PRACTICE INSIGHTS

Key Articles and Guidelines Relative to Intensive Care Unit Pharmacotherapy: 2009 Update

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Compilations of key articles and guidelines in a particular clinical practice area are useful not only to clinicians who practice in that area, but also to all clinicians. We compiled pertinent articles and guidelines pertaining to drug therapy in the intensive care setting from the perspective of experienced critical care pharmacists. A broad assembly of practitioners with expertise in various areas of intensive care unit pharmacology were involved in the compilation of this update.
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The original compilation of key articles and guidelines pertaining to intensive care unit (ICU) pharmacology was published in 2002.[1] That compilation was primarily from the perspective of the general ICU practice of the primary author (B.L.E.); therefore, certain topics were not covered to a significant degree. A subsequent revision in 2004[2] and this 2009 update were compiled by selected members of the Critical Care Practice and Research Network (PRN) of the American College of Clinical Pharmacy. These revisions contain a more diverse range of articles reflective of the authors' interest areas and practice settings. In addition, we evaluated research investigations by using an evidence-based classification system.[3] This classification system is as follows: class I, randomized controlled trials; class II, prospective trials and retrospective studies with reliable data (e.g., case-control studies); and class III, retrospective studies and expert opinion.

The information in this compilation should be particularly useful for trainees, relatively new practitioners, and experienced specialists seeking a broader understanding of critical care–related pharmacotherapy. We hope it also might serve as a useful template for experienced clinicians who have contemplated a similar undertaking in their practice areas.

Authors from the Critical Care PRN were invited to participate based on their recognized areas of expertise. Once written, the sections were compiled and reviewed by all authors to help ensure appropriate article selections and summaries. We could not include every published article we considered important to critical care pharmacotherapy; however, we compiled what we believed were the most representative articles addressing the selected critical care topics.

This bibliography is divided into four general sections. The first focuses on landmark and contemporary pivotal articles and guidelines pertaining to pharmacotherapy in the ICU setting. When these were not available in a specific clinical area, comprehensive reviews or articles were chosen that have generated substantial discussion among ICU practitioners. Some of the headings of this section have been changed since the previous revision.[2] The second section focuses on articles pertaining to medication errors and adverse drug events in the ICU. Since many of the interventions by ICU pharmacists pertain to patient safety, this section could include a large number of citations; however, the intent was to cite investigations that assessed medication errors and adverse drug events, or pharmacists' attempts to prevent or ameliorate them, from a broader system-wide perspective. The third section lists more general articles pertaining to critical care pharmacy services development and justification. The fourth section focuses on literature pertaining to the economic justification of ICU pharmacy services (both supporting and opposing) or, more specifically, the justification for pharmacists in the critical care setting.

Pharmacotherapy in the Intensive Care Unit

Cardiovascular Diseases

The following compilations of key articles and guidelines pertaining to arrhythmias, acute coronary syndromes, and hypertension have been covered in previous issues of *Pharmacotherapy*:

Jackevicius CA, Page RL, Chow S, et al. High-impact articles related to the management of heart failure: 2008 update. Pharmacotherapy 2009;29:82–120.

Dobesh P, Brouse SD, Dager WE, Spinler SA, Stacy Z, Wiggins BS. Key articles and guidelines in the management of acute coronary syndrome and in percutaneous coronary intervention: 2007 update. Pharmacotherapy 2007;27:1722–58.

de Denus S, Hardy AM, Olson KL, Robinette B. Key articles and guidelines in the management of hypertension. Pharmacotherapy 2004;24:1385–99.

Cheng JW, Frank L, Garrett SD, Lu Y, Sanoski CA, White CM. Key articles and guidelines in pharmacotherapeutic management of arrhythmias. Pharmacotherapy 2004;24:248–79.

Dobesh PP, Brouse SD, Johnson DC, et al. Key articles and guidelines relative to treatment of patients with acute coronary syndromes. Pharmacotherapy 2004;24:105–44.

Arrhythmias

Neumar RW, Nolan JP, Adrie C, et al. Post–cardiac arrest syndrome: epidemiology, pathophysiology, treatment, and prognostication. A consensus statement from the International Liaison Committee on Resuscitation (American Heart Association, Australian and New Zealand Council on Resuscitation, European Resuscitation Council, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resuscitation Council of Asia, and the Resuscitation Council of Southern Africa); the American Heart Association Emergency Cardiovascular Care Committee; the Council on Cardiovascular Surgery and Anesthesia; the Council on Cardiopulmonary, Perioperative, and Critical Care; the Council on Clinical Cardiology; and the Stroke Council. Circulation 2008;118:2452–83.

Management of patients resuscitated after cardiac arrest and the related literature are explored, and therapeutic strategies are described in this article.

Goodman S, Weiss Y, Weissman C. Update on cardiac arrhythmias in the ICU. Curr Opin Crit Care 2008;14:549–54.

This review explores the treatment and related outcomes of cardiac arrhythmias occurring in the intensive care unit. Most of the document focuses on atrial fibrillation with limited exploration of ventricular arrhythmias.

Gupta A, Lawrence AT, Krishnan K, Kavinsky CJ, Trohman RG. Current concepts in the mechanisms and management of drug-induced QT prolongation and torsade de pointes. Am Heart J 2007;153:891–9.

This review describes how the QT and QTc are measured and their relationship to selected pharmacologic agents implicated in producing related arrhythmias such as torsade de pointes, or inhibitors of cytochrome P450 (CYP) 3A4 that may prolong their effects. Treatment of arrhythmias related to prolongation of the QT interval is also discussed.

Dager WE, Sanoski CA, Wiggins BS, Tisdale JE. Pharmacotherapy considerations in advanced cardiac life support. Pharmacotherapy 2006;26:1703–29.

The literature describing the use of pharmacologic agents in the setting of advanced cardiac life support and updated advanced cardiac life support recommendations in 2005 were reviewed. This article summarizes the evidence for selection of pharmacologic agents available in specific settings and considerations on how to use them. Also discussed is how to approach pharmacotherapy in the setting of cardiac arrest, including select agents for pharmacologic reversal.

Hypertension

Aronson S, Dyke CM, Stierer KA, et al. The ECLIPSE trials: comparative studies of clevidipine to nitroglycerin, sodium nitroprusside, and nicardipine for acute hypertension treatment in cardiac surgery patients. Anesth Analg 2008;107:1110–21.

This article presents the results of three randomized, parallel, open-label trials comparing clevidipine with nitroglycerin, nitroprusside, and nicardipine for the treatment of perioperative hypertension in patients undergoing cardiac surgery. With 1515 patients meeting inclusion criteria, this is the largest randomized trial to date comparing antihypertensive agents given by continuous infusion. The need for antihypertensive therapy was based on physician discretion, and only the clevidipine group had protocol restrictions—that is, no more than 500 ml or 2.5 g/kg of clevidipine formulated in 20% intravenous lipid emulsion in 24 hours. There were no significant differences between groups in the primary end point (mortality, stroke, or renal dysfunction) at 30 days. Although there were some differences in favor of clevidipine with regard to ability to control blood pressure within the desired range, the results must be considered in light of potential confounders such as prescribing by institutional practice patterns for all of the drugs except clevidipine and the open-label design.

Hoekstra J, Qureshi A. Management of hypertension and hypertensive emergencies in the emergency department: the EMCREG–international consensus panel recommendations. Ann Emerg Med 2008;51:S1–38.

Although these consensus panel recommendations were compiled from the standpoint of emergency medicine, much of the information is applicable to the treatment of hypertensive emergencies in the ICU setting. The recommendations cover a broad range of hypertensive emergencies related to pregnancy, cocaine intoxication, and a variety of disease-specific blood pressure elevations. The tables on drugs include dosage, indications, contraindications, and precautions.

Brooks TW, Finch CK, Lobo BL, Deaton PR, Varner CF. Blood pressure management in acute hypertensive emergency. Am J Health Syst Pharm 2007;64:2579–82.

In this retrospective chart review from a single center, the approach to management of a hypertensive emergency was explored. Appropriate treatment occurred in 32% of patients, whereas 57% were initially excessively treated and 11% failed treatment. Treatment-related adverse events (primarily hypotension) occurred in 94% of patients. This study points out the need to improve the pharmacologic management of hypertensive emergencies from the onset of therapy. (Class III)

Feneck R. Drugs for the perioperative control of hypertension: current issues and future directions. Drugs 2007;67:2023–44.

This is a review article of the literature from 1970–2007 regarding the management of perioperative hypertension. Emphasis is placed on randomized controlled trials in addition to explanations of pharmacology to assist in describing the various classes of agents used and approaches to their use in this setting. How to manage therapy once an agent is selected is not a focus of the review.

Haas CE, LeBlanc JM. Acute postoperative hypertension: a review of therapeutic options. Am J Health Syst Pharm 2004;61:1661–75.

This article reviews the underlying pathophysiology, hemodynamics, potential complications, and treatment options for acute postoperative hypertension. The authors present the pharmacology, clinical response, and supporting evidence for vasodilators and β-blockers commonly used in the management of acute postoperative hypertension, along with the significant limitations of the current literature.

Fluids

Brunkhorst FM, Engel C, Bloos F, et al. Intensive insulin therapy and pentastarch resuscitation in severe sepsis. N Engl J Med 2008;358:125–39.

This multicenter randomized trial investigated two issues important to critical care practitioners: intensive insulin therapy and use of starch products for fluid resuscitation. Various starch products have been used as alternatives to albumin, but there are concerns related to developing a coagulopathy independent of dilutional effects and renal dysfunction. Both increased molecular weight and degree of substitution appear to increase the risk of bleeding with starches; the pentastarch used in this study is low molecular weight. The trial was terminated early for safety reasons, although there was no significant difference in 28-day mortality between the insulin (conventional vs intensive) or fluid (modified Ringer's lactate solution vs pentastarch) groups by using a two-by-two factorial design. There were significantly higher rates of renal failure (p=0.002) and days on renal replacement therapy with pentastarch, and more episodes of severe hypoglycemia (p<0.001) in the intensive insulin group. The authors suggested that all starch products be avoided in critically ill patients until adequately powered studies have demonstrated long-term safety. (Class I)

The National Heart, Lung and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network. Comparison of two fluid-management strategies in acute lung injury. N Engl J Med 2006;354:2564–75.

This randomized study compared a liberal (central venous pressure [CVP] of 10–14 mm Hg or pulmonary artery occlusion pressure [PAOP] of 14–18 mm Hg) with a conservative (CVP < 4 mm Hg or PAOP < 8 mm Hg) fluid administration strategy for patients with acute lung injury. There were no significant differences (p=0.3)

with respect to the primary end point of mortality at 60 days. However, fluid balance, ventilator-free days, and days not spent in the ICU were all significantly lower (p<0.001) in the conservative management group, which supports this approach in patients with acute lung injury. (Class I)

The SAFE Study Investigators. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. N Engl J Med 2004;350:2247–56.

This multicenter, randomized, double-blind comparison of 4% albumin and normal saline for resuscitation of patients admitted to the ICU enrolled 6997 patients; 28-day mortality was the primary end point. No statistically significant differences were observed in death (relative risk [RR] 0.99, 95% confidence interval [CI] 0.91–1.09) or any of the secondary end points under study. The post hoc comparison of the two fluids in patients with severe traumatic brain injury revealed significantly higher mortality (p<0.001) in the albumin group (see Head Injury section). (Class I)

Cooper DJ, Myles PS, McDermott FT, et al. Prehospital hypertonic saline resuscitation of patients with hypotension and severe traumatic brain injury. JAMA 2004;291:1350–7.

This was a double-blind, randomized, controlled trial involving 229 patients with traumatic brain injury (Glasgow Coma Scale score < 9) who experienced hypotension (systolic blood pressure < 100 mm Hg). In addition to conventional resuscitation procedures used by paramedics, patients were randomly assigned to receive rapid intravenous infusions (250 ml) of either 7.5% sodium chloride or Ringer's lactate solution. Patients in both groups were given additional crystalloid or colloid fluids based on a protocol. The major outcome measure was the extended Glasgow Outcome Score at 6 months. Survival rates were similar between the 7.5% sodium chloride and Ringer's lactate groups (55% and 50%, respectively, at discharge, p=0.32; 55% and 47%, respectively, at 6 mo, p=0.23). Similarly, no significant difference was noted between the groups based on neurologic function (p=0.96). The use of the Glasgow Outcome Score as a primary outcome measure in this study is somewhat of a concern in that it is more reflective of unfavorable rather than favorable outcomes. However, as mentioned by the investigators in their response to this criticism

(Cooper DJ et al. JAMA 2004;291:2944–5), a much larger sample would have been needed to investigate the effects of the solutions based on a favorable outcome measure. (Class I)

Sort P, Navasa M, Arroyo V, et al. Effect of intravenous albumin on renal impairment and mortality in patients with cirrhosis and spontaneous bacterial peritonitis. N Engl J Med 1999;341:403–9.

Renal impairment, as a result of cytokine release and decreased arterial blood volume, is common in patients with spontaneous bacterial peritonitis. Albumin may prevent renal dysfunction through its effects on volume expansion and possibly other mechanisms. In this study, 126 patients with cirrhosis and spontaneous bacterial peritonitis were randomly assigned to receive cefotaxime alone or combined with albumin. In the control group, 33% of patients developed renal impairment, versus 10% in the albumin group (p=0.002). Mortality in the hospital and at 3 months was significantly lower in albumin-treated patients than in control patients (p=0.01 and 0.03, respectively). This trial is important because it is one of the few well-controlled trials demonstrating a positive benefit of albumin beyond its effects on surrogate end points. (Class I)

Choi PTL, Yip G, Quinonez LG, Cook DJ. Crystalloids vs colloids in fluid resuscitation: a systematic review. Crit Care Med 1999;27:200–10.

This review of 17 randomized trials compared isotonic crystalloids with colloids for volume resuscitation in 814 adult patients. No significant differences were noted in the frequency of mortality or pulmonary edema, or in the length of hospital stay. However, a subgroup analysis revealed decreased mortality with crystalloid administration in patients who experienced trauma (RR 0.39, 95% CI 0.17–0.89). The authors concluded that more research is necessary to resolve the ongoing controversy regarding the most appropriate and effective method for fluid resuscitation.

Cochrane Injuries Group Albumin Reviewers. Human albumin administration in critically ill patients: systematic review of randomized controlled trials. BMJ 1998;317:235–40.

In this systematic review of 30 randomized controlled trials involving 1419 critically ill patients, albumin administration was associated with one death for every 17 patients treated for hypovolemia, burns, or hypoalbuminemia. Although a significant difference in mortality after albumin administration was not found in each of the categories, the pooled RR of 1.68 for albumin-associated death was significant (95% CI 1.26–2.23). This review, as well as an earlier review in the same journal (Schierhout G et al. BMJ 1998;316:961–4), fueled the colloid-crystalloid debate by pushing the limits of meta-analytic technique.

Bickell WH, Wall MJ, Pepe PE, et al. Immediate versus delayed fluid resuscitation for hypotensive patients with penetrating torso injuries. N Engl J Med 1994;331:1105–9.

Previous studies in animal models have suggested that the volume of intravenous fluid resuscitation may contribute to intraoperative bleeding. In this prospective study, trauma patients with hypotension were randomly assigned to immediate (309 patients) or delayed (289 patients) resuscitation. The primary objective was to determine if the rate of survival would improve when intravenous fluid resuscitation was withheld until the time of surgery. The overall rate of survival was significantly higher in the delayed versus immediate resuscitation group (70% vs 62%, p=0.04). Postoperative complications (acute respiratory distress syndrome, sepsis syndrome, acute renal failure, coagulopathy, wound infection, and pneumonia) also tended to occur less often when fluid administration was delayed, although the difference was not significant. (Class I)

Vasoactive Agents

Mentzelopoulos SD, Zakynthinos SG, Tzoufi M, et al. Vasopressin, epinephrine, and corticosteroids for in-hospital cardiac arrest. Arch Intern Med 2009;169:15–24.

In this single-center, randomized, controlled trial, 100 patients with in-hospital cardiac arrest received either vasopressin plus epinephrine or saline plus epinephrine for five resuscitation cycles. Patients in the vasopressin group also received one dose of methylprednisolone sodium succinate during the first resuscitation cycle. Survivors with postresuscitation shock were randomly assigned to a 7-day course (with taper) of hydrocortisone or saline placebo. Patients in the vasopressin-methylprednisolone group had significantly improved return of spontaneous circulation (p=0.003) and survival to discharge

(p=0.02). Also, patients in the postresuscitation hydrocortisone group had improved survival to discharge (p=0.02) compared with those in the saline control group. (Class I)

Gueugniaud PY, David JS, Chanzy E, et al. Vasopressin and epinephrine vs epinephrine alone in cardiopulmonary resuscitation. N Engl J Med 2008;359:21–30.

In this multicenter, randomized, controlled trial, the combination of epinephrine and vasopressin was compared with epinephrine alone in 2894 patients with out-of-hospital cardiac arrest. No significant difference between the two management strategies was noted; however, over 80% of patients had asystole, less than 15% received amiodarone, and first administration of study drug occurred a mean of 21 minutes after the cardiac event. Potential benefits with either strategy in hospitalized patients remain unclear. (Class I)

Russell JA, Walley KR, Singer J, et al, for the VASST Investigators. Vasopressin versus norepinephrine infusion in patients with septic shock. N Engl J Med 2008;358:877–87.

This multicenter, blinded, randomized trial in 778 patients explored the impact on 28-day mortality of vasopressin 0.01–0.03 U/minute or norepinephrine 5–15 µg/minute, with open-label vasopressor dosages titrated to response. No significant difference was noted in mortality rates (44% with vasopressin vs 42.5% with norepinephrine) in patients with more severe septic shock. In those with less severe sepsis, vasopressin may have an advantage, but this needs to be confirmed in a trial designed to assess this population. Of note is that the mean time of 12 hours to infusion of study drug and presence of additional open-label pressor agents may have minimized the impact of adding vasopressin. (Class I)

Myburgh JA, Higgins A, Jovanovska A, et al. A comparison of epinephrine and norepinephrine in critically ill patients. Intensive Care Med 2008;34:2226–34.

In this prospective, double-blind, randomized trial, epinephrine was compared with norepinephrine in their ability to achieve a mean arterial pressure of 70 mm Hg or higher. Although a greater degree of α-agonism occurred with norepinephrine compared with epinephrine, no significant difference in achieving arterial pressure goals was noted between agents. Multisystem organ failure was present in 25% of

patients, and lack of a sufficient sample may have diminished potential findings. Patients randomly assigned to the epinephrine group experienced a higher frequency of metabolic effects that led to withdrawal from the study. (Class I)

Wenzel V, Krismer AC, Arntz R, Sitter H, Stadlbauer KH, Lindner KH, for the European Resuscitation Council Vasopressor during Cardiopulmonary Resuscitation Study Group. A comparison of vasopressin and epinephrine for out-of-hospital cardiopulmonary resuscitation. N Engl J Med 2004;350:105–13.

The benefits of vasopressin in place of, or as a supplement to, epinephrine in 1186 patients with out-of-hospital cardiac arrest were explored in this double-blind, randomized, controlled trial. Overall, no significant benefit with either agent was observed. A slight benefit in favor of vasopressin in the setting of asystole was noted, but this warrants further investigation. Although it is unclear if any benefit occurs with either agent, there did not appear to be any notable disadvantage with adding vasopressin after starting therapy with epinephrine. This was supported in a subsequent review of randomized controlled trials (Sillberg VAH et al. Resuscitation 2008;79:380–6). One challenge with out-of-hospital cardiac arrest trials is the delay to initiation of therapy, which in this case was a mean of more than 15 minutes after the arrest occurred. (Class I)

Mutlu GM, Factor P. Role of vasopressin in the management of septic shock. Intensive Care Med 2004;30:1276–91.

