

Managing Fluid and Electrolyte Disorders in Renal Failure

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The kidneys are responsible for maintaining homeostasis in the body; kidney failure typically leads to derangements of fluid, electrolyte, and acid-base balance. The goal of treatment is to correct these derangements. Kidney disease is classified into acute and chronic disease, which is a convenient way to view what frequently are markedly different manifestation syndromes. Acute and chronic kidney disease (CKD) may vary from mild to severe. Many patients with acute kidney injury (AKI) require hospitalization for optimal management. Patients with CKD may present in a decompensated state and need hospitalization, or their fluid and electrolyte disturbances may be managed on an outpatient basis. Despite the different types of kidney disease, many of the principles of fluid and electrolyte management are the same regardless of the underlying cause.

Intrinsic renal failure occurs when damage to the renal parenchyma occurs. The damage may be reversible or irreversible and can include damage to the glomeruli, tubules, interstitium, or renal vasculature. Prerenal azotemia occurs when blood flow to the kidney is decreased, as may occur with hypovolemia, hypotension, or increased renal vascular resistance. Prerenal azotemia is rapidly reversible once the underlying disorder has been controlled. Postrenal azotemia occurs when there is an obstruction to urine flow, from the level of the renal pelvis to the urethra, or when urine leaks into surrounding tissue and is reabsorbed (eg, ruptured bladder, ureter, or urethra). Postrenal azotemia also can be reversed rapidly by diverting the urine with a urinary catheter or peritoneal catheter (in cases of an intra-abdominal urinary tract rupture). With prerenal and postrenal causes of azotemia, longstanding problems may progress to intrinsic renal failure. Although substantial renal disease can be present without azotemia, fluid therapy generally is not necessary in those situations. In fact, fluid therapy may not be necessary in cases of compensated chronic renal failure with mild to moderate azotemia.

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FLUID TREATMENT

Normal fluid losses consist of insensible and sensible losses. Insensible losses are those that are not easily measured, such as water lost via respiration, normal stool, or sweating. Sweating is negligible in dogs and cats. Respiratory losses vary, and dogs can lose considerable amounts of fluid by excessive panting, but 22 mL/kg/d is the average. The main sensible fluid loss in the normal patient is urine output. Additional sensible losses include the volume lost from vomiting, diarrhea, body cavity drainage, and burns. In healthy animals, these losses are replaced by drinking water and the fluid contained in food. In sick animals that may not be voluntarily consuming food or water or may be restricted from consumption because of vomiting, fluid therapy is necessary to replace these losses. With renal disease, urine volume frequently is abnormally high or low or inappropriate for the situation, and fluid therapy is tailored for the individual patient to maintain fluid balance.

FLUID THERAPY FOR HOSPITALIZED PATIENTS

Although oliguria and anuria are the classic manifestations of AKI, it may present with polyuria, which frequently portends less severe renal injury [1,2]. AKI also may be indicated by a subtle increase in serum creatinine concentration ($> 50\%$ of baseline) or urine volume inappropriate for the volume of fluid administered. In this early stage of injury, attempts to limit further renal damage are warranted. Patients with CKD may present in a decompensated uremic crisis, which may represent AKI superimposed on chronic disease.

Many drugs have been evaluated for their benefit in treating AKI, and some are helpful in certain settings. The most effective therapy of AKI is careful management of fluid balance, however, which involves thoughtful assessment of hydration, a fluid treatment plan personalized for the specific patient, repeated and frequent reassessment of fluid and electrolyte balance, and appropriate changes in the treatment plan in response to the rapidly changing clinical situation of the patient.

ASSESSING HYDRATION

The key feature to an appropriate fluid plan is accurate determination of hydration status. Blood volume can be measured using indicator dilution techniques, radioactive tracers, bioimpedance spectroscopy, or other methods. Unfortunately, readily available accurate measurement of blood volume is not feasible in general practice settings.

Despite a lack of precise objective data, there are many ways to estimate hydration. A deficit of the extravascular fluid compartment (interstitial and intracellular) causes dehydration. A severe deficit may decrease the intravascular compartment and lead to poor perfusion. Dehydration of less than approximately 5% is difficult to detect clinically. A 5% to 6% deficit leads to tacky mucous membranes. Six percent to 8% dehydration causes dry mucous membranes and decreased skin elasticity. By 8% to 10% dehydration, the eyes may be sunken; with more than 12% dehydration, the corneas are dry, mentation is

dull, and perfusion is impaired [3]. Overhydration may be manifested by wet mucous membranes, increased skin elasticity (heavy or gelatinous), shivering, nausea, vomiting, restlessness, serous nasal discharge, chemosis, tachypnea, cough, dyspnea, pulmonary crackles, pulmonary edema, pleural effusion, ascites, diarrhea, or subcutaneous (SC) edema (especially in the hocks and intermandibular space) [4,5].

Interpretation of these physical findings can be difficult. Patients with uremia frequently have xerostomia, which causes dry mucous membranes independent of hydration status. Hypoalbuminemia or vasculitis may cause interstitial fluid accumulation despite an intravascular volume deficit. Emaciation or advanced age decreases elasticity of the skin.

Central venous pressure (CVP) measurement using a centrally placed intravenous (IV) catheter may provide information about intravascular filling. A volume-depleted animal has a CVP less than 0 cm H₂O. A CVP of more than 10 cm H₂O is consistent with volume overload or right-sided congestive heart failure [6]. Pleural effusion falsely increases CVP, however [7]. An accurate body weight recorded before illness is an invaluable aid to assessing hydration. Body weight should be measured at least twice a day on the same scale to monitor fluid balance. A sick animal may lose up to 0.5% to 1% body weight per day because of anorexia; changes in excess of this amount are caused by changes in fluid status [8]. An increase in blood pressure may indicate a gain of fluid. Conversely, a decrease in blood pressure may indicate a net loss of fluid. Because of the high percentage of patients with hypertension (80% of dogs with severe acute uremia and 20%–30% of dogs and cats with CKD), the trend rather than the absolute value is of more use in assessing changes in hydration status [4,9,10]. Similarly, changes in trends for packed cell volume and total solids may reflect changes in volume in the absence of bleeding or blood transfusion. Because each variable is impacted by factors other than hydration status, these factors must be viewed in aggregate.

