Critical Care CME Program

Module 7

Module 7 of CSA's Critical Care CME Program appears in this issue of the *Bulletin*; the final module will appear in the Winter 2010 issue. To receive CME credit, submit your registration page, answers to the questions, and the evaluation to the CSA office. Your CME certificate will be mailed to you. Alternatively, the full text of each module will be accessible through the CSA Web Site, **www.csahq.org**, in the Online CME Program section. Instructions to complete Module 7 online are given in the Information pages. After completing the assessment, print your CME certificate. Members will need their usernames and passwords to do the modules online.

The following Important Information about Critical Care Module 7 must be read and acknowledged before proceeding to the rest of the module. Check the acknowledgement box on the registration page.

Faculty/Disclosures

All faculty participating in continuing medical education activities sponsored by the CSA are required to disclose any real or apparent conflict(s) of interest related to the content of their presentation(s) or any of the industry sponsors of the meeting. In addition, speakers must disclose when a product is not labeled for the use under discussion or when a product is still investigational.

Michelle Braunfeld, M.D. (Co-author of Module 7)
Clinical Professor of Anesthesiology
Department of Anesthesiology
David Geffen School of Medicine at UCLA

Dr. Braunfeld discloses that she has no relevant financial relationships with any commercial entities.

Anahat K. Dhillon, M.D. (Co-author of Module 7)
Assistant Clinical Professor of Anesthesiology
Anesthesiology Critical Care
University of California, Los Angeles

Dr. Dhillon discloses that she has no relevant financial relationships with any commercial entities.

Nitin Shah, M.D. (Editor and Chair of the Critical Care CME Program)
Clinical Professor of Anesthesiology, Director, Neuroanesthesia
University of California, Irvine, Medical Center, Orange, California
Chief, Combined ICU, Long Beach Veterans Healthcare System
Long Beach, California

Dr. Shah has received honoraria from Masimo, Abbott, and Baxter for his role as speaker. He owns stock in Masimo Corporation.

Registration/Instructions

Method of Participation: The physician will read and study the materials and complete a quiz and an evaluation of the module. Some modules may have slides available online. To register for and complete this module: Complete the registration page, complete the test questions and the evaluation that can be found after the article, and submit your quiz to the CSA office by mail or fax (650-345-3269). Your CME certificate will be mailed to you.

Estimated Time to Complete the Module: One hour

Please check the box on the registration page acknowledging that you have read everything in these introductory pages.

Availability

Module 7: Acute Renal Failure

Release Date: September 30, 2009
Expiration Date: September 30, 2012

CME Sponsor/Accreditation

The California Society of Anesthesiologists is accredited by the Accreditation Council for Continuing Medical Education to sponsor continuing medical education for physicians.

The California Society of Anesthesiologists Educational Programs Division designates this critical care program for a maximum of 8 *AMA PRA Category 1 Credit(s)*™. The program consists of eight modules with 1 credit per module. Physicians should claim credits commensurate with the extent of their participation in the activity.

Fees, Target Audience, Evaluation

The modules are free to CSA members. Nonmembers pay $30 for each module. Each module is worth *one AMA PRA Category 1 Credit*™. This program is intended

for all licensed physicians, including residents. An evaluation of each module of this series is offered after the test questions.

Privacy Policy

CSA has a privacy policy that is a general policy for information obtained regarding all online interactive pages, including online CME activities. To review this policy, please go to www.csahq.org/privacy.vp.html.

Objectives

Upon completion of this activity, participants will be able to:

- Describe the supportive measures to treat renal failure
- Discuss the use of intermittent hemodialysis vs. CVVH for the management of acute renal failure
- Identify the patient with acute kidney injury and stratify him/her according to the RIFLE criteria
- Identify nonconventional biomarkers of acute kidney injury
- Discuss proposed preventive strategies and therapies and determine which ones may be beneficial

Acute Renal Failure

By Michelle Braunfeld, M.D., and Anahat K. Dhillon, M.D.

Michelle Braunfeld, M.D., is currently Clinical Professor of Anesthesiology at the UCLA-David Geffen School of Medicine, where she also completed her training in anesthesiology. She has been a member of the dedicated Liver Transplantation Anesthesiology service at UCLA since 1992.

Anahat Dhillon, M.D., is currently Assistant Professor in the Department of Anesthesia at UCLA. After completing medical school at the University of Rochester, she trained in anesthesia at UCLA and completed her critical care fellowship at Massachusetts General Hospital. Dr. Dhillon is an intensivist in the Liver Transplant ICU, as well as being a part of the general anesthesia team at UCLA.

