Management of Acute Kidney Injury

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Case Presentation

A 58-year-old female with a history of obesity, type 2 diabetes mellitus, essential hypertension and locally advanced uterine cancer was admitted to the intensive care unit with fevers, malaise, nausea and decreased urine output over the last 2 days. Her initial evaluation was relevant for a blood pressure of 87/48, pulse of 92/min and temperature of 101.3 F (38.5 C). She was alert, but appeared ill and confused. There was an implantable venous infusion 'port' in the right chest, no rales, costovertebral angle tenderness or lower extremity edema. Laboratory exam revealed a WBC count of 17.8 × 10^9/L, Hemoglobin of 8.8 g/dL, Platelets of 212,000 × 10^6/L. Serum sodium was 135 mEq/L, potassium 6.3 mEq/L, chloride 100 mEq/L, total carbon dioxide 12 mEq/L, blood urea nitrogen (BUN) 97 mg/dL and serum creatinine (SCr) 4.3 mg/dL. Serum glucose was 270 mg/dL and lactic acid 4.6 mEq/L. She had an indwelling urinary catheter placed which yielded 50 cc of urine. Blood and urine cultures were sent. She was started on broad-spectrum intravenous antibiotics and a continuous infusion of insulin.

Question What are the basics of management of Acute Kidney Injury (AKI) in this case?

Answer Ascertainment and treatment of the underlying cause together with prevention of further injury and supportive care including renal replacement therapy.

In this patient with septic shock the treating physician must simultaneously resuscitate and treat the source of sepsis while ruling out other treatable causes of AKI. This patient is in shock as evidenced by a low arterial blood pressure (made more profound by the history of hypertension) and hyperlactatemia which in a resting patient is evidence of cellular stress likely a function of inadequate tissue perfusion. The initial management involves the infusion of intravenous isotonic crystalloids and if necessary, vasopressors may be added to preserve tissue perfusion, if hypotension persists despite restoration of intravascular volume. Care should be taken to avoid fluid overload which is a significant risk in a patient with AKI. At the same time unresuscitated shock will injure multiple tissues including the kidneys.

Sepsis is a leading cause of AKI and the most likely etiology given the case presented. However, other etiologies need to be excluded. For example, what medications was the patient taking? In addition, timely detection and relief

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of urinary obstruction is important, especially in this patient with a history of locally advanced gynecologic cancer, which puts her at risk for ureteral obstruction.

Complications of AKI such as hyperkalemia, volume overload and metabolic acidosis are managed concomitantly. Attention must be paid to prevent further injury to the kidneys (discontinuation of angiotensin converting enzyme [ACE] inhibitors, aldosterone receptor blockers [ARBs], non-steroidal anti-inflammatory drugs (NSAIDs), avoidance of radiographic contrast media etc.) and to adjust dosage of renally excreted medications. Renal replacement therapy should be instituted when (or preferably before) complications from AKI arise despite medical management. This patient was treated with intravenous boluses of lactated Ringer's (a physiologically balanced crystalloid solution), but her mean arterial pressure (MAP) remained low despite fluid resuscitation. She was started on norepinephrine with a goal to keep her MAP above 65–70 mmHg. Insulin and isotonic fluids were used to correct hyperkalemia. Repeat potassium was 5.2 mEq/L. A renal ultrasound showed normal kidney size with no hydronephrosis. Twenty-four hours after presentation, she became hypoxic (requiring 6 l of oxygen) with chest x-ray showing pulmonary edema. She was given IV loop diuretics, but remained oliguric, and her SCr increased to 5.1 mg/dL. A temporary hemodialysis catheter was placed and she was started on continuous venovenous hemodiafiltration (CVVHDF) at a dose of 25 cc/Kg/h. Five days after admission, she was no longer requiring vasopressor support and was no longer volume overloaded. Urine output progressively increased, renal replacement therapy was discontinued, and SCr returned to her baseline value of 1.1 mg/dL.

