13 Special Consideration on Fluid and Electrolytes in Acute Kidney Injury and Kidney Transplantation

Oluwatoyin Fatai Bamgbola

Key Words: Acute kidney injury; Pre-renal azotemia; pRIFLE; post-transplant kidney injury; children

A normal kidney regulatory function is essential in order to maintain optimal body fluid dynamics and preserve electrolyte homeostasis. Similarly, a good kidney function is dependent on adequacy of its perfusion. The initial phase of this review will highlight the progress made so far in a consensus definition of acute kidney injury (AKI). Emphasis on the prospect of a future application of tissue biomarkers as a more accurate diagnostic tool will follow. Second, the pathogenesis and clinical outcome of pre-renal azotemia and intrinsic AKI will be differentiated. The mechanisms of renal injury in the course of fluid and electrolyte disorders are then discussed. Finally, clinical management of AKI and the challenges of fluid and electrolyte status in surgical kidney transplantation are delineated.

1. DEFINITION

Acute kidney injury is an abrupt and sustained decline in renal function that occurs over a period of few hours or days, resulting in a buildup of nitrogenous toxins, and loss of fluid, electrolyte, and acid–base homeostasis. The impairment of glomerular filtration causes fluid and salt retention leading to oliguria while excessive urine output is the likely outcome in a predominant tubular injury.

Partly because of a wide variation in operational definition, epidemiological data on AKI are often inaccurate. Indeed it is estimated that there are more than 30 definitions of AKI in the literatures *(1)*. In an effort to standardize clinical evaluation and promote comparison of research studies, AKI Network proposed a consensus definition by modifying the previously recommended RIFLE criteria. The pediatric version of RIFLE criteria is shown in the Table 1. Loss of kidney function is graded by severity into three categories on the basis of creatinine clearance [derived from Schwartz formula] and per-

From: *Nutrition and Health: Fluid and Electrolytes in Pediatrics*
Edited by: L. G. Feld, F. J. Kaskel, DOI 10.1007/978-1-60327-225-4_13,

Table 1
Pediatric RIFLE Criteria

pRIFLE criteria		*Estimated creatinine clearance*	*Urine output*
Early	R (risk)	↓ 25%	<0.5 ml/kg/h × 8 h
	I (injury)	↓ 50%	<0.5 ml/kg/h × 12 h
	F (failure)	↓ 75%	<0.5 ml/kg/h × 24 h or anuria
Late	L (loss)	Renal failure > 4 weeks	
	E (end stage)	Renal failure > 3 months	

sistence of oliguria *(2, 3)*. The late manifestations of kidney dysfunction, namely acute renal loss and acute renal failure, are recommended as outcome variables *(2, 4)*.

Furthermore, AKI qualitatively describes a spectrum of renal dysfunction that includes an asymptomatic elevation in serum creatinine concentration on one end and acute kidney failure (AKF) at the other end of the spectrum. Because of its severity, AKF has the highest probability of evolving into a permanent structural renal damage. In support of its validity, subjects with AKI as defined are hospitalized for longer duration (14 vs. 7 days, $p < 0.01$) and sustain a higher mortality rate (45.8 vs. 16.4%, $p < 0.01$) compared to the control *(4)*.

2. DIAGNOSTIC CHALLENGES

Kidney is a highly adaptive organ, with an efficient auto-regulatory mechanism and is therefore able to withstand an extreme variation in hemodynamic changes. In addition, because of a substantial renal reserve, there may be no immediate increase in serum creatinine with impairment in kidney function. Furthermore, tubular secretion of creatinine increases with severe reduction in glomerular filtration leading to an over-estimation of its clearance *(5)*. In view of these, serial evaluation of trend rather than absolute values of serum creatinine may lead to early detection of AKI *(6)*. Unfortunately, baseline information on serum creatinine value is seldom available in clinical practice. Nevertheless, highlighting its limitation as a diagnostic tool for an early kidney injury, even a marginal increase in serum creatinine value is associated with a high mortality rate in critical illness *(7)*.

Unlike creatinine, serum cystatin C does not vary with skeletal muscle mass or is it secreted by the renal tubules and may serve as a better index of glomerular filtration *(8)*. However, a multidimensional diagnostic approach that takes into account different phases of kidney injury may be more accurate than a single index. Such candidate biomarkers are cystatin C for glomerular filtration, kidney injury molecule-1 (KIM-1) for tubular function, cysteine-rich protein (CYP 61) and neutrophil gelatinase-associated lipocalin (UNGAL) for ischemia, and interlukin-18 for inflammation *(9–12)*. This novel technique may facilitate early diagnosis of AKI giving a hope for a timely therapeutic intervention and an improved mortality outcome (that had otherwise remained stagnant in the last two to three decades).

3. PRE-RENAL AZOTEMIA: PATHOPHYSIOLOGY

Pre-renal azotemia is an adaptive physiological response to an inadequate perfusion pressure that may result from either extracellular (EC) fluid depletion (e.g., acute gastroenteritis) or an ineffective circulatory volume (e.g., congestive heart failure). Normally, systemic blood flow is protected by the vascular activity of baroreceptors, which respond to hypovolemia by amplifying signal transmission to the vasomotor centers. This results in an activated sympathetic outflow, which increases the systemic arteriolar resistance and stimulates intra-renal β-adrenoreceptors for plasma renin release. In addition, release of vasopressin and aldosterone with a reduction of atrial natriuretic peptides causes salt and water retention in an effort to restore the blood volume *(13*, *14)*.