ROUTE OF FLUID ADMINISTRATION

In most hospitalized patients, the IV route is the most appropriate route of fluid administration. In some situations, such as with extremely small patients, including neonates or young puppies or kittens, IV catheterization may be difficult. Intraosseous fluid administration can be used in that setting. In dehydrated patients, fluids administered into the peritoneal cavity are readily absorbed, but this method is not reliable for promoting diuresis or in patients with oliguria. Fluid administered SC may not be absorbed rapidly or completely, and it is not possible to administer a large volume by this route, which makes SC fluid administration inappropriate for the hospital setting. It may, however, play a role in outpatient therapy (see later discussion).

TYPE OF FLUID

A balanced polyionic solution (eg, lactated Ringer's solution, Plasmalyte-148, Normosol-R) is an appropriate choice for initial volume resuscitation and

replacement of the dehydration deficit. Physiologic (0.9%) NaCl contains no potassium and is a suitable initial choice for patients with hyperkalemia. After rehydration, maintenance fluids with a lower sodium concentration are more appropriate (eg, 0.45% NaCl with 2.5% dextrose, half-strength lactated Ringer's solution with 2.5% dextrose). Dextrose 5% in water is rarely appropriate as the sole fluid choice, but it may be combined with lactated Ringer's solution or 0.9% saline to make half- or three-quarter-strength sodium solutions (25 mL lactated Ringer's solution + 25 mL dextrose 5% in water = 50 mL half-strength lactated Ringer's solution + 2.5% dextrose).

Colloidal solutions (eg, hydroxyethyl starch, 6% dextran) may be appropriate if hypoalbuminemia is present. Hypoalbuminemia may be present with protein-losing nephropathy, diseases associated with vasculitis, or severe gastrointestinal losses or bleeding. The recommended dosage is 20 mL/kg/d, and it may be used to replace the insensible portion when using the “ins-and-outs” method (see later discussion). Higher dosages may be associated with coagulopathy. An alternative to synthetic colloids is human albumin, but use of this product carries a risk of anaphylaxis [11,12].

Treatment of the patient with acute uremic crisis caused by protein-losing nephropathy with severe hypoalbuminemia presents additional considerations. The increased intravascular volume and hydrostatic pressure from crystalloid infusion are not balanced by adequate colloid osmotic (oncotic) pressure in the plasma, which enhances interstitial edema in the periphery. Even with concurrent administration of a colloid, aggressive diuresis with a crystalloid may not be possible without creating peripheral edema. Loss of antithrombin III in the urine causes a hypercoagulable state, which may cause complications associated with IV catheterization.

Anemia may be present in acute and chronic renal failure. Red cell survival is shorter in the uremic environment, blood sampling may create substantial losses, and erythropoietin production generally is suppressed. Gastrointestinal bleeding can acutely cause anemia, and if bleeding is brisk, hypotension and hypovolemia may occur and require rapid infusion of crystalloid or synthetic colloid solutions. Red blood cell transfusion may be indicated if symptomatic anemia is present. Intensive diuresis may exacerbate high output heart failure in cats with anemia. Conversely, rapid blood transfusion may cause congestive heart failure. In patients with compromised cardiovascular function or incipient volume overload, red blood cell transfusion may need to be given more slowly than usual.

A sometimes overlooked fluid choice is water given enterally. Because vomiting is a common problem with uremia, enteral food or water frequently is contraindicated, and many patients with uremia do not voluntarily consume water. Water administered through a feeding tube should be included in water calculations, however.

Ultimately, the fluid choice must be guided by monitoring the patient's fluid and electrolyte balance. A major determining factor in the appropriate fluid choice is the serum sodium concentration, because the degree of free water loss relative to sodium loss varies greatly in patients with AKI. The guiding

principle in treating a sodium disorder is to reverse it at the same rate at which it developed, because rapid increases or decreases in serum sodium concentration may cause central nervous system dysfunction (see later discussion).

VOLUME AND RATE

Some patients may present in hypovolemic shock, which is manifest as dull mentation, hypotension (systolic blood pressure < 80 mm Hg), poor perfusion of the periphery (eg, cold extremities, pale or gray mucous membranes with slow capillary refill time), hypothermia, and tachycardia [6]. Immediate correction of shock is necessary to prevent irreversible organ damage. The standard dosage of crystalloids is 60 to 90 mL/kg for dogs and 45 to 60 mL/kg for cats, of which 25% is given over 5 to 15 minutes [13]. If hemodynamic parameters do not improve sufficiently with the first 25% dose, a second dose should be given. Resuscitation efforts are continued until the patient is hemodynamically stable. If the patient remains hypotensive and there are concerns about volume overload, CVP monitoring may be helpful. A CVP less than 0 cm H₂O indicates hypovolemia, whereas a CVP more than 10 cm H₂O is a contraindication to further fluid therapy. A 10- to 15-mL/kg bolus of crystalloid or 3- to 5-mL/kg bolus of colloid does not change CVP in patients with hypovolemia but transiently increases CVP by 2 to 4 cm H₂O in patients with euvolemia and causes an increase of more than 4 cm H₂O in patients with hypervolemia [6]. Adequate resuscitation (as assessed by achievement of identifiable goals) decreases renal morbidity in people as compared to standard resuscitation doses [14].

For patients that present with dehydration, the dehydration deficit is calculated as body weight (in kilograms) \times estimated % dehydration = fluid deficit in liters. Because dehydration less than 5% cannot be detected by clinical examination, a 5% dehydration deficit is assumed in patients with AKI that appear normally hydrated. If a fluid bolus was used for initial resuscitation, that volume is subtracted from the dehydration deficit.

The rate at which to replace the dehydration deficit depends on the clinical situation. In patients with AKI that presumably have become dehydrated over a short period of time, rapid replacement is indicated. This approach restores renal perfusion to normal and may prevent further damage to the kidneys. In situations in which urine output may be decreased, rapid replacement of the dehydration deficit to normalize fluid status allows the clinician to quickly determine if oliguria is an appropriate response to volume depletion or is a pathologic change arising from renal damage. In this setting, replacing the deficit in 2 to 4 hours is recommended. If diastolic cardiac function is impaired, a rapid fluid bolus may precipitate congestive heart failure, and a more gradual rehydration rate (ie, over 12–24 hours) may be prudent. In patients with chronic dehydration, a more gradual replacement of the fluid deficit is acceptable to minimize the risk of cardiac problems or excessively rapid changes in serum electrolyte concentrations; 24 hours is a commonly selected time frame. In severely dehydrated, chronically debilitated patients, it may take up to 48 hours to achieve rehydration.

