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Critical issues in nephrology

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Renal and electrolyte complications are commonplace in intensive care. This article will focus on selected issues of interest to practicing of critical care physicians. It is not meant to be a comprehensive review of critical care nephrology. Instead, we have selected topics that relate to recent advances in the evolution and management of acute renal failure, and in the approach to relevant acid-base and electrolyte problems.

Acute renal failure

Approximately 1% to 5% of hospitalized patients develop acute renal failure (ARF) [1], a number that can be much higher in surgical patients and in the intensive care unit (ICU) where the incidence varies from 2.5% to 15% [2]. The variability in incidence is dependent on the definitions used, but most investigators would agree that an acute decrease in glomerular filtration rate that is greater than 50% compared with baseline or the need for dialysis constitutes bona fide ARF [1]. When restricted to the ICU, ARF is alarming because of its associated morbidity and mortality. Mortality in this setting can be as high as 78% in patients who require dialysis; as many as one third of survivors may remain on chronic dialysis [3]. Furthermore, there seems to be a difference between having ARF on admission and developing it during the ICU stay. In a large multi-center study that was done in France, 1086 cases of ARF were studied according to the timing of development of ARF: on admission through the second day in ICU (736 cases), from the third through sixth day in ICU (202 cases), or after the seventh day in ICU (148 cases) [2]. Mortality was significantly lower in those who had ARF on admission (61%, 71%, and 81%, respectively), and so was the need for dialysis (51%, 58%, and 64%, respectively). These data reflected a larger number of patients who had reversible PRA as the cause of ARF in the "ARF on admission" group [2]. Thus, ARF development in the ICU is marked by poor prognosis and increased long-term complications; prevention whenever possible and aggressive management are essential to the minimization of these ominous consequences.

Prevention of acute renal failure in the ICU

There are few circumstances in which the ICU physician is able to actively prevent ARF, a few of which deserve mention. A few common situations deserve mention.

Nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors, and angiotensin-2 receptor blockers

Nonsteroidal anti-inflammatory drugs (NSAIDs), angiotensin-converting enzyme (ACE) inhibitors, and angiotensin-2 receptor blockers alter intrarenal hemodynamics and are common causes of acute renal dysfunction in patients who have associated volume depletion. Judicious use of these drugs in critically ill patients will prevent such episodes.

Crush injuries

Crush injuries are often associated with severe rhabdomyolysis and myoglobinuric renal failure. Ag-

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gressive volume repletion with a solution that includes bicarbonate for concomitant urinary alkalinization (decreases myoglobin precipitation in tubules) and mannitol (decreases myoglobin precipitation and provides free radical scavenging) reduced the risk of development of ARF [4].

Amphotericin B

Amphotericin B is often needed in the management of critically ill patients who have systemic fungal infections. In a large retrospective study, this drug was associated with ARF in about 25% of cases, with higher estimates for patients who received more than 60 mg/day, those in the ICU, and those who received cyclosporine [5]. Other risk factors that were previously reported include low body weight, diuretic use, baseline renal insufficiency, and total amphotericin dose [6,7]. No single preventive maneuver is effective in completely eliminating the risks of ARF, but several strategies are effective in reducing the risk. The most commonly used approach is pretreatment with saline, which suppresses the vasoconstrictive effect of the tubuloglomerular feedback mechanism [8]. Another approach is the use of one of several lipid formulations of amphotericin B, which has been associated with a 30% to 50% risk reduction compared with standard amphotericin B deoxycholate [9]. These preparations should be specifically considered in patients who have baseline renal insufficiency and in those who develop renal dysfunction on amphotericin B and must remain on therapy. Lastly, a recent randomized, open-label trial demonstrated that infusion of amphotericin B over 24 hours found that the reduction in creatine clearance was 60% less compared with the conventional 4-hour infusion rate [10]. Unfortunately, the actual rates and severity of ARF were not presented in the paper. This slow infusion of amphotericin B may be a simple, inexpensive approach to decrease nephrotoxicity.

Aminoglycosides

Aminoglycoside antibiotics cause ARF in 10% to 15% of patients who receive them for more than several days. Current antibiotic choices allow for limited use of these agents, and adjustments according to antimicrobial sensitivities limit exposure to aminoglycosides, which reduces toxicity. In patients who are treated with these agents for more than several days, however, appropriate measures must be undertaken to limit toxicity. The most important intervention is adequate monitoring of levels and dose adjustment for renal function [11]. Secondly, available evidence from two meta-analyses and one systematic review shows that once daily dosing results in a 13% to 26% reduction in the risk of nephrotoxicity compared with multiple daily doses [12–14]. This trend did not achieve statistical significance in any of these studies. Given the similar clinical efficacy and decreased need for monitoring (only trough levels used as an index of renal dysfunction to adjust dosing interval), single daily dosing seems to be the most rational approach.