Similarly, low tubular sodium delivery from impaired renal perfusion induces plasma renin release by the stimulation of macula densa (within the juxtaglomerular apparatus). In turn, plasma renin stimulates an increased synthesis of angiotensin II, a potent vasoconstrictor. With the dilatation of afferent arteriole by prostaglandin E and I_2, and an efferent vasoconstriction by angiotensin II, greater fraction of the (otherwise poor) glomerular capillary flow is filtered. This auto-regulatory process is sometimes called tubulo-glomerular feedback *(14*, *15)*.

4. INTRINSIC AKI: PATHOGENESIS

Etiology of AKI includes renal vascular obstruction [e.g., hemolytic–uremic syndrome], acute nephritis, acute tubular necrosis (ATN), toxic nephropathy, interstitial nephritis, and post-renal obstruction. Acute tubular necrosis is a term that is broadly applied to all instances of kidney injury outside of arterial, glomerular, or obstructive nephropathy. Common causes of ATN are severe hypovolemia, endotoxemia, and exposure to toxins. Acute kidney injury, arising from drug toxicity, irradiation injury, sepsis, and dehydration, is a potential complication of bone marrow transplantation *(16)*. Similarly, pathogenesis of ATN in critical illness is multi-factorial and may include drugs, hypovolemia, sepsis, coagulopathy, and major organ failure. Furthermore, association of AKI with a major organ failure (or sepsis) increases the attributed mortality rate by a factor of 7–10 *(7*, *13–17)*.

Failure of auto-regulatory mechanism with inadequate restoration of hemodynamic status ultimately results in loss of tubular function and structural integrity. The blood flow to the medullary kidney falls short of its intense metabolic demand, making the distal third of proximal tubules and the loop of Henle most susceptible to ischemic injury. Nephrotoxic and ischemic injuries, by increasing the local synthesis of endothelin, induce vasoconstriction by binding to ETa receptor. In addition, pro-inflammatory cytokine up-regulates endothelial wall adhesion molecules and increases activity of migratory leucocytes. Finally, the tubular injury causes a disruption of the epithelial cytoskeleton and promotes cell apoptosis and necrosis. Debris from the desquamated epithelial cells causes obstruction of the tubular lumen resulting in a backleak of its filtrate contents. The recovery phase is heralded by histological de-differentiation and regeneration of the tubular cells, which may be clinically associated with an increased urine output *(13*, *14*, *18)*.

5. NORMAL FLUID AND ELECTROLYTE DYNAMICS

Water constitutes close to 80% of the body weight of a newborn infant. With the growth of skeletal muscle and fat mass, water content is reduced to 50–60% of the body weight by the end of puberty. Greater amount of total body water (TBW) is situated in the intracellular (IC) space (30–40%) while EC fluid shares 20–25% of the volume. Extracellular fluid consists of plasma water (5% of TBW) and interstitial space is derived from 15% of the body fluids. To maintain adequate plasma flow, sufficient hydrostatic force must be generated by cardiac output to counteract the opposing effect of the interstitial (oncotic) pressure. Although EC and IC fluid spaces are separated by cellular membrane, osmotic equilibrium is maintained by free water permeability across the two compartments. Sodium and chloride ions are the major solutes in the EC fluid while potassium and phosphate anions are predominant in the IC unit *(19)*.

6. EXTRACELLULAR FLUID LOSS AND ACUTE KIDNEY INJURY IN CHILDREN

Children are more prone to dehydration than adults because of their unique physiological characteristics. Thus there is a greater insensible water loss in young children due to a high body surface area to weight ratio. In addition, children have a higher incidence of gastroenteritis while they depend on caregivers for an adequate access to water. Common sources of EC fluid loss are gastrointestinal tract (diarrhea, emesis), skin (fever, deep burns), and urine (forced diuresis) *(18*, *19)*.

Hyper-oncotic kidney injury: Hyperglycemia, as in diabetic ketoacidosis, causes osmotic induced diuresis and severe dehydration. Poor renal perfusion is followed by azotemia in the short term while a prolonged course may lead to ischemic injury *(20)*. ATN may be prevented by an early and aggressive fluid resuscitation *(19)*. Particularly at high risk for permanent kidney injury are diabetic patients with poorly controlled hyperglycemia and a pre-existing nephropathy.

Similarly, the use of hyper-osmolar substances for forced diuresis such as mannitol in cerebral edema and 25% albumin in severe nephrotic syndrome is a potential source of AKI. Osmotic-induced renal toxicity was a common complication of sucrose-based intravenous gamma globulin (IVIG) therapy. Over the years, incidence of IVIG-mediated nephrotoxicity has been minimized with the avoidance of the sucrose medium *(21)*.

Ineffective circulatory volume: Renal perfusion may be compromised because of poor circulatory volume in spite of a positive gain in total body water. Accumulation of body fluid at the expense of plasma water deficit occurs in congestive heart failure due to reduction in cardiac output, diminished hydrostatic pressure, and expansion of venous capacitance. Similarly, low plasma oncotic pressure from severe hypoalbuminemia in nephrotic syndrome invariably results in excessive fluid retention. Cumulative gain in total body water is facilitated by pituitary vasopressin (VP) release, thirst stimulation, activated sympathetic nervous system, and induction of renin–angiotensin mechanism. Indeed there is correlation between mortality attributable to the predisposing disease and dilutional hyponatremia *(18)*.

Surgery and AKI: The incidence of an AKI after cardiac surgery in children ranges from 5 to 20%. Mortality associated with post-cardiac renal injury has remained essentially unchanged in the last two decades *(22)*. Extracorporeal diversion of blood (or cardiopulmonary bypass) during cardiac surgery may potentiate low tissue oxygen delivery and causes acute ischemic kidney injury *(23)*. To avoid life-threatening post-operative complications, a pre-emptive placement of peritoneal dialysis catheter during surgical repair of complex cardiac anomaly is desirable *(24)*. Furthermore, strategies to prevent hypovolemia are necessary in order to minimize sources of kidney injury, including rhabdomyolysis, in critically ill surgical patients. In addition to surgical hemorrhage, poor circulatory volume from capillary leaks may result from ischemic-reperfusion phenomenon, elaboration of free oxygen radicals, and cytokine-mediated endothelial injury *(22, 25)*.