The pharmacology and role of vasopressin for circulatory support in the setting of septic shock were explored in this review. Use of vasopressin infusions at 0.01 U/minute to reestablish plasma levels is discussed, noting limited risk of myocardial ischemia if the dose is less than 0.04 U/minute. The authors caution that higher doses may carry additional risks, and in either case evidence is limited on the benefits and optimal dosing approach.

Hollenberg SM, Ahrens TS, Annan D, et al. Practice parameters for hemodynamic support of sepsis in adult patients: 2004 update. Crit Care Med 2004;32:1928–48.

This is a review by the American College of Critical Care Medicine of the evidence related to hemodynamic support in patients with sepsis. Specific recommendations are provided for monitoring parameters and end points for

therapy. Areas discussed include fluid resuscitation, vasopressor therapy, and inotropic therapy for adult patients with sepsis (also see Surviving Sepsis Campaign Guidelines in the Sepsis section).

Holmes CL, Walley KR. Bad medicine: low-dose dopamine in the ICU. Chest 2003;123:1266–75.

The authors reviewed the 30-year history of low-dose dopamine treatment in the ICU. Based on the collective evidence, they concluded that this therapy does not have a beneficial effect in critically ill patients with oliguria. In addition, substantial evidence indicates that low-dose dopamine may have significant detrimental effects. The authors concluded that there is no justification for the use of low-dose dopamine in treating critically ill patients.

Endocrinology

The NICE-SUGAR Study Investigators. Intensive versus conventional glucose control in critically ill patients. N Engl J Med 2009;360:1283–97.

This prospective, multicenter, randomized parallel group, controlled trial was designed to evaluate the hypothesis that intensive glucose control reduces mortality at 90 days among critically ill patients who were expected to be in the ICU for more than 3 days. Subjects were stratified based on type of admission (surgical vs nonsurgical) and region (Australia, New Zealand, North America) and then randomly assigned to receive either intensive (target glucose values 81–108 mg/dl, 3054 patients) or conventional (target glucose values < 180 mg/dl, 3050 patients) glucose control. Blood glucose control for all patients was guided by a Web-based treatment algorithm. Assessment of the primary end point at 90 days in 6022 patients (intensive control group 3010 patients, conventional control group 3012 patients), revealed that significantly more patients died in the intensive insulin group (27.5%) compared with the conventional glucose control group (24.9%). No significant differences in the treatment effect were detected between the surgical and nonsurgical patient populations. Severe hypoglycemia (glucose level < 40 mg/dl) occurred significantly more frequently in the patients in the intensive glucose control group (6.8% of patients) compared with the conventional glucose control group (0.5% of patients). This study raises serious questions regarding the role of intensive insulin therapy in the management of critically ill patients. (Class I)

Marik PE, Pastores SM, Annane D, et al. Recommendations for the diagnosis and management of corticosteroid insufficiency in critically ill adult patients: consensus statements from an international task force by the American College of Critical Care Medicine. Crit Care Med 2008;36:1937–49.

Experts from the Society of Critical Care Medicine and the European Society of Intensive Care Medicine developed a consensus statement regarding the diagnosis and management of corticosteroid insufficiency by using a modified Delphi method. In addition to defining critical illness–related corticosteroid insufficiency, the panel provided evidence-based guidelines regarding how to approach the diagnosis of this condition, as well as treatment (i.e., who to treat and how to treat). Each recommendation was rated in terms of the strength of the recommendation (strong or weak) and the quality of the evidence, by using the Modified Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system.

Brunkhorst FM, Engel C, Bloos F, et al. Intensive insulin therapy and pentastarch resuscitation in severe sepsis. N Engl J Med 2008;358:125–39.

A summary of this article, which highlights the serious adverse events related to hypoglycemia with intensive insulin therapy, is presented in the Fluids section. (Class I)

Krinsley JS. Glycemic variability: a strong independent predictor of mortality in critically ill patients. Crit Care Med 2008;36:3008–13.

This retrospective cohort study of 3242 critically ill patients evaluated whether or not glycemic variability had an independent effect on mortality. Patients admitted to the medical-surgical adult ICU between October 1999 and October 2007 who had at least three venous glucose sample measurements were included in the analysis. Of note, a standard glucose protocol was instituted in February 2003. Increased glycemic variability was a strong independent risk factor for mortality. The relationship was strongest for patients in the euglycemic range, with mortality ranging from 5.9% for the first quartile of glycemic variability to 30.1% for the fourth quartile of glycemic variability. This study raises the issue as to the appropriate end point for glucose control in critically ill patients. Is it the absolute glucose value or is it glycemic variability (or both)? (Class III)

Sprung CL, Annane D, Keh D, et al, for the CORTICUS Study Group. Hydrocortisone therapy for patients with septic shock. N Engl J Med 2008;358:111–24.

This multicenter, randomized, double-blind, placebo-controlled trial evaluated the safety and efficacy of low-dose hydrocortisone therapy. The primary outcome, death at 28 days, among patients who did not have a response to corticotropin was not significantly different between the two groups (hydrocortisone group 28.8% vs placebo group 27.7%, p=1.0). In addition, no significant differences in mortality were detected between any of the subgroups. Although no significant differences were seen in the proportions of patients with reversal of shock between hydrocortisone and placebo among all patients, shock was reversed more quickly in the hydrocortisone group compared with the placebo group. An increased frequency of superinfections, hyperglycemia, and hypernatremia was noted among patients receiving hydrocortisone. (Class I)

Wiener RS, Wiener DC, Larson RJ. Benefits and risks of tight glucose control in critically ill adults: a meta-analysis. JAMA 2008;300:933–44.

This meta-analysis, which included 29 randomized controlled trials in a total of 8432 patients, evaluated the benefits and risks of tight glucose control compared with usual care among critically ill adult patients. No significant difference was detected in mortality between tight glucose control and usual care (21.6% vs 23.3%). However, tight glucose control was associated with a significant increased risk for hypoglycemia compared with usual care (13.7% vs 2.5%, RR 5.3, 95% CI 4.09–6.43). Although a significantly reduced risk for septicemia was noted in the tight glucose control group compared with usual care, this was limited to trials conducted in the surgical ICU.

Lipiner-Friedman D, Sprung CL, Laterre PF, et al. Adrenal function in sepsis: the retrospective Corticus cohort study. Crit Care Med 2007;35:1012–18.

This retrospective multicenter cohort study evaluated the relationship of baseline and corticotropin-simulated cortisol levels to mortality in patients with severe sepsis or septic shock. A total of 477 patients had undergone corticotropin stimulation tests at the onset of sepsis. Results revealed that nonsurvivors had higher baseline cortisol levels, similar peak cortisol levels, and thus lower changes in cortisol level (peak value – baseline value = change in cortisol level) compared with survivors. Patients with a baseline cortisol level of 15 μg/dl or lower, or a change in cortisol level of 9 μg/dl or lower had an increased likelihood of dying. This study demonstrates the prognostic importance of change in cortisol level. (Class III)

Van den Berghe G, Wilmer A, Hermans G, et al. Intensive insulin therapy in the medical ICU. N Engl J Med 2006;354:449–61.

This prospective, randomized, controlled study evaluated the efficacy and safety of intensive glucose therapy (blood glucose levels 80–110 mg/dl) with an insulin infusion or conventional therapy (insulin administered when blood glucose was > 215 mg/dl) in patients who were expected to be in the medical ICU for more than 3 days. Intensive insulin therapy significantly reduced morbidity but not in-hospital mortality (mortality rate in intensive insulin group 37.3% vs conventional treatment group 40%, p=0.33). Subgroup analysis revealed that intensive insulin therapy reduced in-hospital mortality for patients who stayed in the ICU for more than 3 days; however, these patients could not be identified at the onset of the trial. (Class I)

Adler SM, Verbalis JG. Disorders of body water homeostasis in critical illness. Endocrinol Metab Clin N Am 2006;25:873–94.

Disorders of sodium and water homeostasis commonly occur in critically ill patients. This article summarizes normal water homeostasis and subsequently reviews the diagnosis and treatment of hyponatremia and hypernatremia in intensive care patients.

Annane D, Bellissant E, Bollaert PE, Briegel J, Keh D, Kupfer Y. Corticosteroids for treating severe sepsis and septic shock. Cochrane Database Syst Rev 2009;(2):CD002243.

This systematic review of 15 randomized or quasirandomized controlled trials of corticosteroids versus placebo or support treatment evaluated the effects of corticosteroids on the risk of death in patients with sepsis and septic shock. Corticosteroids did not significantly alter 28-day all-cause mortality (RR 0.92, 95% CI 0.75–1.14) or hospital mortality (RR 0.89, 95% CI 0.71–1.11); however, significant heterogeneity among trials was noted. Subanalysis examining trials in which corticosteroids were continued for 5 or more days revealed that the agents reduced all-cause mortality, ICU mortality, and hospital

mortality. Of note, this analysis did not include the recent prospective Corticosteroid Therapy of Septic Shock (CORTICUS) study, discussed above, which showed no effect of hydrocortisone on mortality.

Annane D, Sebille V, Bollaert P-E, et al. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. JAMA 2002;288:862–71.

This randomized, double-blind, placebo-controlled, parallel-group, multicenter trial evaluated the effects of treatment with intravenous hydrocortisone 50 mg every 6 hours and enteral fludrocortisone 50 µg once/day for 7 days on 28-day mortality. Patients were classified as either responders or nonresponders based on the results of a corticotropin test. For non-responders, mortality was 63% in the placebo group and 53% in the treatment group (adjusted odds ratio [OR] 0.54, 95% CI 0.31–0.97, p=0.04). For responders, as well as for all patients regardless of corticotropin test results, there was no significant effect of corticosteroids on survival. For nonresponders, the time to withdrawal of vasopressor support was a median of 3 days shorter with corticosteroid therapy than placebo (p=0.001). No significant differences in the frequency of adverse events were noted between treatment groups. These data support corticotropin testing in patients with septic shock and the administration of replacement cortico-steroids in patients with adrenal insufficiency. The results of this trial contrast with the findings of the CORTICUS trial, previously discussed. (Class I)

Van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in critically ill patients. N Engl J Med 2001;345:1359–67.

This prospective, randomized, controlled trial involving 1548 mechanically ventilated surgical patients with hyperglycemia compared the effects of intensive insulin therapy with conventional treatment. The goals for blood glucose levels were 80–110 mg/dl with intensive insulin therapy and 180–200 mg/dl with conventional treatment. At 12 months, mortality rate was significantly lower in the intensive insulin therapy group compared with the conventional treatment group (4.6% vs 8%, p<0.04). The benefits of intensive insulin therapy were greatest in the patients whose ICU stay exceeded 5 days; mortality rate was 10.6% in the intensive insulin therapy group versus 20.2% in the conventional

treatment group (p<0.005). This trial also reported significant reductions in morbidity in the intensive insulin therapy group. (Class I)

Gastroenterology

Intestinal Transit

Fruhwald S, Holzer P, Metzler H. Gastrointestinal motility in acute illness. Wien Klin Wochenschr 2008;120:6–17.

Although this review article is similar in content to that published in 2007 by these authors, this review elaborates on effective strategies to treat gastrointestinal motility disorders, including general therapeutic recommendations (electrolyte balance, fluid management, early enteral feeding, laxative use), as well as specific therapeutic modalities for the various types of disturbances. An algorithm for the management of acute colonic pseudo-obstruction is also provided.

Traut U, Brugger L, Kunz K, et al. Systemic prokinetic pharmacologic treatment for post-operative adynamic ileus following abdominal surgery in adults. Cochrane Database Syst Rev 2008;(1):CD004930.

This systematic review evaluated 39 randomized controlled trials to assess the efficacy and safety of systemic prokinetic agents used to treat adynamic ileus in patients undergoing open or laparoscopic abdominal surgery. Drugs evaluated included cholinergic agonists (bethanechol, neostigmine), benzamides (cisapride, metoclopramide), peptide hormones (ceruletide, vasopressin, cholecystokinin), dopamine antagonists (domperidone), adrenergic antagonists (propranolol), macrolide antibiotics (erythromycin), lidocaine, prostaglandins, pathothenic acid, dexpanthenol, and selective gastrointestinal opioid antagonists (alvimopan). A wide variety of outcome measures were assessed. Many of the studies included in the meta-analysis enrolled only small numbers of patients and often showed moderate or poor methodologic characteristics such as lack of reporting of allocation concealment. Six trials supported the use of alvimopan (vs placebo), with five of the trials assessing the composite end point of maximum time to either first bowel movement or tolerance of solid food (pooled hazard ratio 1.59, 95% CI 1.33–1.90). Erythromycin showed an absence of effect, whereas insufficient evidence was available to recommend the use of cholecystokinin-like

agents, cisapride, domperidone, propranolol, or vasopressin. Additional trials are needed to further explore the potential effects of lidocaine or neostigmine. This meta-analysis did not evaluate the efficacy or safety of methylnaltrexone. Of note, the indication by the United States Food and Drug Administration (FDA) for alvimopan is only to accelerate time to upper and lower gastrointestinal recovery after partial large- or small-bowel resection in patients with primary anastomosis, and it can only be used by hospitals that have registered for and met the access support requirements (Entereg Access Support and Education program).

McNicol ED, Boyce D, Schumann R, Carr DB. Mu-Opioid antagonists for opioid-induced bowel dysfunction. Cochrane Database Syst Rev 2009;(2):CD006332.

This meta-analysis assessed the efficacy and safety of traditional and peripherally active opioid antagonists compared with conventional interventions for the management of opioid-induced bowel dysfunction. Twenty-three randomized controlled trials met the stated inclusion criteria, yielding data on 2871 patients treated with opioid antagonists (alvimopan, methylnaltrexone, naloxone, and nalbuphine). The analysis revealed that methylnaltrexone and alvimopan were superior to placebo in reversing opioid-induced constipation; however, there was insufficient data to support the safety or efficacy of naloxone or nalbuphine. Of note, although opioid-induced constipation is a common problem among critically ill patients, the studies assessing the efficacy of mu-opioid antagonists have predominantly been conducted in healthy volunteers, postoperative patients (after hysterectomy, bowel resection, or abdominal surgery), and patients receiving long-term opioid therapy (malignant or nonmalignant pain, methadone maintenance). Only two studies included in this meta-analysis were conducted in mechanically ventilated critically ill patients who were receiving opioids, and these patients were then randomly assigned to receive placebo or naloxone therapy. Of note, alvimopan or methylnaltrexone are not approved for use in critically ill patients. Alvimopan is FDA indicated to speed gastrointestinal recovery after partial large- or small-bowel resection in patients with a primary anastomosis, whereas methyl-naltrexone is FDA indicated for the management of opioid-induced constipation in patients with advanced illness who are receiving palliative care and have not sufficiently responded to laxative therapy.

Fruhwald S, Holzer P, Metzler H. Intestinal motility disturbances in intensive care patients: pathogenesis and clinical impact. Intensive Care Med 2007;33:36–44.

This detailed review describes normal gastrointestinal motility patterns as well as motility disturbances commonly seen in critically ill patients (esophageal, gastric emptying, and digestive motility disturbances; acute colonic pseudo-obstruction). The authors also review the mechanisms by which various pharmacologic agents can cause alterations in intestinal motility. A brief review on therapeutic options for managing motility disturbances in critically ill patients is included; however, for a more detailed review readers should refer to a subsequent article by these authors (Fruhwald S et al. Wien Klin Wochenschr 2008;120:6–17).

Stress Ulcer Prophylaxis

Guillamondegui O, Gunter O, Bonadies JA, et al. Practice management guidelines for stress ulcer prophylaxis: eastern association for the surgery of trauma. Available from http://www.east .org/tpg/stressulcer.pdf. Accessed January 20, 2008.

The Practice Management Guideline Committee of the Eastern Association for the Surgery of Trauma (EAST) developed this guideline, which is available at the EAST Web site. This evidence-based guideline addresses which patients should receive stress ulcer prophylaxis, whether or not there is a preferred agent for stress ulcer prophylaxis, and the duration of therapy. The guideline provides a table summarizing each of the studies that support the recommendations. The guideline provides concise information and categorizes the recommendations regarding the level of evidence, but it is not as detailed as a guideline published by the American Society of Health-System Pharmacists (Am J Health Syst Pharm 1999;56:347–79.) or recent reviews on this topic.

Somberg L, Morris J, Fantus R, et al. Intermittent intravenous pantoprazole and continuous cimetidine infusion: effect on gastric pH control in critically ill patients at risk for developing stress-related mucosal disease. J Trauma 2008;64:1202–10.

This multicenter, randomized, open-label, dose-ranging pilot trial was designed to evaluate

the ability of various doses of intermittent intravenous pantoprazole to control gastric pH compared with continuous infusion cimetidine in critically ill patients at risk for stress-related mucosal disease. Patients were enrolled within 24 hours of the precipitating event and randomly assigned to receive intravenous pantoprazole 40 mg every 24 hours (32 patients), 40 mg every 12 hours (38), 80 mg every 24 hours (23), 80 mg every 12 hours (39), 80 mg every 8 hours (35), or a continuous bolus infusion of cimetidine 300 mg, followed by 50 mg/hour for at least 48 hours (35). All patients were not allowed anything by mouth for the initial 24-hour period. Gastric aspirates were collected every 2 hours for determination of gastric pH for 2–7 days. The primary outcome measure was percentage of time gastric pH values were above 4. Secondary end points included occurrences of upper gastro-intestinal bleeding and pneumonia.

The mean percentage of time gastric pH was 4 or greater was significantly lower in the two groups that received pantoprazole 40 mg (i.e., every 24 hrs or every 12 hrs) compared with the cimetidine group on day 1 of trial participation. From day 1 to day 2 the percentage of time gastric pH was 4 or greater decreased in the cimetidine group, potentially the result of tolerance or cimetidine's inability to control food-mediated acid secretion in the enterally fed patients. In contrast, from day 1 to day 2, the percentage of time gastric pH was 4 or greater increased in all pantoprazole groups. No patients in the trial developed clinically important gastrointestinal bleeding. The frequency of pneumonia was not significantly different between the pantoprazole (9.6%) and cimetidine (8.6%) groups. As this study was only a pilot dose-ranging trial to assess the primary end point based on gastric pH, it is difficult to use these data to determine the appropriate dosage of intravenous pantoprazole to be used in patients at risk for stress-related mucosal bleeding. Because of the differences in the patients' pH control observed on the first day on the study, the authors provocatively suggest that gastric pH may be adequately controlled with one of the pantoprazole 80-mg dosage regimens, followed by 40 mg every 12 hours thereafter; however, clearly more studies evaluating the efficacy of these regimens are needed. (Class I)

Conrad SA, Gabrielli A, Margolis B, et al. Randomized, double-blind comparison of immediate-release omeprazole oral suspension versus intravenous cimetidine for the prevention of upper gastrointestinal bleeding in critically ill patients. Crit Care Med 2005;33:760–5.