The concept of the maintenance fluid rate is based on average fluid losses from insensible (eg, respiration) and sensible (eg, urine output) sources. There are various published values for maintenance fluid therapy, the most commonly quoted of which is 66 mL/kg/d. Ignoring normal individual variation, the assumption with this value is that urine output is normal and there are no other sources of fluid loss, which is rarely the case in patients with renal failure. This figure provides a reasonable starting point for calculating fluid administration volumes, however. If accurate measurement of urine output and ongoing losses can be documented, fluid therapy can be adjusted precisely (see “ins-and-outs” method later). If these variables cannot be measured accurately, an estimate of the loss should be included in the fluid administration rate. In practical terms, after initial fluid resuscitation for shock, the volume of fluid to administer is calculated by adding average maintenance fluid needs (66 mL/kg/d) plus replacement of dehydration (over a selected time frame) plus ongoing losses (eg, estimated volume of polyuria, vomiting).

Because uremic toxins are retained in renal failure, administration of a volume of fluid that exceeds “maintenance” can improve excretion of some uremic toxins in animals with the ability to increase urine output in response to a fluid challenge. The volume is varied based on the clinical situation and clinician preferences, but generally ranges from 2.5% to 6% of body weight per day in addition to the maintenance fluid administration rate. In practical terms, twice the maintenance fluid rate is equivalent to a maintenance rate plus a 6% “push” for diuresis ($60 \text{ mL/kg/d} = 6\%$ of body weight).

If the urine output deviates substantially from normal—whether oliguria ($< 0.5 \text{ mL/kg/h}$) or polyuria ($> 2 \text{ mL/kg/h}$)—a fluid plan based on these assumptions may be inadequate. Animals with renal failure may have urine output in the normal range ($0.5\text{--}2.0 \text{ mL/kg/h}$), but if their kidneys are unable to alter urine volume to excrete a fluid load, the patient has “relative oliguria.” The “ins-and-outs” method of fluid administration is appropriate in these situations. It should be used only after rehydration is complete and is not appropriate if the patient is still dehydrated. The three components of volume calculations in the “ins-and-outs” method consist of (1) insensible loss (fluid lost via respiration and normal stool = 22 mL/kg/d), (2) urine volume replacement calculated by actual measurement (see later discussion for measuring techniques), and (3) ongoing losses (eg, vomiting, diarrhea, body cavity drainage) that are usually estimated.

To write treatment orders for “ins-and-outs” using two IV catheters, divide the daily insensible loss by 4 to determine the every-6-hour dose of IV fluid for one catheter (Box 1). One may then use this fluid dose to deliver any drugs that need to be given by constant rate infusion (CRI) (eg, metoclopramide, furosemide, mannitol), being cognizant of drug incompatibilities. For the starting fluid dose, select a volume based on an estimate of the patient’s needs. The fluid rate is then recalculated every 6 hours. Use the previous 6-hour urine output volume plus an estimate of losses during that time period (eg, vomiting, diarrhea) as the volume to deliver over the next every-6-hours treatment in the second

Box 1: Sample calculations for “ins-and-outs” method of intravenous fluid administration

Without fluid pump

Insensible loss: $4.5 \text{ kg cat} \times 22 \text{ mL/kg/d} = 100 \text{ mL/d}$

$100 \text{ mL/day} \div 4 \text{ treatment periods per day} = 25 \text{ mL per } 6 \text{ hours}$

Urine output: 30 mL urine over previous 6 hours

Ongoing loss: vomiting approximately 3 times a day (approximately 8 mL each time) = 6 mL over 6 hours

Total: $25 + 30 + 6 \text{ mL} = 61 \text{ mL to administer over next } 6 \text{ hours}$

Readjust volume every 6 hours based on urine output and ongoing losses

With fluid pump

Insensible loss: $4.5 \text{ kg cat} \times 22 \text{ mL/kg/d} = 100 \text{ mL/d}$

$100 \text{ mL/day} \div 24 \text{ h per day} = 4 \text{ mL/h}$

Urine output: $30 \text{ mL urine over previous } 6 \text{ hours} \div 6 \text{ h} = 5 \text{ mL/h}$

Ongoing loss: vomiting approximately 3 times a day (approximately 8 mL each time) = 1 mL/h

Total: $4 + 5 + 1 \text{ mL} = 10 \text{ mL/h}$

Readjust volume every 6 hours based on urine output and ongoing losses

catheter. This method avoids the need to recalculate the dosage for the CRI drugs every 6 hours. If only one IV catheter is available, calculate the amount of medication to be administered by CRI over 6 hours. Add this amount to the fluid volume required over the next 6 hours (6 hours of insensible losses + previous 6-hour urine output). Divide the total volume by 6 to get the hourly rate for the CRI. If a fluid pump is available, calculate daily insensible fluid needs and divide by 24 to get the hourly rate. Add to this number the hourly volume of urine output over the previous monitoring interval plus an estimate of ongoing losses.

A patient with anuria should receive fluid administration to replace insensible loss only. If the patient is overhydrated, withhold the insensible loss. Overhydration in a patient with anuria or inability to induce diuresis in a patient with oliguria or anuria is an indication for dialysis, which is the only other effective therapeutic option.

CONVERTING OLIGURIA TO NONOLIGURIA

A decrease in urine production may be caused by prerenal, intrinsic renal, or postrenal factors. An appropriate renal response to inadequate renal perfusion from hypovolemia or hypotension includes fluid retention with a concomitant decrease in urine volume. Renal perfusion should be optimized by ensuring adequate hydration before determining whether oliguria is pathologic or physiologic. A volume of fluid equal to 3% to 5% of body weight should be administered to patients that seem normally hydrated because dehydration less than

5% cannot be detected clinically. In patients that are clearly volume overexpanded, this fluid administration is not necessary. Healthy kidneys can autoregulate renal blood flow at perfusion pressures between 80 and 180 mm Hg, but renal perfusion may be more linear in damaged kidneys [8,15]. The mean arterial pressure should be maintained above 60 to 80 mm Hg or the systolic pressure above 80 to 100 mm Hg when measured by Doppler technology. Apparent anuria caused by obstruction of the urinary tract or leakage into the peritoneal, retroperitoneal, or SC tissues should be excluded before determining that a lack of urine is caused by intrinsic renal damage.