7. LABORATORY EVALUATION

Serum analysis: Serial analysis showing the trend of hematocrit, hemoglobin, and serum albumin may be a useful adjunct in the evaluation of severe dehydration and adequacy of the following rehydration therapy. Metabolic acidosis may result from stool bicarbonate loss in diarrhea, and lactic acid may be generated from poor tissue perfusion in hypovolemia, sepsis, and multi-organ failure. Serum biochemistry is seldom necessary in assessing most cases of dehydration. If serum analysis is obtained, a bicarbonate concentration less than 16 mEq/L may discriminate moderate and severe dehydration from the milder form *(26)*.

Blood urea nitrogen (BUN)/serum creatinine (Cr) ratio: Extracellular fluid depletion with poor renal blood flow causes an increase re-absorption of urea by the proximal tubules. Compared with the elevation in serum creatinine, renal retention of urea is an earlier manifestation of poor kidney perfusion. Hence, BUN/Cr ratio is often greater than 20 in pre-renal azotemia. Unfortunately, blood urea nitrogen is not a reliable index of glomerular filtration as it may vary with skeletal muscle catabolism, gastrointestinal bleeding, and dietary protein intake. Similarly, serum uric acid is a sensitive but poorly specific index of renal perfusion, its concentration increases with arterial volume contraction and decreases with its expansion *(27)*.

Urine analysis and biochemistry: Urine sample is not only easy to collect; its random analysis often indicates the degree of volume deficit. In the absence of poor concentrating capacity or osmotic diuresis, a specific gravity in excess of 1015 may signify dehydration while values that are less than 1010 may suggest adequate hydration.

Urine microscopy in acute tubular necrosis may demonstrate a non-specific finding of hyaline and granular casts, few white and red blood cells, and mild proteinuria. These urinary sediments of tubular injury are reversible, subsiding few days after a successful restoration of fluid status.

In severe dehydration, poor renal perfusion with impaired glomerular filtration causes an adaptive increase in tubular sodium and water absorption, leading to a fall in urine sodium concentration (UNa) to a value less than 20 mEq/L (Table 2). The fractional excretion of urinary sodium (FENa) is less than 1% (or <2.5% in neonates), tubular concentration capacity (U/Osmol > 500 mOsm/kg) is preserved while urinary creatinine

Table 2
Diagnostic Urinary Indices to Differentiate Pre-renal Azotemia and Intrinsic Kidney Injury

Urine test	*Pre-renal AKI*	*Intrinsic AKI*	*SIADH*
UNa (mEq/L)	<20	>40	>40
U/SG	>1020	<1010	Generally >1020
U/Osmol (mOsm/kg)	>500	<350	Generally >500
U/P Osmol	>1.3	<1.3	Generally >2
U/Cr (mg/dL)	>40	<20	>30
FENa	<1%	>1%	~1%

UNa = urine sodium, U/SG = urine specific gravity, U/Osmol = urine osmolality, U/P Osmol = urine: plasma osmolality ratio, U/Cr = urine creatinine, FENa = fractional excretion of sodium, AKI = acute kidney injury, SIADH = syndrome of inappropriate anti-diuretic hormone secretion.
FENa = [Urine Na/Plasma Na] × [Plasma Cr/ Urine Cr] × 100

(U/Cr) is greater than 40 mg/dL. On the other hand, the loss of tubular function in intrinsic AKI results in salt wasting (FENa > 3% or > 5–10% in neonates) and poor renal concentration (U/Osmol < 350 mOsm/kg) while impaired glomerular filtration causes a reduction in urine creatinine to a value below 20 mg/dL *(18*, *27)*.

Because of its correction for creatinine clearance, FENa is more sensitive (96% vs. 90%) and specific (95% vs. 82%) than urinary Na in differentiating pre-renal azotemia from intrinsic AKI. Unfortunately, accuracy of urine indices is confounded by excessive Na excretion in forced diuresis (e.g., furosemide and saline infusion). Therefore, these tests are only reliable when performed prior to institution of fluid challenge. However, given the limited diagnostic yield, therapeutic intervention should not be delayed on the account of these urinary indices *(18*, *27)*.

8. CLINICAL MANAGEMENT

Pre-renal AKI: To prevent irreversible kidney injury prompt correction of EC fluid depletion is mandatory. Clinical approach is a function of the underlying cause of renal hypoperfusion. While volume restoration is critical in hypovolemia, forced diuresis and ionotropic supports (e.g., milrinone) are needed in cardiac failure. Because kidney injury in sepsis syndrome is multi-factorial, therapeutic intervention must include correction of volume deficit, hypotension (e.g., dopamine and dobutamine), coagulopathy, and endotoxemia. In addition to the repair of fluid deficit in diabetic ketoacidosis, normoglycemia must be restored with insulin therapy. Immediate restoration of plasma oncotic pressure with slow infusion of 25% albumin and furosemide therapy will improve renal perfusion in severe nephrotic syndrome complicated by fluid overload. Exposure to therapeutic and diagnostic agents with a potential for renal insult such as hypotensive substances, renal vasoconstrictors (e.g., nonsteroidal anti-inflammatory drugs), radiopharmaceutical agents, and antibiotics (e.g., gentamicin) must be avoided or minimized. If toxic therapeutic agent (e.g., vancomycin) must be used, serum trough levels must be monitored to avoid renal injury *(18*, *27)*. At high risk of a permanent kidney injury are patients with a pre-existing glomerular impairment and a limited renal reserve, e.g., solitary

kidney, renal transplant, hypoplastic–dysplastic kidney, renal artery stenosis, and use of angiotensin receptor inhibitor.