Principles of Management

Intravenous Fluids and Vasopressors

The classic paradigm that explains acute reduction in glomerular filtration rate (AKI) in critically ill patients is centered on decreased renal perfusion that exceeds the ability of kidneys to auto-regulate in the setting of shock. Septic shock, major surgery, hypovolemia and heart failure are the leading causes of AKI in the ICU setting [1] and are all characterized by hypotension and shock. Our understanding of the pathophysiology of AKI has markedly improved over the last decade, and factors in addition to decreased renal perfusion such as inflammation and microcirculation dysfunction – to name a few – have surfaced as important contributors to AKI. Few strategies are available in clinical practice to counteract those newly recognized factors, and reversal of shock while avoiding harm from fluid overload remains the most widely accepted first step in management of AKI in such settings. This is done through administration of isotonic intravenous fluids in hypovolemic conditions or in vasoplegic shock (septic shock, severe pancreatitis, anaphylaxis, burns). Several factors should be kept in mind when administering intravenous fluids to a patient with AKI. First, that vasoplegic shock might or might not be fluid-responsive. Second, that restoration of renal tissue perfusion might or might not reverse AKI, especially in the presence of established "damage" to the kidneys. In addition, once kidneys are injured, resuscitation milestones like resolution of oliguria may be unreliable [2]. Lastly, intravenous fluids can lead to fluid overload, which is a negative prognostic factor in AKI. This is especially true for elderly individuals, or when heart failure or cardiogenic shock is suspected.

Initial concerns that the use of vasoactive medications (such as norepinephrine and vasopressin) might cause further vasoconstriction and worsening AKI by reducing renal blood flow are not valid [3]. An increase in renal blood flow was demonstrated in experimental models of sepsis when dogs were infused with norepinephrine at clinically relevant doses. This is thought to be a result of an improvement in blood pressure, which through the baroreceptor reflex decreases sympathetic tone and improves renal blood flow [4]. Norepinephrine and vasopressin have also been used in conjunction with intravenous albumin for treatment of the hepatorenal syndrome, where splanchnic vasodilation is thought to play an essential role in the development of AKI. A meta-analysis including 154 patients with type I hepatorenal syndrome showed similar rates of resolution of AKI with norepinephrine plus

albumin when compared to terlipressin (a vasopressin analogue) plus albumin, with lower cost and complication rates [5]. It is important to note that despite potential reversal of AKI, vasopressors have a questionable effect on mortality in patients with type I hepatorenal syndrome, and that liver transplantation remains the mainstay of therapy in this condition.

Consider Alternative Etiologies and Specific Treatments for AKI

While septic shock is the most likely etiology of AKI in this patient, care should be taken not to miss other important causes. Drugs and radiographic contrast media are among the most common causes of AKI, and nephrotoxicity from antimicrobial agents is an important contributor [6]. Obstructive uropathy is an uncommon cause of AKI in the ICU setting [1]. Nevertheless, it is a potentially reversible cause of AKI, and should be suspected and alleviated in the appropriate clinical setting (solitary kidney, active gynecologic, gastrointestinal or urological cancer, known nephrolithiasis). Systematic use of renal ultrasonography to detect hydronephrosis in patients with AKI is not recommended, as it is unlikely to change management or to be cost-efficient [7]. Primary or secondary glomerular diseases are also uncommon causes of AKI in the ICU. On the other hand, It is essential to suspect glomerular disease in the appropriate clinical setting (proteinuria, hematuria, multi-organ involvement), as specific treatments like immunosuppressive agents and plasma exchange can often alter the course of AKI [8]. Similarly, specific treatments may exist for other etiologies of AKI, such as the hepatorenal syndrome, cardiorenal syndrome or acute interstitial nephritis, but are beyond the scope of this chapter.

Prevention of Further Injury

The lack of effective therapies to reverse AKI makes prevention of further kidney damage an essential step in management. Radiocontrast agent use is avoided whenever possible. This can be done through use of alternate imaging modalities or use of non-nephrotoxic radiocontrast agents such as carbon dioxide if available [9]. In cases where use of radiocontrast agent is unavoidable, the dose of contrast agent administered is minimized, and isotonic intravenous fluids are given before and after radiocontrast administration. In patients with AKI, drugs such as NSAIDs, ACE inhibitors, ARBs, aminoglycosides, amphotericin B and intravenous acyclovir should be avoided whenever possible. Scleroderma renal crisis is an exception to this rule, as ACE inhibitors (captopril) are considered the treatment of choice despite the common presence of AKI. Failing to adjust dosage of renally eliminated medications in AKI is common and frequently leads to adverse drug events. Worsening AKI and hypotension appear to be the most common preventable adverse drug events [10]. Special attention to medication dosage is therefore essential in AKI, especially for certain medication classes such as antimicrobials, opiates and antithrombotics (Fig. 43.1).