Various values have been used to define oliguria, including less than 0.25 mL/kg/h, less than 0.5 mL/kg/h, and less than 1 to 2 mL/kg/h [4]. In a hydrated, well-perfused patient, less than 1.0 mL/kg/h can be considered absolute oliguria, and urine production between 1 and 2 mL/kg/h in a patient on fluid therapy is considered relative oliguria [4,8]. Anuria is defined as essentially no urine production [4]. Urine volume more than 2 mL/kg/h is generally considered polyuria.

If pathologic oliguria or anuria persists despite correcting prerenal factors, most clinicians attempt to convert oliguria to nonoliguria using diuretics. There is no evidence that diuretics improve outcome in acute renal failure (ARF), and some believe that the ability to respond to diuretics indicates less severe renal injury, which is associated with a better prognosis. In people, an increase in urine output with diuretic use delays referral for dialysis, perhaps inappropriately [16]. In veterinary medicine, however, in which dialysis is not as readily available to control fluid status, an increase in urine output from diuretic use may allow other medications or nutrition to be administered in larger volumes, and treatment with diuretics may be justified even without improvement in renal function.

Mannitol is an osmotic diuretic that causes extracellular volume expansion, which can increase glomerular filtration rate (GFR) and inhibit sodium reabsorption in the kidney by inhibiting renin. Mannitol also increases tubular flow, which may relieve intratubular obstruction from casts and debris. Mannitol decreases vascular resistance and cellular swelling, increases renal blood flow, GFR, and solute excretion, protects from vascular congestion and red blood cell aggregation, scavenges free radicals, induces intrarenal prostaglandin production and vasodilatation, and induces atrial natriuretic peptide release [4,8,17,18]. Mannitol may blunt the influx of calcium into mitochondria in sublethally injured renal cells, thus decreasing the risk of sublethal injury progressing to lethal damage. Despite theoretical advantages, no randomized studies have shown a better clinical response with the use of mannitol and volume expansion than with volume expansion alone in people or healthy cats [17,19].

Mannitol is administered as a slow IV bolus of 0.25 to 1.0 g/kg. If urine production increases, mannitol may be administered as a CRI of 1 to 2 mg/kg/min IV or 0.25 to 0.5 g/kg every 4 to 6 hours [4]. Doses in excess of 2 to 4 g/kg/d may cause ARF. Mannitol should not be given to patients that are dehydrated because it further exacerbates intracellular dehydration. Conversely, it is also contraindicated if overhydration is present, and it may worsen pulmonary edema. Hypertonic dextrose can be used as an osmotic diuretic if mannitol is

not available. A total daily dose of 22 to 66 mL/kg of a 20% dextrose solution should cause hyperglycemia and glucosuria [20].

Loop diuretics, such as furosemide, can increase urine flow without increasing GFR [17,19,21–23]. Despite the increase in urine output, loop diuretics do not improve outcome, which suggests that patients that respond have less severe renal failure, resulting in a better outcome for recovery independent of drug therapy [17,21–24]. In one study, for example, human patients who could be converted from oliguric to nonoliguric renal failure had better Acute Physiology And Chronic Health Evaluation (APACHE) scores and higher creatinine clearance before treatment, which suggested that they had less severe renal injury [24]. Because of a perception that there is a low complication rate associated with loop diuretic administration, they often are used despite lack of proven benefit. Loop diuretics inhibit the $\text{Na}^+2\text{Cl}^- \text{K}^+$ pump in the luminal cell membrane of the loop of Henle, decreasing transcellular sodium transport. Basal $\text{Na}^+ \text{K}^+ \text{ATPase}$ activity becomes less crucial and renal medullary oxygen consumption decreases, which is hypothesized to protect the kidney from further injury [24,25]. The amount of structural damage to the thick ascending limb of the loop of Henle consequently is decreased in isolated perfused kidneys [25]. Loop diuretics also have renal vasodilatory effects [26]. Despite the theoretical reasons to use loop diuretics, one retrospective study in people showed an increased risk of death or failure of renal recovery in the furosemide treatment group. Potential reasons for this finding include a detrimental effect of the drug, delay in recognizing the severity of renal failure with subsequent delay in starting dialysis, or preferential use of loop diuretics in patients with a more severe course of disease [16,21]. Loop diuretics may make fluid management easier in people without changing the outcome [24]. In animals, loop diuretics may play a larger role in management because dialysis is not universally available. Established indications for the use of furosemide in veterinary medicine include treatment of overhydration or hyperkalemia [4]. Furosemide should not be given to patients with aminoglycoside-induced ARF [8].

An increase in urine output should be apparent 20 to 60 minutes after an IV dose of furosemide of 2 to 6 mg/kg. Ototoxicity has been reported at high doses in people, and doses of 10 to 50 mg/kg may cause adverse effects in animals (eg, apathy and anorexia in cats; hypotension, apathy, and staggering in dogs) [8]. If there is no response to high doses of furosemide, therapy should be discontinued. If a response does occur, the effective dose can be administered every 6 to 8 hours. A CRI provides a more sustained diuresis with a lower cumulative dose compared to bolus administration [21]. In people, the time to maximal effect using a CRI without a loading dose is 3 hours and 1 hour with a loading dose. The dosage used in people is usually 1 to 9 mg/h (approximately 0.01–0.15 mg/kg/h), with some reports using dosages as high as 0.75 mg/kg/h [27]. In normal dogs, 0.66 mg/kg/h resulted in diuresis [28,29], and dosages of 0.25 to 1.0 mg/kg/h have been used in dogs and cats with naturally occurring renal failure [4]. Because electrolyte and fluid balance disorders can develop rapidly if a brisk diuresis ensues, frequent monitoring is necessary.