This prospective, multicenter, randomized, double-blind, double-dummy, parallel, non-inferiority trial evaluated the efficacy of omeprazole immediate-release suspension 40 mg for two doses on day 1, then 40 mg once/day, compared with a 300-mg bolus of cimetidine, followed by a continuous intravenous infusion of 50 mg/hour. The primary noninferiority end point was clinically significant upper gastro-intestinal bleeding. Secondary end points included percentage of patients with median gastric pH greater than 4 on each trial day, the percentage of patients with inadequate pH control, and the frequency of pneumonia. The frequency of clinically significant upper gastrointestinal bleeding was 3.9% in the immediate-release omeprazole group compared with 5.5% in the cimetidine group, meeting the threshold to conclude noninferiority. Significant differences were detected in the frequency of any overt bleeding (omeprazole 19.1% vs cimetidine 32%), and inadequate pH control (18% vs 58%). There was no significant difference in the frequency of nosocomial pneumonia between the two groups. Overall, this well-designed trial demonstrated that a suspension of immediate-release omeprazole is as effective as a continuous infusion of cimetidine in preventing clinically significant upper gastrointestinal bleeding and was superior to cimetidine in controlling gastric pH. Based on results of this trial, immediate-release omeprazole oral suspension gained FDA approval for the reduction of upper gastrointestinal bleeding in critically ill patients. (Class I)

Cook DJ, Griffith LE, Walter SD, et al. The attributable mortality and length of intensive care unit stay of clinically important gastrointestinal bleeding in critically ill patients. Crit Care 2001;5:368–75.

Although this study is from several years ago, it provides support for why stress ulcer prophylaxis is used despite the fairly low rate of clinically important gastrointestinal bleeding among critically ill patients. Specifically, this study demonstrated that profound morbidity and mortality are associated with clinically important gastrointestinal bleeding. Based on data from two multicenter databases, and using three different modeling strategies, data from 1666 mechanically ventilated patients were used to estimate mortality and length of stay in the ICU

attributable to clinically important upper gastrointestinal bleeding. Clinically important gastrointestinal bleeding developed in 3.5% of the patients. The risk of death was increased in patients with bleeding, RR ranged from 1.8 (95% CI 1.1–2.9) to 4.1 (95% CI 2.6–6.5), dependent on the modeling strategy used. The median length of ICU stay attributable to clinically important upper gastrointestinal bleeding ranged from 3.8–7.9 days based on the model used. (Class II)

Cook D, Guyatt G, Marshall J, et al. A comparison of sucralfate and ranitidine for the prevention of upper gastrointestinal bleeding in patients requiring mechanical ventilation. N Engl J Med 1998;338:791–7.

This landmark, multicenter, randomized, double-blind, double-dummy, controlled trial compared the efficacy of sucralfate versus ranitidine for the prevention of clinically important upper gastrointestinal bleeding in 1200 mechanically ventilated, critically ill patients. The study demonstrated a lower frequency of clinically important upper gastrointestinal bleeding in the ranitidine group compared with the sucralfate group (RR 0.44, 95% CI 0.21–0.92). No significant infusion differences were noted in rates of ventilator-associated pneumonia, length of ICU stay, or survival between the two groups. This study demonstrated the superiority of ranitidine 50 mg given intravenously every 8 hours compared with sucralfate 1 g administered by nasogastric tube every 6 hours for prevention of clinically important upper gastrointestinal bleeding. (Class I)

Cook DJ, Fuller HD, Guyatt GH, et al. Risk factors for gastrointestinal bleeding in critically ill patients. N Engl J Med 1994;330:377–81.

This prospective, multicenter, observational study was designed to identify risk factors for stress ulceration in critically ill patients. The two major independent risk factors identified by multivariate analyses for clinically important upper gastrointestinal bleeding were respiratory failure (OR 15.6) and coagulopathy (OR 4.3). Although clinically important gastrointestinal bleeding occurred in only 1.5% of patients, another analysis discussed above (Cook DJ et al. Crit Care 2001;5:368–75) demonstrated that bleeding is associated with significant morbidity and mortality. However, because the study involved a critically ill patient population

predominantly composed of patients undergoing cardiovascular surgery, these should not be considered the only risk factors for stress-related mucosal bleeding. Specifically, earlier literature suggests that patients with head injury, burns, multiple trauma, sepsis, or shock may also be at risk. Of note, few patients with these conditions were included in this trial. (Class II)

Upper Gastrointestinal Bleeding

Van Rensburg C, Barkun AN, Racz I, et al. Clinical trial: intravenous pantoprazole vs ranitidine for prevention of peptic ulcer rebleeding: a multicentre, multinational, randomized trial. Aliment Pharmacol Ther 2009;29:497–507.

This multicenter, randomized, controlled, double-blind, parallel-group trial evaluated the efficacy of high-dose intravenous pantoprazole (80-mg loading dose followed by 8 mg/hr for 72 hrs) compared with high-dose intravenous ranitidine therapy (50-mg loading dose followed by 13 mg/hr for 72 hrs) in preventing repeat ulcer bleeding after endoscopic hemostasis in patients with major stigmata (Forrest Ia, Ib, IIa) of ulcer hemorrhage. The primary outcome was an overall outcome ordinal score: no bleeding, rebleeding with or without subsequent hemostasis, surgery, and mortality. There was no significant difference in the overall outcomes scores between the two groups. In patients with an initial diagnosis of Forrest 1a (arterial spurting), pantoprazole therapy was associated with significantly fewer outcome events (i.e., rebleeding with or without subsequent hemostasis, surgery, and mortality) compared with the ranitidine group (pantoprazole 13.9%, 95% CI 6.6–24.7% vs ranitidine 33.9%, 95% CI 22.1–47.4%, p=0.01). Pantoprazole also significantly reduced the outcome events among patients with gastric ulcers (pantoprazole 6.7%, 95% CI 4.0–10.4% vs ranitidine 14.3%, 95% CI 10.3–19.2%). A similar U.S. trial (Jensen DM et al. Am J Gastroenterol 2006;101:1991–9), which assessed the efficacy of high-dose intravenous pantoprazole compared with intravenous ranitidine therapy (50-mg loading dose followed by 6.25 mg/hr for 72 hrs) in preventing repeat ulcer bleeding after endoscopic hemostasis in patients with major stigmata of ulcer hemorrhage and which was stopped prematurely due to slow enrollment, also showed no significant difference between the two treatments. In a trial discussed below (Zarger SA et al. J Gastroenterol Hepatol

2006;21:716–21), pantoprazole given as a continuous infusion was superior to placebo for reducing repeat ulcer bleeding after endoscopic hemostasis in high-risk patients with peptic ulcer. In contrast, the lack of overall differences in this Van Rensburg trial and the U.S. trial by Jensen may reflect issues concerning the choice of outcome (i.e., ordinal score vs frequency of rebleeding), the selection of the comparator (high-dose ranitidine vs placebo), and/or sample size issues. (Class I)

Andruilli A, Loperfido S, Focareta R, et al. High- versus low-dose proton pump inhibitors after endoscopic hemostasis in patients with peptic ulcer bleeding: a multicentre, randomized study. Am J Gastroenterol 2008;103:3011–18.

This prospective, multicenter, randomized, double-blind trial assessed the efficacy of high-dose proton pump inhibitor therapy (80-mg loading dose followed by 8 mg/hr) compared with low-dose proton pump therapy (40 mg given intravenously once/day) after endoscopic hemostasis in patients at high risk for repeat peptic ulcer bleeding. After 3 days of therapy, all patients were switched to an oral proton pump inhibitor (20 mg twice/day) until discharge. The frequency of rebleeding was not significantly different between the two dosing groups (high dose 11.8% vs low dose 8.1%, difference 3.8%, 95% CI -1.7–9.1%). Although this study indicates that low-dose proton pump inhibitor therapy is effective in preventing repeat ulcer bleeding in high-risk patients, it should be noted that concerns exist, as the choice of the proton pump inhibitor (omeprazole vs pantoprazole) was left to the discretion of the investigator and 50% of patients received only epinephrine injection as endoscopic management, which has been shown to be less effective than the combination of epinephrine injection and thermocoagulation. Moreover, the results of this study are contrary to those of other studies (Lin HJ et al. Am J Gastroenterol 2006;101:500–5; Simon-Rudler M et al, Aliment Pharmacol Ther 2007;25:949–54) and current consensus guidelines (Barkun A et al. Ann Intern Med 2003;139:843–57). Controversy continues regarding the optimal proton pump inhibitor dosage regimen to prevent repeat peptic ulcer bleeding after endoscopic hemostasis. (Class I)

Lau JY, Leung WK, Wu JCY. Omeprazole before endoscopy in patients with gastrointestinal bleeding. N Engl J Med 2007;356:1631–40.

These authors previously demonstrated that high-dose intravenous omeprazole was superior to placebo in preventing repeat ulcer bleeding after endoscopic hemostasis in high-risk patients (Lau JY et al. N Engl J Med 2000;343:310–16). The present study was designed to evaluate the efficacy of empiric intravenous omeprazole therapy given before endoscopic management compared with placebo. With use of a double-blind, placebo-controlled design, consecutive patients who had overt signs of upper gastro-intestinal bleeding at presentation were randomly assigned to either intravenous omeprazole 80-mg loading dose followed by 8 mg/hour or placebo before endoscopy. Patients who were receiving long-term aspirin therapy were excluded from the trial. At endoscopy, rates of actively bleeding ulcers were noted to be significantly lower in the omeprazole group (6.4%) compared with the placebo group (14.7%). The primary end point—need for interventional endoscopic treatment—was significantly lower in the omeprazole group (19.1%) than in the placebo group (24.8%, p=0.007). Although this study indicates high-dose intravenous omeprazole therapy is superior to placebo when given before endoscopy, this study should not be overextrapolated to suggest proton pump inhibitors can replace endoscopy. Rather, prompt evaluation, resuscitation, and endoscopic treatment in conjunction with empiric proton pump inhibitor therapy should be used to minimize the risk of rebleeding in high-risk patients. The results from this well-designed prospective trial are similar to those reported in a Cochrane review (Dorward S et al. Cochrane Database Syst Rev 2009;(2): CD005415). Another group performed an economic decision analysis (Tsoi KK et al. Gastrointest Endosc 2008;67:1056–63) using data from this Lau et al trial that suggested that preemptive use of intravenous proton pump inhibitors before endoscopy is a cost-effective strategy.

Zarger SA, Javid G, Khan AB, et al. Pantoprazole infusion as adjuvant therapy to endoscopic treatment in patients with peptic ulcer bleeding: prospective randomized controlled trial. J Gastroenterol Hepatol 2006;21:716–21.

This prospective, single-center, double-blind, placebo-controlled study assessed the efficacy of intravenous pantoprazole (80-mg bolus followed by 8 mg/hr) or placebo for 72 hours in patients at high risk for repeat peptic ulcer bleeding who had undergone endoscopic hemostasis with epinephrine injection and thermocoagulation.

Randomization was stratified based on the location of the ulcer. Rebleeding was significantly lower in the pantoprazole group versus the placebo group (7.8% vs 19.8%). In addition, patients in the pantoprazole group required fewer transfusions and had a shorter duration of hospital stay compared with the placebo group. This study is similar to the previously mentioned landmark trial (Lau JY et al. N Engl J Med 2000;343:310–16), which demonstrated that high-dose intravenous omeprazole (80-mg loading dose followed by 8 mg/hr) was superior to placebo in preventing repeat ulcer bleeding after endoscopic hemostasis in high-risk patients. (Class I)

Leontiadis GI, Sharma VK, Howden CW. Proton pump inhibitor treatment for acute peptic ulcer bleeding. Cochrane Database Syst Rev 2006;(1): CD002094.

This systematic review evaluated 24 randomized controlled trials to assess the efficacy of proton pump inhibitors (intravenous and oral) in a total of 4373 patients with ulcer bleeding. Overall, pooled results revealed that compared with placebo or histamine$_2$-receptor antagonists, proton pump inhibitors significantly reduced rebleeding (OR 0.49, 95% CI 0.37–0.65) and need for surgery (OR 0.61, 95% CI 0.48–0.78), but not all-cause mortality (OR 1.01, 95% CI 0.74–1.40). There was no evidence to suggest the rebleeding or surgery results were influenced by the quality of the studies, the route of administration, or type of initial endoscopic hemostatic treatment. The analysis did suggest that proton pump inhibitor treatment was more efficacious in studies conducted in Asia compared with those of other countries, which may relate to the higher prevalence of slow CYP2C19 metabolizers in this population.

Barkun A, Bardou M, Marshall JK, for the Nonvariceal Upper GI Bleeding Consensus Conference Group. Consensus recommendations for patients with nonvariceal upper gastrointestinal bleeding. Ann Intern Med 2003;139: 843–57.

These consensus guidelines for the management of nonvariceal upper gastrointestinal bleeding recommend that institution-specific protocols be developed. Initial management should include categorizing patients by risk of rebleeding (i.e., high risk vs low risk) and of death based on clinical, endoscopic, and prognostic factors. Early endoscopy serves to aid in diagnosis and risk stratification, and to facilitate hemostasis in patients with stigmata suggesting high risk of rebleeding. A combination of injection and thermal coagulation is recommended as it provides superior endoscopic hemostasis in patients with high-risk stigmata compared with either treatment alone. High-dose intravenous therapy with a proton pump inhibitor is recommended for patients who have undergone endoscopic hemostasis and who are at high risk for rebleeding. Recommendations were graded according to the level and strength of available evidence at the time the guidelines were developed.

Miscellaneous

Leonard J, Marshall JK, Moayyedi P. Systematic review of the risk of enteric infection in patients taking acid suppression. Am J Gastroenterol 2007;102:2047–56.

Controversy exists regarding the potential association between proton pump inhibitor therapy and the development of enteric infections such as *Clostridium difficile*. There have been several small observational studies assessing this potential association in hospitalized patients. This systematic review of observational studies was conducted to evaluate the potential association between acid suppression and enteric infection. Twelve observational studies evaluating 2948 patients with *C. difficile* were included in the meta-analysis. The analysis revealed that there was an increased risk of taking antisecretory therapy in those infected with *C. difficile* (pooled OR 1.94, 95% CI 1.37–2.75), which was greater for those receiving proton pump inhibitors (OR 1.96, 95% CI 1.28–3.00) compared with those receiving histamine$_2$-receptor antagonists (OR 1.40, 95% CI 0.85–2.29). This systematic review also assessed the association between other enteric infections (e.g., *Salmonella*, *Campylobacter*) and antisecretory therapy and found similar results. A recent case-control study assessing the potential association between antisecretory therapy and *C. difficile* infection, which was published after this meta-analysis, also showed similar results (Aseeri M et al. Am J Gastroenterol 2008;103:2308–13). Looking at the studies as a composite, there appears to be an association between acid suppressant therapy (especially proton pump inhibitor use) and *C. difficile* infection. However, because of the study designs used, causality cannot be concluded.

Devlin JW, Welage LS, Olsen KM. Proton pump inhibitor formulary considerations in the acutely ill. I. Pharmacology, pharmacodynamics and available formulations. Ann Pharmacother 2005;39:1667–77.

Devlin JW, Welage LS, Olsen KM. Proton pump inhibitor formulary considerations in the acutely ill. II. Clinical efficacy, safety and economics. Ann Pharmacother 2005;39:1844–51.

This two-part series provides a detailed review of formulary considerations for the various proton pump inhibitors. Of note, to those interested in critical care, the articles summarize the evidence regarding the use of proton pump inhibitors for prevention of stress-related mucosal bleeding, as well as prevention of repeat ulcer bleeding.

Hematology

Antithrombotics

American College of Chest Physicians. The eighth ACCP consensus conference on anti-thrombotic and thrombolytic therapy: evidence-based guidelines. Chest 2008;133(suppl):S71–968.

This report from the American College of Chest Physicians provides an extensive evidence-based review of the management of thrombo-embolic disorders. Application to the ICU has some limitations because many of the clinical trials supporting the recommendations excluded critically ill patients.

Dager WE, Dougherty JA, Nguyen PH, Militello MA, Smythe MA. Heparin-induced thrombocytopenia: treatment options and special considerations. Pharmacotherapy 2007;27:564–87.

This review focuses on approaches to managing heparin-induced thrombocytopenia. It includes application in distinct patient populations such as those undergoing surgical procedures, those with renal or hepatic failure, those with acute coronary syndromes, and children.

Dong B, Jirong Y, Liu G, Wang Q, Wu T. Thrombolytic therapy for pulmonary embolism. Cochrane Database Syst Rev 2006;(2):CD004437.

The safety and efficacy of thrombolytic therapy in the presence of an acute pulmonary embolism were evaluated using reports published up to February 2006. Although thrombolytic therapy is more likely to be used in the setting of pulmonary embolism–related hemodynamic instability, limited evidence is available supporting any advantage over heparin therapy.

This, in part, is the challenge of doing clinical trials in more uncommon situations and the process of randomization and selection when urgent therapy is necessary.

Blood Conservation and Transfusion

Fergusson DA, Hébert PC, Mazer CD, et al, for the BART Investigators. A comparison of aprotinin and lysine analogues in high-risk cardiac surgery. N Engl J Med 2008;358:2319–31.

Aprotinin was a commonly used antifibrinolytic agent during cardiac surgery to reduce bleeding and blood transfusion requirements. Reports of potential complications with its use led to a multicenter, blinded trial that compared aprotinin with two other agents—tranexamic acid and aminocaproic acid. Although the rate of massive bleeding was lower with aprotinin than with tranexamic acid and aminocaproic acid (9.5% vs 12.1% and 12.1%, respectively), the secondary outcome of death at 30 days from any cause was higher (6% vs 3.9% and 4%, respectively). The benefits and risks of aprotinin were recently reviewed (Kristeller JL, Roslund BP, Stahl RF. Pharmacotherapy 2008;28:112–24). Aprotinin has subsequently been removed from the market. (Class I)

Corwin HL, Gettinger A, Fabian TC, et al, for the EPO Critical Care Trials Group. Efficacy and safety of epoetin alfa in critically ill patients. N Engl J Med 2007;357:965–76.

The benefit of reducing red blood cell transfusions with the use of erythropoietin 40,000 units/week in critically ill patients was explored in this prospective, randomized, placebo-controlled trial. This trial was the third in a series of studies investigating the value of erythropoietin in critically ill patients; however, the previous trials suggested benefits with erythropoietin (Corwin HL et al. JAMA 2002;288:2827–35; Corwin HL et al. Crit Care Med 1999;27:2346–50). In this latest trial, the use of erythropoietin was not associated with a reduction in red blood cell transfusion and was associated with a significant increase in thromboembolic complications (hazard ratio 1.41, 95% CI 1.06–1.86). A mortality benefit was observed in a subset of trauma patients, suggesting a potential benefit in this specific population that warrants further investigation. (Class I)

Hajjar LA, Auler Junior JO, Santos L, Galas F. Blood transfusion in critically ill patients: state of

the art. Clinics 2007;62:507–24.

Blood transfusions carry the risk of associated complications. Recent experiences have challenged the threshold for which transfusions should be considered. In this review article, key studies combined with reported experiences with blood transfusion are explored. The threshold of transfusing at a hemoglobin level of 10 g/dl is challenged, and the potential to reduce this parameter while focusing on meeting the individual needs of the patient is explored. The use of conservative red blood cell transfusion strategies has also reduced transfusion-related adverse events.

O'Connell KA, Wood JJ, Wise RP, Lozier JN, Braun MM. Thromboembolic adverse events after use of recombinant human coagulation factor VIIa. JAMA 2006;295:293–8.

Reports from the FDA Adverse Event Reporting System from 1999–2004 of thromboembolic complications after administration of recombinant activated factor VII (rFVIIa) in nonhemophiliac patients are explored. Although not balanced with the frequency of use, this report points out potential risks associated with rFVIIa. Randomized controlled trials are needed to determine the benefits of rFVIIa compared with drug-related adverse events, particularly for off-label use. (Class III)

Corwin HL, Gettinger A, Pearl RG, et al. The CRIT study: anemia and blood transfusion in the critically ill—current clinical practice in the United States. Crit Care Med 2004:32:39–52.