Diuretics

Loop diuretics have been hypothesized to improve AKI through washing the debris blocking renal tubules and decreasing oxygen consumption at the tubular level [11]. Those theories have been disproved by randomized controlled trials, and Kidney Disease Improving Global Outcomes (KDIGO) guidelines recommends against the use of diuretics for prevention or treatment of AKI [12]. Nevertheless, diuretics are still commonly used in patients with AKI[14], usually to help manage volume overload. Patients with both AKI and acute lung injury, for example, might benefit from loop diuretics as part of a lung-protective ventilation strategy [14]. Another possible role for loop diuretics in AKI is in patients with decompensated heart failure or the cardiorenal syndrome. Response to diuretics in this syndrome varies, as SCr might increase, stay the same or improve. Two explanations have been proposed for the improvement in SCr in patients with decompensated heart failure and AKI that receive diuretics: reduction in intra-abdominal and renal venous pressure, and

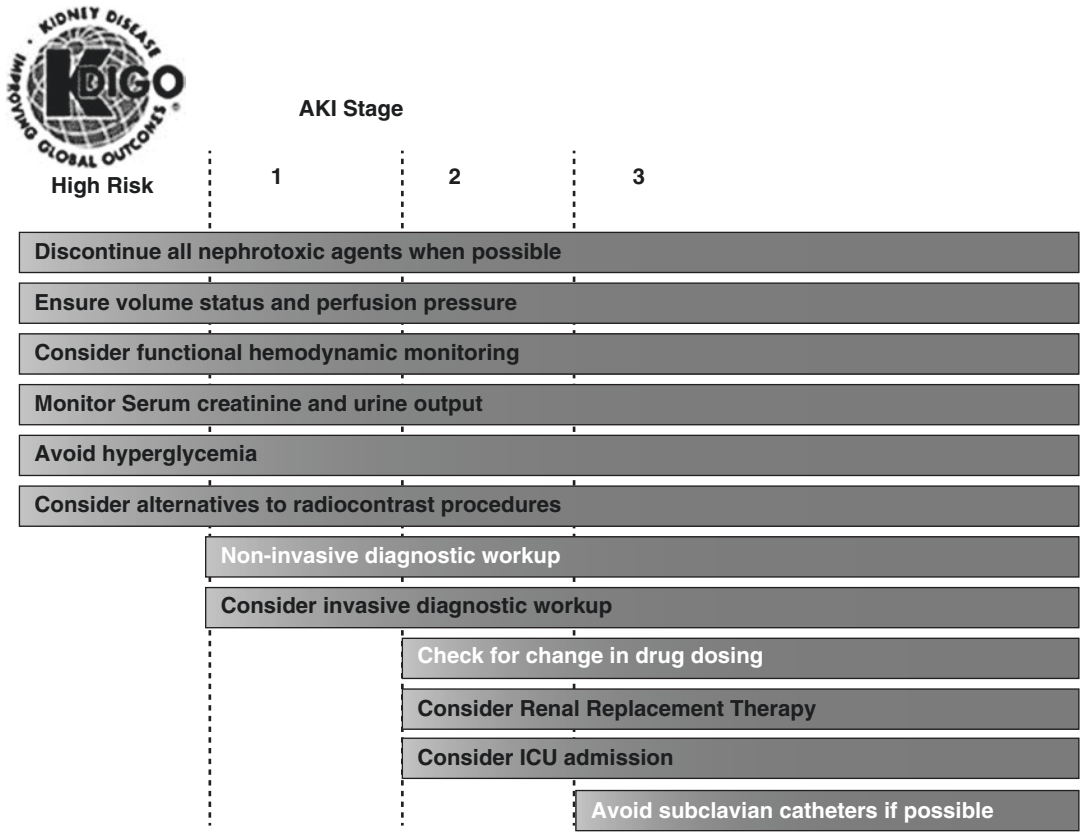

Fig. 43.1 Stage-based management of AKI (From Section 2: AKI Definition. *Kidney Int Suppl* 2012;2(1):19–36. Reprinted with permission from Elsevier)