Dopamine has been shown to convert some human patients from oliguria to nonoliguria, but it does not increase GFR or improve outcome in people [17,23,30,31]. Because of lack of efficacy and adverse effects associated with dopamine, it is no longer recommended for treatment of oliguric renal failure, except for pressor control [4,32]. Selective dopamine agonists may have better efficacy and fewer adverse effects compared to dopamine. There are two dopaminergic receptors, DA-1 and DA-2. Fenoldopam is a selective DA-1 receptor agonist, and as such, it selectively increases renal cortical and medullary blood flow, sodium excretion, and urine output while maintaining GFR in people. It does not have DA-2 or alpha or beta adrenergic activity, so it does not cause vasoconstriction, tachycardia, or arrhythmias as seen with dopamine [17,26]. Although no clear benefit has been observed, studies with fenoldopam in people are encouraging, and larger clinical trials are needed [26]. Although some studies in dogs treated with fenoldopam have demonstrated an improvement in GFR, GFR may decrease within the first few hours after administration [33–35].

Calcium channel antagonists have been used to decrease damage after renal transplantation [36]. Calcium channel antagonists presumptively reverse renal vasoconstriction by causing predominantly preglomerular vasodilatation, inhibiting vasoconstriction induced by tubuloglomerular feedback mechanisms, and causing natriuresis independent of GFR [36]. Although the results of one study using diltiazem in addition to standard care in dogs with AKI caused by leptospirosis were not statistically significant, there was a trend toward increased urine output and more complete resolution of azotemia [36]. Whether calcium channel antagonists will prove beneficial is still to be determined.

Atrial natriuretic peptide increases tubular excretion of salt and water and stimulates afferent arteriolar dilatation and efferent arteriolar constriction, which increases GFR. Although atrial natriuretic peptide decreases the severity of experimental ARF from ischemic but not nephrotoxic causes, it has not been effective in clinical trials thus far [17].

MONITORING FLUID THERAPY

Monitoring fluid status is an ongoing process that must be repeated throughout the day. Physical examination and body weight should be assessed at least twice daily and the fluid plan adjusted accordingly. Blood pressure also should be monitored. Urine output and other fluid losses should be monitored and correlated with other findings of volume status.

Determining urine volume can be performed by various methods, including placing an indwelling urinary catheter with a closed collection system, collecting naturally voided urine, using a metabolic cage, and weighing cage bedding or litter pans (1 mL of urine = 1 g). An indwelling catheter is usually the most precise method, but technical issues such as urine leakage around the catheter and inadvertent disconnection may artifactually decrease measured volumes. The risk of iatrogenic urinary tract infection from the catheter can be decreased by careful attention to catheter and patient hygiene, including cleaning the external portions of the catheter with an antiseptic solution several times daily

and changing the collection bag and tubing daily [37]. Complete collection of voided urine may be difficult in many patients because of lack of patient cooperation or urinary incontinence in obtunded or recumbent patients. An accurate scale is necessary to measure small volumes of urine in cats and small dogs, but weighing cage bedding or litter pans before and after use may provide adequate and noninvasive assessment of urine volume in some patients. Fluid losses from vomiting and diarrhea usually are estimated, and other losses such as body cavity drainage (eg, ascites, pleural effusion) or nasogastric tube suctioning can be measured.

DISCONTINUING FLUID THERAPY

With AKI, once a diuresis has been established, polyuria can be marked. Monitoring urine production to prevent inadequate fluid administration is necessary in this phase just as monitoring was necessary during oliguria or anuria to prevent overhydration. Weaning these patients from IV fluids is a crucial step. When azotemia has resolved or reached a plateau, the fluid dose can be decreased by 25% per day. If urine output decreases by a corresponding amount and azotemia does not return, tapering of fluid administration over 2 to 3 days should continue. If urine output does not decrease, the kidneys are not yet able to regulate fluid balance and further reduction in fluid administered will lead to dehydration. Attempts to taper fluid administration can be made again after several days, but generally at a slower rate (10%–20% per day). It can take weeks for the kidneys to regain the ability to control fluid volume in rare cases.

With CKD, once the prerenal component of the azotemia has resolved, serum creatinine concentration (generally monitored every 48 hours) usually decreases by at least 1 mg/dL/d. When serum creatinine concentration reaches a baseline value (ie, when it no longer decreases despite IV fluid therapy), fluids should be tapered in preparation for patient discharge. After a period of intensive diuresis, fluid administration should be tapered gradually over approximately 2 to 3 days.

OUTPATIENT FLUID THERAPY

Despite widespread use of SC fluid therapy, its role in managing kidney disease has never been evaluated rigorously. Empirically, chronic dehydration and persistent signs of uremia are rational indications for chronic SC fluid administration. The dosage is empirical, based on subjective assessment of the patient's well-being and hydration status. A typical starting dose for cats is 100 to 150 mL daily or every other day. Cats subjectively seem to respond more favorably to SC fluid therapy compared to dogs. Lactated Ringer's solution and 0.9% saline are appropriate fluids choices. Dextrose-containing fluids increase the risk of abscess formation, and Plasmalyte is reported to sting when administered SC. Many owners can be taught to administer fluids at home, using a new needle for each administration. An administration tube can be implanted in the SC space for fluid administration without a needle, but this method increases the risk of infection at the site where the tube exits

the skin, and SC fibrosis with subsequent pain during fluid administration and decreased capacity to accommodate fluid has been observed.

NUTRITIONAL SUPPORT

Renal failure is highly catabolic. Although it is hard to identify clearly the contribution of nutritional management to outcome, poor nutritional status is a major factor that increases patient morbidity and mortality [38]. Early enteral feeding can help preserve gastrointestinal mucosal integrity [39]. Although renal diets, characterized by restricted phosphorus and restricted quantities of high-quality protein, are indicated for treating CKD, the ideal diet for ARF has not been identified [40,41]. In the absence of information, enteral diets for critically ill animals or people have been used [8].

Anorexia is a common problem in hospitalized patients that have renal failure. If appetite does not return within a few days of therapy, feeding tube placement may allow administration of an appropriate quantity of the desired diet and easy administration of oral medications. It is strongly recommended in animals not voluntarily consuming adequate calories. If vomiting cannot be controlled, partial or total parenteral nutrition may be necessary.