This prospective, multicenter, observational, cohort study of 4892 patients, conducted in 2000–2001, serves as an important historical control to compare current patterns of blood use. The patients' mean ± SD hemoglobin level was 11 ± 2.4 g/dl, with a progressive decrease through-out the ICU stay. Overall, 44% of patients received at least one transfusion of red blood cells. Most transfusions were given in the first week and thereafter at a rate of 1–2 units/week. Mean ± SD time to first transfusion was 2.3 ± 3.7 days (median 1 day). Transfusion of red blood cells was associated with worsened patient outcomes. These data were similar to Western European ICU data collected in 1999, which evaluated baseline hemoglobin levels, hemoglobin levels at the time of transfusion, and any association between mortality and transfusion (Vincent JL et al. JAMA 2002;288: 1499–507). (Class II)

Rudis MI, Jacobi J, Hassan E, Dasta JF. Managing anemia in the critically ill patient. Pharmacotherapy 2004;24:229–47.

This literature review focuses on the use of transfusions for acute management of anemia in critically ill patients. The risks and benefits of red blood cell transfusion and the use of blood substitutes are reviewed. Despite measures to reduce blood wastage, many patients develop anemia of critical illness, characterized by low red blood cell production despite normal-to-high concentrations of erythropoietin and, in some cases, inadequate erythropoietin production for the degree of anemia. The authors make recommendations for therapy based on the limited data and expert opinion available.

Taylor RW, Manganaro L, O'Brien J, et al. Impact of allogeneic packed red blood cell transfusion on nosocomial infection rates in the critically ill patient. Crit Care Med 2002;30: 2249–54.

The authors searched their clinical database for information regarding nosocomial infection in 1717 patients in their medical-surgical-trauma ICU for admissions from October 1998–August 2000. Risk of infection was calculated based on the entire cohort—patients receiving or not receiving red blood cell transfusion. The overall nosocomial infection rate was 5.94%, and the rates were significantly different between the patients who received (15.3%) and those who did not receive (2.9%) transfusion (p<0.005). This difference persisted after adjusting for severity of illness with scores from the Mortality Prediction Model. In addition, an association was noted between the number of units administered and risk of infection. Patients receiving transfusions had longer ICU and hospital stays (p<0.0005). The risk of nosocomial infection, although not proven to be the direct result of red blood cell transfusion, may be the result of transfusion-related immunosuppression. Similar results have been documented in other populations, such as trauma patients (Claridge JA et al. Am Surg 2002;68:566–72). (Class II)

Goodnough LT, Brecher ME, Kanter MH, AuBuchon JP. Transfusion medicine. N Engl J Med 1999;340:438–47.

This article, the first of a two-part series, extensively reviews the risks of blood transfusion, such as human immunodeficiency virus, hepatitis B and C, and other hepatitis viruses. Other risks, such as hemolytic reactions, red blood cell

bacterial contamination, transfusion-related lung injury, and immunomodulation, are also reviewed. The indications for transfusion reflect the thinking at the time, although these have been altered by subsequent report, as described below.

Hébert PC, Wells G, Blajchman MA, et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. N Engl J Med 1999;340:409–17.

These investigators randomly assigned patients either to a liberal transfusion strategy designed to maintain a hemoglobin level of 10–12 g/dl or to a restrictive strategy designed to maintain a hemoglobin level of 7–9 g/dl. More red blood cell transfusions were given to the liberal group, and although the primary outcome of all-cause mortality was not significantly different between the groups, the in-hospital mortality and multiple-organ dysfunction score were significantly higher in the liberal group. These data indicate that a transfusion threshold as low as 7 g/dl was at least as effective and possibly superior to a more liberal transfusion strategy. A trend toward a lower survival was noted in a subset of patients with cardiovascular disease from the restrictive transfusion group. This led the authors to suggest that patients with unstable coronary ischemic syndromes may not benefit from a restrictive transfusion strategy (Hébert PC et al. Crit Care Med 2001;29:227–34). (Class I)

Infectious Diseases

Bacterial and Fungal

Pappas PG, Kauffman CA, Andes D, et al. Clinical practice guidelines for the management of candidiasis: 2009 update by the Infectious Diseases Society of America. Clin Infect Dis 2009;48:503–35.

These are updated guidelines from the Infectious Diseases Society of America (IDSA) that expand on the first edition published in 2004. The update includes information on echinocandins and expanded spectrum azoles in evidenced-based trials, in addition to other, older antifungal therapy. Evidence-based recommendations are included for the diagnosis and treatment of candidemia in nonneutropenic and neutropenic patients; empiric treatment for suspected invasive candidiasis in neutropenic patients; treatment for neonatal candidiasis; and antifungal prophylaxis for solid-organ transplant

recipients, patients hospitalized in ICUs, neutropenic patients receiving chemotherapy, and stem cell transplant recipients at risk of candidiasis. Recommendations were graded based on the quality of evidence available, based on the IDSA–U.S. Public Health Service Grading System for ranking recommendations in clinical guidelines. A review of available antifungal agents is included. These guidelines provide considerable direction on empiric treatment of candidal diseases and offer recommendations for managing patients in the ICU setting.

Zilberberg MD, Shorr AF, Kollef MH. Increase in adult *Clostridium difficile*–related hospitalizations and case-fatality rate, United States, 2000–2005. Emerg Infect Dis 2008;14:929–31.

Using data from the Agency for Healthcare Research and Quality, this analysis identified *C. difficile*–associated disease (CDAD)-related hospitalizations from 2000–2005. The number of adults with a CDAD diagnosis rose by nearly 160,000, from 134,361 in 2000 to 291,303 in 2005. This equates to an approximately 23% average crude growth rate annually, compared with approximately 1.3% growth in overall hospitalizations annually during the same time period. The crude case-fatality rate rose from 1.2% in 2000 to 2.3% in 2004; age-adjusting the 2004 estimate resulted in a similar case-fatality rate of 2.2%. This report helps to put in perspective the observed increasing mortality rates related to CDAD in the United States. (Class III)

O'Grady NP, Barie PS, Bartlett JG, et al. Guidelines for evaluation of new fever in critically ill adult patients: 2008 update from the American College of Critical Care Medicine and the Infectious Diseases Society of America. Crit Care Med 2008;36:1330–49.

This update of 1998 guidelines is focused on promotion of the rational consumption of resources and an efficient evaluation of new fever in adult patients in the ICU. The recommendations are based on the quality of the evidence in the literature following the Society of Critical Care Medicine rating system. The recommendations include measuring temperature and defining fever, obtaining and interpreting cultures, the role of intravascular devices, pulmonary infections and ICU-obtained pneumonia, stool evaluation, urinary tract infection, sinusitis, postoperative fever, surgical site infections, central nervous system infection, noninfectious

causes of fever, and empiric therapy for new fever. These guidelines provide comprehensive methods for evaluating fever in the critically ill patient.

Aarts MA, Hancock JN, Heyland D, McLeod RS, Marshall JC. Empiric antibiotic therapy for suspected ventilator-associated pneumonia: a systematic review and meta-analysis of randomized trials. Crit Care Med 2008;36:108–17.

This meta-analysis examined the effectiveness of various treatment regimens, as well as monotherapy compared with combination therapy in the empiric treatment of suspected ventilator-associated pneumonia. Data from 41 randomized controlled trials conducted in more than 30 countries and published between 1984 and 2006 were reviewed. A total of 7015 patients receiving 29 different regimens of antibiotics were compared. There was no evidence that any particular regimen improved survival. Individual pooled subgroup analyses demonstrated some differences in one regimen over others (e.g., meropenem over ceftazidime-aminoglycoside regimens). There was no significant difference in mortality in the 11 trials evaluating monotherapy versus combination therapy (RR 0.94, 95% CI 0.76–1.16). These data seem to refute the recommendation of combination antimicrobial therapy for empiric treatment of ventilator-associated pneumonia, although the authors do not recommend routine monotherapy for empiric treatment.

Zar FA, Bakkanagari SR, Moorthi KM, Davis MB. A comparison of vancomycin and metronidazole for the treatment of *Clostridium difficile*–associated diarrhea, stratified by disease severity. Clin Infect Dis 2007;45:302–7.

This prospective, randomized, double-blind, placebo-controlled trial compared oral vancomycin and oral metronidazole for the treatment of *C. difficile*–associated diarrhea, stratified by disease severity. Patients with *C. difficile*–associated diarrhea were stratified according to whether they had mild or severe disease based on clinical criteria. The overall rate of cure was 84% (66/79) in the metronidazole group and 97% (69/71) in the vancomycin group (p=0.006). Among the patients with mild disease, treatment resulted in clinical cure in 90% (37/41) of patients treated with metronidazole and in 98% (39/40) of patients treated with vancomycin (p=0.36). Among the patients with severe disease, treatment resulted in clinical cure in 76% of

patients treated with metronidazole and in 97% of patients treated with vancomycin (p=0.02). This trial gives pause to clinicians who might routinely treat critically ill patients who have *C. difficile*–associated diarrhea with metronidazole. (Class I)

Silvestri L, van Saene HK, Milanese M, Gregori D, Gullo A. Selective decontamination of the digestive tract reduces bacterial bloodstream infection and mortality in critically ill patients: systematic review of randomized, controlled trials. J Hosp Infect 2007;65:187–203.

This is a systematic review and meta-analysis of randomized controlled trials of selective decontamination of the digestive tract (SDD) to determine the impact on bacterial bloodstream infection and mortality. Trials included compared oropharyngeal and/or intestinal administration of antibiotics as part of the SDD protocol, with or without a parenteral component, with no treatment or placebo in the controls. Fifty-one trials conducted between 1987 and 2005, with 8065 critically ill patients, were included in the review; 4079 patients received SDD and 3986 were controls. In the SDD versus control groups, SDD significantly reduced overall bloodstream infections (11.5% vs 15%, OR 0.73, 95% CI 0.59–0.90, p=0.0036), gram-negative bloodstream infections (2.2% vs 7.1%, OR 0.39, 95% CI 0.24–0.63, p<0.001), and overall mortality (19.3% vs 23.8%, OR 0.80, 95% CI 0.69–0.94, p=0.0064). Gram-positive bloodstream infections were not affected. These data demonstrate the value of SDD in critically ill patients, but potential long-term resistance concerns likely explain the lack of widespread SDD use in the United States.

Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis 2007;44(suppl 2): S27–72.

This is a consensus guideline from the IDSA and the American Thoracic Society for the management of community-acquired pneumonia. It follows publication of separate guidelines from each society and represents consensus recommendations from both groups. The guideline was created by using a three-tiered scale to evaluate evidence for each recommendation, using the IDSA rating system. The guideline covers use of local treatment pathways, diagnostic testing,

empiric antibiotic therapy, other noninfectious treatment considerations, management of nonresponders, and prevention strategies. The guideline provides a thorough and evidenced-based approach to managing community-acquired pneumonia in ambulatory, hospitalized, and intensive care patients.

Fowler VG Jr, Boucher HW, Corey GR, et al. Daptomycin versus standard therapy for bacteremia and endocarditis caused by *Staphylococcus aureus*. N Engl J Med 2006;355:653–65.

This unusually large trial studied 246 patients with bacteremia, with or without endocarditis, caused by *Staphylococcus aureus*. Patients were randomly assigned to daptomycin or an antistaphylococcal penicillin plus low-dose gentamicin or vancomycin. Treatment success at 42 days of therapy was 44.2% for daptomycin compared with 41.7% (absolute difference 2.4%, 95% CI -10.2–15.1%) for the alternative therapy. Success rates favored daptomycin over vancomycin among patients who were infected with methicillin-resistant *S. aureus* ([MRSA] 44.4% for daptomycin vs 31.8% for standard therapy, p=0.28) but were higher among patients receiving standard therapy for methicillin-sensitive *S. aureus* infection (44.6% for daptomycin vs 48.6% for standard therapy, p=0.74). The success rates were similar in subgroups of patients with endocarditis. This work generated the FDA-approved indication for daptomycin for bacteremia and endocarditis. (Class I)

McDonald LC, Killgore GE, Thompson A, et al. An epidemic, toxin gene-variant strain of *Clostridium difficile*. N Engl J Med 2005;353: 2433–41.

This report described the emergence of a new strain of *C. difficile* with increased virulence, resistance, or both. A total of 187 *C. difficile* isolates were collected from eight health care facilities in six states (Georgia, Illinois, Maine, New Jersey, Oregon, and Pennsylvania) in which outbreaks of CDAD had occurred between 2000 and 2003. This outbreak strain was the same as the strain responsible for recent outbreaks outside the United States. It is classified by restriction-endonuclease analysis (REA) typing as BI and by pulsed-field gel electrophoresis as NAP1, and is distinct from the J strain (REA type J7/9) that was responsible for outbreaks during the period from 1989 through 1992. The current isolates were more likely to be resistant to fluoroquinolones. There was evidence of higher white blood cell counts and more severe disease in patients infected with BI/NAP1 strains than in those infected with non-BI/NAP1 strains. Pseudomembranous colitis was more frequent among patients infected with the BI/NAP1 strain, suggesting that this toxin type is associated with increased severity of the disease. (Class III)

Shorr AF, Chung K, Jackson WL, Waterman PE, Kollef MH. Fluconazole prophylaxis in critically ill surgical patients: a meta-analysis. Crit Care Med 2005;33:1928–35.

This meta-analysis determined the impact of fluconazole prophylaxis on the rate of fungal infections and on mortality among critically ill surgical patients. Four randomized studies comparing fluconazole with placebo for prevention of fungal infections in the surgical ICU were included (626 patients). Fluconazole administration significantly reduced the rate of fungal infections (OR 0.44, 95% CI 0.27–0.72, p<0.001) but did not have a statistically significant effect on mortality (OR 0.87, 95% CI 0.59 –1.28). Fluconazole did not affect the rate of candidemia, which was low. The authors commented that use of fluconazole may affect both resistance to and emergence of non-*albicans* isolates.

DiazGranados CA, Zimmer SM, Klein M, Jernigan JA. Comparison of mortality associated with vancomycin-resistant and vancomycin-susceptible enterococcal bloodstream infections: a meta-analysis. Clin Infect Dis 2005;41:327–33.

This meta-analysis of studies investigated the clinical impact of vancomycin resistance among patients with enterococcal bloodstream infections. The meta-analysis was performed due to the conflicting results found in the literature on this topic. The nine studies included a total of 1614 enterococcal bloodstream infections; 683 were caused by vancomycin-resistant enterococci (VRE), and 931 were caused by vancomycin-susceptible enterococci. Although the individual results from these nine trials were conflicting, the combined studies demonstrated an independent risk of mortality caused by VRE, with an OR of 2.52 (95% CI 1.9–3.4). The authors suggest that the conflicting results of previous reports may be explained in part by lack of sufficient power among several studies to reach a statistically significant association between vancomycin resistance and mortality. These data provide

some clarity on the increased risk of death in patients with VRE.

Bliziotis IA, Samonis G, Vardakas KZ, Chrysanthopoulou S, Falagas ME. Effect of aminoglycoside and β-lactam combination therapy versus β-lactam monotherapy on the emergence of antimicrobial resistance: a meta-analysis of randomized, controlled trials. Clin Infect Dis 2005;41:149–58.

This meta-analysis of available randomized controlled trials examined the use of β-lactam monotherapy versus aminoglycoside–β-lactam combination therapy and presented data regarding the emergence of antimicrobial-resistant organisms during treatment or during the follow-up period. Eight trials were included in the analysis. Treatment failure was less common in the β-lactam monotherapy arm than in the combination arm (OR 0.62, 95% CI 0.38–1.01). No significant difference in mortality was identified between the two treatment groups (OR 0.70, 95% CI 0.40–1.25). No significant difference in the emergence of antimicrobial resistance was observed between monotherapy and combination therapy. Monotherapy treatment was associated with a lower number of superinfections than was combination treatment (OR 0.62, 95% CI 0.42–0.93). These data do not support the widespread belief among clinicians of a mortality benefit of aminoglycoside–β-lactam combination therapy compared with β-lactam monotherapy.

Wisplinghoff H, Bischoff T, Tallent SM, Seifert H, Wenzel RP, Edmond MB. Nosocomial bloodstream infections in U.S. hospitals: analysis of 24,179 cases from a prospective nationwide surveillance study. Clin Infect Dis 2004;39: 309–17.

This nationwide surveillance study described trends in the epidemiology and microbiology of nosocomial bloodstream infections over a 7-year period from 1995–2002. The most commonly identified organisms in bloodstream infection were coagulase-negative staphylococci, *S. aureus*, *Enterococcus* sp, *Candida* sp, *Escherichia coli*, *Klebsiella* sp, *Pseudomonas aeruginosa,* and *Enterobacter* sp. The proportion of *S. aureus* isolates with methicillin resistance increased from 22% in 1995 to 57% in 2001 (p<0.001, trend analysis). The proportion of *P. aeruginosa* isolates resistant to ceftazidime increased from 12% in 1995 to 29% in 2001 (p<0.001, trend analysis). Vancomycin resistance was seen in 2%

of *Enterococcus faecalis* isolates and in 60% of *Enterococcus faecium* isolates. For *Candida* bloodstream infection, *C. albicans* was the most common, accounting for 54% of cases of *Candida* bloodstream infection, followed in rank order by *C. glabrata* (19%), *C. parapsilosis* (11%), and *C. tropicalis* (11%). Bacteremia occurred more commonly in the ICU than in a non-ICU setting (50.5%). (Class II)

Baddour LM, Yu VL, Klugman KP, et al. Combination antibiotic therapy lowers mortality among severely ill patients with pneumococcal bacteremia. Am J Respir Crit Care Med 2004;170:440–4.

This study examined the effect of combination antibiotic therapy compared with monotherapy on mortality in a prospective, multicenter, international observational study of 844 adult patients with bacteremia due to *Streptococcus pneumoniae.* Overall, 16.5% of patients died by day 14. The risk of death was significantly greater for critically ill patients compared with non–critically ill patients (54.6% vs 7.3%, p=0.0001). The 14-day mortality was not significantly different for all patients receiving combination therapy versus monotherapy (10.4% vs 11.5%). Among 94 critically ill patients, however, combination antibiotic therapy was associated with lower mortality than was monotherapy (14-day mortality 23.4% vs 55.3%, p=0.0015). This difference in mortality remained significant when analyzed according to in vitro activity of the drug regimen. When all treatments were active in vitro, mortality in critically ill patients was 19.4% versus 60%, in the combination therapy versus monotherapy groups, respectively (p=0.0006). When at least one of the drugs of the combination therapy was active in vitro, mortality in critically ill patients was 18.2% versus 60%, respectively (p=0.0003). These data suggest that the administration of combination antibiotic therapy results in increased survival among critically ill patients with pneumococcal bacteremia. (Class II)

Chastre J, Wolff M, Fagon J-Y, et al. Comparison of 8 vs 15 days of antibiotic therapy for ventilator-associated pneumonia in adults. JAMA 2003;290:2588–98.

A prospective, randomized, double-blind, clinical trial in 401 patients with ventilator-associated pneumonia conducted in 51 French ICUs found no significant difference in mortality or recurrent infection in patients treated with

antibiotics for 8 days compared with those treated for 15 days. No significant differences were noted in time to fever resolution, leukocyte count, ratio of partial pressure of arterial oxygen to fraction of inspired oxygen, proportion of patients with organ dysfunction, or radiologic scores between the two treatment groups. In a secondary analysis, there were more patients with nonfermenting gram-negative bacilli infections treated with 8 days of antibiotics who had pulmonary infection recurrence. These data demonstrated that for patients in the ICU who have ventilator-associated pneumonia, there is no clinical advantage in prolonging antimicrobial therapy to 15 days compared with 8 days. (Class I)

Solomkin JS, Mazuski JE, Baron EJ, et al. Guidelines for the selection of anti-infective agents for complicated intra-abdominal infections. Clin Infect Dis 2003;37:997–1005.