improvement of LV filling and therefore cardiac output through reduction of RV dilation (ventricular interdependence). The effect of diuretic therapy on survival in patients with the cardiorenal syndrome is not well established and requires further exploration. It is important to remember that judicious use of intravenous fluids will often avoid the need for diuretics.

Medical Management of Complications of AKI

Volume overload, hyperkalemia, metabolic acidosis, hyperphosphatemia, hypocalcemia and bleeding disorders are the main complications of AKI. Their management is an integral part of treating AKI. Volume overload is often managed with IV loop diuretics (see "Diuretics" above). Nevertheless, a trial of diuretics should not be viewed as a mandatory prerequisite prior to the initiation of renal replacement therapy. Prompt initiation of dialysis in an anuric patient with severe volume overload would be a good example. Hyperkalemia is commonly seen in oliguric patients with active tissue breakdown, such as tumor lysis syndrome and rhabdomyolysis. Because hyperkalemia is often asymptomatic, its first manifestations can often be ventricular dysrhythmias and death, which is why it should rapidly be recognized and promptly treated. Transient and rapidly acting therapies include intravenous insulin plus glucose (if serum glucose is less than 250 mg/dL) and beta-2 agonists such as high-dose nebulized albuterol (10–20 mg). A continuous infusion of intravenous bicarbonate can lower potassium levels after 4–6 h in patients with metabolic acidosis [15]. It is

not efficacious in the first hour of infusion and is not recommended for rapid treatment of hyperkalemia [16]. A calcium infusion is administered to decrease the incidence of cardiac dysrhythmias when EKG changes such as prolonged QRS interval or absence of P waves are present. Metabolic acidosis often complicates AKI, but can also result from shock and lactic acidosis, or chloride administration, all of which are commonly present with AKI. Use of exogenous bicarbonate for the treatment of metabolic acidosis is very controversial, and is usually reserved for severe acidosis with an arterial pH < 7.1. Bicarbonate infusions can cause symptomatic hypocalcemia (decreased ionized calcium through increased binding of calcium to albumin) with potential cardiotoxicity, hypernatremia, volume overload and an increase in arterial and tissue capillary PCO_2. The rationale behind the use of bicarbonate therapy is that severe acidemia (pH < 7.1) is associated with hemodynamic instability and impaired response to catecholamines [17]. Severe hyperphosphatemia can potentially cause symptomatic hypocalcemia through precipitation of calcium and phosphate. Use of oral phosphate binders to treat hyperphosphatemia in AKI is based on expert opinion as there is no clear evidence that such treatment improves outcomes.

Renal Replacement Therapy

Dialysis is the treatment of choice for severe AKI, or when complications of AKI fail to respond to medical therapy. Commonly accepted indications for initiation of renal replacement therapy (RRT) include hyperkalemia (potassium > 6.5 mEq/L or rapidly increasing despite medical therapy), metabolic acidosis (pH < 7.1 despite bicarbonate therapy), volume overload unresponsive to diuretics, uremic symptoms and signs (pericarditis, altered mental status without an alternative explanation to uremia) and AKI in the setting of certain intoxications (such as ethylene glycol, methanol or lithium). KDIGO guidelines recommend considering the clinical context and trend of laboratory exams rather than a single cutoff for BUN and SCr when making the decision to initiate RRT [12]. The two commonly used modalities for RRT in the ICU setting are intermittent hemodialysis (iHD) and continuous renal replacement therapy (CRRT). The use of hemofiltration in CRRT offers the theoretical advantage of "convective" clearance of middleweight molecules, which is not well achieved with "diffusive" clearance of iHD. Inflammatory mediators and cytokines are examples of middle-sized molecules that are thought to have a deleterious role in septic patients. Randomized prospective trials have failed to show any superiority of CRRT to iHD in terms of survival and recovery of renal function [18, 19]. CRRT offers the potential advantages of less hypotension and more efficient volume removal in hemodynamically unstable patients [20], but this does not translate into increased survival compared to iHD. The choice of modality remains dependent on staff and equipment availability and differences in comfort level and expertise. Higher intensity hemodialysis does not seem to improve mortality or recovery of renal function and is associated with more electrolyte abnormalities such as hypophosphatemia [21]. A delivered effluent volume of 20–25 cc/Kg/h is recommended for CRRT (Fig. 43.2).