Whether supplementation is enteral or parenteral, the volume that can be administered may be limited in patients that are anuric or oliguric. Most liquid diets suitable for administration via a nasoesophageal or nasogastric tube have a caloric density of approximately 1 kcal/mL [42]. Provision of 100% of the basal energy requirements general requires a volume of approximately twice the insensible fluid requirement. Common formulas for calculation of total parenteral nutrition also encompass almost twice the insensible fluid requirements [43]. Dialysis can remove fluid from the patient by ultrafiltration, which may be necessary to prevent volume overload in an oliguric or anuric patient receiving nutritional support.

ELECTROLYTE ABNORMALITIES

Sodium and Chloride

The serum sodium concentration may be normal, increased, or decreased with renal failure. Hypernatremia before fluid therapy indicates excessive free water loss. Administration of sodium bicarbonate or hypertonic saline may contribute to hypernatremia. Hyponatremia may indicate excessive sodium loss associated with vomiting or may represent transient dilutional hyponatremia after administration of mannitol, hypertonic dextrose, or colloid solutions. Sodium-poor solutions (eg, 5% dextrose, total parenteral nutrition, enteral formulations) may contribute to hyponatremia. In many situations, dehydration initially is caused by isonatremic fluid loss, and the patient's serum sodium concentration is normal [4,8].

The initial fluid deficit should be replaced by an isonatremic solution such as lactated Ringer's solution, 0.9% saline, or Plasmalyte-148. Continued administration of these solutions over several days may lead to hypernatremia. A sodium-poor fluid, such as half-strength lactated Ringer's solution or 0.45%

saline with 2.5% dextrose, may be a more appropriate fluid choice after the initial rehydration phase. The serum sodium concentration should be monitored regularly and the fluid choice adjusted as needed.

Clinical signs of sodium disorders are unlikely unless rapid changes in serum sodium concentration occur, and signs generally are related to neurologic dysfunction. The rate of change in serum sodium concentration should not exceed 1 mEq/L/h [44]. Changes in serum chloride concentration tend to parallel changes in serum sodium concentration.

Potassium

Hypokalemia

Hypokalemia is more likely to be present in CKD compared to AKI and is more likely in cats compared to dogs. Between 20% and 30% of cats with CKD have hypokalemia [45–47]. Multiple mechanisms may contribute to the development of hypokalemia, including excessive renal wasting associated with polyuria. Alkalemia worsens hypokalemia because potassium shifts intracellularly in response to translocation of hydrogen ions out of the cells. Vomiting and loop diuretics can cause additional potassium loss. Decreased oral intake alone generally does not cause hypokalemia, but prolonged anorexia exacerbates hypokalemia. Hypokalemia may be present at admission, particularly with polyuric CKD, or it may develop during hospitalization, particularly in the diuretic phase of recovery from AKI or with effective diuretic therapy. Hypokalemia is a cause and effect of renal dysfunction; hypokalemia interferes with urinary concentrating ability, but the renal dysfunction generally is reversible with normalization of serum potassium concentration [48].

Signs of hypokalemia include muscle weakness (eg, stiff, stilted gait in hind limbs, cervical ventroflexion, respiratory muscle paralysis). Cardiac abnormalities occur inconsistently but may include ventricular and supraventricular arrhythmias. Rarely, U waves are noted on the electrocardiogram. Other signs include fatigue, vomiting, anorexia, and gastrointestinal ileus [4,49]. Clinical signs of hypokalemia are likely when serum potassium concentration is less than 2.5 mEq/L; a concentration of less than 2.0 mEq/L may be life threatening [4,8]. By definition, hypokalemia is diagnosed by detecting a low serum potassium concentration. Evaluation of the fractional excretion of potassium may help distinguish renal potassium loss (fractional excretion > 4%) from nonrenal loss (fractional excretion < 4%) [50,51].

Because excretion of potassium may be impaired with renal failure, treatment in this setting requires judicious supplementation with careful monitoring. Because normalization of hypokalemia can improve renal function and decrease clinical signs, treatment of hypokalemia should not be overlooked [48]. In hospitalized patients unable to tolerate orally administered medications, potassium chloride may be added to the IV fluids. The rate of supplementation is based on a patient's serum potassium concentration using an empirically derived scale (Table 1). The rate of potassium supplementation should not exceed 0.5 mEq/kg/h. Serum potassium concentration may decrease during initial fluid

Table 1
Sliding scale of potassium supplementation

Serum potassium concentration (mEq/L)	Potassium concentration in fluids (mEq/L)
3.5–4.5	20
3–3.5	30
2.5–3	40
2–2.5	60
< 2	80

therapy despite supplementation because of extracellular fluid volume expansion, increased distal renal tubular flow, and cellular uptake, especially if potassium is administered with dextrose-containing fluids.

In a life-threatening hypokalemic emergency (eg, respiratory muscle weakness with hypoventilation, cardiac arrhythmias), some clinicians recommend administering an IV bolus of KCl. This approach should be undertaken only with constant electrocardiographic monitoring because a rapid potassium bolus potentially could cause a fatal arrhythmia. To calculate the amount of potassium to administer, subtract the patient's serum potassium concentration from a desired serum potassium concentration of 3 mEq/L. Calculate the blood volume (8% of body weight in kg in dogs or 6% of body weight in kg in cats) and multiply the blood volume by 60% to estimate the plasma volume. Multiply the plasma volume by the difference between the measured and desired potassium concentrations to determine the number of milliequivalents of KCl to administer as an IV bolus over 1 to 5 minutes through a central vein. Check the patient's serum potassium concentration 5 minutes later. A second bolus—calculated from the new serum potassium concentration—can be administered, but caution must be used and it should be administered more slowly as the patient's serum potassium concentration approaches 3 mEq/L [49].

Once oral intake is possible, potassium gluconate can be administered. A dose of 5 to 10 mEq/d divided into two to three doses is used to replenish potassium, followed by 2 to 4 mEq/d for maintenance [50]. Potassium citrate (40–60 mg/kg/d divided into two to three doses) is an alternative to potassium gluconate that also helps to correct acidosis. Potassium chloride can be added to SC fluids at concentrations up to 35 mEq/L.

Frequent monitoring (once to several times daily) is recommended for patients on IV potassium supplementation. During potassium repletion on an outpatient basis, monitoring every 7 to 14 days is recommended until a stable maintenance dose is determined [48]. If hypokalemia persists after standard supplementation, hypomagnesemia may be present and magnesium supplementation may be necessary.