Introduction

Acute renal failure (ARF) has long been recognized as a potentially disastrous complication that is associated with increased costs of hospitalization[1] and in-hospital mortality.[1-3] Until recently, however, studies on ARF have been hampered by the lack of a clear definition. An

excellent illustration of this was made in a study by Chertow, et al., on a single center population of 9,210 patients in whom at least two serum creatinine levels were obtained. Using a range of common definitions of ARF from the most sensitive (increase in SCreat > 0.3 mg/dl) to the most specific (increase in SCreat > 2.0 mg/dl), this study found that the odds ratio for mortality ranged from 4.1% to 16.4% and the associated costs from $8,902 to $33,161.[4]

Defining/Diagnosing ARF

Clearly, the "I know it when I see it" approach to diagnosing ARF was not compatible with robust conclusions. As with other important but difficult to define entities such as ARDS and sepsis, a consensus definition was needed.

The Acute Dialysis Quality Initiative (ADQI) proposed such a definition, as a diagnosis termed "acute Kidney Injury" or AKI, rather than ARF. AKI was described by three stages of increasingly severe injury (Risk, Injury, Failure) and two outcomes (Loss and End-stage renal disease) on the basis of increases in creatinine and decreases in urine output (Figure 1). This definition, known by its acronym, RIFLE, has since been validated as a predictor of hospital mortality and ICU length of stay (LOS)[5-8] and has been employed increasingly in renal studies to describe outcomes.

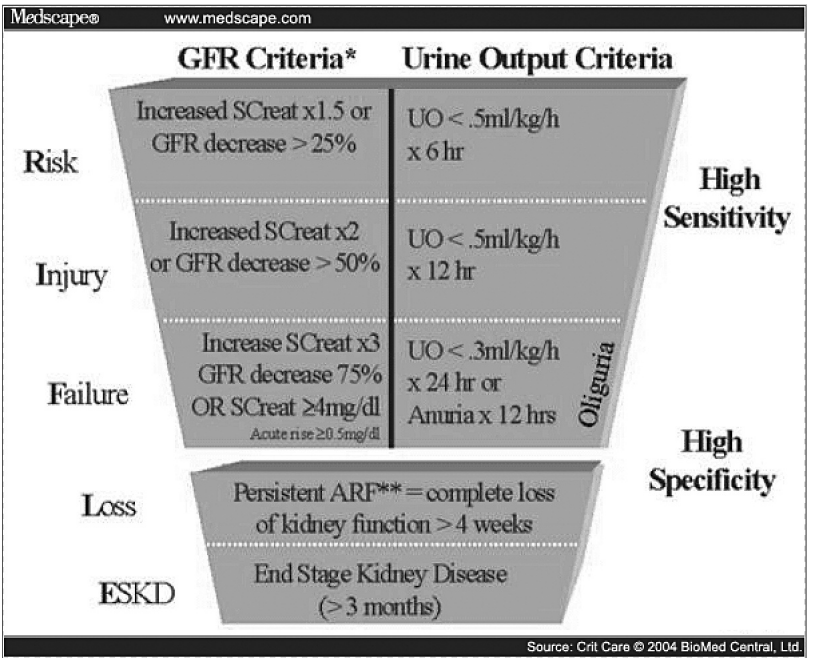

Figure 1.

Proposed classification scheme for acute renal failure (ARF). The classification system includes separate criteria for creatinine and urine output (UO). A patient can fulfill the criteria through changes in serum creatinine (SCreat) or changes in UO, or both. The criteria that lead to the worst possible classification should be used. Note that the F component of RIFLE (Risk of renal dysfunction, Injury to the kidney, Failure of kidney function, Loss of kidney function and End-stage kidney disease) is present even if the increase in SCreat is under threefold, as long as the new SCreat is greater than 4.0 mg/dl (350 μmol/l) in the setting of an acute increase of at least 0.5 mg/dl (44 μmol/l). The designation RIFLE-F_C should be used in this case to denote "acute-on-chronic" disease. Similarly, when the RIFLE-F classification is achieved by UO criteria, a designation of RIFLE-F_O should be used to denote oliguria. The shape of the figure denotes the fact that more patients (high sensitivity) will be included in the mild category, including some without actually having renal failure (less specificity). In contrast, at the bottom of the figure the criteria are strict and therefore specific, but some patients will be missed. *GFR = Glomerular Filtration Rate; ARF = Acute Renal Failure. Bellomo et al. *Critical Care* 2004 8:R204 doi:10.1186/cc2872. (*Critical Care* lists articles by R number rather than by pages.)