Evidence Contour

Choice of Intravenous Fluid Solution

The best type of intravenous fluids for management of AKI has been intensely investigated but remains controversial. KDIGO recommends using isotonic crystalloids rather than colloids for volume expansion, in the absence of hemorrhagic shock [12]. This is based on higher cost of intravenous albumin solutions and a randomized control trial of nearly 7000 patients that showed no difference in outcomes between resuscitation with 4 % human albumin and isotonic saline 28 days after randomization [22]. Other colloid formulations such as hydroxyethylstarch (HES) have no added benefit to isotonic crystalloids [23] and should be avoided, as there is a concern

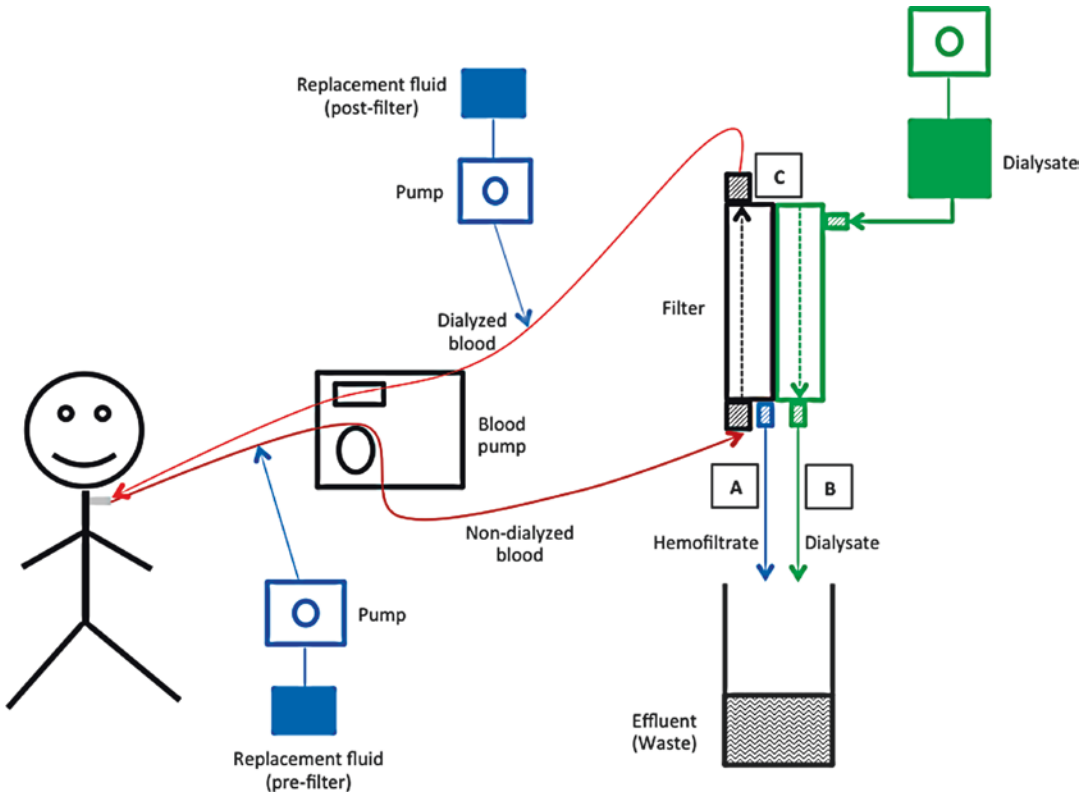

Fig. 43.2 Continuous renal replacement therapy circuits. (**a**) In continuous veno-venous hemofiltration (CVVH – *blue*), blood purification is achieved through "convection". The blood pump generates a pressure that allows passage of plasma water through the filter. Water drags toxins and electrolytes (solvent drag). Replacement fluids are given before and/or after the filter to prevent volume and electrolyte losses. (**b**) In continuous veno-venous hemodialysis (CVVHD – *green*), blood purification is achieved through "diffusion". A toxin-free fluid with appropriate amounts of electrolytes (dialysate) is pumped across the filter. Blood circulates inside the filter's hollow fibers, while dialysate circulates countercurrently outside of those fibers. Toxins and electrolyte follow a concentration gradient across this semi-permeable membrane and are eliminated through diffusion. There is no need for replacement fluids as there is no water loss or hemofiltration (**c**) Continuous veno-venous hemodiafiltration (CVVHDF – *blue* and *green*) is a combination of both methods. Both diffuse and convection are used for blood purification

for increased risk of AKI and mortality when such solutions are used in sepsis [24]. Isotonic normal saline has supra-physiologic contents of chloride: normal plasma has roughly 100 mEq/L of chloride compared to 142 mEq/L of chloride added to the plasma when 1 L of 0.9 % sodium chloride is administered (only 92 % of plasma is water). In a prospective study, a chloride-liberal strategy was associated with higher rates of AKI and need for RRT [25]. Avoidance of hyperchloremia and chloride-induced metabolic acidosis is an argument used by proponents of more physiologic or "balanced" solutions. Lactated Ringer's is a commonly used balanced solution (contains 109 mEq/L of chloride), but is slightly hypotonic, and is limited by the fact that it contains calcium, which prevents its