These guidelines from the IDSA, Surgical Infection Society, American Society for Microbiology, and Society of Infectious Disease Pharmacists contain evidence-based recommendations for selection of antimicrobial therapy for adult patients with complicated intraabdominal infections. Recommendations were graded based on the quality of evidence available. Recommendations included patient selection for therapy, timing of empiric antibiotic therapy, selection of the empiric antibiotic regimen, identification of high-risk patients, duration of therapy, laboratory testing, health care–associated infections, culture and sensitivity testing, antifungal therapy, and enterococcal coverage. The guideline demonstrates the need for additional research in intraabdominal infection treatment.

Wunderink RG, Rello J, Cammarata SK, Croos-Dabrera V, Kollef MH. Linezolid vs vancomycin: analysis of two double-blind studies of patients with methicillin-resistant *Staphylococcus aureus* nosocomial pneumonia. Chest 2003;124:1789–97.

This is a post hoc analysis of two randomized, double-blind, multicenter studies of linezolid versus vancomycin for gram-positive nosocomial pneumonia. Data on 1019 patients were combined; 339 patients had documented *S. aureus* pneumonia, and 160 had documented MRSA pneumonia. Clinical cure rates for MRSA pneumonia were 50% for linezolid-treated patients and 35.5% for vancomycin-treated patients (p<0.01). The 28-day survival rate for

patients with MRSA pneumonia was 80% with linezolid versus 63.5% with vancomycin (p=0.03). After adjusting for baseline variables, the difference favoring linezolid remained significant. The methodology of this study, a retrospective subgroup analysis of combined data, has been criticized. Despite the criticism, this is the first study to demonstrate a survival advantage for one antibiotic regimen over another in patients treated for MRSA pneumonia, and it generates a hypothesis for testing in future trials. (Class III)

Sepsis

Dellinger RP, Levy MM, Carlet JM, et al, for the International Surviving Sepsis Campaign Guidelines Committee. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock—2008. Crit Care Med 2008;36:296–327.

This update of the 2004 comprehensive guidelines was prepared by critical care and infectious diseases experts from 14 international organizations. The guidelines cover initial resuscitation, diagnosis, antibiotic therapy, source control, fluid therapy, vasopressors, inotropic therapy, steroids, drotrecogin alfa (activated), blood product administration, mechanical ventilation, glucose control, renal replacement therapy, bicarbonate therapy, deep vein thrombosis prophylaxis, stress ulcer prophylaxis, considerations for limitations of support, considerations for pediatric patients, and sedation, analgesia, and neuromuscular blockade. This guideline update provides an evidenced-based approach to management of sepsis, septic shock, and critical illness.

Turgeon AF, Hutton B, Fergusson DA, et al. Meta-analysis: intravenous immunoglobulin in critically ill adult patients with sepsis. Ann Intern Med 2007;146:193–203.

This is a meta-analysis of 20 trials of polyclonal intravenous immunoglobulin in patients with sepsis or septic shock. Only six of the trials were published since 2000, and none reflect practice changes since sepsis guidelines were published in 2004. Polyclonal intravenous immunoglobulin use was associated with a clinically and statistically significant lower mortality rate than placebo or no intervention (risk ratio 0.74, 95% CI 0.62–0.89). The number needed to treat for benefit was 9. This survival benefit was consistently observed in sensitivity analyses, and

although the data analyzed were published between 1981 and 2006, the more recent trials were associated with an increased survival benefit compared with earlier trials. The authors projected that routine use of intravenous immunoglobulin in patients with sepsis could save an additional 20,000 lives every year in the United States, at an average cost of $4000–5000/patient. Use of polyclonal intravenous immunoglobulin has not become a standard of treatment for sepsis, but this meta-analysis highlights the need to evaluate further the role of intravenous immunoglobulin in future randomized trials.

Kumar A, Roberts D, Wood KE, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Crit Care Med 2006;34:1589–96.

This retrospective database review of septic shock cases was compiled from three separate cohorts—two Canadian and one American. The relationship between timing of initiation of effective antimicrobial therapy and survival from septic shock was determined. There were 2731 cases that met definitions for septic shock, but 558 were receiving effective antimicrobial therapy at the time of hypotension onset and thus were excluded from the primary analysis. Overall mortality was 56.2%. Survival was 79.9% if effective antimicrobial therapy was begun within the first hour of the onset of hypotension, and 42% if begun in the sixth hour. Each hour of delay in initiation of effective antimicrobial therapy was associated with a mean decrease in survival of 7.6%. When confounding variables were controlled for, time to effective antimicrobial therapy was most strongly associated with outcome (p<0.0001). This article supports the timely use of broad-spectrum antimicrobial therapy as an initial component of resuscitation of septic shock. (Class III)

MacArthur RD, Miller M, Albertson T, et al. Adequacy of early empiric antibiotic treatment and survival in severe sepsis: experience from the MONARCS trial. Clin Infect Dis 2004;38:284–8.

The Monoclonal Anti-TNF: Randomized Controlled Sepsis (MONARCS) trial was a double-blind, placebo-controlled trial designed to evaluate the safety and efficacy of afelimomab, an anti–tumor necrosis factor antibody, on patients with sepsis. Since the trial is the largest randomized sepsis trial to date, it presented an opportunity to determine the relationship between mortality and the adequacy of early empiric antibiotic treatment. In the MONARCS trial, 91% of enrolled patients received adequate antibiotic support, with an overall mortality rate of 34%. Mortality rates were 33% for patients receiving adequate and 43% for patients receiving inadequate antibiotic treatment (p<0.001). These data supplement much earlier foundational research demonstrating the necessity of early adequate antimicrobial therapy for patients with sepsis. (Class I)

Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 2001;345:1368–77.

This prospective, randomized trial involved 263 patients with severe sepsis or septic shock in an emergency department. Results showed a significant 16% absolute improvement in in-hospital survival for patients receiving 6 hours of early goal-directed therapy compared with standard therapy before admission to the ICU. Early goal-directed therapy consisted of achieving a central venous pressure of 8–12 mm Hg or greater, mean arterial pressure of 65–90 mm Hg, and central venous oxygen saturation of 70% or greater. A protocol for achieving these goals was used. Urine output of 0.5 ml/kg/hour or greater was also a goal, but there was no specific therapy in the protocol directed toward urine output. Goals were achieved in 99.2% of the early therapy group, compared with 86.1% of the standard therapy group. The authors suggested that goal-directed therapy provided at the earliest stages of severe sepsis and septic shock has significant short- and long-term benefits. These results may affect the quality and timing of resuscitation before enrollment in future trials of sepsis and septic shock. (Class I)

Bernard GR, Vincent J-L, Laterre P-F, et al. Efficacy and safety of recombinant human activated protein C for severe sepsis. N Engl J Med 2001;344:699–709.

This randomized, double-blind, placebo-controlled, multicenter trial involved 1690 patients with severe sepsis. The authors found that drotrecogin alfa (activated), which is recombinant human activated protein C, infused at 24 µg/kg/hour for 96 hours reduced all-cause 28-day mortality from 30.8% to 24.7% (p<0.005). Reduced RR of death was 19.4%. For patients at high risk of death, as predefined by Acute

Physiology and Chronic Health Evaluation II score, drotrecogin alfa (activated) produced an absolute reduction in mortality of 13%, from 44% to 31%. The frequency of severe bleeding was higher in the treatment than placebo group (3.5% vs 2.0%, p=0.06). Drotrecogin alfa (activated) was approved by the FDA for treatment of severe sepsis on the basis of this trial. (Class I)

Neurosurgery and Neurology

Spinal Cord Injury

Consortium for Spinal Cord Medicine. Early acute management in adults with spinal cord injury: a clinical practice guideline for health-care professionals. J Spinal Cord Med 2008;31: 403–79.

These guidelines provide recommendations for the overall management of the patient with a spinal cord injury. The pharmacy-related topics include resuscitation, neuroprotection, anesthetic concerns, pain, anxiety, and secondary prevention. These guidelines provide a general recommendation and succinct rationale for each topic and provide references for supporting evidence.

Furlan JC, Fehlings MG. Cardiovascular complications after acute spinal cord injury: pathophysiology, diagnosis, and management [online exclusive article]. Neurosurg Focus 2008;25:E13.

This is an excellent overview of the patho-physiology and management of cardiovascular complications after spinal cord injury. Detailed recommendations are provided for the prevention and treatment of cardiac and hemodynamic dysfunction, autonomic dysreflexia, and venous thromboembolism.

Sayer FT, Kronvall E, Nilsson OG. Methylprednisolone treatment in acute spinal cord injury: the myth challenged through a structured analysis of published literature. Spine J 2006;6:335–43.

There has been much debate over the use of steroids for treatment of acute spinal cord injury. In this article, the National Acute Spinal Cord Injury Studies (NASCIS) II and III are highly criticized because the authors did subgroup analyses of the study population, the results were inconsistent indicating that the conclusions were based on statistical artifact, and the functional recovery shown in these studies was not clinically significant. Other published studies have been unable to support the conclusions

from NASCIS II and III, and high-dose methylprednisolone complications are concerning. This systematic review of the literature suggests there is insufficient evidence to support the use of high-dose methylprednisolone as a standard of care for spinal cord injury.

American Association of Neurological Surgeons and Congress of Neurological Surgeons Joint Section on Disorders of the Spine and Peripheral Nerves. Blood pressure management after acute spinal cord injury: guidelines for the management of acute cervical spine and spinal cord injuries. Neurosurgery 2002;50(3 suppl): S58–62.

The authors state that evidence is insufficient to support treatment standards or guidelines for blood pressure management for patients with acute spinal cord injury. They do, however, recommend avoiding hypotension (systolic blood pressure < 90 mm Hg) and maintaining mean arterial pressure at 85–90 mm Hg for 7 days after injury to improve spinal cord perfusion.

American Association of Neurological Surgeons and Congress of Neurological Surgeons Joint Section on Disorders of the Spine and Peripheral Nerves. Pharmacological therapy after acute cervical spinal cord injury: guidelines for the management of acute cervical spine and spinal cord injuries. Neurosurgery 2002;50(3 suppl):S63–72.

This is one of the most controversial chapters in the guidelines, and the authors recommend that readers review the data and comments to formulate their own opinions regarding treatment options. They state that there is insufficient evidence for treatment standards or guidelines for using corticosteroid therapy. The group recommends that methylprednisolone administered for 24–48 hours can be considered a treatment option for patients with acute spinal cord injury; however, the authors first acknowledge that the evidence suggesting harmful side effects is more consistent than evidence supporting clinical benefit.

American Association of Neurological Surgeons and Congress of Neurological Surgeons Joint Section on Disorders of the Spine and Peripheral Nerves. Deep venous thrombosis and thromboembolism in patients with cervical spinal cord injuries: guidelines for the management of acute cervical spine and spinal cord injuries. Neurosurgery 2002;50(3 suppl):S73–80.

In this chapter, prophylaxis of deep vein

thrombosis is recommended as a standard of care for patients with acute spinal cord injury. The authors support the use of low-molecular-weight heparins, rotating beds, adjusted-dose heparin, or a combination of these modalities, as well as low-dose heparin in combination with pneumatic compression stockings or electrical stimulation as treatment strategies for prophylaxis. The guidelines state that low-dose heparin therapy alone and oral anticoagulation alone are not recommended. Other suggestions include the administration of various diagnostic tests, 3 months of prophylactic treatment, and vena cava filters for patients not responding to anticoagulation or who have contraindications to anticoagulation and/or mechanical devices.

Bracken MB, Shepard MJ, Holford TR, et al. Administration of methylprednisolone for 24 or 48 hours or tirilazad mesylate for 48 hours in the treatment of acute spinal cord injury: results of the third national acute spinal cord injury randomized controlled study. JAMA 1997;277: 1597–604.

The NASCIS III was a double-blind, randomized, controlled trial involving 499 patients with acute spinal cord injury. At 6-week and 6-month follow-up, a significant neurologic recovery persisted with the 48-hour methyl-prednisolone regimen that had been started within 3–8 hours after injury compared with the 24-hour regimen (neurologic change scores at 6 wks: 7.6 vs 12.5, p=0.04; at 6 months: 11.2 vs 17.6, p=0.01). No significant difference in recovery was found when treatment was started within 3 hours of injury. In a third study group, tirilazad demonstrated efficacy similar to that of the 24-hour methylprednisolone regimen and was well tolerated. The authors concluded that methylprednisolone therapy should be continued for 24 hours if started within 3 hours of injury, but continued for 48 hours if started 3–8 hours after injury. (Class I)

Bracken MB, Shepard MJ, Collins WF, et al. A randomized, controlled trial of methylprednisolone or naloxone in the treatment of acute spinal-cord injury: results of the second national acute spinal cord injury study. N Engl J Med 1990;322:1405–11.

In the NASCIS I trial, methylprednisolone in dosages up to 1000 mg/day did not improve neurologic recovery (sensory or motor function) in 330 patients with acute spinal cord injury. This article describes NASCIS II, a double-blind, placebo-controlled trial involving 487 patients

treated within 8 hours of injury. Treatment consisted of a high-dose methylprednisolone intravenous bolus of 30 mg/kg followed by continuous infusion of 5.4 mg/kg/hour for 23 hours. Significant motor function and sensation were maintained at 6 weeks and 6 months with methylprednisolone compared with placebo or a naloxone bolus of 5.4 mg/kg followed by infusion of 4 mg/kg/hour for 23 hours. Complication rates were similar among the three groups. (Class I)

Head Injury

Bilotta F, Caramia R, Cernak I, et al. Intensive insulin therapy after severe traumatic brain injury: a randomized clinical trial. Neurocrit Care 2008:9:159–66.

In this prospective, randomized, single-center study, 97 patients with severe traumatic brain injury were randomly assigned to receive conventional insulin therapy (continuous insulin infusion to maintain blood glucose level < 220 mg/dl) or intensive insulin therapy (continuous infusion to maintain blood glucose level 80–120 mg/dl). The aim of the study was to determine the risks and benefits of intensive insulin therapy and strict glucose control in patients with severe traumatic brain injury. A significantly higher rate of hypoglycemia (defined as blood glucose level below 80 mg/dl, median 7 vs 15 episodes, p<0.0001) and a shorter ICU length of stay (median 7.3 vs 10 days, p<0.05) occurred in the intensive insulin therapy group versus the conventional therapy group; no significant differences were found in ICU infection rate, neurologic outcome scores, or mortality at 6 months. All but one patient in the intensive therapy group had at least one episode of hypoglycemia during the study period. The study was not powered to determine differences in mortality. The study protocol for insulin titration is included in the article. The authors concluded that intensive insulin therapy increases the risk of hypoglycemia without a beneficial effect on outcome. (Class I)

Brain Trauma Foundation, American Association of Neurological Surgeons (AANS), Congress of Neurological Surgeons (CNS), and the AANS/CNS Joint Section on Neurotrauma and Critical Care. Guidelines for the management of severe traumatic brain injury. J Neurotrauma 2007;24:S1–199.

These guidelines are the joint project of the

Brain Trauma Foundation, American Association of Neurological Surgeons (AANS), Congress of Neurological Surgeons (CNS), and the AANS-CNS Joint Section on Neurotrauma and Critical Care. This third edition includes pharmacy-related topics, such as hyperosmolar therapy; infection prophylaxis; deep vein thrombosis prophylaxis; anesthesia, analgesics and sedatives; nutrition; seizure prophylaxis; and steroids. These guidelines are evidence based and were developed by experts in the field of neurotrauma.

The SAFE Study Investigators. Saline or albumin for fluid resuscitation in patients with traumatic brain injury (SAFE–TBI). N Eng J Med 2007;357:874–84.

This study is a post hoc analysis of the patients with traumatic brain injury included in the Saline versus Albumin Fluid Evaluation (SAFE) database and original study—a multicenter, double-blind, randomized, controlled trial that was conducted from 2001–2003. In the original study, patients with traumatic brain injury had a higher mortality rate at 28 days if they were resuscitated with albumin 4% versus normal saline. Therefore, this post hoc study was conducted in 480 patients with traumatic brain injury to determine mortality differences at 24 months. The study patients were similar at baseline; however, the mortality rate was significantly higher in the patients receiving albumin (33.2%) versus saline (20.4%, p=0.003). Patients classified as having severe traumatic brain injury (Glasgow Coma Scale scores of 3–8) also had a higher rate of mortality if they received albumin (41.8%) versus saline (22.2%, p<0.001). The majority of deaths occurred by hospital day 28 in both groups. The authors concluded that fluid resuscitation with albumin was associated with higher mortality rates than resuscitation with normal saline in critically ill patients with traumatic brain injury. (Class II)

Vincent JL, Berre J. Primer on medical management of severe brain injury. Crit Care Med 2005;33:1392–9.

In this review, the authors provide an overview of severe brain injury pathophysiology and clinical evaluation, as well as a step-wise approach to the management of intracranial hypertension in patients with severe brain injury. Other topics discussed include seizure prophylaxis, sedation, nutrition support, use of hypothermia, and corticosteroids.

The CRASH Trial Collaborators. Effect of intravenous corticosteroids on death within 14 days of 10,008 adults with clinically significant head injury (MRC-CRASH trial): randomised placebo-controlled trial. Lancet 2004;364:1321–8.

The Medical Research Council's Corticosteroid Randomization After Significant Head Injury (MRC CRASH) trial was a multicenter, randomized, placebo-controlled trial involving 10,008 adults with severe head injury. The goal was to determine the effect of early administration of methylprednisolone on risk of death at 2 weeks or disability at 6 months. Patients were randomly assigned to receive intravenous methylprednisolone 2 g followed by 0.4 g/hour for 48 hours, or placebo, within 8 hours of injury. The study was stopped prematurely because an interim analysis showed a significant increase in RR of all-cause death in the methylprednisolone-treated group (RR 1.18, 95% CI 1.09–1.27, p=0.0001). The relative increase in mortality in the methylprednisolone group did not significantly differ by the severity or time of injury. The exact mechanism for the increased mortality is unknown. This is the first study that clearly refutes the mortality benefit of corticosteroids in the treatment of patients with severe head injury. (Class I)

Temkin NR, Dikmen SS, Wilensky AJ, Keihm J, Chabal S, Winn HR. A randomized, double-blind study of phenytoin for the prevention of post-traumatic seizures. N Engl J Med 1990;323: 497–502.

This randomized, double-blind, placebo-controlled study is the landmark article supporting short-course phenytoin therapy for seizure prophylaxis in patients with severe head injury. A phenytoin 20-mg/kg loading dose or placebo was administered within 24 hours of injury, and maintenance doses were continued for 12 months. Phenytoin dosages were adjusted to maintain free phenytoin levels within a target range of 0.75–1.5 mg/L. Patients were followed for 24 months. One week after injury, the seizure rates were 3.6% and 14.2% in the phenytoin and placebo groups, respectively (p<0.001). The differences in the frequency of late-onset seizures (day 8–year 2) between groups was not statistically significant (p>0.2). The authors concluded that phenytoin is effective only for prevention of early-onset (< 7 days) seizures after severe head injury. (Class I)

Hemorrhagic Stroke

Bederson JB, Connolly ES, Batjer HH, et al. Guidelines for the management of aneurysmal subarachnoid hemorrhage: a statement for health care professionals from a special writing group of the Stroke Council, American Heart Association. Available from http://stroke.ahajournals.org. Accessed January 22, 2009.

These guidelines provide a classification of recommendations and level of evidence for the management of subarachnoid hemorrhage. Evidence for the medical, surgical, and endovascular treatment of subarachnoid hemorrhage and management of subarachnoid hemorrhage–associated cerebral vasospasm are summarized.