Normal saline bolus with 10–20 ml/kg over 30 min to correct peripheral circulatory failure is of utmost priority *(28)*. Assessment of mental alertness, pulse rate, blood pressure, central venous pressure (CVP), and urine output (UOP) may signify adequacy of fluid resuscitation. Lack of urine output within 2 h of fluid resuscitation should warrant examination of bladder for distension. If unsure of bladder findings, urethral catheterization is performed to determine if there is urinary retention. For patients with central vascular access, in the absence of cardiac insufficiency CVP (5–10 cm H_2O) may indicate if there is adequate volume status. If there is no urine output in spite of adequate resuscitation, diuretic challenge may be attempted with an intravenous administration of 2–4 mg/kg furosemide. If oliguria persists (UOP < 0.5 ml/kg/h) furosemide dose may be repeated either as a bolus or as a continuous infusion. Failure of diuretic fluid challenge may indicate there is an intrinsic rather than pre-renal AKI *(18*, *27)*.

After a successful fluid resuscitation, volume deficit in severe dehydration is replaced as 10–15% of the body weight, moderate dehydration as 6–10%, and mild dehydration as 3–5%. Many cases of dehydration are treated with oral rehydration therapy (see Chapter 7).

Oliguric intrinsic AKI: Once there is an established kidney injury, modality of treatment will depend on the severity of glomerular filtration loss. To avoid fluid overload, intake is restricted to replace ongoing output (ml-for-ml) and the insensible water loss (400 ml/m^2/24 h) in oliguric kidney injury. To avoid sodium retention and fluid overload, metabolic acidosis is corrected only if severe (arterial pH < 7.15; serum bicarbonate <12 mEq/L). In addition, rapid correction of acidosis may decrease ionization of calcium and therefore precipitate hypocalcemic tetany. In the event of a concomitant metabolic acidosis and hyperkalemia, infusion of 1–2 mEq/kg of sodium bicarbonate over 5–10 min may normalize the serum potassium. Acidosis promotes hyperkalemia by supplying hydrogen ions for an exchange with intracellular potassium. Although furosemide diuresis does not increase renal survival in oliguric AKI, it may improve fluid control and increases renal clearance of potassium and hydrogen ions. Nebulization with albuterol solutions produces beta-agonist effect to stimulate intracellular uptake of potassium. Additional means of correcting hyperkalemia (>6 mEq/L) is the infusion of 0.1 units of regular insulin and 1 ml/kg 50% glucose over 1 h (drives potassium into the cells). Furthermore, oral or rectal administration of sodium polystyrene sulfonate resin (1 g/kg kayexalate) causes an exchange of Na for a fecal elimination of potassium *(18*, *27*, *29)*.

The risk of aggressive use of furosemide for volume control may outweigh its potential benefit, as it does not decrease the need for dialysis use and may in fact increase the risk of death because of delayed onset of dialysis therapy *(29)*.

Non-oliguric intrinsic AKI: In general, AKI without oliguria has a more favorable renal survival. Non-oliguric kidney injury requires a liberal fluid supply to replace the loss from the associated water diuresis. Furthermore, fluid requirement may vary with the phase of renal injury; thus the initial oliguria in ATN may give way to polyuria during the recovery phase. Hence frequent but scheduled evaluation of urine output and body weight is necessary to guide the amount of fluid requirement *(18*, *27)*.

Hyperhydration and reno-protection: Generous hydration may be required to enhance renal excretion of potentially toxic endogenous or exogenous substances. Thus there is a lower incidence of contrast nephropathy with the infusion of normal saline prior to cardiac catheterization than the control. Additionally, renal sparing benefit is observed with intravenous saline support (for volume expansion) and the use of non-ionic contrast agents (290–850 mOsm/kg) in radio-imaging studies *(29)*. Adequate hydration is also a necessity to minimize possible kidney injury from acute tumor lysis during chemotherapy. The same precaution is needed to protect kidney from oncologic irradiation injury. Furthermore, renal survival is increased with an early and aggressive fluid support in traumatic rhabdomyolysis *(27)*.

Renal replacement modality: Development of fluid overload, severe hyperkalemia (>6.5 mEq/L), intractable metabolic acidosis, and inability to maintain basic nutritional needs may necessitate a renal replacement therapy. The options available in AKI are acute peritoneal dialysis (PD), acute hemodialysis (HD), and continuous renal replacement therapy (CRRT). Acute PD is a practical choice for infants because of the limited option for vascular access. Although not as technologically advanced as CRRT, it may be used in an unstable patient with hypotension. Because solute clearance is remarkably slow, PD is of no use in rapid removal of poisons or toxic metabolites (inborn errors of metabolism). Hemodialysis is the treatment of choice in systemic intoxication (e.g., acetyl salicylate poisoning) or in a sudden fluid overload. Dialysis is not an appropriate modality in the removal of any toxic substance with a wide body tissue distribution. Patients with unstable hemodynamic status (e.g., sepsis) are preferably managed with CRRT rather than a conventional dialysis. Because of improved technology, modern conventional hemodialysis may be run slowly and for longer hours to achieve a bio-equivalent outcome with the CRRT in selected patients. Although quite efficient for ultrafiltration and dialysis, use of CRRT in AKI does not improve renal outcome or mortality rate *(18*, *27*, *30)*.