Tumor lysis syndrome

Tumor lysis syndrome (TLS) is marked by the development of severe hyperuricemia, hyperkalemia, hyperphosphatemia, and ARF in patients who have hematologic malignancies, especially at the time of initiation of therapy [15]. TLS also can occur spontaneously in hematologic malignancies with high turnover [16], or as a rare complication of therapy of solid tumors [17]. ARF occurs mostly as a result of tubular deposition of uric acid produced by massive lysis of tumor cells (acute uric acid nephropathy). Prevention strategies are effective, and include allopurinol in higher than usual dosages (600 mg/day) and alkalinization of the urine, although the latter may be associated with an increased risk of tubular deposition of phosphate. Thus, many physicians have resorted solely to aggressive hydration without bicarbonate, unless baseline uric acid levels are still high at the time therapy is initiated. Available data indicate a significantly increased risk of ARF in patients who have high pretreatment uric acid and lactate dehydrogenase levels and underlying renal insufficiency [18,19]. Prophylactic hemodialysis is indicated in high-risk patients (especially if uric acid is higher than 15 mg/dL) even if baseline renal function is normal. After ARF is established, management is supportive and dialysis is generally required. Continuous dialysis modalities are often needed to match the high rates of uric acid, potassium, and phosphate generation [20]. The use of recombinant urate oxidase is an effective way of rapidly (within 4 hours) reducing uric acid levels, but is not yet available commercially [15,21].

Prevention of contrast nephropathy

Nephropathy that is induced by iodinated radiocontrast is a preventable renal insult in patients who are in the ICU. The most relevant predisposing factor to contrast nephropathy (CN) is baseline renal dysfunction; this is further amplified by the presence of volume depletion and diabetes. In patients who have renal insufficiency, exposure to dye results in ARF in up to 30% of cases [22]. The pathogenesis of CN involves vasoconstriction with resulting ischemic injury as well as direct cellular toxicity. Thus, strategies

that are directed at these mechanisms have been widely tested, especially in subjects who had pre-existing renal dysfunction. Current effective approaches include peri-procedural hydration, and the use of N-acetylcysteine, low osmolality contrast media, and, perhaps, fenoldopam. Other therapies (dopamine; atrial natriuretic peptide (ANP); methylxanthines; diuretics, including mannitol; calcium channel blockers) have not been demonstrated to be of value [23].

Hydration

Peri-procedure hydration has been well demonstrated to decrease the risk of CN in patients who have underlying renal insufficiency [24], although no study has compared hydration with no hydration. Based on the data from Solomon et al [24], standard hydration regimens of 0.45% NaCl at 1 mL/kg/hour started 12 hours before the procedure and continued for another 12 hours after the administration of contrast. Because such an approach often resulted in a need for admission to the hospital, a pilot study evaluated the differences in ARF in 18 patients who were treated with the Solomon protocol before cardiac catheterization and 18 patients who were treated with liberal oral hydration (1000 mL clear liquids over 10 hours preceding the procedure followed by 6 hours of intravenous 0.45% NaCl at 300 mL/hour starting "on call" to the catheterization laboratory) [25]. In this trial, which included patients who had serum creatinine between 1.4 and 3.0 mg/dL and only patients with left ventricular ejection fraction that was higher than 30%, there were no differences in incidence of ARF or net changes in serum creatinine. This led the investigators to conclude that hospitalization for peri-procedure hydration was unwarranted in the setting of mild to moderate renal insufficiency and preserved left ventricular function to allow for the brisk pace of post-contrast hydration. A recent study compared 0.45% NaCl with 0.9% NaCl that was started in the morning of coronary angiography and continued for 24 hours in 1620 patients (288 of whom had baseline renal insufficiency) [26]. CN developed in 0.7% of the patients who were given 0.9% NaCl and in 2.0% of the patients who were given 0.45% NaCl ($P = 0.04$); the differences were more marked in women, diabetics, and patients who received more than 250 mL of contrast [26]. No difference was noted in the subgroup of patients who had baseline renal insufficiency. These data indicate that hydration should be used whenever possible; 0.9% NaCl leads to better outcomes and when preprocedure hydration is not initiated in a timely fashion, a brisk infusion is justified as long as underlying left ventricular function is adequate to tolerate the infusion.