A further complicating factor of the attempts to define and diagnose AKI is the emerging recognition that not all AKI is alike. Broadly speaking, cell death can be either necrotic or apoptotic. In contrast to necrotic cell death, which is a passive process resulting from overwhelming cellular energy loss, apoptetic cell death is an energy requiring genetically directed process which may be triggered by factors other than ischemia, such as nitric oxide, tumor necrosis factor-alpha (TFN-α), and glucocorticoids. Thus, results from patient studies or animal models that have ischemic or nephrotoxic injury may not be applicable to apoptotic injury. This may explain the different outcomes of studies in different populations.

Although currently separate from the work on defining AKI, the search for new biomarkers to diagnose AKI dovetails with it, and it may eventually replace the traditional biomarkers used currently. Many *factors* unrelated to renal function affect urine output and SCreat, and change in SCreat is a late indicator of injury. Identifying a serum marker of glomerular function or of tubular damage that is unaffected by non-renal factors, and is an early indicator whose levels correlate with severity of injury would revolutionize the study—and likely the management—of AKI. Several candidates have been studied, among them cystatin-C, Neutrophil gelatinase-associated lipocalin, Interleukin-18, and Kidney injury molecule -1.

Cystatin-C is an enzyme present in all nucleated cells of the body. It is almost entirely renally eliminated, being > 99% filtered by the glomeruli and essentially completely metabolized by the proximal tubular cells. Because it is neither secreted nor resorbed, serum levels correlate well with glomerular function. Because it should be entirely metabolized by the tubular cells, its presence in urine suggests proximal tubular injury. Studies of serum cystatin-C suggest that elevations sufficient to diagnose AKI (defined as > 50% over baseline) occur 24-48 hours before similar changes in *SCreat*.[9,10]

Neutrophil gelatinase-associated lipocalin is a protein that normally exists at low serum levels but which is rapidly induced by epithelial injury. In studies on postcardiopulmonary bypass patients who developed AKI, plasma NGAL more than doubled[11] and urine NGAL increased 15-fold[12] within two hours after CPB. In contrast, the diagnostic rise in SCreat in these patients did not appear until 2 to 3 days after CPB. It is unclear whether NGAL would still have predictive value in a broader population of patients.

Interleukin-18 is an inflammatory cytokine that is induced and activated in renal tubular cells, after which it appears in the urine. Studies in postrenal transplant, cardiac surgery, and critically ill patients show poor sensitivity for early diagnosis of AKI, but good specificity.[13] Thus, normal levels have no predictive value, but elevations in urine levels are rarely seen in patients who do not develop AKI.

Kidney injury molecule-1 is a protein expressed by proximal tubular cells after ischemic injury, which can be measured in the urine. A single study in cardiac surgery patients showed moderate sensitivity and excellent specificity (0.74/0.90) for the early diagnosis of AKI.[14] Additionally, this study also showed that higher urinary levels of KIM-1 could differentiate patients with AKI from those with chronic kidney disease.

Maintaining Renal Perfusion

Given the compelling evidence that AKI is associated with increased mortality and hospital costs, there is no doubt that it should be prevented. What remains controversial is how to do it. Earlier renal protective strategies were aimed at enhancing renal blood flow or urine production. A demonstrated increase in these endpoints was interpreted as benefit of therapy. These endpoints, however, are only proxies for GFR. Transient changes in these parameters have not been shown to predict clinically meaningful outcomes such as need for renal replacement therapy (RRT), increased length of stay, or mortality. Although it seems obvious that increasing renal blood flow should prevent renal ischemia,

renal physiology belies this assumption because renal oxygenation is not homogenous.

Contemporary studies still attempt to improve the oxygen supply-demand balance by either increasing supply (renal perfusion) or decreasing demand (tubular agents), but also include agents to limit ischemia-reperfusion injury. More important, these studies use clinically relevant endpoints such as changes in SCreat over at least 24 to 48 hours, need for RRT, and mortality.

Maintaining renal perfusion can be achieved through pharmacologic and non-pharmacologic means. The chief *nonpharmacologic* intervention is hydration. Although there are no randomized controlled trials (RCT) comparing maintenance of adequate circulating volume to nonintervention, it is generally accepted that hypovolemia is a risk factor for AKI.