9. KIDNEY TRANSPLANTATION: FLUID AND ELECTROLYTES

During the immediate pre-operative care of renal transplant recipients efforts should be made to avoid dehydration in order to minimize the risk of allograft hypoperfusion. Similarly, the potential recipients on chronic dialysis are prone to peri-operative pulmonary edema because of a cumulative fluid retention. The need for a pre-transplant dialysis must be individualized depending on the fluid status, time of the last dialysis, presence of residual renal function, and type of electrolyte disorders. Immediate dialysis should be instituted to correct pre-operative hyperkalemia [serum $K > 5.5$] or metabolic acidosis [serum $HCO_3 < 18$]. Fluid removal is minimized during pre-operative dialysis to protect the transplanted kidney from poor perfusion and a delayed graft function *(31*, *32)*.

A pre-requisite for successful kidney transplantation is an optimal cooperation between nephrology and transplant surgical teams. An adequate knowledge of the peculiar clinical characteristics of both the allograft recipient and donor is invaluable. For an example, the nature of the primary renal disease may influence the fluid status of the recipient. Thus a poor tubular concentrating capacity in children with a previous

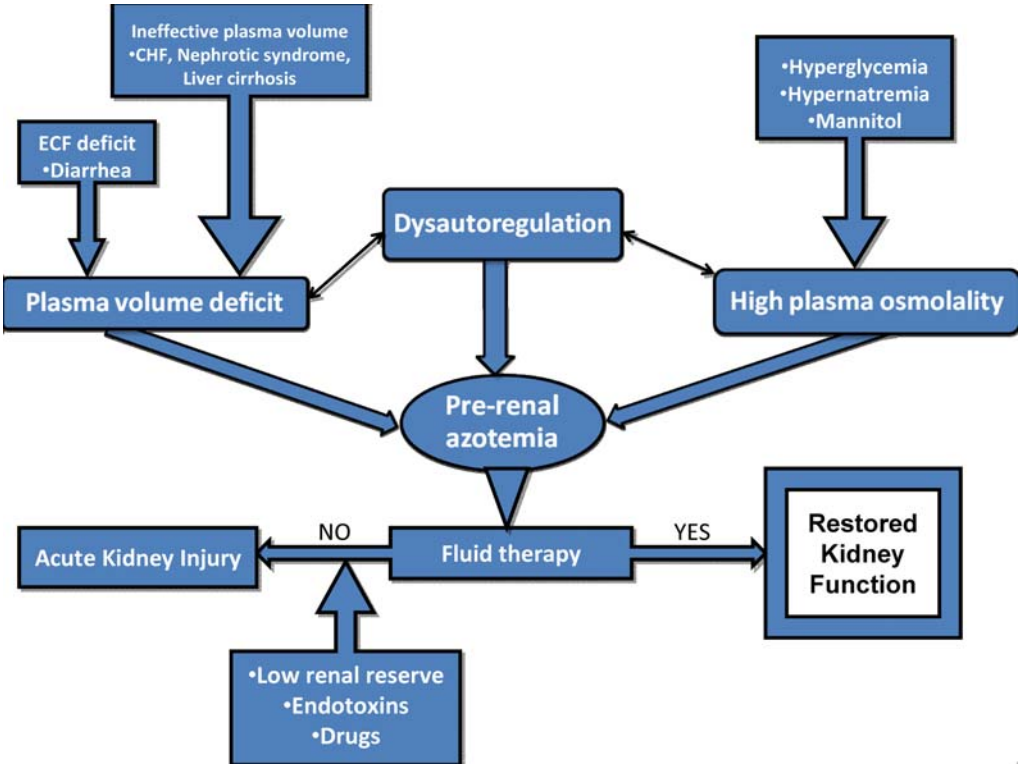

Fig. 1. Schematic illustration of the relationship between fluid and electrolyte dysregulation and acute kidney injury.

obstructive uropathy may result in a negative fluid balance. On the other hand, increased total body water is likely in hypoalbuminemia from a pre-existing nephrotic syndrome. Furthermore, patients with long-standing kidney disease may have a limited cardiac reserve due to uremic-induced diastolic dysfunction, dysautonomia, and chronic hypertension *(32)*.

Small-sized pediatric patients (<10 kg) are particularly at risk of allograft vein thrombosis because of the disparity between body mass, kidney volume, and size of the renal vessels. Adequate perfusion of the donor kidney is readily undermined by the diminutive systemic pressure and low blood volume that are typical of pediatric recipients. Consequently, the transplanted kidney is prone to vascular thrombosis from poor plasma perfusion, ischemic endothelial injury, and surgery-related mechanical stress. To minimize the occurrence of vascular thrombosis, enough fluid is administered during surgery to maintain CVP at 16–20 cm H_2O prior to allograft vascular anastomosis. Use of 5% albumin may be preferred if serum albumin is <2.5 g/dL. Sometimes, the volume of intra-operative fluid required to sustain an adequate perfusion may lead to the development of post-operative pulmonary edema (29%) and a need for assisted ventilation (8.3%) *(33, 34)*.

Intra-operative administration of (hypertonic) mannitol solution has the potential not only to enhance allograft perfusion but it also minimizes oxidative stress (as a free

oxygen radical scavenger) from ischemic reperfusion injury. Pulse steroid therapy, though primarily used for immuno-suppression, may increase vasoactivity and improve renal blood flow. Immediate UOP after allograft vascular anastomosis is a good indicator of an adequate renal perfusion. In the absence of prolonged ischemia, brisk diuresis occurs within few minutes of surgical anastomosis. Initial urine output is massive because of osmotic effect of urea nitrogen load, intra-operative fluid challenge, and mobilization of retained body water from chronic kidney disease *(32, 35)*.