N-acetylcysteine

Tubular damage due to oxidative stress is a possible mechanism that contributes to the development of CN [27]. N-acetylcysteine (NAC) provides scavenging properties that decreased the incidence of CN following 75 mL of intravenous contrast in patients who had baseline renal insufficiency [28], although there are conflicting results in the literature regarding its efficacy in higher risk procedures, such as intra-arterial procedures with higher amounts of contrast [29]. In this setting, four of six available studies showed a beneficial effect, whereas two studies showed no difference protecting from contrast induced ARF [29]. Kay et al [30] recently published the largest randomized, controlled, double-blind trial to date in patients who were undergoing cardiac catheterization [30]. In this study, 200 patients who had a mean calculated creatinine clearance of 43.5 mL/minute were randomized to four doses of NAC, 600 mg (three doses precatheterization and 1 dose postcatheterization) or placebo, in addition to 0.9 normal saline (NS) pericatheterization infusion. The mean contrast volume was 2.2 mL/kg and 2.1 mL/kg in the groups who received NAC and placebo, respectively. NAC resulted in a lower incidence of ARF (4% versus 12%, $P = 0.03$) and shorter duration of hospitalization (3.4 days 3.9 days, $P = 0.02$) [30]. NAC is well tolerated and inexpensive; therefore, it should be offered as a prophylactic agent despite the lack of absolute uniformity in the data.

Low-osmolality contrast media

The osmolar load that is presented by iodinated contrast media leads to vasoconstriction and altered erythrocyte deformability, factors that may contribute to tubular ischemia [31]. The use of contrast media with osmolality that is one third to one half lower ("low-osmolality," 600–850 mOsm/kg) than conventional contrast media (1500–1800 mOsm/kg) resulted in less nephrotoxicity and other adverse reactions [31,32]. The protective effect for ARF was more pronounced in patients who had baseline renal dysfunction [32]; most radiology services use low osmolality contrast agents in this patient population despite the higher costs. One recent advance is the use of an agent that is iso-osmolar to plasma (iodixanol, 290 mOsm/kg) and resulted in less episodes of ARF (3% versus 26%, $P = 0.002$) compared with iohexol, a "low osmolality" agent (780 mOsm/kg), following angiography in 129 patients who had serum creatinine between 1.5 mg/dL and 3.5 mg/dL [33]. No patient required dialysis in either group. Despite the higher cost of this agent, these are encouraging results that

may lead to a change in practice if the data are reproduced by other groups.

Fenoldopam

Fenoldopam is a dopamine DA-1 receptor agonist that is approved for the treatment of hypertensive emergencies. Animal data demonstrated that the vasodilatory effect of DA-1 receptors is effective in preventing contrast-associated vasoconstriction [34]. Accordingly, fenoldopam has been used in doses lower than those used for blood pressure reduction to prevent CN. In the only randomized clinical trial, Tumlin et al [35] showed that fenoldopam (started 1 hour before contrast and continued for another 4 hours) fully prevented the decrease in renal blood flow immediately following contrast injection and was associated with a lower incidence of CN (21% versus 41% in the group that received 0.45% NaCl alone, $P = 0.148$) [35]. Hypotension was more common in the group that received fenoldopam, despite the lower dosages used (0.1 μg/kg/minute). A larger, adequately powered study is needed to confirm the value of fenoldopam, especially because uncontrolled studies reached positive [36,37] and negative results [38].

The diagnostic approach to acute renal failure

The initial approach to the patient who has ARF should be uniform and meticulous. A close review of medications that are used by the patient is one of the most relevant parts of this initial approach, especially in individuals who develop ARF after hospitalization [39]. The spectrum of drug-induced ARF is broad; Table 1 lists many of the drugs that are frequently associated with ARF and their respective mechanisms.

Another important aspect that is often overlooked is ruling out obstruction. A simple bladder scan or straight catheterization can provide immediate information about the bladder outlet, which is the most common cause of acute urinary obstruction. If clinically indicated, this can be further evaluated with imaging of the urinary tree with an ultrasound, CT scan, or MRI [40].