Pharmacologic agents used to maintain renal perfusion are primarily vasodilators that increase renal blood flow. These include dopamine agonists (dopamine and fenoldopam), natriuretic peptides, and calcium channel blockers. As a group, the vasodilators have not generally shown clinical benefit, perhaps because not all renal failure is the result of inadequate global renal perfusion, as discussed earlier. In fact, recent evidence suggests that, similarly to septic AKI, apoptosis may have a significant role in contrast nephropathy.[15] Thus, two large, frequently studied patient groups are thought to have AKI on the basis of mechanisms other than ischemic necrosis.

Dopamine at "dopaminergic" doses (usually 0.5-2.0 mcg/kg/min) has been studied extensively both in preventing and treating established AKI. Two review articles[16,17] and three meta-analyses[18-20] have evaluated these studies and each has concluded that "renal-dose" dopamine has *no* value in the prevention of AKI.

The value of *fenoldopam*, a selective DA-1 agonist, is uncertain. A large RCT in patients receiving contrast *failed* to show benefit,[21] as did a meta-analysis of RCT for preventing contrast nephropathy.[22] However, a meta-analysis of studies in various settings other than contrast administration suggested that fenoldopam reduced the need for RRT and mortality.[23] Thus, although there is no evidence to recommend fenoldopam to prevent contrast nephropathy, it may yet prove beneficial in other settings.

Calcium channel-blockers have been studied primarily in the renal transplant population. One large RCT using isradipine vs. placebo concluded that there was no difference in delayed function or rejection between the two groups, but a significant difference in mean SCreat at three and at 12 months.[24] A very

unsatisfying meta-analysis of calcium channel-blockers in renal transplant recipients came to similar conclusions, although the included studies used different agents, doses, and routes of administration.[25] A persistent question about the value of calcium channel blockers in the transplant population is how much effect is attributable to intrinsic renal protection and how much to the antagonism of the renal vasoconstrictive effects of cyclosporine.

Natriuretic peptides (including atrial natriuretic peptide and urodilantin) promote GFR by dilating afferent, and constricting efferent glomerular arterioles. They have primarily been studied in patients with established AKI. A large, multicenter RCT showed no benefit to atrial natriuretic peptide in terms of dialysis-free survival or days of RRT in oliguric critically ill patients.[26] A single study examining ANP for preventing contrast nephropathy also concluded that there was no benefit on the basis of serial SCreat over 48 hours post-contrast administration.[27]

Agents such as *furosemide* and *mannitol*, which limit tubular resorption, theoretically reduce oxygen demand and improve supply-demand balance. Unfortunately, in two separate meta-analyses evaluating diuretic therapy to prevent AKI, need for RRT, and mortality, they failed to show benefit.[28,29] More unfortunately, they have also shown harm in the form of increases in SCreat compared to hydration alone[30] and, in two observational studies, increased mortality and nonrecovery of renal function.[31,32]

Ischemic injury may not be limited simply by restoring renal perfusion. Continued renal hypoperfusion because of microvascular dysfunction, together with cellular dysoxia due to mitochondrial dysfunction, propagate damage. This has led to investigation into the contributions of ischemia-reperfusion events and inflammatory mediators to AKI. It has also suggested new avenues for prevention.

An agent that may be beneficial for its free-radical scavenging properties to limit ischemia-reperfusion injury is *N-acetylcysteine* (NAC), a glutathione precursor with easily oxidized sulfhydryl groups. It has been studied in cardiac and vascular surgery, and extensively for preventing contrast nephropathy. No benefit has been ascribed to NAC in cardiac or vascular surgery.[33,34] Five meta-analyses of NAC administration to prevent contrast nephropathy[22,35-38] have concluded that it appears beneficial, although perhaps of borderline value.[38] Nonetheless, consensus of these meta-analyses is that NAC is an inexpensive and benign drug whose use is supported in at-risk patients (chronic renal disease, diabetes, sepsis, liver disease, etc.) to prevent contrast nephropathy.

Although mannitol also has theoretic radical-scavenging properties, except for a single study in renal transplant recipients, it has not been shown to have clinically significant benefit.[39]

AKI in Sepsis

Investigation into the mechanisms of AKI in sepsis has yielded some very intriguing results. Whereas septic AKI was once thought to be due to global renal hypoperfusion, it now seems that other mechanisms contribute. In fact, a recent review of studies on the histopathology of septic AKI concluded that, although a characteristic histology is lacking, ATN is an uncommon finding.[40] Endotoxemia causes release of inflammatory mediators (TNFα, cytokines, adhesion molecules, etc.), generation of oxygen free radicals, and expression of inducible nitric oxide synthase (iNOS), which promotes renal microvascular dysfunction. Animal models of sepsis suggest that antagonists of these pathways can be protective,[41,42] but there is not yet any patient data. In vitro studies of renal tubular cells show that apoptotic changes are associated with endotoxin and TNF administration, evidence that apoptosis may be a significant part of the pathophysiology of septic AKI.[42]

Treatment of AKI

As with the prevention of renal failure, the studies investigating treatment modalities for acute kidney injury have resulted in conflicting data and few definitive answers. The goals in caring for a patient with acute kidney injury are to avoid further renal injury, manage the complications of renal failure, and if possible, increase the chance of dialysis-free recovery. Preventing further injury involves avoiding nephrotoxic medications and other conditions associated with renal injury. The common complications of renal failure such as volume overload, hyperkalemia, and acidosis can be managed either medically or with the institution of renal replacement therapy.