Sillberg VAH, Wells GA, Perry JJ. Do statins improve outcomes and reduce the incidence of vasospasm after aneurysmal subarachnoid hemorrhage: a meta-analysis. Stroke 2008;39: 2622–6.

Although this is a meta-analysis, the article is beneficial as it provides information on the three small double-blind, randomized, controlled trials published to date on the use of statins for reducing the occurrence of vasospasm after aneurysmal subarachnoid hemorrhage, and it evaluated differences in morbidity and mortality. The studies included were ones in which one treatment group received statin therapy and another received placebo; 78 patients received statin therapy and 80 received placebo. This analysis showed a reduction in the incidence of vasospasm (RR 0.73, 95% CI 0.54–0.99), delayed ischemic deficits (RR 0.38, 95% CI 0.17–0.83), and mortality (RR 0.22, 95% CI 0.06–0.82) in the statin group; with a number needed to treat of 6.25, 5, and 6.7, respectively. This article also provides a summary of the clinical studies of statin use and related subarachnoid hemorrhage outcomes. The authors concluded that these data support the use of statins as a standard of care in patients with aneurysmal subarachnoid hemorrhage.

Anderson CS, Huang Y, Wang JG, et al. Intensive blood pressure reduction in acute cerebral haemorrhage trial (INTERACT): a randomised pilot trial. Lancet Neurol 2008;7: 391–9.

This multicenter, open-label, randomized, non–United States pilot study of 404 patients with acute spontaneous intracerebral hemorrhage was conducted to determine the safety and efficacy of early, aggressive blood pressure reduction. Patients presenting within 6 hours of symptom onset with a systolic blood pressure of 150–200 mm Hg were included in the trial and were randomly assigned to a management strategy of intensive blood pressure lowering (target systolic blood pressure 140 mm Hg, 203 patients) or standard guideline-based blood pressure management (target systolic blood pressure 180 mm Hg, 201 patients). In the intensive blood pressure group, the goal was to achieve the target blood pressure within 1 hour of randomization and maintain this target for at least 7 days. The results showed no significant differences in the absolute reduction in hematoma growth at 24 hours and no significant difference in mortality or dependency between groups at 90 days. This study provides support for the safety of intensive blood pressure lowering in patients with intracerebral hemorrhage; however, a larger study (INTERACT2) is underway to determine the effects of intensive blood pressure management on clinical outcomes. (Class I)

Mayer SA, Brun NC, Begtrup K, et al. Efficacy and safety of recombinant activated factor VII for acute intracerebral hemorrhage (FAST). N Eng J Med 2008;358:2127–37.

This phase III trial randomly assigned 841 patients to placebo, rFVIIa 20 µg/kg, or rFVIIa 80 µg/kg within 4 hours of intracerebral hemorrhage. The primary objective was to determine the effects of rFVIIa on the rates of death or severe disability after intracerebral hemorrhage. Results showed a significant reduction in hematoma volume growth with rFVIIa 80 µg/kg, but there was no significant difference among the three treatment groups with regard to poor outcome. The overall rate of thromboembolic serious adverse events was similar in all three groups, but there was a statistically significant increase in arterial thromboembolic events in the patient receiving rFVIIa 80 µg/kg compared with the placebo group (8% vs 4%, p=0.04). The outcome results of this study are contradictory to the results of a previous phase IIb rFVIIa trial (Mayer SA et al. N Engl J Med 2005;352:777–85). The authors suggest that these outcome result differences may be due to clinically important baseline imbalances in the phase III study groups, with patients in the rFVIIa 80 µg/kg group having larger intracerebral and intraventricular hemorrhage volumes, and greater frequency of coma and left ventricular

hypertrophy compared with those in the placebo group. The investi-gators also conducted a series of unplanned exploratory post hoc analyses that showed rFVIIa may have benefited patients younger than 70 years, with a baseline intracerebral hemorrhage volume of less than 60 ml, an intraventricular hemorrhage volume less than 5 ml, and time to treatment of less than 2.5 hours. The authors concluded that rFVIIa reduced hematoma growth but did not reduce the rate of death or severe disability in patients with intracerebral hemorrhage, and further study of a subgroup of patients at high risk for active bleeding is warranted. (Class I)

Goldstein JN, Rosand J, Schwamm LH. Warfarin reversal in anticoagulant-associated intracerebral hemorrhage. Neurocrit Care 2008;9:277–83.

The authors review the incidence of warfarin-induced intracerebral hemorrhage and the treatment options for warfarin reversal. Strategies for reversal discussed include vitamin K, fresh frozen plasma, prothrombin complex concentrate, and rFVIIa. A summary of international guidelines for warfarin reversal in patients with intracerebral hemorrhage is also provided.

Broderick J, Connolly S, Feldmann E, et al. Guidelines for the management of spontaneous intracerebral hemorrhage in adults: 2007 update. Stroke 2007;38:2001–23.

These guidelines were developed by the American Heart Association–American Stroke Council, High Blood Pressure Research Council, and the Quality of Care and Outcomes in Research Interdisciplinary Working Group. It is an update of the 1999 guidelines for the diagnosis and treatment of acute spontaneous intracerebral hemorrhage and includes literature published up to 2006. These guidelines provide recommendations for diagnosis, urgent treatment, medical management, surgical treatment, and prevention of intracerebral hemorrhage.

Chumnanvej S, Dunn IF, Kim DH. Three-day phenytoin prophylaxis is adequate after subarachnoid hemorrhage. Neurosurgery 2007;60:99–103.

This retrospective study of prospectively collected data compared the seizure rates and adverse events of 453 patients with subarachnoid hemorrhage who received phenytoin seizure prophylaxis for the duration of hospitalization (first period group, 79 patients) with those receiving prophylaxis for only 3 days (second period group, 370 patients) unless patients had a history of epilepsy (four patients). All patients received a phenytoin 1000-mg loading dose, followed by 100 mg 3 times/day, without therapeutic drug monitoring. Most patients had aneurysmal subarachnoid hemorrhage and a mild-to-moderate severity subarachnoid hemorrhage (Hunt and Hess grade $\leq$ 3). The seizure rate was not significantly different between the first and second period groups during hospitalization (1.3 % vs 1.9%, p=0.06) or within 3–12 months after discharge (5.7% vs 4.6%, p=0.57). There was a statistically significant reduction in the rate of adverse events (hypersensitivity reactions) in the 3-day group (8.8% vs 0.5%, p=0.002). This study supports the use of short-term seizure prophylaxis in patients with aneurysmal subarachnoid hemorrhage. (Class II)

Liu-DeRyke X, Rhoney DH. Cerebral vasospasm after aneurysmal subarachnoid hemorrhage: an overview of pharmacologic management. Pharmacotherapy 2006;26:182–203.

One of the leading causes of mortality in patients with subarachnoid hemorrhage is cerebral vasospasm. This review discusses the pathophysiology of vasospasm, summarizes the published data for the prevention and treatment of vasospasm, and provides the rationale and limitations for each therapy.

Sen J, Belli A, Albon H, Morgan L, Ptezold A, Kitchen N. Triple-H therapy in the management of aneurysmal subarachnoid haemorrhage. Lancet Neurol 2003;2:614–21.

Vasospasm, a major complication after subarachnoid hemorrhage, is associated with high morbidity and mortality. Hypervolemia, hypertension, and hemodilution (triple-H) therapy is accepted as a standard of care; however, no randomized controlled trials have been conducted to prove efficacy in the treatment of vasospasm. The authors review the literature and discuss the rationale for triple-H therapy.

Ischemic Stroke

Hacke W, Kaste M, Bluhmki, et al, for the ECASS Investigators. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke: ECASS III. N Eng J Med 2008;359:1317–29.

The European Cooperative Acute Stroke Study (ECASS) investigators conducted a double-bind, parallel-group, multicenter study of 821 patients

with acute stroke who had a National Institutes of Health Stroke Scale (NIHSS) score less than 25 (excluded patients with severe stroke). Patients were treated with alteplase 0.9 mg/kg (maximum 90 mg) or placebo between 3 and 4.5 hours after the onset of symptoms. This study showed that patients treated with alteplase were more likely to experience minimal to no disability at 90 days compared with those receiving placebo (52.4% vs 45.2%, p=0.04), representing an absolute reduction of 7.2%. There was a higher rate of intracranial hemorrhage with alteplase than with placebo (asymptomatic 27.0% vs 17.6%, p=0.001; symptomatic 2.4% vs 0.2%; p=0.008); there was no significant difference in mortality (7.7% and 8.4%, respectively; p=0.68). These results support extending the window for the use of alteplase to within 4.5 hours after symptom onset in patients with mild-to-moderate acute ischemic stroke, which will increase the possibilities of receiving thrombolytic therapy and improving patient outcomes. (Class I)

Albers GW, Amarenco P, Easton JD, et al. Antithrombotic and thrombolytic therapy for ischemic stroke: American College of Chest Physicians evidence-based clinical practice guidelines, 8th ed. Chest 2008;133;630–69.

These guidelines provide graded recommendations for the prevention and treatment of acute ischemic stroke. The focus of this article is on antithrombotic agents for short- and long-term prevention and thrombolytic therapy for treatment of acute ischemic stroke.

Khajha AM, Grotta JC. Established treatments for acute ischaemic stroke. Lancet 2007;369: 319–30.

This article is a concise review of the treatment of acute ischemic stroke and the medical and neurologic complications of stroke. The authors discuss acute ischemic stroke diagnosis and initial management, and provide recommendations for examination and monitoring of oxygenation, fever, blood pressure, and blood glucose concentrations. Treatment with tissue plasminogen activator (t-PA), complications of t-PA, and an approach to t-PA complications are also discussed.

Sherman DG, Albers GW, Bladin C, et al. The efficacy and safety of enoxaparin versus unfractionated heparin for the prevention of venous thromboembolism after acute ischaemic stroke (PREVAIL study): an open-label randomised comparison. Lancet 2007;369:1347–55.

This multinational, randomized study compared the efficacy and safety of subcutaneous enoxaparin 40 mg/day with subcutaneous unfractionated heparin 5000 U every 12 hours, started within 48 hours of onset of stroke symptoms, in 1762 patients with acute stroke who were unable to walk unassisted. Patients were also stratified into two stroke groups: severe stroke (NIHSS score ≥ 14) and less severe stroke (NIHSS score < 14). Only 1096 patients were included in the efficacy analysis; enoxaparin and unfractionated heparin were given for a mean ± SD of 10.5 ± 3.2 days. At day 14, enoxaparin reduced the occurrence of venous thromboembolism by 43% compared with unfractionated heparin (68 patients receiving enoxaparin [10%] vs 121 patients receiving heparin [18%], p=0.0001). The reduction continued to be significant at 90 days. There was a significantly higher rate of venous thromboembolism in patients with severe stroke compared with those with less severe stroke; however, the reduction in risk was also seen for patients receiving enoxaparin compared with those receiving unfractionated heparin. The bleeding risk was similar for both groups. The authors concluded that enoxaparin was preferable to unfractionated heparin because of its benefit:risk ratio and convenience of administration. This study did not compare enoxaparin with every-8-hour dosing of unfractionated heparin, so the difference in efficacy and safety between these two treatments is still unknown for this patient population. (Class I)

Adams H, Adams R, Del Zoppo G, et al. Guidelines for the early management of patients with ischemic stroke: 2005 guidelines update. A scientific statement from the Stroke Council of the American Heart Association/American Stroke Association. Stroke 2005;36:916–21.

These guidelines, which update the original 2003 guidelines, are intended to guide clinicians in the diagnosis and management of patients during the first 24–48 hours after ischemic stroke. Recommendations are provided for diagnostic testing and examination, general supportive care and treatment of complications, use of thrombolysis, role of anticoagulation, surgical interventions, and management of neurologic complications. Each recommendation is graded based on the level of supporting evidence.

Clark WM, Wissman S, Albers GW, Jhamandas

JH, Madden KP, Hamilton S. Recombinant tissue-type plasminogen activator (alteplase) for ischemic stroke 3 to 5 hours after symptom onset: the ATLANTIS study: a randomized controlled trial. JAMA 1999;282:2019–26.

Recombinant t-PA (rt-PA) originally was studied when administered within 3 hours of symptom onset in patients with acute ischemic stroke. However, only a few patients received the drug within this time frame. In this randomized, placebo-controlled trial, alteplase 0.9 mg/kg was started 3–5 hours after symptom onset. Outcomes were neurologic recovery at 90 days, functional outcome measures at 30 and 90 days, and serious adverse events. Neurologic recovery, functional recovery, and mortality were similar in both groups. Asymptomatic, symptomatic, and fatal intracranial hemorrhages were significantly higher in the alteplase group ($p<0.05$). The authors concluded that there was no benefit to administering alteplase 3–5 hours after symptom onset. (Class I)

Hacke W, Kaste M, Fieschi C, et al. Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II). Lancet 1998;352:1245–51.

The primary objective of this multicenter trial was to determine whether alteplase 0.9 mg/kg given within 6 hours of symptom onset would improve overall function in 800 patients with acute ischemic stroke. Efficacy of alteplase was independent of administration time (no significant difference when given < 3 vs 3–6 hrs after stroke). No significant difference in efficacy or mortality was observed between alteplase and placebo at the 30- and 90-day end points. As seen in the first European Cooperative Acute Stroke Study (ECASS I) and the National Institute of Neurological Disorders and Stroke (NINDS) trial, symptomatic intracranial hemorrhage was higher in the alteplase group (8.8%) than in the placebo group (3.4%). (Class I)

The NINDS t-PA Stroke Study Group. Intracerebral hemorrhage after intravenous t-PA therapy for ischemic stroke. Stroke 1997;28:2109–18.

Administration of t-PA has been associated with increased risk of intracranial hemorrhage when used to treat ischemic stroke. The authors investigated whether any variables collected in the NINDS t-PA stroke trial were associated with intracranial hemorrhage. Severity of neurologic deficit (OR 1.8, 95% CI 1.2–2.9) and brain edema and mass effect by computed tomography (OR 7.8, 95% CI 2.2–27.1) were the only independent variables associated with intracranial hemorrhage. Patients with severe neurologic deficits had more favorable outcomes at 90 days in the treatment group than in the placebo group (OR 4.3, 95% CI 1.6–11.9). The authors concluded that these patients were still candidates for t-PA if the agent was administered within 3 hours of symptom onset. (Class II)

National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. N Engl J Med 1995;333:1581–7.

Previous trials have suggested that early intervention with thrombolytic therapy improves clinical outcomes in patients with acute ischemic stroke, although the therapy is associated with a risk of symptomatic intracranial hemorrhage. In this prospective, randomized, double-blind, placebo-controlled trial, 624 patients were treated with rt-PA 0.9 mg/kg or a maximum dose of 90 mg. The results demonstrated significantly decreased neurologic deficit at 3 months in patients treated within 3 hours of stroke onset (OR 1.7, 95% CI 1.2–2.6). Symptomatic intracranial hemorrhage occurred more frequently in the rt-PA group (6.4%) than in the placebo group (0.6%) during the first 36 hours ($p<0.001$). No significant difference in mortality was detected. (Class I)

Hacke W, Kaste M, Fieschi C, et al. Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke: the European cooperative acute stroke study (ECASS). JAMA 1995;274:1017–25.

Restoration of cerebral blood flow is the goal of thrombolytic therapy in patients with stroke. This randomized controlled trial compared rt-PA with placebo in 620 patients with acute ischemic stroke. The patients presented within 6 hours of symptom onset and had experienced a stable (moderate to severe) stroke without signs of infarction at computed tomography. No significant difference in the primary outcome of functional scores at 90 days was found with the intent-to-treat analysis. The target population analysis revealed that one of the functional scores (Rankin score) was in favor of rt-PA ($p<0.05$). Mortality was similar between the two groups, but parenchymal hemorrhages and mortality occurred significantly more often in the rt-PA group. The

authors concluded that rt-PA was effective, and that the risk of bleeding and death does not outweigh the positive effects of t-PA. They recommended more stringent criteria for patient selection to reduce adverse effects. (Class I)

Seizures

Von Winckelmann SL, Spriet I, Willems L. Therapeutic drug monitoring of phenytoin in critically ill patients. Pharmacotherapy 2008;28: 1391–400.

Phenytoin is a commonly used antiepileptic and requires therapeutic drug monitoring to ensure safety and efficacy. This review covers the difficulties of phenytoin monitoring, including physiologic conditions and drug interactions that can alter phenytoin pharmacokinetics in critically ill patients.

Khaled KJ, Hirsch LJ. Updates in the management of seizures and status epilepticus in critically ill patients. Neurol Clin 2008;26:385–408.

This review discusses the diagnosis and management of seizures and status epilepticus in various types of critically ill patients, including those with liver disease, renal disease, and transplants. Topics include the pathophysiology of status epilepticus, the etiology of seizures, drugs associated with decreased seizure threshold, and sequelae of status epilepticus. An algorithm for the treatment of status epilepticus is also provided.

Liu KC, Bhardwaj A. Use of prophylactic anticonvulsants in neurologic critical care: a critical appraisal. Neurocrit Care 2007;7:175–84.

This is an excellent literature review of the use of seizure prophylaxis in multiple neurocritical care clinical conditions, such as traumatic brain injury, subarachnoid hemorrhage, brain tumors, spontaneous intracranial hemorrhage, and ischemic stroke. The authors summarize the existing literature, highlight the important controversies concerning anticonvulsant use in these disease states, and provide evidence-based recommendations for seizure prophylaxis.

Lowenstein DH. The management of refractory status epilepticus: an update. Epilepsia 2006;47: 35–40.

This review article addresses issues concerning the management of refractory status epilepticus, epidemiology, clinical course, and outcome. The author provides a review of the literature comparing effectiveness of current antiepileptic

agents and an algorithm for current approaches to treatment, as well as a discussion of intravenous anesthetic agents and emerging therapies with oral and intravenous antiepileptic agents.

Chen JW, Wasterlain CG. Status epilepticus: pathophysiology and management in adults. Lancet Neurol 2006;5:246–56.

This is a review of the physiologic and cellular changes of status epilepticus that result in the development of time-dependent pharmaco-resistance. The authors also include a treatment algorithm for patients with status epilepticus from before hospitalization to admittance to the ICU, as well as a discussion of the preferred therapeutic agents.

Claasen J, Hirsch LJ, Emerson RG, Mayer SA. Treatment of refractory status epilepticus with pentobarbital, propofol, or midazolam: a systematic review. Epilepsia 2002;43:146–53.

The absence of controlled, prospective studies comparing available treatment options for patients with refractory status epilepticus makes it difficult to compare the relative efficacy and safety of these options. This article provides a systematic review of peer-reviewed publications reporting the treatment of adults with status epilepticus refractory to at least two standard anticonvulsants. Outcome measures evaluated were the frequency of short-term treatment failure (within 1–6 hrs), mortality, and drug titration goals. Twenty-eight case reports or series describing 193 patients receiving pentobarbital, propofol, or midazolam were included in the analysis. Of the 193 patients, 48% died, with no significant differences based on the treatment received. Although pentobarbital dosage was usually titrated to electroencephalogram background suppression, propofol and midazolam were titrated to the dosage needed to achieve seizure suppression. Overall, the limited data reviewed in this article suggest that treatment with pentobarbital or titration of any agent to electroencephalogram background suppression may be the most effective strategy for managing refractory status epilepticus. However, there was no obvious improvement in mortality. Prospective, controlled evaluations of this issue are needed.

Treiman DM, Meyers PD, Walton NY, et al. A comparison of four treatments for generalized convulsive status epilepticus. N Engl J Med 1998;339:792–8.