co-administration with blood products. Non-calcium containing physiologic solutions such as plasmalyte are gaining popularity but have yet to show superiority compared to normal saline using hard outcomes such as mortality or need for RRT. A recent RCT that compared small volumes (approximately 2 L) of saline to plasmalyte in relatively low-risk patients failed to demonstrate any advantage with plasmalyte [26]. The amount of potassium that lactated Ringer's or plasmalyte contain is too small to cause clinically significant

Table 43.1 Composition of commonly used crystalloid and colloid solutions

	0.9 % saline	Lactated Ringer's	Plasmalyte	Albumin (human) 5 %
Sodium (mEq/L)	154	130	140	130–160
Chloride (mEq/L)	154	109	98	
Acetate (mEq/L)			27	
Lactate (mEq/L)		28		
Gluconate (mEq/L)			23	
Calcium (mEq/L)		3		
Potassium (mEq/L)		4	5	
Magnesium (mEq/L)			1.5	
Protein (g/L)				50

increases in serum potassium values. In kidney transplant recipients for example, normal saline was found to be associated with more hyperkalemia compared to lactated Ringer's [27]. This can be due to transcellular shifts of potassium associated with hyperchloremic acidosis (Table 43.1).

Nutrition in AKI

Initial reports suggested that early enteral nutrition (within 48 h from illness) could be beneficial in critically ill patients, at least in decreasing the rate of infections [28]. This remains controversial, especially with a recent large randomized trial showing no difference in mortality or infections between early nutrition through the enteral or parenteral routes [29]. Patients with AKI, especially those who require RRT, have protein hypercatabolism, which is driven by inflammation, stress and acidosis. They frequently have protein-calorie malnutrition [30], which is why they have been thought to be a group that might particularly benefit from early nutrition. This was confirmed by a large prospective study examining predictors of mortality in AKI patients, where patients who received enteral nutrition had an increased chance of survival [31].

Tight Glycemic Control

Hyperglycemia is associated with worse outcomes in critically ill patients, including patients with AKI [32]. Whether hyperglycemia is a contributor to those outcomes or only a marker of disease severity is unclear. Initial reports indicating less need for RRT with intensive insulin therapy in patients with AKI [33] were disproved by a large randomized controlled trial [34]. Glycemic control is probably beneficial in patients with AKI, but blood sugar values of 140–180 mg/dL should be targeted rather than 80–110 mg/dL. The latter target is associated with a higher risk of hypoglycemia and death [35].