One of the commonly used medications for treating AKI has been loop diuretics, in particular, furosemide. There have not been many randomized controlled trials; however, several meta-analyses have shown that, while loop diuretics will decrease the length of time patients are oliguric, there is no survival benefit or decrease in chronic dialysis rates.[43,44] Other pharmacological therapies, such as fenoldapam, atrial naturetic peptide, and anti-inflammatory agents, have not shown benefit in terms of renal recovery or mortality.

Often, when medical management of the complications of AKI fail, patients are considered for RRT that has been traditionally considered in patients with refractory volume overload, hyperkalemia, signs of uremia (usually a BUN of

80-100), or severe metabolic acidosis. The timing, the dosing, and the type of renal replacement therapy have been an area of extensive research.

There is scarce data to guide the optimal timing of dialysis in AKI. Of two randomized trials, one found no difference in mortality or dialysis dependence in 106 patients,[45] and another found a reduction in mortality with early dialysis but only included 28 patients.[46] The largest prospective, multicenter cohort trial to date demonstrated an increased risk of death at 60 days in those patients who were started on dialysis after the BUN was greater than 76.[47] Pending a large randomized controlled trial that is powered for mortality difference, there might be some benefit to initiating RRT early in AKI, although it may vary based on the etiology of the AKI.

Once the decision has been made to institute RRT, the type of RRT has to be selected by the clinician. Peritoneal dialysis is rarely used for AKI in the United States, given the general availability of other modalities. The classic choice has been between traditional intermittent hemodialysis and continuous RRT. CRRT tends to take the form of continuous venovenous hemofiltration or hemodialysis. Continuous venoarterial dialysis carries increased risks associated with arterial access without any benefits and is thus not commonly used. Several meta-analyses and one large prospective multi-center study have all found no significant difference in mortality or overall rate of dialysis dependence.[48-50] There is some suggestion that there is a trend to decreased rates of chronic dialysis dependence among survivors, although this difference is lost when combined with mortality data. Some of the advantages cited for CRRT include greater hemodynamic stability in some patients, increased net salt and water removal, enhanced clearance of inflammatory mediators that may play a role in sepsis, and possibly better cerebral perfusion in patients with acute brain injury. Disadvantages of CRRT are the cost of the equipment as well as the cost of dedicated, specially trained personnel. While on CRRT, patients need to be anti-coagulated, which can result in an increase in bleeding episodes or, if the filter clots, loss of blood to the circuit. Additionally, CRRT decreases the mobility of the patient, which can have a significant impact on the recovery of critically ill patients. The choice of modality then has to be based on the availability at the practitioner's institution as well as the severity of the patient's illness. With advancement in technology, hybrid modalities such as slow intermittent hemodialysis or extended daily dialysis need further evaluation as possible optimal modalities.

The final decision facing the clinician is the dosing of the dialysis. With intermittent hemodialysis, the dosing is dependent on the amount dialyzed per session as well as the frequency of the sessions. One study of daily hemodialysis vs. every other day showed a significant decrease in mortality

with daily dialysis.[51] However, the group assigned to conventional dialysis had a lower than usual dose, making the data difficult to interpret. The recent study from the VA/NIH acute renal failure trial in a randomized parallel group trial of hemodynamically stable patients, found no difference in mortality or kidney function between an intensive daily dialysis group and conventional dialysis.[52] With CRRT the dialysis dose is measured in ml per kilogram per hour. Although controversial, earlier meta-analysis and small trials had suggested that a higher dosing at the rate of 35 ml/kg/hr resulted in improved survival.[48,53] The VA study also looked at hemodynamically unstable patients that were treated with intensive vs. conventional CRRT and again found no difference in mortality or recovery of renal function. These latest data suggest that with either IHD or CRRT, high dose dialysis offers little benefit over conventional dosing in the generalized population of AKI.