Prolonged cold ischemia, inadequate renal perfusion, and loss of autoregulation in a denervated graft are predisposing factors for a delayed function. Post-operatively, adequate fluid input must be maintained by keeping CVP between 8 and 10 cm H_2O. Estimated from the average daily urinary Na excretion (>40 mEq/L) and gastric Na secretion (20–80 mEq/L), post-transplant loss of urine or nasogastric secretions is replaced ml-for-ml with half-normal saline (77 mEq/L). The insensible water loss is replaced with 5% dextrose water as 45–50 ml/100 kcal of daily energy expenditure. Insensible water loss may also be crudely estimated as 40–50% of the maintenance fluid requirements *(31, 32)*.

Frequent evaluation of fluid status is essential to allow for adjustment in intake if necessary. Normal saline fluid boluses (10–20 ml/kg body weight) is given if there is a fall in CVP below 7 cm H_2O and/or reduction in UOP below 1–2 ml/kg/h and/or progressive fall in BP below the baseline. If there is no increase in UOP after 2–3 boluses of NS, forced diuresis with furosemide may be attempted. Absence of urine output in spite of an elevated CVP is another reason for a furosemide diuresis. It should be noted that forced diuresis does not necessarily improve graft outcome; its major advantage is to forestall fluid overload and postpone an immediate need for dialysis *(31, 32)*.

The rate of intravenous fluid infusion is reduced by 25% every 1 h if urine output exceeds 5 ml/kg/h. Urine volume should be maintained at 2–5 ml/kg/h. Post-ischemic diuresis may follow the recovery of renal allograft from ATN. Therefore, inadequate fluid support may compromise long-term allograft function *(31)*.

CASE SCENARIO

AR is an 11-year-old African American female who was previously healthy until few months prior to the presentation at a local emergency room (ER). She had anorexia, sleepiness, body weakness, and close to 15 kg weight loss in the last five months. She had an increased frequency of emesis in the last few weeks, and an associated diarrhea for 3 days. Her current medications included "apple cider vinegar" and an unidentified "enzyme supplement;" both of which were obtained from a health food store for symptomatic relief. Her perinatal history was uneventful and immunization was up to date.

What in the history suggests a possible diagnosis of kidney injury?

The history highlights a common clinical scenario in the presentation of chronic kidney disease. This girl had been sick for a minimum of 5 months. She presented with protracted uremic symptoms but apparently because of an adequate renal reserve visit to the ER was avoided until the later phase of the illness. Uremia alters the control of

hunger–satiety cycle by increasing brain secretion of anorectic serotonin, and causing a decreased synthesis of (appetite stimulant) neuropeptide Y. In addition to low caloric intake, catabolism with weight loss is promoted by pro-inflammatory cytokines (IL-1), elaboration of leptin, and metabolic acidosis. Anemia and metabolic acidosis are contributory to body weakness and somnolence. The protracted symptoms, in the setting of a poor accessibility to health care services, may promote risky behavior such as seeking homeopathic medicine or over-the-counter therapy. Often, these non-FDA approved alternative agents (largely untested for nephrotoxicity) may cause further kidney injury. Medication such as nonsteroidal anti-inflammatory drug may also cause a rapid loss in renal function leading to deterioration in a compensated kidney disease. Her symptoms progressively worsen over the months, and in the last 1 week an acute deterioration necessitates urgent medical services.

What are the common chronic kidney diseases in which family history could be helpful in making diagnosis?

Common kidney diseases with strong family history are Alport nephritis (X-linked or autosomal inheritance), polycystic kidney disease (autosomal recessive or dominant), and nephrogenic diabetes insipidus (X-linked or autosomal). Focal segmental glomerulosclerosis (FSGS) is a common cause of nephrotic syndrome particularly in African American population. FSGS is heterogeneous kidney disease, some of which have clearly defined genetic mutation that involves functional integrity of podocytes (a component of foot process in the glomerulus; important for ultrafiltration).

The family history in this patient is highly suspicious of a possible diagnosis of FSGS. Both parents and a maternal aunt were on dialysis for end-stage kidney disease. Except for the maternal aunt who had a preceding nephrotic syndrome the etiology of end-stage kidney disease was unknown in both parents. Her paternal grandmother died of chronic kidney disease. Her 20-year-old brother and 14-year-old sister were healthy, and both had tested negative for proteinuria. Review of the system was unremarkable.

If this is an acute on chronic kidney injury, what are the expected physical findings?

Protracted fluid loss might have resulted in dehydration. On the other hand, long standing oliguria may predispose to fluid retention including body edema, congestive heart failure (CHF), and pulmonary edema. Severe hypertension with or without encephalopathy is a likely complication. Advanced kidney disease may present with anemia because of erythropoietin deficiency or dilutional effect of fluid retention. Deficient 1-alpha hydroxylation of 25-vitamin D and secondary hyperparathyroidism may result in hypocalcemia. Impaired glomerular filtration reduces renal phosphate clearance. Metabolic acidosis may lead to lethargy and acidotic hyperventilation. Hyperkalemia is a possible complication due to impaired potassium clearance and an extracellular shift of potassium in exchange for hydrogen ions. On the other hand, she may also have hypokalemia because of the protracted emesis and total body potassium depletion from skeletal muscle wasting.

Her clinical and laboratory findings reflect a number of the projected possibilities: she had a normal mental status, good nutritional status, moderate pallor, mild–moderate dehydration, but there was no jaundice, body edema, or peripheral adenopathy. Her axillary temperature was 99°F, pulse rate 75/min, RR 20/ min, BP 162–177/100–115 mmHg,

and pulse oximetry was 99% in room air. Her height was 153 cm and weight was 48.7 kg. Other physical findings were not clinically significant.

Laboratory analysis: WBC was 5.1, hemoglobin 8.1 gm/dL, hematocrit 22.6%, and platelet count was 145,000. Serum Na was 137 mEq/L, K 2.6 mEq/L, Cl 97 mEq/L, HCO_3 19 mEq/L, glucose 77 mg/dL, BUN 93 mg/dL, Cr 18.7 mg/dL, Ca 4.3 mg/dL, P 9.6 mg/dL, and albumin 4.1 gm/L. Urine had a pH of 6.5, protein was >300 mg/dL, was positive for ketones, but glucose was negative. EKG showed a prolonged QTc interval with no arrhythmia. Echocardiogram showed a mild decrease in ventricular contractility.