Hyperkalemia

Renal excretion is the major mechanism for removing potassium from the body, and chronic hyperkalemia is unlikely to occur with normal renal function. Hyperkalemia is more likely to develop in cases of oliguric or anuric ARF and

usually does not occur in cases of CKD unless oliguria or severe metabolic acidosis is present [8]. Metabolic acidosis from mineral acids (eg, NH_4Cl , HCl) but not organic acids (eg, lactic acid, ketoacids) causes translocation of potassium out of cells as hydrogen ions enter the cells. Patients that have CKD may have decreased ability to tolerate an acute potassium load and may take 1 to 3 days to re-establish external potassium balance after a potassium load [51]. Mild hyperkalemia is relatively common in stable patients being treated with angiotensin-converting enzyme inhibitors. My experience is that most patients on angiotensin-converting enzyme inhibitors do not develop serum potassium concentrations in excess of 6.5 mEq/L, and the clinical relevance of mild hyperkalemia in these patients is uncertain. Hyperkalemia and azotemia are common with hypoadrenocorticism and acute tumor lysis syndrome [50].

Hyperkalemia is a potentially life-threatening electrolyte disorder. The increase in extracellular potassium changes the electrical potential of excitable cells. The myocardium is relatively resistant compared to the conducting system of the heart. Typical electrocardiographic changes include bradycardia, tall spiked T waves, shortened QT interval, wide QRS complex, and small, wide, or absent P waves. Severe hyperkalemia can lead to a sinoventricular rhythm, ventricular fibrillation, or ventricular standstill. Muscle weakness may be present in patients with serum potassium concentrations more than 8 mEq/L [50]. Characteristic electrocardiographic changes may require emergency therapy before serum potassium concentration results are available from the laboratory. Pseudohyperkalemia may occur *ex vivo* if red cell potassium content is high, as may occur in Akita dogs.

Calcium gluconate 10% (0.5–1.0 mL/kg IV to effect, given slowly) can be used in critical situations to restore cardiac membrane excitability, but it does not decrease serum potassium concentration. During infusion, the electrocardiogram must be monitored and administration slowed or stopped if the arrhythmia worsens. The cardiac effects should be apparent within minutes. Despite a rapid onset of action, the duration of effect after administration of calcium gluconate is less than 1 hour [51]. Calcium administration increases the risk of soft tissue mineralization if hyperphosphatemia is present.

Several methods can be used to translocate potassium intracellularly. Regular insulin (0.5 U/kg IV) has an effect within 20 to 30 minutes. Dextrose (1–2 g/U insulin as an IV bolus, then 1–2 g/U insulin in IV fluids administered over the next 4–6 hours) is necessary to prevent hypoglycemia when insulin is used. Dextrose induces endogenous insulin release in patients that do not have diabetes and can be used at a dosage of 0.25 to 0.5 g/kg IV to control mild to moderate hyperkalemia without concurrent insulin administration.

Metabolic acidosis from mineral acids causes an extracellular shift of K^+ as H^+ increases intracellularly. Correction of metabolic acidosis with bicarbonate allows an intracellular shift of K^+ as the H^+ is combined with HCO_3^- and removed. The dose of sodium bicarbonate used to treat hyperkalemia is based on the base deficit, or an empirical dosage of 1 to 2 mEq/kg IV over 10 to 20 minutes can be used. Sodium bicarbonate is contraindicated if the partial

pressure of carbon dioxide (PCO_2) is increased or metabolic alkalosis is present, and it may contribute to hypernatremia or paradoxical central nervous system acidosis. If serum ionized calcium concentration is low, dextrose is preferred to bicarbonate because alkalemia exacerbates hypocalcemia [8].

The beta-agonist albuterol has been used to treat hyperkalemia in people because it causes an intracellular shift of potassium [8]. The cation exchange resin sodium polystyrene sulfonate (Kayexalate) can be administered orally or by enema at a dosage of 2 g/kg in three to four divided doses as a suspension in 20% sorbitol [4]. This substance binds potassium in the gastrointestinal tract and releases sodium. It takes several hours to work, and adverse effects include hypernatremia and constipation.

The potassium-lowering effects of these drugs, with the exception of polystyrene sulfonate, are temporary. Serum potassium concentrations gradually increase again within several hours after administration unless urine production increases. Once even minimal urine production resumes, serum potassium concentrations usually decrease. Peritoneal dialysis or hemodialysis may be necessary to ultimately control serum potassium concentration if oliguria or anuria persists.

Drugs and other treatments that contribute to hyperkalemia should be avoided, including nonspecific beta-blockers, digoxin, angiotensin-converting enzyme inhibitors, angiotensin receptor antagonists, nonsteroidal anti-inflammatory drugs, potassium-sparing diuretics (eg, spironolactone, amiloride, triamterene), high doses of trimethoprim, cyclosporine, and total parenteral nutrition [50].

Calcium

Most of the body's calcium is found in the skeleton as hydroxyapatite. Serum calcium concentration consists of three fractions: (1) ionized calcium (55%), which is the biologically active form, (2) protein-bound (35%), a storage form generally bound to albumin, and (3) complexed calcium (10%), which is bound to citrate, lactate, bicarbonate, or phosphate in serum. Serum total calcium concentration (including all three fractions) is most commonly measured, but measurement of serum ionized calcium concentration is becoming more readily available in practice settings.

Disturbances of serum calcium concentration may occur in renal failure for several reasons. An acute decrease in GFR may lead to an abrupt increase in serum phosphorus concentration, causing a decrease in serum calcium concentration by the law of mass action. The decrease in serum ionized calcium concentration stimulates parathyroid hormone synthesis and release, which act to increase the calcium concentration back to normal. On the other hand, chronic renal failure may cause parathyroid hyperplasia which rarely leads to hypercalcemia. Metabolic acidosis increases the ionized calcium fraction, but more than 50% of dogs with CKD and metabolic acidosis were hypocalcemic [52].

Based on serum ionized calcium concentration, 36% to 56% of dogs with CKD are hypocalcemic, 20% to 55% are normocalcemic, and 9% to 24% are

hypercalcemic [52,53]. Based on serum total calcium concentration, 8% to 19% are hypocalcemic, 60% to 76% are normocalcemic, and 16% to 22% are hypercalcemic. The concordance between serum ionized calcium and serum total calcium concentrations is poor, especially in dogs with CKD [52,53].