Conclusion

AKI is a complex, multifactorial pathology that still has a high mortality despite contemporary medical care. Although there is a wealth of literature on AKI, until recently the lack of a consensus definition has made it difficult to compare and draw conclusions. Moreover, as our understanding of the mechanisms of injury evolves, new approaches to prevention and management are suggested. For the moment, however, care is still largely supportive, with the hope that future studies will yield effective therapies.

References

1. Chertow G, Burdick E, et al. Acute kidney injury, mortality, length of stay, and costs in hospitalized patients. *J Am Soc Nephrol* 2005; 16:3365-70.
2. Dasta J, Kane-Gill S, et al. Cost and outcomes of acute kidney injury (AKI) following cardiac surgery. *Nephron Dial Trans* 2008; 23:1970-74.
3. Uchino S, Kellum J, et al. Acute renal failure in critically ill patients: a multinational, multicenter study. *JAMA* 2005; 294:813-818.
4. Chertow G, Levy E, et al. Independent association between acute renal failure and mortality following cardiac surgery. *JAMA* 1998; 104:343-348.
5. Bellomo R, Kellum J, et al. Defining and classifying acute renal failure: from advocacy to consensus and validation of the RIFLE criteria. *Int Care Med* 2007; 33:409-413.
6. Ricci Z, Cruz D, et al. The RIFLE criteria and mortality in acute kidney injury: a systematic review. *Kidney Int* 2008; 73:538-546.
7. Bagshaw S, George C, et al. A multi-centre evaluation of the RIFLE criteria for early acute kidney injury in critically ill patients. *Nephron Dial Trans* 2008; 23:1203-1210.

8. Hoste E, Clermont G, et al. RIFLE criteria for acute kidney injury are associated with hospital mortality in critically ill patients: a cohort analysis. *Crit Care* 2006; 10(3): R73.

9. Herget-Rosenthal S, Marggraf G, et al. Early detection of acute renal failure by serum Cystatin C. *Kidney Int* 2004; 66:1115-22.

10. Ahlstrom A, Tallgren M, et al. Evolution and predictive power of serum cystatin C in acute renal failure. *Clin Nephrol* 2004; 62:344-50.

11. Dent C, Ma Q, et al. Plasma neutrophil gelatinase-associated lipocalin predicts acute kidney injury and mortality after pediatric cardiac surgery: a prospective uncontrolled cohort study. *Crit Care* 2007; 11:R127.

12. Bennett M, Dent C, et al. Urine NGAL predicts severity of acute kidney injury after cardiac surgery: a prospective study. *Clin J Am Soc Nephrol* 2008; 3:665-73.

13. Coca S, Yalavarthy R, et al. Biomarkers for the diagnosis and risk stratification of acute kidney injury: a systematic review. *Kidney Int* 2008; 73:1008-16.

14. Han W, Waikar Sk, et al. Urinary biomarkers for detection of acute kidney injury. *Kidney Int* 2008; 73:863-9.

15. Itoh Y, Yano T, et al. Clinical and experimental evidence for prevention of acute renal failure induced by radiographic contrast media. *J Pharm Sci* 2005; 97:473-88.

16. Debaveye Y, VandenBerghe G. Is there still a place for dopamine in the modern intensive care unit? *Anesth Analg* 2004; 98:461-8.

17. Holmes C, Whalley K. Bad medicine: low dose dopamine in the ICU. *Chest* 2003; 123:1266-75.

18. Kellum J, Decker J. Use of dopamine in acute renal failure: A meta-analysis. *Crit Care Med* 2001; 29:1526-31.

19. Marik P. Low-dose dopamine: a systematic review. *Int Care Med* 2002; 28:877-83.

20. Friedrich J, Adhikari N, et al. Meta-analysis: low dose dopamine increases urine output but does not prevent renal dysfunction or death. *Ann Int Med* 2005; 142:510-24.

21. Stone G, McCullough P, et al. Fenoldopam mesylate for the prevention of contrast-induced nephropathy: a randomized controlled trial. *JAMA* 2003; 290:2284-91.

22. Kelly A, Dwamena B, et al. Meta-analysis: effectiveness of drugs for preventing contrast-induced nephropathy. *Ann Int Med* 2008; 148:284-94.

23. Landoni G, Biondi G, et al. Beneficial impact of fenoldopam in critically ill patients with or at risk for acute renal failure: a meta-analysis of randomized clinical trials. *Am J Kidney Dis* 2007; 49:56-68.

24. van Riemsdijk I, Mulder P, et al. Addition of isradipine (Lomir) results in a better renal function after kidney transplantation: a double-blind, randomized, placebo-controlled, multi-center study. *Transpl* 2000; 70:122-6.