In this multicenter, randomized, double-blind trial, four intravenous antiepileptic regimens were compared for in-hospital treatment of generalized convulsive status epilepticus. A total of 570 patients were randomly assigned to receive lorazepam 0.1 mg/kg, phenobarbital 15 mg/kg, phenytoin 18 mg/kg, or diazepam 0.15 mg/kg followed by phenytoin 18 mg/kg. Treatment success was defined as the absence of motor and electrical activity within 20 minutes of drug infusion, with no evidence of recurrence over the next 40 minutes. Intent-to-treat analysis revealed no statistically significant differences among regimens. For 384 patients with overt generalized convulsive seizures, lorazepam was more effective than phenytoin (p=0.02) but did not significantly differ from the diazepam-phenytoin and phenobarbital regimens. Based on at least comparable safety and efficacy for the four regimens, the authors concluded that for patients with generalized convulsive status epilepticus, lorazepam should be the initial treatment because of its ease of administration and improved response compared with phenytoin. (Class I)

Nutrition

Martindale RG, McClave SA, Vanek VW, et al. Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: Society of Critical Care Medicine and American Society for Parenteral and Enteral Nutrition. Crit Care Med 2009;37:1–30.

These are evidence-based guidelines compiled by two professional organizations with an interest in providing multidisciplinary nutritional support of the critically ill patient. The guidelines pertain to adult patients with an expected ICU stay of at least 2 days. The guidelines provide information in the form of a recommendation followed by rationale for the recommendation. All major aspects of nutrition support for critically ill patients are covered.

Doig GS, Simpson F, Finfer S, et al. Effect of evidence-based feeding guidelines on mortality in critically ill adults: a cluster randomized controlled trial. JAMA 2008;300:2731–41.

Intensive care units in Australia and New Zealand were randomly assigned to implement a guideline composed of 18 interventions with associated educational visits to help change practice or to a control group. The recommendations in the guideline were based on available evidence that included an algorithm shown to increase the days of enteral nutrition and reduce length of hospital stay in a previous study (Martin CM et al. CMAJ 2004;70:197–204). The authors estimated that 1386 patients would be needed to demonstrate an 8% reduction in mortality. Total enrollment was 1118 patients. Although practice changes such as reduced time to enteral (p<0.001) and parenteral (p=0.04) feeding start and attainment of caloric feeding goals (p=0.03) were identified in the intervention group, there were no significant differences in hospital mortality (p=0.75), or hospital (p=0.97) or ICU (p=0.42) length of stay. As discussed in an accompanying editorial (Jones NE, Heyland DK, JAMA 2008;300:2798–9), the lack of change in mortality or length of stay may have been due to the relatively rapid attainment of enteral feeding goals in both groups (95% by 1.6 days of admission), the types of interventions actually used in each ICU, and lack of barrier assessment in each of the institutions. The latter two limitations restrict the generalizability of the results of this investigation. (Class 1)

Elke G, Schadler D, Engel C, et al. Current practice in nutritional support and its association with mortality in septic patients: results from a national, prospective, multicenter study. Crit Care Med 2008;36:1762–7.

This cross-sectional study involving 454 ICUs in Germany found an increased risk of death in patients with severe sepsis or septic shock who received parenteral nutrition (OR 2.09, 95% CI 1.29–3.37) when other factors were adjusted with use of regression analysis. Furthermore, mortality was significantly lower in patients receiving enteral (38.9%) compared with parenteral (62.3%) or mixed (57.1%) nutrition (p=0.005). Although the study had limitations related to details of caloric intake and infectious complications, it is important not only because of the number of patients studied (415 patients), but also because mean blood glucose concentrations were similar between enteral and parenteral groups (unlike many previous studies). An accompanying editorial makes the point that most patients in the ICU have no contraindications to early enteral feeding and this route should be used regardless of ventilator status (Marik PE. Crit Care Med 2008;36:1964–5). (Class II)

Radrizzani D, Bertolini G, Facchini R, et al. Early enteral immunonutrition vs parenteral nutrition in critically ill patients without severe

sepsis: a randomized clinical trial. Intensive Care Med 2006;32:1191–8.

This was a multicenter, randomized trial conducted in Italian ICUs that was originally designed to compare three forms of nutrition: standard enteral formulation, immune-modulating enteral formulation, and parenteral nutrition. Unfortunately, a lack of funding forced the investigators to drop the standard enteral formulation arm of the trial. An interim analysis revealed increased mortality in severely septic patients receiving the immune-modulating formulation, so recruitment of these subjects was stopped (Bertolini G et al. Intensive Care Med 2003;29:834–40). No significant difference was noted in overall 28-day mortality between immune-modulating enteral and parenteral nutrition; however, immune-modulating nutrition did result in a reduction in the other primary end point of first major septic complication (p=0.022) in the stratified group of patients defined as nonseverely septic on admission. Length of ICU stay in this group was also reduced by immune-modulating nutrition (p=0.047). Because of the exclusion of the standard enteral feeding group, it is not clear if the positive findings are due to the specific immune-modulating enteral formula under investigation or the choice of route (i.e., enteral vs parenteral). This study is included because it illustrates the difficulties of conducting and interpreting research that involves complex immune-modulating enteral formulations. The generalizability of the results of this trial and similar investigations (Pontes-Arruda A et al. Crit Care Med 2006;34:2325–33) is limited. (Class I)

Kreymann KG, Berger MM, Deutz NEP, et al. ESPEN guidelines on enteral nutrition: Intensive Care. Clin Nutr 2006;25:210–23.

These are evidence-based guidelines developed by the European Society for Clinical Nutrition and Metabolism. The guidelines give recommendations based on indication, application, route, and type of formula with further classification by admission category (burns, medical, sepsis, surgical, transplant, trauma). The guidelines provide clear-cut recommendations with references to the supporting literature for retrieval by the reader.

Jacobs DG, Jacobs DO, Kudsk KA, et al. Practice management guidelines for nutritional support of the trauma patient. J Trauma 2004;57:660–79.

This guideline was developed by a working group of EAST. Each of the six guideline subsections (route, timing, site, macronutrients, monitoring, and type of nutritional support) is a freestanding, evidence-based document. References and evidence tables associated with the guideline can be obtained on the EAST Web site (http://www.east.org). The guideline contains an algorithm summarizing the nutritional management of trauma patients.

Barr J, Hecht M, Flavin KE, et al. Outcomes in critically ill patients before and after the implementation of an evidence-based nutritional management protocol. Chest 2004;125:1446–57.

The primary end point of this before-and-after, prospective investigation (100 patients in each phase) was to evaluate the impact of a nutritional management protocol on the time to initiation of feeding of patients in two medical-surgical ICUs. The protocol was evidence based but lacked high-level evidence for some recommendations. Enteral versus parenteral nutrition, ability to reach caloric goals, and length of ICU stay were evaluated. Patients in the postimplementation group were more likely than those in the preimplementation group to be fed enterally, and their mean duration of mechanical ventilation was decreased. However, the results were statistically significant (p=0.009 and p=0.03, respectively) only after adjusting for a variety of covariates, such as baseline nutritional status and severity of illness. The logic behind this adjustment was questioned in an editorial accompanying the article (Zaloga GP et al. Chest 2004;125:1195–7). No other significant differences between groups were noted, probably because of the comparable number of patients receiving enteral nutrition in the preimplementation and postimplementation groups (68% and 78%, respectively, p=0.08). This study is notable because of its prospective design and comprehensive approach to the nutritional management of critically ill patients. (Class II)

Heyland DK, Dhaliwal R, Drover R, et al. Canadian clinical practice guidelines for nutrition support in mechanically ventilated, critically ill adult patients. J Parenter Enter Nutr 2003;27:355–73.

These guidelines were initially promulgated by an interdisciplinary stakeholder group that convened in 2001. The broad representation of stakeholders, the use of a systematic evidence-based approach to guideline development, the use of clinically important outcome measures

(mortality, length of stay, quality of life, and complications), and the focus on critically ill patients distinguishes this document from others. The results are presented as a series of questions followed by a presentation of available evidence and interpretation of the evidence by committee members along with a final recommendation. The questions address the important issues relative to nutritional support in the critically ill patient including enteral versus parenteral nutrition, early versus late feedings, dose and composition of formulations, and adjunctive interventions. Areas in need of further research are identified.

American Society of Parenteral and Enteral Nutrition Board of Directors and the Clinical Guidelines Task Force. Guidelines for the use of parenteral and enteral nutrition in adult and pediatric patients. J Parenter Enter Nutr 2002;26(suppl):1SA–96.

Based on an extensive review of the literature, an interdisciplinary, technical advisory group of nutrition support specialists updated the 1993 guidelines to assist clinicians in managing patients in both outpatient and inpatient settings. Each topic is presented in the same format: background, evidence, special considerations (if applicable), and graded recommendations for specialized nutrition support. The guidelines have a section on critical illness.

Veterans Affairs Total Parenteral Nutrition Cooperative Study Group. Perioperative total parenteral nutrition in surgical patients. N Engl J Med 1991;325:525–32.

This was the first large randomized controlled trial that attempted to define the appropriate indications for parenteral nutrition based on clinically important end points. The primary objective of this trial was to determine whether perioperative parenteral nutrition decreased serious complications secondary to major abdominal or thoracic surgery. A total of 395 patients were randomized: 192 to the parenteral nutrition group and 203 to the control group. Rates of major complications, mortality, and noninfectious complications were not statistically significantly different between the two groups. Patients receiving parenteral nutrition had more infectious complications than controls (14.1% vs 6.4%, RR 2.20, 95% CI 1.19–4.05). Severely malnourished patients, however, experienced an overall benefit from total parenteral nutrition, since a significantly lower rate of infectious

complications was found in this group (RR 0.12, 95% CI 0.02–0.91). (Class I)

Pulmonary Diseases

Severe Asthma (status asthmaticus)

National Asthma Education and Prevention Program Expert Panel. Expert panel report 3: guidelines for the diagnosis and management of asthma. Section 5. Managing exacerbations of asthma. National Heart, Lung and Blood Institute, National Institutes of Health, 2007: 373–417. Available from http://www.nhlbi.nih. gov/guidelines/asthma/11_sec5.exacerb.pdf. Accessed December 20, 2008.

The National Heart, Lung and Blood Institute asthma guidelines were fully updated in 2007, and this section provides evidence-based recommendations for the diagnosis, classification, evaluation, treatment goals, and management of acute exacerbations of asthma, including emergency and ICU care. Information is presented in easy-to-follow tables and figures as well as parenthetic details, and includes recommended agents, doses, and regimens for the treatment of acute exacerbations. Evidence tables are also available at the Web site for more detailed summaries of the primary literature.

Bogie AL, Towne D, Luckett PM, Abramo TJ, Weibe RA. Comparison of intravenous terbutaline versus normal saline in pediatric patients on continuous high-dose nebulized albuterol for status asthmaticus. Pediatr Emerg Care 2007;23:355–61.

Despite the continued use of intravenous β_2-agonists for children with a severe asthma exacerbation, there have been very few well-designed clinical trials documenting the value or safety. This double-blind, randomized, placebo-controlled trial describes 46 children (aged 2–17 yrs) who were treated with continuous infusion terbutaline or placebo in combination with high-dose continuous inhaled albuterol and intravenous corticosteroids. All patients were admitted to the pediatric ICU for refractory asthma exacerbations. There were no significant differences in rate of improvement of the clinical asthma severity score, although there was a trend toward more rapid improvement with intravenous terbutaline. Duration of continuous inhaled albuterol and ICU length of stay tended to be shorter with intravenous terbutaline but did not reach statistical significance. Six patients in the terbutaline group had transiently elevated

troponin I levels, and one patient discontinued treatment due to supraventricular arrhythmias. This study was limited by a small sample size and some deviations from the intended protocol; however, it failed to show a clinically important advantage for intravenous terbutaline and raises some important safety concerns. (Class I)

Travers AH, Rowe BH, Barker S, Jones A, Camargo CA. The effectiveness of IV β-agonists in treating patients with acute asthma in the emergency department: a meta-analysis. Chest 2002;122:1200–7.

This meta-analysis included 15 controlled trials available through 2000 that evaluated patients receiving intravenous β$_2$-agonists for severe acute asthma in an emergency department. Despite several limitations due to heterogeneity of the outcome variables, the authors concluded that the use of intravenous β$_2$-agonists does not appear to improve the outcome of severe asthma and may contribute to adverse effects. The recommendation is that intravenous β$_2$-agonists be limited to patients in whom inhaled therapy is not feasible or in the context of a clinical trial.

Ream RS, Loftis LL, Albers GM, et al. Efficacy of IV theophylline in children with severe status asthmaticus. Chest 2001;119:1480–8.

Theophylline use in patients with severe acute asthma is controversial and generally not recommended; however, most trials excluded critically ill children. This study enrolled 49 pediatric patients in the ICU who were receiving β$_2$-agonists, corticosteroids, and inhaled anticholinergics and who were randomly assigned to open-label theophylline or a control group. Assessment was performed in a blinded fashion by the investigator. Children receiving theophylline had significantly more rapid improvement in their clinical asthma score. There were no significant differences in time to meet ICU discharge criteria, or ICU and hospital length of stay, and no significant difference in the frequency of adverse events. This study was limited by sample size; however, it did not demonstrate a clear clinical advantage of adding theophylline to standard therapy. (Class I)

Acute Lung Injury–Acute Respiratory Distress Syndrome

Raghavendran K, Pryhuber GS, Chess PR, Davidson BA, Knight PR, Notter RH. Pharmacotherapy of acute lung injury and acute respiratory distress syndrome. Curr Med Chem 2008;15:1911–24.

This recent comprehensive review (364 references) of pharmacotherapy for acute lung injury–acute respiratory distress syndrome (ALI-ARDS) provides an overview of the current state of research on this topic. The authors review the many factors that make drug development for ALI-ARDS difficult, provide a summary of relevant biologic targets during both the exudative and fibroproliferative stages of ALI-ARDS, and describe the current evidence for specific therapeutic agents in the treatment of the two major stages of ALI-ARDS. They also make an argument for the potential future value of combination-therapy strategies for ALI-ARDS.

Deal EN, Hollands JM, Schramm GE, Micek ST. Role of corticosteroids in the management of acute respiratory distress syndrome. Clin Ther 2008;30:787–99.

The authors present a systematic review of controlled clinical trials of corticosteroid therapy for the prevention and treatment of ARDS. The authors review the methodology and limitations of the studies published before January 2008 and conclude that low-to-moderate dose corticosteroids may impart some benefit for treating ARDS up to 14 days. Use of short-course high-dose corticosteroids for prevention of ARDS or treatment of early-stage ARDS is not supported and may be harmful.

Meduri GU, Marik PE, Chrousos GP, et al. Steroid treatment in ARDS: a critical appraisal of the ARDS network trial and the recent literature. Intensive Care Med 2008:34:61–9.

This critical review incorporates a meta-analysis of five controlled trials that evaluated prolonged, low-dose corticosteroids in the treatment of ALI-ARDS. The authors provide a critical analysis of the limitations of the data from the ARDS Network trial and provide alternative explanations for subgroup analyses from that pivotal trial. The authors conclude that prolonged corticosteroid therapy should be administered to patients with persistent ALI-ARDS within 14 days of onset and should be combined with intensive infectious disease surveillance, neuromuscular blocking agents should be avoided, and therapy should be tapered over a prolonged period after extubation to derive maximal benefit from treatment.

Peter JV, John P, Graham PL, Moran JL, George IA, Bersten A. Corticosteroids in the prevention and treatment of acute respiratory distress syndrome (ARDS) in adults: meta-analysis. BMJ

2008;336:1006–9.

This publication reports the results of a formal meta-analysis including nine qualifying prospective, controlled clinical trials of corticosteroid therapy for ARDS: four trials evaluated prevention and five trials evaluated treatment. The authors concluded that some evidence does exist for the efficacy of corticosteroids for the treatment of ARDS, but they could not dismiss a null effect. The limitations of the analysis due to study heterogeneity are discussed. This meta-analysis does not support a definitive role for corticosteroids in the treatment of ARDS.

Adhikari NK, Burns KE, Friederich JO, Granton JT, Cook DJ, Meade MO. Effect of nitric oxide on oxygenation and mortality in acute lung injury: systematic review and meta-analysis. BMJ 2007;334:779–86.

The use of inhaled nitric oxide for treatment of ALI-ARDS remains controversial. This most recent meta-analysis from the group at McMaster University, Hamilton, Canada, included 12 randomized controlled studies of nitric oxide; nine evaluated mortality as their primary outcome measure. In this analysis, nitric oxide did not affect mortality (with a consistent trend toward increased mortality), duration of mechanical ventilation (three trials), ventilator-free days (five trials), or pulmonary artery pressure (four trials). Nitric oxide was associated with a short-term beneficial effect on oxygenation parameters but an increased frequency of renal dysfunction (four trials). The authors concluded that nitric oxide is not beneficial in the treatment of ALI-ARDS and may be harmful. They also acknowledged that its value in severe, life-threatening hypoxemia is difficult to evaluate and represents clinician judgment. Routine use of nitric oxide for patients with ALI-ARDS is not recommended.

Angus DC, Clermont G, Linde-Zwirble WT, et al. Healthcare costs and long-term outcomes after acute respiratory distress syndrome: a phase III trial of inhaled nitric oxide. Crit Care Med 2006;34:2883–90.

This article reports a planned 1-year follow-up of a previously published prospective, randomized trial (Taylor RW et al. AMA 2004;291:1603–9) that evaluated the efficacy of nitric oxide in patients with ARDS and enrolled 385 previously healthy patients without multiple organ failure or severe sepsis. Acute respiratory distress syndrome was associated with high hospital costs and resource use, a mortality rate exceeding 30% that continued beyond 1 month, decreased functional status at 1 year, and poor quality of well-being. There were no significant differences in outcome between the treatment and control groups, demonstrating no short- or long-term benefits in this study sample from treatment with nitric oxide. (Class I)

National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network. Efficacy and safety of corticosteroids for persistent acute respiratory distress syndrome. N Engl J Med 2006;354:1671–84.

This represents the largest prospective, controlled trial of moderate-dose corticosteroids for late-stage ARDS. This study enrolled 180 patients who were 7–28 days past the onset of ARDS and who continued to meet clinical criteria. Overall, there was no significant difference in 60- or 180-day mortality. In patients with ARDS for more than 13 days at the time of enrollment, methylprednisolone therapy was associated with increased mortality. Steroid treatment was associated with an increase in ventilator-free days and an increase in ICU-free days during the first 28 days of study. Steroids were not associated with an increased risk of infections; however, there were more severe adverse effects from neuromyopathy in the steroid group (overall frequency of neuromyopathy was similar between groups). The authors concluded that their data did not support the routine use of moderate-dose corticosteroids for the treatment of late-phase ARDS. (Class I)

Pulmonary Hypertension

Winterhalter M, Simon A, Fischer S, et al. Comparison of inhaled iloprost and nitric oxide in patients with pulmonary hypertension during weaning from cardiopulmonary bypass in cardiac surgery: a prospective randomized trial. J Cardiothorac Vasc Anesth 2008:22:406–13.