Her calculated GFR (cGFR) by Schwartz formula is

$$\text{cGFR} = \text{k} \times \text{Ht (cm)}/\text{Serum Cr (mg/dL)} = 0.55 \times 153/18.7 = 4.7\,\text{ml/min/1.73m}^2$$

(k; proportionality constant for age and sex = 0.55)

$$\%\,\text{loss in GFR} = \text{eGFR} - \text{cGFR}/\text{eGFR} \times 100 = 127 - 4.7/127 \times 100 = 96.3\%$$

(where eGFR = estimated normal GFR for age)

Using the pRIFLE criteria (see Table 1), she has a stage 3 AKI or acute kidney failure (AKF). Thus, most likely she has an acute loss in GFR on a pre-existing kidney injury. Because there is hardly any chance for renal recovery, a chronic maintenance dialysis will be ultimately required.

Note that she presented with a weight of 48.7 kg which is >90th percentile for height. With the loss of 15 kg in the course of the illness her real weight exceeds 64 kg (>99th, percentile for height). Using the baseline weight to calculate her body mass index (BMI), the value equals 28.4 kg/m^2 (which is >95th percentile = 26 kg/m^2). Thus obesity is a contributing factor to the kidney failure. The ensuing weight-loss in the course of her illness is an adaptive mechanism by the kidney to minimize the metabolic load of obesity. This is one of the reasons why kidney may be so resilient, and why kidney injury may last long before obvious clinical manifestation.

What are the immediate and long-term therapeutic concerns?

Life-threatening complications must be addressed immediately including cardiac toxicity (prolonged QTc) from hypocalcemia and/or hypokalemia and correction of fluid deficiency. Infusion of bicarbonate was not a priority because of its less severe deficit and due to the danger of hypocalcemic tetany. Blood transfusion may be avoided if there are no symptoms attributed to anemia. Otherwise, it may be given during dialysis to avoid fluid overload in the presence of oliguric kidney injury. Severe hypertension should be reduced slowly (50–75% over 24 h) with oral antihypertensive agents in the absence of symptoms. If there is hypertensive encephalopathy, immediate intravenous therapy with nicardipine, labetalol, diazoxide, or sodium nitroprusside is administered. After the initial hemodynamic stability, central dialysis catheter is inserted and acute hemodialysis is provided. To maintain fluid and electrolyte homeostasis, and restore important renal function deficit, chronic dialysis is offered while supportive care is instituted for anemia, Vitamin D deficiency, hyperphosphatemia, hypertension, and nutritional deficit. Dialysis modality is not an end in itself but a transitional procedure that will allow for eventual renal allograft transplantation.

Acute therapy for the patient included infusion of 5% dextrose and half saline with 20 mEq/L per liter of potassium chloride to correct dehydration and hypokalemia, intravenous Ca gluconate for severe hypocalcemia (restoring EKG changes back to normal), and thereafter acute hemodialysis. Chronic supportive care included home peritoneal dialysis, sevelamer hydrochloride as phosphate binder, erythropoietin for anemia, nifedipine for hypertension, and 1, 25 Vitamin D as maintenance therapy for Ca deficiency.

After an extensive pre-transplant work up, she was placed on a waiting list for cadaveric transplantation. Ten months after the initial diagnosis, she was offered the kidney of a 31-year-old head injury victim of a motor vehicle accident. Cold ischemic time for the allograft was 10 h. She had oliguria in the first 3 h of surgery with urine output of 15–20 ml/h. Although BP was 150/95 mmHg, CVP was low, 2–5 cm H_2O. She received three boluses of normal saline, which was followed by a prompt increase in rate of UOP to 100–150 ml/h. Blood urea nitrogen was 48 mg/dL, while serum Cr was 18.8 mg/dL shortly after the graft surgery. By post-operative day 3, serum creatinine had decreased to 7.4 mg/dL while by the 7th day the Cr was 1.6 mg/dL.

REFERENCES

1. Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P and the ADQI workgroup. Acute renal failure – definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference on the Acute Dialysis Quality Initiative (ADQI) Group. Crit Care 2004, 8 (4): R204–R212
2. Mehta RL, Kellum JA, Shah SV, Mollitoris BA, Ronco C, Warnock DG, Levin A. Acute kidney injury network: report of an initiative to improve outcomes in acute kidney injury. Crit Care 2007, 11(2): R31
3. Akcan-Arikan A, Zappitelli M, Loftis LL, Washburn KK, Jefferson LS, Goldstein SL. Modified RIFLE criteria in critically ill children with acute kidney injury. Kidney Int 2007, 71(10): 1028–1035
4. Barrantes F, Tian J, Vazquez R, Amoateng-Adjepong Y, Manthous CA. Acute kidney injury criteria predict outcomes of critically ill patients. Crit Care Med 2008, 36(5): 1397–1403
5. Doolan PD, Alpen EL, Theil GB. A clinical appraisal of the plasma concentration and endogenous clearance of creatinine. Am J Med 1962, 32: 65–72
6. Lassnigg A, Schmid ER, Hiesmayr M, Falk C, Druml W, Baeuer P, Schmidlin D. Impact of minimal increase in serum creatinine on outcome in patients after cardiothoracic surgery: do we have to revise current definitions of acute renal failure? Crit Care Med 2008, 36(4): 1129–1137
7. Chertow GM, Burdick E, Honour M, Bonventre JV, Bates DW. Acute kidney injury, mortality, length of stay, and costs in hospitalized patients. J Am Soc Nephrol 2005, 16:3365–3370
8. Herrero-Morin JD, Malaga S, Fernandez N, Rey C, Dieguez MA, Solis G, Concha A, Medina A.. Cystatin C and beta2-microglobulin: markers of glomerular filtration in critically ill children. Crit Care 2007, 11: R59
9. Bennett M. Urine NGAL predicts severity of acute kidney injury after cardiac surgery: a prospective study. Clin J Am Soc Nephrol 2008, 3(3): 665–673
10. Parikh CR, Devarajan P. New bio-markers of acute kidney injury. Crit Care Med 2008, 36: S159–S165
11. Mehta RL, Chertow GM. Acute renal failure definitions and classification: Time for change? J Am Soc Nephrol 2003, 14: 2178–2187
12. Zappitelli M, Washburn KK, Arikan AA, Loftis LL, Ma Q, Devarajan P, Parikh CR, Goldstein SL. Urine neutrophil gelatinase-associated lipocalin is an early marker of acute kidney injury in critically ill children: A prospective cohort study. Crit Care 2007, 11(4): R84
13. Galloway E, Doughty L. Electrolyte emergencies and acute renal failure in pediatric critical care. Clin Pediatr Emerg Med 2007, 8(3): 176–189