25. Shilliday I, Sherif M. Calcium channel blockers for preventing acute tubular necrosis in kidney transplant recipients. *Cochrane Rev* 2004; 1.

26. Lewis J, Salem M, et al. Atrial natriuretic factor in oliguric acute renal failure. *Am J Kidney Dis* 2000; 36:767-74.

27. Kurnik B, Allgren R, et al. Prospective study of atrial natriuretic peptide for the prevention of radiocontrast-induced nephropathy. *Am J Kidney Dis* 1998; 31:674-80.

28. Kellum J. The use of diuretics and dopamine in acute renal failure: a systematic review of the evidence. *Crit Care* 1997; 1:53-9.

29. Ho K, Sheridan M. Meta-analysis of furosemide to prevent or treat acute renal failure. *BMJ* 2006; 333:420.

30. Solomon R, Werner C, et al. Effects of saline, mannitol, and furosemide to prevent acute decreases in renal function induced by radiocontrast agents. *NEJM* 1994; 331:1416-20.

31. Mehta R, Pascual M, et al. Diuretics, mortality, and non-recovery of renal function in acute renal failure. *JAMA* 2002; 288:2547-53.

32. Uchino S, Doig G, et al. Diuretics and mortality in acute renal failure. *Crit Care Med* 2004; 32:1669-77.

33. Koyner J, Ali R, et al. Antioxidants: Do they have a place in the prevention or therapy of acute kidney injury? *Exp Nephr* 2008; 109:e109-e117.

34. Adabag A, Ishani A, et al. Efficacy of N-acetylcysteine in preventing renal injury after heart surgery: a systematic review of randomized trials. *Eur Heart J* epub March 11, 2009.

35. Isenbarger D, Kent S, et al. Meta-analysis of randomized clinical trials on the usefulness of acetylcysteine for prevention of contrast nephropathy. *Am J Card* 2003; 92:1454-8.

36. Misra D, Leibowitz K, et al. Role of acetylcysteine in prevention of contrast-induced nephropathy after cardiovascular procedures: a meta-analysis. *Clin Card* 2004; 27: 607-10.

37. Birck R, Krzorsok S, et al. Acetylcysteine for prevention of contrast nephropathy: meta-analysis. *Lancet* 2003; 362:598-603.

38. Pannu N, Manns B, et al. Systematic review of the impact of N-acetylcysteine on contrast nephropathy. *Kidney Int* 2004; 65:1366-74.

39. Van Valkenburg P, Hoitsma A, et al. Mannitol as an indispensable constituent of an intravenous hydration protocol for the prevention of acute renal failure after cadaveric renal transplantation. *Transpl* 1987; 44:784-88.

40. Langenberg C, Bagshaw S, et al. The histopathology of acute kidney injury: a systematic review. *Crit Care* 2008; 12:R38.

41. Wan L, Bagshaw S, et al. Pathophysiology of septic acute kidney injury: what do we really know? *Crit Care Med* 2008; 36(4 Suppl):S198-203.

42. Schrier R, Wang W. Acute renal failure and sepsis. *NEJM* 2004; 351:159-69.

43. Bagshaw SM, Hasse M, et al. Loop diuretics in the management of acute renal failure: A systematic review and meta-analysis. *Crit Care Resusc* 2007; 9:60-68.

44. Sampath S, Moran J, et al. The efficacy of loop diuretics in acute renal failure: Assessment using Bayesian evidence synthesis techniques. *Crit Care Med* 2007: 35: 2516-2524.

45. Bousman CSC, Oudemans-Van Straaten HM, et al. Effects of early high-volume continuous venovenous hemofiltration on survival and recovery of renal function in intensive care patients with acute renal failure. *Crit Care Med* 2002; 30:2205-2211.

46. Sughara S, Suzuki H. Early start on continuous hemodialysis therapy improves survival rate in patients with acute renal failure following coronary bypass surgery. *Hemodial Int* 2004; 8:320-325.

47. Liu KD, Himelfarb J, et al. Timing of initiation of dialysis in critically ill patients with acute kidney injury. *Clin J Am Soc Nephrol* 2006; 15:915-919.

48. Pannu N, Kiarenbach S, et al. Renal replacement therapy in patients with acute renal failure: A systematic review. *JAMA* 2008; 299:793-805.

49. Bagshaw S, Berthiaume L, et al. Continuous versus intermittent renal replacement therapy for critically ill patients with acute kidney injury: A meta-analysis. *Crit Care Med* 2008; 36:610-617.