Symptomatic hypocalcemia (tetany) occurs infrequently in renal disease. Hypocalcemia may be more severe with ethylene glycol-induced ARF, because antifreeze contains phosphate that can cause severe hyperphosphatemia, and ethylene glycol is converted to oxalate, which complexes with calcium. Treatment with calcium increases the risk of soft tissue mineralization in patients with hyperphosphatemia. The minimal dose of calcium gluconate that controls clinical signs should be used when therapy is needed. A 10% solution of calcium gluconate can be used at a dosage of 0.5 to 1.5 mL/kg IV over 20 to 30 minutes. As when treating hyperkalemia, the electrocardiogram should be monitored during infusion.

In patients with renal failure, hypercalcemia based on total serum calcium concentration usually is mild and associated with normal serum ionized calcium concentration. No specific treatment is necessary. If serum ionized calcium concentration is increased, treatment is warranted. Hypercalcemia may respond to fluid therapy, although calcium-containing fluids (eg, lactated Ringer's solution) should be avoided. Normal saline (0.9% NaCl) is an ideal fluid choice because its high sodium content facilitates calciuresis. Furosemide also promotes urinary calcium loss. Sodium bicarbonate therapy decreases serum ionized calcium concentration as more calcium ions bind to serum proteins. Hypercalcemia associated with renal failure is not likely to be glucocorticoid responsive [54]. Calcitonin or bisphosphonates could be considered if hypercalcemia is severe, although bisphosphonates also can induce renal failure [54].

MAGNESIUM

Serum magnesium concentrations may be increased in severe renal failure because the kidneys are the major route of excretion of magnesium, but specific therapy generally is not necessary. Supplemental magnesium, such as that found in some phosphate binders, should be avoided in these situations. Hypomagnesemia may occur with polyuric renal failure. Hypokalemia may be refractory to therapy if concurrent hypomagnesemia is present. In this situation, correction of the magnesium deficit may be necessary before correction of the hypokalemia can occur. Magnesium sulfate or magnesium chloride can be used for IV supplementation, and various formulations of magnesium are available for oral supplementation [55].

PHOSPHORUS

Dietary phosphorus is readily absorbed from the gastrointestinal tract and excreted by the kidneys. Decreased excretion commonly leads to hyperphosphatemia in patients with ARF and chronic renal failure. Intravenous fluid therapy may partially control serum phosphorus concentration by improving renal blood flow and correcting prerenal azotemia. No other specific treatments are

available to decrease serum phosphorus concentration in the early stages of ARF. A phosphate-restricted diet is recommended for long-term control of hyperphosphatemia. Because protein is phosphate-rich, adequate phosphorus restriction necessitates a protein-restricted diet. Although diet may be sufficient to control serum phosphorus concentration in mild to moderate renal failure, diet alone generally is not sufficient as renal disease progresses.

Phosphate binders prevent absorption of dietary phosphorus in the gastrointestinal tract. Aluminum-containing phosphate binders are commonly used in veterinary medicine. They are rarely used in people because of the potential for complications from long-term exposure to aluminum, including anemia and neurologic disorders. These effects are rarely noted in animals unless they are receiving chronic hemodialysis. Aluminum hydroxide or aluminum carbonate can be administered at a dosage of 30 to 90 mg/kg/d divided and given with meals. Calcium acetate and calcium carbonate are alternatives to aluminum-containing phosphorus binders. They may cause hypercalcemia and should be avoided in patients with increased serum calcium concentrations. Calcium carbonate combined with chitosan is a veterinary product for binding phosphorus. Several newer phosphate binders, such as sevelamer hydrochloride and lanthanum carbonate, are available for people, but there is limited veterinary experience with them. With all phosphate binders, the dosage is adjusted by serial determination of serum phosphorus concentration. Because of their binding properties, they can interfere with absorption of orally administered medications, especially antibiotics.

METABOLIC ACIDOSIS

Metabolic acidosis is a common acid-base disturbance in renal failure. The daily H^+ load is excreted in the urine with NH_3 as NH_4^+ or with phosphate as $H_2PO_4^-$. With renal failure, the kidneys are less able to excrete H^+ and cannot reabsorb adequate amounts of HCO_3^- . Lactic acidosis from dehydration and poor tissue perfusion also may contribute to acidosis in some patients with renal failure. If acidosis persists after correcting dehydration and perfusion, IV sodium bicarbonate therapy can be considered. Sodium bicarbonate therapy usually is reserved for patients with pH less than 7.2 or HCO_3^- less than 12 mEq/L. Treatment with sodium bicarbonate causes H^+ to combine with HCO_3^- to form H_2CO_3 , which dissociates into H_2O and CO_2 . If the lungs are unable to adequately eliminate the CO_2 , treatment is not effective. Bicarbonate administration in this situation can increase PCO_2 and lead to paradoxical central nervous system acidosis because of the ability of CO_2 to more easily diffuse into the central nervous system and lower pH. Sodium bicarbonate treatment also is contraindicated in patients with hypernatremia. The bicarbonate dose can be calculated from the formula: $0.3 \times \text{body weight (kg)} \times \text{base deficit}$, where the base deficit = $24 - \text{the patient's serum bicarbonate concentration}$. Give 25% to 50% of the dose IV and an additional 25% to 50% of the dose in the IV fluids over the next 2 to 6 hours. Adjust any subsequent doses based on serial evaluation of blood gas determinations.

Oral alkalinizing agents can be used for treatment of chronic acidosis. Potassium citrate (40–75 mg/kg orally every 12 hours) simultaneously addresses metabolic acidosis and hypokalemia. Oral sodium bicarbonate (8–12 mg/kg orally every 12 hours) is more palatable in tablet form compared to powder. Doses should be adjusted based on the individual patient response.

SUMMARY

Careful fluid therapy is the most important aspect of treating a uremic crisis and involves careful assessment of hydration status with frequent reassessment, use of the appropriate fluid type and rate, and flexibility to respond to changes in the patient's clinical status. Electrolyte and acid-base disturbances are common with renal failure and frequently require specific therapy.

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