antimicrobials (4 days) with a longer course (antimicrobial therapy continued for 1–3 calendar days after the resolution of fever, gastrointestinal symptoms, or leukocytosis or for a maximum of 10 days) for the management of complicated intraabdominal infection (cIAI) in patients 16 years of age or older.\(^ {106} \) The primary outcome was a composite of death within 30 days of source control, recurrent IAI, and surgical-site infection (SSI). Patients with cIAI were included in the study if they had signs of sepsis or gastrointestinal dysfunction at presentation; patients were excluded if there was a high likelihood of death at 72 hours or they had IAI requiring less than 24 hours of treatment per published guidelines.\(^ {105} \) After adequate source control, patients were randomly assigned to the experimental group or the control group. Secondary outcomes included duration of antimicrobial therapy and rate of subsequent infections.

A total of 518 patients were randomly assigned to the experimental (\( n = 260 \)) and control (\( n = 258 \)) groups. The mean \( \pm \) S.E. APACHE II score was 10.1 \( \pm \) 0.3, and the most common origin of infection was the colon or rectum (34.2%). Culture data were not obtained in 107 patients (20.7%). Protocol adherence was 72.7% in the control group versus 81.8% in the experimental group (\( p = 0.02 \), with the greatest source of protocol deviation being prolonged duration of therapy. There was no significant difference between the groups in the frequency of the composite primary outcome (21.8% in the experimental group versus 22.3% in the control group, \( p = 0.92 \)). The median duration of antimicrobial therapy for the index infection was shorter in the experimental group (4 days versus 8 days, \( p < 0.001 \)), and the mean times to diagnosis of SSI and recurrent IAI were also significantly shorter in the experimental group (8.8 days versus 15.1 days \( p < 0.001 \) and 10.8 days versus 15.1 days \( p < 0.001 \), respectively). There were no significant between-group differences in other secondary outcomes.

Although adequate source control remains the primary treatment for IAI, antimicrobial therapy is often used adjunctively. Current guidelines recommend a treatment course of 4–7 days after source control, but the duration of therapy is often extended in clinical practice due to prolonged symptoms.\(^ {105,106} \) Smaller studies have evaluated shorter durations of antimicrobial therapy in IAI,\(^ {107,108} \) but the STOP-IT trial was the largest to date. However, there are several limitations to this study. First, it was terminated early due to futility after the first interim analysis. Second, the median duration of antibiotic therapy among patients in the experimental group who received non–protocol-adherent therapy (18% of the ITT population) was 11 days. Furthermore, cultures were not required, and empirical use of antimicrobials followed guideline recommendations. It is unknown whether antimicrobial therapy was tailored to target a cultured organism, as this information was not provided.

Third, given the high mean APACHE II score for the overall study population, the observed mortality rate of <1% was lower than the rates of 7–10% reported in other studies of cIAI.\(^ {109} \) Lastly, the rates of MDRO infections have increased dramatically over the past few years, with reported rates of MDRO resistance to commonly used antimicrobials of up to 25% in some cases.\(^ {110} \) However, only 8 patients (1.5%) in this study were reported to harbor an MDRO.

The STOP-IT study was a large, well-designed study whose findings warrant further investigation of a shorter duration of antibiotic therapy after adequate source control in cIAI. However, clinicians should also be cognizant of the need to tailor empirical antibiotic therapy selection to local resistance patterns and culture susceptibilities.

**Skolnick et al. A clinical trial of progesterone for severe traumatic brain injury\(^ {17} \)**

**Wright et al. Very early administration of progesterone for acute traumatic brain injury\(^ {18} \)**

The SYNAPSE\(^ {17} \) and PROTECT III\(^ {18} \) studies were both multicenter,
double-blind RCTs. The SYNAPSE trial was performed in 21 countries from July 2010 to September 2013. The PROTECT III study was conducted in 49 U.S. trauma centers from April 2010 to October 2013. Both studies enrolled adult patients with nonpenetrating traumatic brain injury (TBI) and had a primary endpoint of favorable outcome at 6 months (defined in the SYNAPSE trial as good recovery or moderate disability per Glasgow Outcome Scale [GOS] scoring and in the PROTECT III study as functional recovery per a stratified dichotomy of scores on the extended version of the GOS). Secondary outcomes included mortality at 6 months and Disability Rating Scale score. In the SYNAPSE study, a progesterone i.v. bolus (0.71 mg/kg) and continuous infusion of progesterone (0.5 mg/kg/hr) were initiated within 8 hours of TBI and continued for 5 days; in the PROTECT III trial, progesterone therapy was initiated within 4 hours and then tapered and continued for 4 days.

Neither study demonstrated a benefit with progesterone use in terms of the primary or secondary outcomes. The PROTECT III trial was halted at the second interim analysis due to futility. There was no difference in the proportion of progesterone-treated patients versus placebo recipients with a favorable outcome in either the SYNAPSE study (OR, 0.96; 95% CI, 0.77–1.18) or the PROTECT III study (relative benefit with progesterone use, 0.95; 95% CI, 0.85–1.06; \( p = 0.35 \)). These disappointing results contrasted with findings of research using multiple animal models and several single-center placebo-controlled studies that found reduced mortality with progesterone use.\(^{111}\) Meta-analyses that included data from the SYNAPSE and PROTECT III trials also did not show a benefit with progesterone use.\(^{112,113}\)

Progesterone produces neuroprotective effects by inhibiting inflammatory cytokines, decreasing levels of inflammation-related factors, preventing excitotoxicity, and reducing apoptosis and vasogenic edema.\(^{117}\) Potential reasons for the reported lack of benefit from progesterone use in the SYNAPSE and PROTECT III studies include confounding preexisting conditions, heterogeneity of injury, a lack of biomarkers for use in determining clinical improvement, multiple concomitant direct and indirect injury mechanisms, and variability in routine care across sites; the positive findings in Phase II trials may be attributable to unrecognized bias, small sample size, and low odds of a true association between progesterone use and improved outcomes in patients with TBI, as those studies demonstrated a reduction in mortality but only a modest benefit in terms of functional outcomes.\(^{114-117}\) A truly effective treatment for patients with TBI remains to be found. Efforts are underway to improve the quality of studies, better characterize the disease process, and identify appropriate targets of therapy.\(^{115,118,119}\)

**Conclusion**

Important recent additions to the critical care pharmacy literature include updated joint clinical practice guidelines on the management of spontaneous ICH, ACLS, and SVT.

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**Additional information**

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