Vasodilators and Growth Factor Interventions

Use of agents that cause renal vasodilation has been attempted to treat AKI. Low-dose dopamine has been studied in patients with AKI in different clinical settings. A placebo-controlled randomized study confirmed previous findings that low-dose dopamine offers no benefit in the treatment of AKI [36]. Other agents such as fenoldopam, atrial natriuretic peptide (ANP) and growth factors (recombinant human IGF-1) do not appear to be beneficial neither, and KDIGO recommends against their use in clinical practice [12].

Early Initiation of Dialysis

Prophylactic dialysis is the initiation of RRT in critically ill patients with AKI prior the development of "life-threatening complications" such as hyperkalemia, volume overload and acidosis. The role of such practice remains controversial and has not been validated in well-designed and adequately powered prospective randomized trials.

Retrospective analyses of large observational cohorts indicated that initiation of dialysis with a lower level of BUN (less than 76 mg/dL) provided a survival benefit [37]. Another report indicated that initiation of dialysis if urine output was less than 100 cc for 8 h after cardiac surgery was associated with better survival [38]. This contrasts to a randomized controlled trial that included 208 patients with AKI, and failed to show a survival benefit or a decrease in need for RRT after 3 months in the group that received early dialysis [39]. The small number of patients included in this trial does not make it powered enough to refute the potential benefit of early initiation of dialysis.

References

1. Uchino S et al. Acute renal failure in critically ill patients: a multinational, multicenter study. JAMA. 2005;294:813–8.
2. Srisawat N et al. Urinary biomarkers and renal recovery in critically ill patients with renal support. Clin J Am Soc Nephrol. 2011;6:1815–23.
3. Bellomo R, Wan L, May C. Vasoactive drugs and acute kidney injury. Crit Care Med. 2008;36:S179–86.
4. Bellomo R, Kellum JA, Wisniewski SR, Pinsky MR. Effects of norepinephrine on the renal vasculature in normal and endotoxemic dogs. Am J Respir Crit Care Med. 1999;159:1186–92.
5. Nassar Junior AP, Farias AQ, D' Albuquerque LAC, Carrilho FJ, Malbouisson LMS. Terlipressin versus norepinephrine in the treatment of hepatorenal syndrome: a systematic review and meta-analysis. PLoS One. 2014;9:e107466.
6. Bellomo R. The epidemiology of acute renal failure: 1975 versus 2005. Curr Opin Crit Care. 2006;12:557–60.
7. Licurse A et al. Renal ultrasonography in the evaluation of acute kidney injury: developing a risk stratification framework. Arch Intern Med. 2010;170:1900–7.
8. Kidney Disease: Improving Global Outcomes (KDIGO) Glomerulonephritis Work Group. KDIGO clinical practice guideline for glomerulonephritis. Kidney Inter Suppl. 2012;2;139–274.
9. Shaw DR, Kessel DO. The current status of the use of carbon dioxide in diagnostic and interventional angiographic procedures. Cardiovasc Intervent Radiol. 2006;29:323–31.
10. Cox ZL et al. Adverse drug events during AKI and its recovery. Clin J Am Soc Nephrol. 2013;8:1070–8.
11. Karajala V, Mansour W, Kellum JA. Diuretics in acute kidney injury. Minerva Anestesiol. 2009;75:251–7.
12. Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO clinical practice guideline for acute kidney injury. Kidney Int Suppl. 2012;2:1–138.
13. Mehta RL, Pascual MT, Soroko S, Chertow GM. Diuretics, mortality, and nonrecovery of renal function in acute renal failure. JAMA. 2002;288:2547–53.
14. Grams ME, Estrella MM, Coresh J, Brower RG, Liu KD. Fluid balance, diuretic use, and mortality in acute kidney injury. Clin J Am Soc Nephrol. 2011;6:966–73.
15. Blumberg A, Weidmann P, Ferrari P. Effect of prolonged bicarbonate administration on plasma potassium in terminal renal failure. Kidney Int. 1992;41:369–74.
16. Allon M, Shanklin N. Effect of bicarbonate administration on plasma potassium in dialysis patients: interactions with insulin and albuterol. Am J Kidney Dis. 1996;28:508–14.
17. Marsh JD, Margolis TI, Kim D. Mechanism of diminished contractile response to catecholamines during acidosis. Am J Physiol. 1988;254:H20–7.
18. Vinsonneau C, et al. Continuous venovenous haemodiafiltration versus intermittent haemodialysis for acute renal failure in patients with multiple-organ dysfunction syndrome: a multicentre randomised trial. Lancet (London, England). 2006;368:379–85.
19. Schneider AG et al. Choice of renal replacement therapy modality and dialysis dependence after acute kidney injury: a systematic review and meta-analysis. Intensive Care Med. 2013;39:987–97.
20. Augustine JJ, Sandy D, Seifert TH, Paganini EP. A randomized controlled trial comparing intermittent with continuous dialysis in patients with ARF. Am J Kidney Dis. 2004;44:1000–7.
21. Palevsky PM et al. Intensity of renal support in critically ill patients with acute kidney injury. N Engl J Med. 2008;359:7–20.
22. Finfer S et al. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. N Engl J Med. 2004;350:2247–56.
23. Brunkhorst FM et al. Intensive insulin therapy and pentastarch resuscitation in severe sepsis. N Engl J Med. 2008;358:125–39.
24. Wiedermann CJ. Systematic review of randomized clinical trials on the use of hydroxyethyl starch for fluid management in sepsis. BMC Emerg Med. 2008;8:1.
25. Yunos NM et al. Association between a chloride-liberal vs chloride-restrictive intravenous fluid administration strategy and kidney injury in critically ill adults. JAMA. 2012;308:1566–72.
26. Young P, et al. Effect of a buffered crystalloid solution vs saline on acute kidney injury among patients in the intensive care unit. JAMA. 2015;1. doi:10.1001/jama.2015.12334.
27. O'Malley CMN, et al. A randomized, double-blind comparison of lactated Ringer's solution and 0.9 % NaCl during renal transplantation. Anesth Analg. 2005;100;1518–24, table of contents.
28. Marik PE, Zaloga GP. Early enteral nutrition in acutely ill patients: a systematic review. Crit Care Med. 2001;29:2264–70.