50. Vinsonneau C, Camus C, et al. Continuous venovenous hemodiafiltration versus intermittent hemodialysis for acute renal failure in patients with multiple-organ dysfunction syndrome: a multicentre, randomized trial. *Lancet* 2006; 368:379-385.

51. Schiffl H, Lang SM, et al. Daily hemodialysis and the outcome of acute renal failure. *N Eng J Med* 2002; 346:305-310.

52. The VA/NIH Acute Renal Failure Trial Network: Intensity of renal support in critically ill patients with acute kidney injury. *N Engl J Med* 2008; 359:7-20.

53. Ricci Z, Ronco C: Dose and efficiency of renal replacement therapy: Continuous renal replacement therapy versus intermittent hemodialysis versus slow extended daily dialysis. *Crit Care Med* 2008: 36 (suppl):229-237.

Critical Care CME Program

In this issue of the *Bulletin*, Module 7 of the Critical Care CME Program is available. There will be one more module for a total of eight modules for this program. After each module is published in the *CSA Bulletin* (one per season), it is posted on the CSA Web Site at www.csahq.org. Each online module uses a self-assessment and evaluation; once these are completed, you may print your CME certificate. You may also contact the CSA office at 800-345-3691 to obtain the materials by fax or mail.

Questions

1. Your patient, Ms. M, is a diabetic with hypertension and nephropathy. She is scheduled to undergo a radiocontrast study. Therapy to reduce the likelihood that she will suffer AKI includes:
    a. Mannitol
    b. Hydration
    c. N-acetylcysteine
    d. b and c
    e. a, b, and c

2. The day after her radiocontrast study, Ms. M's creatinine increases from a baseline of 1.5 mg/dl to 2.0 mg/dl. This increase is sufficient to diagnose AKI by the RIFLE criteria.
    a. True
    b. False

3. On the following day, Ms. M's creatinine increases further to 2.5 mg/dl. This corresponds to what category of AKI by the RIFLE criteria?
    a. Risk
    b. Injury
    c. Failure

4. You had given Ms. M IV hydration and N-acetylcysteine prophylactially for this procedure. A colleague suggests that fenoldopam might also have helped prevent AKI. Does the literature support this?
    a. Yes
    b. No

5. You are providing anesthesia for a patient undergoing an aorto-occlusive procedure. A few minutes before he cross-clamps the aorta, the surgeon asks you to start some renal-dose dopamine to protect the patient's kidneys. Does the literature support this?
    a. Yes
    b. No

6. Agents that promote septic AKI include:
    a. Inflammatory mediators
    b. Oxygen free radicals
    c. Inducible nitric oxide synthetase
    d. All of the above

7. The management of a patient with acute kidney injury includes:
    a. Avoid further renal injury
    b. Medically manage complications of renal failure
    c. Institute RRT
    d. All of the above

8. In AKI, research supports the use of continuous renal replacement over intermittent hemodialysis.
   a. True
   b. False

9. If RRT is instituted, high-dose therapy is definitively indicated.
   a. True
   b. False

Evaluation of Module 7

As part of the CSA Educational Programs Division's ongoing efforts to offer continuing medical education, the following evaluation of this program is requested. This is a useful tool for the EPD in preparing future CME programs.

1. How well were the learning objectives of this program met?

Very Well	5	Above Average	4
Average	3	Below Average	2
Not Well at All	1		

2. How relevant was the information in this program to your clinical practice?

Very Relevant	5	Above Average	4
Average	3	Below Average	2
Not Relevant	1		

3. How would you rate this program overall?

Excellent	5	Above Average	4
Average	3	Below Average	2
Poor	1		

4. Did you detect any commercial bias in this module? Yes No

Registration

Complete this form, the test, and the evaluation, and **mail or fax** all three to the CSA office at 951 Mariner's Island Boulevard #270, San Mateo, CA 94404 or FAX to 650-345-3269. The CSA CME journal courses are also available on the CSA Web Site at www.csahq.org.

Critical Care CME Course, Module 7

Available September 30, 2009, to September 30, 2012

Name _____M.D. D.O.

Address _____

City/State/Zip _____

Phone ( ) _____

E-mail _____

❑ CSA Member No Fee

❑ Non-CSA Physician $30

Total $_____

Please charge my: ❑ MasterCard ❑ Visa

Card # _____ Exp. Date _____

I authorize the California Society of Anesthesiologists to charge my account for the registration.

Signature: _____

OR

Mail with a check made payable to California Society of Anesthesiologists

❑ **I acknowledge that I have read the Important Information about Module 7.**