14. Bailey D, Phan V, Litalien C et al. Risk factors of acute renal failure in critically ill children: A prospective descriptive epidemiological study. Pediatr Crit Care Med 2007, 8: 29–35
15. Iglesias J, Lieberthal W. Clinical evaluation of acute renal failure. In: Johnson RJ, Feehaly J, eds. Comprehensive clinical nephrology, 1st edn. London: Mosby, 2000, (4): 15.1–15.16
16. Detaille T, Anslot C, de Clety SC. Acute kidney injury in pediatric bone marrow patients. Acta Clin Belg Suppl 2007, 2:401–404
17. Wolfson RG, Hillman K. Causes of acute renal failure. In: Johnson RJ, Feehaly J, eds. Comprehensive clinical nephrology, 1st edn. London: Mosby, 2000, (4): 16.1–16.15
18. Khalil P, Murty P, Palevsky PM. The patient with acute kidney injury. Primary Care: Clinics in Office Practice 2008, (35): 239–264
19. Greenbaum LA. The pathophysiology of body fluids and fluid therapy. In: Kliegman RM, Behrman RE, eds. Nelson textbook of pediatrics, 18th edn. Philadelphia, PA: Saunders Elsevier, 2007, (52): 300–319
20. Moritz ML, Ayus JC. Preventing neurological complications from dysnatremias in children. Pediatr Nephrol 2005, 20(12): 1687–1700
21. Orbach H, Katz U, Sherer Y, Shoenfeld Y. Intravenous immunoglobulin: adverse effects and safe administration. Clin Rev Allergy Immunol 2005, 29(3): 173–184
22. Thakar CV, Worley S, Arrigain S, Yared JP, Paganini EP. Improved survival in acute kidney injury after cardiac surgery. Am J Kidney Dis 2007, 50(5): 703–711
23. Ranucci M. Perioperative renal failure: hypoperfusion during cardiopulmonary bypass? Semin Cardiothorac Vasc Anesth 2007, 11(4): 265–268
24. Alkan T, Akcevin A, Turkoglu H, Paker T, Sasmazel A, Bayer V, Ersoy C, Askn D, Aytac A. Preoperative prophylactic peritoneal dialysis in neonates and infants after complex congenital cardiac surgery. ASAIO J 2006, 52(6): 693–697
25. Sharp LS, Rozycki GS, Feliciano DV. Rhabdomyolysis and secondary renal failure in critically ill surgical patients. Am J Surg 2004, 188(6): 801–806
26. Wathen JE, MacKenzie T, Bothner JP. Usefulness of the serum electrolyte panel in the management of pediatric dehydration treated wit intravenously administered fluids. Pediatrics 2004, 114(5): 1227–1234
27. Vogt BA, Avner ED. Acute renal failure. In: Kliegman RM, Behrman RE, eds. Nelson Textbook of Pediatrics, 18th edn. Philadelphia, PA: Saunders Elsevier, 2007, (535): 2206–2209
28. Neville KA, Verge CF, Rosenberg AR, O'Meara MW, Walker JL. Isotonic is better than hypotonic saline for intravenous rehydration of children with gastroenteritis: a prospective randomized study. Arch Dis Child 2006, 91(3): 226–232
29. Venkataraman R. Can we prevent acute kidney injury? Crit Care Med 2008, 36(4): S166–S171
30. 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(4): 229–237
31. Brenan DC. Immediate postoperative management of the kidney transplant recipient. In: Norman DJ, Turka LA eds. Primer on Transplantation 2nd edn. New Jersey: American Transplantation Society, 2001, (54): 440–451.
32. Urizar RE.. Renal Transplantation. In: Kliegman RM, Behrman RE, eds. Nelson Textbook of Pediatrics, 18th edn. Philadelphia, PA: Saunders Elsevier, 2007, (536): 2214–2219
33. Chavers B, Najarian JS, Humar A. Kidney transplantation in infants and small children. Pediatr Transplant 2007, 11(7): 702–708
34. Sprung J, Kapural L, Bourke DL, O'Hara JF Jr. Anesthesia for kidney transplant surgery. Anesthesiol Clin North Am 2000, 18(4): 919–951
35. Markmann JF, Yeh H, Naji A, Olthoff KM, Shaked A, Barker CF. Transplantation of abdominal organs. In: Townsend CM Jr. ed., Sabiston Textbook of Surgery, 18th ed. Philadelphia, PA: Saunders Elsevier 2008, (28): 692–707