29. Harvey SE et al. Trial of the route of early nutritional support in critically ill adults. N Engl J Med. 2014;371:1673–84.
30. Fiaccadori E et al. Prevalence and clinical outcome associated with preexisting malnutrition in acute renal failure: a prospective cohort study. J Am Soc Nephrol. 1999;10:581–93.
31. Metnitz PGH et al. Effect of acute renal failure requiring renal replacement therapy on outcome in critically ill patients. Crit Care Med. 2002;30:2051–8.
32. Krinsley JS. Association between hyperglycemia and increased hospital mortality in a heterogeneous population of critically ill patients. Mayo Clin Proc. 2003;78:1471–8.
33. Van den Berghe G et al. Intensive insulin therapy in critically ill patients. N Engl J Med. 2001;345:1359–67.
34. Finfer S et al. Intensive versus conventional glucose control in critically ill patients. N Engl J Med. 2009;360:1283–97.
35. Finfer S et al. Intensive versus conventional glucose control in critically ill patients. N Engl J Med. 2009;360:1283–97.
36. Bellomo R, Chapman M, Finfer S, Hickling K, Myburgh J. Low-dose dopamine in patients with early renal dysfunction: a placebo-controlled randomised trial. Australian and New Zealand Intensive Care Society (ANZICS) Clinical Trials Group. Lancet (London, England). 2000;356:2139–43.
37. Liu KD et al. Timing of initiation of dialysis in critically ill patients with acute kidney injury. Clin J Am Soc Nephrol. 2006;1:915–9.
38. Demirkiliç U, et al. Timing of replacement therapy for acute renal failure after cardiac surgery. J Card Surg. 2004;19:17–20.
39. Jamale TE et al. Earlier-start versus usual-start dialysis in patients with community-acquired acute kidney injury: a randomized controlled trial. Am J Kidney Dis. 2013;62:1116–21.