Evidence from prospective, controlled studies for the treatment of pulmonary hypertension in critically ill patients is quite limited. Several studies enrolled patients undergoing cardiothoracic surgery for whom therapy was started in the operating room and then often continued into the critical care setting. These studies do not typically involve patients with pulmonary artery hypertension, so extrapolating the results to other classes of patients with pulmonary

hypertension should be done cautiously. This study enrolled 46 patients with known pulmonary hypertension undergoing cardiac surgery who were equally randomized to inhaled iloprost or inhaled nitric oxide. Hemodynamic response was evaluated at 30 and 90 minutes after start of drug therapy. Iloprost was given as a single 20-µg dose nebulized over 4–6 minutes, and nitric oxide was administered at a concentration of 20 parts/million. Both agents resulted in a significant reduction in mean pulmonary artery pressure and pulmonary vascular resistance and an increase in cardiac output at 30 and 90 minutes. The hemodynamic changes were significantly greater with iloprost. Both drugs resulted in an unexpected significant reduction in systemic vascular resistance with a greater response observed with iloprost. There were no adverse effects. Differences in clinical outcomes were not reported. Both drugs were efficacious and safe. (Class I)

Rubenfire M, Bayram M, Hector-Word Z. Pulmonary hypertension in the critical care setting: classification, pathophysiology, diagnosis, and management. Crit Care Clinics 2007;23:801–34.

This article provides a comprehensive review of pulmonary hypertension in critically ill patients. In addition to a review of the pathophysiology, classification, and diagnosis of pulmonary hypertension, this article describes the treatment standards for pulmonary hypertension as well as recommendations for the pharmacotherapy for acute complications of pulmonary hypertension in critically ill patients.

Zamanian RT, Haddad F, Doyle RL, Weinacker AB. Management strategies for patients with pulmonary hypertension in the intensive care unit. Crit Care Med 2007;35:2037–50.

This article provides a systematic and comprehensive review (163 references) of the available literature for the management of pulmonary hypertension in critically ill patients, including treatment of the patient with decompensated pulmonary hypertension.

Fattouch K, Sbraga F, Sampognaro R, et al. Treatment of pulmonary hypertension in patients undergoing cardiac surgery with cardiopulmonary bypass: a randomized, prospective, double-blind study. J Cardiovasc Med 2006;7:119–23.

This study included 58 patients undergoing cardiac surgery who had severe mitral stenosis and pulmonary hypertension. Patients were randomly assigned to one of three treatment groups: inhaled nitric oxide, inhaled prostacyclin, and a control group treated with intravenous vasodilators. Both groups treated with inhaled therapy experienced a significant reduction in mean pulmonary artery pressure and pulmonary vascular resistance and improvement in right and left ventricular performance that was not observed in the control group. Patients receiving inhaled therapies were weaned from mechanical ventilation and discharged from the ICU sooner than the control group, and required lower doses of inotropes and vasopressors. The study drugs were well tolerated. Unfortunately, this study did not describe how study blinding was maintained, and did not provide any details about how the control group was treated. In addition, the inhaled drugs were given in a fixed dose, but the dose administered was not provided. (Class I)

DeWet CJ, Affleck DG, Jacobsohn E, et al. Inhaled prostacyclin is safe, effective, and affordable in patients with pulmonary hypertension, right heart dysfunction, and refractory hypoxemia after cardiothoracic surgery. J Thorac Cardiovasc Surg 2004;127:1058–67.

This case series discusses 126 patients who underwent cardiothoracic surgery and experienced pulmonary hypertension, hypoxemia, or right heart dysfunction that was treated with inhaled prostacyclin. Hemodynamics were collected at 30–60 minutes and 4–6 hours after start of therapy. The drug consistently decreased mean pulmonary artery pressure without affecting mean arterial pressure. The average duration of therapy was 45.6 hours, and no adverse events were noted. The authors concluded that inhaled prostacyclin was a safe and effective treatment option that did not require any specific equipment and was markedly less expensive than inhaled nitric oxide. (Class III)

Sedation, Analgesia, Delirium, Sleep, and Neuromuscular Blockade

Riker RR, Shehabi Y, Bokesch PM, et al. Dexmedetomidine vs midazolam for sedation of critically ill patients: a randomized controlled trial. JAMA 2009;301:489–99.

This double-blind, controlled study, conducted at 68 centers in five countries, compared sedation with dexmedetomidine 0.2–1.4 µg/kg/hour and midazolam 0.02–0.1 mg/kg/hour, titrated to achieve light sedation (Richmond Agitation Sedation Scale [RASS] score between -2 and +1) in 375 patients in the medical-surgical ICU with

expected mechanical ventilation of more than 24 hours. Although previous benzodiazepine use was permitted, the exclusion criteria in the study were extensive and thus the proportion of patients at any ICU who would be eligible for this study was likely small. Although there was no significant difference in the percentage of time spent within the RASS target between the groups, use of dexemedetomidine was associated with a lower rate of delirium during treatment (54% vs 76.7%, p<0.001) and a shorter duration of mechanical ventilation (3.7 vs 5.6 days, p=0.01) but a greater rate of bradycardia (42.2% vs 18.9%, p<0.001). (Class I)

Sessler CN, Varney K. Patient-focused sedation and analgesia in the ICU. Chest 2008;133:552–65.

This recent review thoroughly summarizes key principles and recent evidence surrounding the evaluation of pain and agitation, choices when providing analgesic or sedation therapy, and the use of sedation titration strategies and sedation protocols. This article will be of particular use to clinicians who wish to obtain an overview of sedation and analgesia therapy in the ICU before delving into the ever-increasing primary literature on this topic.

Girard TD, Kress JP, Fuchs BD, et al. Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (awake and breathing controlled trial): a randomised controlled trial. Lancet 2008;371:126–34.

This randomized controlled trial demonstrates that use of paired spontaneous awakening and breathing results in better outcomes, including a lower mortality rate and a shorter length of ICU stay, than spontaneous breathing alone. Unlike other sedation interruption studies, this study included patients from multiple institutions and who were admitted to a surgical service, incorporated a standardized weaning strategy, and was large enough to measure a difference in mortality. (Class I)

Ahlers SJ, van Gulik L, van der Veen Am, et al. Comparison of different pain scoring systems in critically ill patients in a general ICU [online exclusive article]. Crit Care 2008;12:R15.

This well-done, ICU observational study sought to determine the interrater reliability of the Numerical Rating Scale (NRS) and the Behavioral Pain Scale (BPS) and compare the NRS, BPS, and the visual analog scale between observers and patients. Whereas each scale demonstrated high reliability, observer-based patient evaluation often underestimated pain, particularly when the NRS was deemed to be high (≥ 4) by the patient. The authors concluded that in mechanically ventilated patients, the BPS should be used to measure pain only in conjunction with the NRS. (Class III)

Fong JJ, Sylvia L, Ruthazer R, Schumaker G, Kcomt M, Devlin JW. Predictors of mortality in patients with suspected propofol infusion syndrome. Crit Care Med 2008;36:2281–7.

This evaluation of the FDA MedWatch database is the largest study completed to date that characterizes predictors of mortality in patients suspected to have propofol infusion syndrome. Among 1139 suspected cases of propofol infusion syndrome that were identified, 342 patients died. Multivariate modeling demonstrated that presence of cardiac symptoms, rhabdomyolysis, metabolic acidosis, renal failure, and age each affected survival. The authors developed a mortality scoring system for patients at risk for propofol infusion syndrome. (Class III)

Friese RS. Sleep and recovery from critical illness and injury: a review of theory, current practice, and future directions. Crit Care Med 2008;36: 697–705.

Clinicians are increasingly realizing the importance that normal sleep plays in recovery from critical care illness. This review, by a recognized expert in this field, describes the deleterious effects of sleep deprivation, characterizes the various abnormalities that can occur during critical care illness and their causes, and proposes an integrated strategy to improve sleep in the critical care environment.

Marshall J, Finn CA, Theodore AC. Impact of a clinical pharmacist–enforced intensive care unit sedation protocol on duration of mechanical ventilation and hospital stay. Crit Care Med 2008;36:427–33.

This before-after study is important given that it documents a substantial benefit in having clinical pharmacists support an institutional ICU sedation protocol. During the postintervention period, pharmacists made 210 sedation-related interventions (91% accepted) supporting the sedation protocol that resulted in a decrease in both the duration of mechanical ventilation (from 14.0 to 7.4 days, p<0.001) and ICU stay (from 15.8 to 9.9 days, p=0.001). (Class III)

Girard TD, Pandharipande PP, Ely EW. Delirium

in the intensive care unit [online exclusive article]. Crit Care 2008;12(suppl 3):S3.

This article, authored by leaders in the field of ICU delirium, thoroughly reviews the pathogenesis and epidemiology of delirium in the ICU and highlights strategies that can be used to both prevent and treat delirium in the critical care setting. This well-organized article will be of particular interest to ICU clinicians who may not yet be familiar with the ever-increasing body of literature on this topic.

Pandharipande PP, Pun BT, Herr DL, et al. Effect of sedation with dexmedetomidine vs lorazepam on acute brain dysfunction in mechanically ventilated patients: the MENDS randomized controlled trial. JAMA 2007;298:2644–53.

This double-blind, randomized, controlled study, conducted at two academic centers and enrolling both medical and surgical populations, found that compared with continuous lorazepam, patients treated with dexmedetomidine spent more days alive without delirium or coma, had a lower prevalence of coma, and spent more time closer to their desired sedation goal. It remains unclear whether the benefit found with dexmedetomidine may be partially attributable to the fact that lorazepam was administered as a continuous infusion (rather than intermittently) and that a strategy of daily sedation interruption was not used. This study is also the first to demonstrate that a high dose of dexmedetomidine up to 1.5 μg/kg/hour for 5 days does not lead to adverse cardiac effects. (Class I)

Patanwala AE, Duby J, Waters D, Erstad BL. Opioid conversions in acute care. Ann Pharmacother 2007;41:255–66.

This article demonstrates that clinicians should use caution when applying standard opioid conversion tables in the ICU, given the fact that the conversion ratios in these tables do not correspond with data from the clinical trials that have evaluated opioid therapy. The authors recommend instead that clinicians should base opioid conversion recommendations on patient response to therapy, as well as both the agent and route of administration that is being used.

Devlin JW, Fong JJ, Fraser GL, Riker RR. Delirium assessment in the critically ill. Intensive Care Med 2007;33:929–40.

This review highlights the challenges of screening for delirium in the ICU and compares available instruments for assessing delirium in

critically ill adults by reviewing the background behind their development and the psychometric evaluations that have been conducted regarding their use. This article also provides clinicians with practical strategies that can be used to boost delirium screening efforts in clinical practice by using these validated instruments.

Payen JF, Chanques G, Mantz J, et al. Current practices in sedation and analgesia for mechanically ventilated critically ill patients: a prospective multicenter patient-based study. Anesthesiology 2007;106:687–95.

In this large observational study of sedation practices in 44 French ICUs, the authors concluded that less than half of patients had their level of sedation evaluated by a standardized assessment tool and that more than half were deeply sedated. This study highlights the importance for clinicians to be involved in educational efforts surrounding the use of sedation monitoring, down-titration strategies, and protocolization in order to decrease the occurrence of oversedation in ICU(s). (Class III)

Barnes BJ, Gerst C, Smith JR, Terrell AR, Mullins ME. Osmol gap as a surrogate marker for serum propylene glycol concentrations in patients receiving lorazepam for sedation. Pharmacotherapy 2006;26:23–33.

This observational study of patients in the ICU who were receiving lorazepam demonstrates that the osmol gap, and the amount of propylene glycol administered (from lorazepam injection) before serum sampling, predict serum propylene glycol concentrations (r^2=0.692, p<0.05). Although the osmol gap alone also predicts serum propylene glycol concentrations (r^2=0.532, p<0.05), serum lactate concentrations did not correlate with serum propylene glycol concentrations. This study, along with others that have attempted to characterize propylene glycol toxicity in patients in the ICU who are receiving lorazepam, suggests that an osmol gap should be routinely checked in all patients who receive lorazepam at rates of 6 mg/hour or greater for longer than 24 hours. (Class III)

Playfor S, Jenkins I, Boyles C, et al. Consensus guidelines on sedation and analgesia in critically ill children. Intensive Care Med 2006;32:1125–36.

These are the first clinical practice guidelines for analgesia, sedation, and neuromuscular blockade in children and are a product of a multidisciplinary working group from the United Kingdom Paediatric Intensive Care Society.

These easy-to-read guidelines, developed through use of a modified Delphi technique, and of interest to any clinician working in a pediatric critical care environment, highlight the substantial need for further research surrounding the use of analgesics and sedatives in critically ill children.

Carson SS, Kress JP, Rodgers JE, et al. A randomized trial of intermittent lorazepam versus propofol with daily interruption in mechanically ventilated patients. Crit Care Med 2006;34:1326–32.

This randomized, open-label study of mechanically ventilated medical patients that was conducted at two academic centers demonstrated that lorazepam, even when administered on a scheduled intermittent basis, leads to a longer duration of mechanical ventilation than does propofol (8.4 vs 5.8 days, p=0.04). A well-performed pharmacoeconomic analysis of this study demonstrated that propofol, despite having an acquisition cost far greater than that of intermittent lorazepam, is, on average, $6378 less costly per patient (Cox CE et al. Crit Care Med 2008;36:706–14). (Class II)

Pandharipande P, Shintani A, Peterson J, et al. Lorazepam is an independent risk factor for transitioning to delirium in intensive care unit patients. Anesthesiology 2006;104:21–6.

In this robust cohort analysis, investigators found that sedation with lorazepam is an independent risk factor for daily transition to delirium (OR 1.2, 95% 1.1–1.4). The use of fentanyl, morphine, or propofol is associated with a higher but not statistically significant increased risk for delirium. This study is the first to suggest that avoidance of benzodiazepine sedation therapy in the ICU may decrease the risk for delirium and the numerous serious sequelae associated with its development. (Class III)

Pun BT, Gordon SM, Peterson JF, et al. Large-scale implementation of sedation and delirium monitoring in the intensive care unit: a report from two medical centers. Crit Care Med 2005;33:1199–205.

Despite the ever-increasing evidence demonstrating that delirium is associated with negative sequelae, clinicians do not routinely screen for its presence—even at centers where delirium screening efforts are formally documented in protocols (Devlin JW et al. Am J Crit Care 2008;17:555–65). This report describes a process improvement effort surrounding delirium screening at two centers. The investigators found that after comprehensive training, the compliance of the bedside nurse with a delirium screening protocol was excellent and that agreement between the bedside nurse and a reference standard rater was high. (Class III)

Breen D, Karabinis A, Malbrains M, et al. Decreased duration of mechanical ventilation when comparing analgesia-based sedation using remifentanil with standard hypnotic-based sedation for up to 10 days in intensive care unit patients: a randomized trial. Crit Care 2005;9:R200–10.

This is the first large study to demonstrate the benefit of using a remifentanil-only sedation regimen in the ICU (a practice that is widely used in Europe). This randomized, open-label study, in a population of mixed medical-surgical patients, found that duration of mechanical ventilation was shorter by more than 2 days (53.5 hrs, p=0.003) with continuous remifentanil (along with as-needed boluses of midazolam) compared with a regimen of continuous midazolam and fentanyl. (Class II)

Skrobik Y, Bergeron N, Dumont M, Gottfried SB. Olanzapine vs haloperidol: treating delirium in a critical care setting. Intensive Care Med 2004;30:444–9.

This study, using a randomized design, evaluated the role of an atypical antipsychotic agent for the treatment of delirium in critically ill patients. Over the 5-day study period, olanzapine 5 mg/day was found to be equivalent to oral haloperidol 5 mg/day in terms of change in the Delirium Index and the administered dose of benzodiazepines. No adverse effects were noted in the olanzapine group, whereas haloperidol was associated with greater extrapyramidal effects. Future studies that evaluate atypical antipsychotics for delirium should be placebo controlled and blinded, use a standardized dosage-titration schedule, and evaluate post-ICU cognitive function. (Class II)

Murray MJ, Cowen J, DeBlock H, et al. Clinical practice guidelines for sustained neuromuscular blockade in the adult critically ill patient. Crit Care Med 2002;30:142–56.

Although use of continuous neuromuscular blockade continues to decrease, this class of agents is still occasionally required to optimize care for patients not able to be managed with deep sedation alone. These consensus guidelines

remain the most recent practice guidelines for the sustained use of neuromuscular blockers in adults and are very unlikely to be updated in the future. The authors describe the mechanism of action and the pharmacology of the individual agents. They also describe the appropriate indications and recommended agents, along with suggestions for how to monitor for effectiveness and adverse effects. The article also reviews the syndromes and risk factors leading to delayed muscle recovery after treatment with these agents. A template for evaluation of the pharmacoeconomic impact of individual agents is provided.

Jacobi J, Fraser GL, Coursin DB, et al. Clinical practice guidelines for the sustained use of sedatives and analgesics in the critically ill adult. Crit Care Med 2002;30:119–41.

These guidelines, although more than 6 years old, summarize much of the foundational literature regarding the provision of analgesia and sedation to critically ill patients, with an emphasis on patient assessment, therapeutic options, and protocolization. Examples of assessment tools are provided along with an algorithmic approach to developing a sedation plan for different critically ill patient populations. Associated topics include management of delirium and issues related to nonpharmacologic therapy and sleep. These guidelines are undergoing revision with publication expected in 2010.

Kress JP, Pohlman AS, O'Connor MF, Hall JB. Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. N Engl J Med 2000;342:1471–7.

This landmark randomized study was the first to demonstrate that daily interruption of sedative infusion reduces the duration of mechanical ventilation (from 7.3 to 4.9 days, p=0.004) without compromising patient safety or comfort. Subsequent reports from this study demonstrate that the benefit of daily sedation interruption is observed regardless of whether midazolam or propofol is used (Kress JP et al. J Clin Outcomes Manag 2001;8:33–9) and is associated with neither deleterious psychological or cardiac effects (Kress JP et al. Am J Resp Crit Care Med 2003;168:1457–61; Kress JP et al. Crit Care Med 2007;35:365–71). (Class I)

Toxicology

Alapat PM, Zimmerman JL. Toxicology in the critical care unit. Chest 2008;133:1006–13.

This review provides relevant updates on the treatment of common poisonings and overdoses managed in the critical care setting. Beyond the usual agents, this review includes references to iatrogenic toxicity that may be related to ICU care including propofol infusion syndrome, propylene glycol accumulation, and drug-induced methemogobinemia.

Zimmerman JL. Poisonings and overdoses in the intensive care unit: general and specific management issues. Crit Care Med 2003;31:2794–801.

This article provides a general overview of the diagnosis and management of poisonings and overdoses that commonly lead to the need for intensive care unit admission. The author presents information on general supportive care, specific antidotes where applicable, and a discussion of limitations of the recommendations.

Mokhlesi B, Leiken JL, Murray P, Corbridge TC. Adult toxicology in critical care. I. General approach to the intoxicated patient. Chest 2003;123:577–92.

Mokhlesi B, Leikin JB, Murray P, Corbridge TC. Adult toxicology in critical care. II. Specific poisonings. Chest 2003;123:897–922.

This two-part series provides a very comprehensive and thorough discussion of adult toxicology for critical care patients, including the epidemiology, diagnosis, and general and specific management of poisonings and overdoses.

Medication Errors and Adverse Drug Events in the Intensive Care Unit

Thomas AN, Panchagnula U. Medication-related patient safety incidents in critical care: a review of reports to the UK National Patient Safety Agency. Anaesthesia 2008;63:726–33.

Kane-Gill S, Rea RS, Verrico MM, Weber RJ. Adverse-drug-event rates for high-cost and high-use drugs in the intensive care unit. Am J Health Syst Pharm 2006;63:1876–81.

Pronovost PJ, Thompson DA, Holzmueller CG, et al. Toward learning from patient safety reporting systems. J Crit Care 2006;21:305–15.

Rothschild JM, Landrigan CP, Cronin JW, et al. The critical care safety study: the incidence and nature of adverse events and serious medical errors in intensive care. Crit Care Med 2005;33:1694–700.

Osmon S, Harris CB, Dunagan C, Prentice D, Fraster VJ, Kollef MH. Reporting of medication

errors: an intensive care unit experience. Crit Care Med 2004;32:727–33.

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