The urinalysis is essential in the evaluation of ARF [41]. The presence of dysmorphic red blood cells and red blood cell casts point toward a glomerulonephritis or vasculitis. Sterile pyuria or white blood cell casts suggests the presence of an interstitial nephritis. ‘‘Muddy brown,’’ pigmented casts are typical of acute tubular necrosis (ATN) and often allow for the distinction between ATN and PRA, which is marked by a normal sediment or occasional hyaline casts. Eosinophiluria, which is often used to look for interstitial nephritis [42], is fraught with limited specificity and positive predictive value, because it can be seen in other conditions that are associated with ARF, such as acute glomerulonephritis and atheroembolic renal disease, as well as other common diseases in acutely ill patients, such as pyelonephritis and prostatitis [42,43].

Perhaps the most explored topic in the diagnosis of ARF is the differentiation between PRA and ATN. Unfortunately, the physical examination is often misleading in the setting of mild volume depletion or overload [44], and the precise evaluation of volume status in ARF often requires the judicious use of central hemodynamic monitoring. Of all techniques used to date, the use of urinary indices has fared best in this distinction. Table 2 presents the commonly used urinary indices to distinguish PRA from ATN. The test with the best descriptive ability is the fractional excre-

Table 1
The spectrum of drug-induced acute renal failure

Type of renal injury	Drugs
Systemic capillary leak	Interleukin-2
Changes in intrarenal hemodynamics	NSAIDs (including selective COx-2 inhibitors), ACE inhibitors, angiotensin-2 receptor blockers, cyclosporine/tacrolimus, vasopressor agents
Glomerular injury	
Glomerulonephritis	NSAIDs, gold, penicillamine, captopril ticlopidine,
Microangiopathy	clopidogrel, cyclosporine, oral contraceptives
Tubular necrosis	Iodinated contrast, aminoglycosides, amphotericin B, pentamidine, foscarnet, cisplatinum, acetaminophen, cidofovir, ritonavir
Interstitial nephritis	NSAIDs, β-lactams, quinolones, sulfonamides, phenytoin, allopurinol, diuretics, indinavir
Obstruction due to crystal deposition	Indinavir, sulfadiazine, sulfamethoxazole, methotrexate, high-dose acyclovir
Obstruction due to retroperitoneal fibrosis	Methysergide, methyldopa

Table 2
Urinary indices used in the distinction between prerenal azotemia and acute tubular necrosis

	Prerenal azotemia	Acute tubular necrosis
Serum SUN/creatinine ratio	>20:1, especially if >40:1	<20:1
Urine osmolality	>500 mOsm/kg	<350 mOsm/kg
Urine Na	<20 mmol/L	>40 mmol/L
FENa	<1%	>3%
FEUrea	<35%	>50%
FEUric acid	<7%	>15%

Abbreviations: FEUric acid,= fractional excretion of uric acid; SUN, serum urea nitrogen.

tion of sodium (FENa) (FENa = urine/plasma [U/P] Na: U/P creatinine × 100), although one must remember that the overlap is greater when evaluating patients who are nonoliguric [45–47]. A frequent problem is the interpretation of the FENa in patients who take diuretics, in whom this index may be high despite a decrease in effective plasma volume. A recent prospective study confirmed this observation and showed that using the fractional excretion of urea (FEUrea) (FEUrea = U/P urea nitrogen: U/P creatinine × 100) identifies patients who have PRA despite the use of diuretics [48] and confirmed previous retrospective observations [49]. Acute glomerulonephritis presents with urinary indices that are indistinguishable from PRA [47]. The differential diagnosis, however, is made simple by the analysis of clinical features and abnormalities of the urinary sediment.

A recent advance in the differential diagnosis of ARF is the identification of a kidney injury molecule-1 (KIM-1), which is a biomarker of proximal tubular injury [50]. In an exploratory study, six patients who had biopsy-proven ATN had markedly increased expression of KIM-1 in proximal tubules, as well as increased urinary excretion of the molecule in comparison with patients who has other causes of ARF [50]. Confirmatory studies and the commercial availability of this marker will determine its clinical value in the future.

The use of erythropoietin in the ICU and in acute renal failure

Anemia is a common complication in the ICU; it is estimated that by the third day of admission to the ICU, 95% of patients have hemoglobin concentrations that are below normal [51]. Although the anemia of critical illness is multi-factorial, inappropriately low levels of erythropoietin (EPO) have an important role in the process [51]. Thus, the idea of using EPO in critically ill patients was developed as a possible alternative to the frequently used blood transfusions, especially in the face of evidence that suggested that more frequent transfusions targeting a higher hemoglobin level (10–12 g/dL versus 7–9 g/dL) were associated with worse outcomes [52]. There is compelling evidence that EPO decreases transfusion requirements in critically ill patients without renal failure. Similar to the results from two previous small studies [53,54], Corwin et al [55] published data from a large (n = 1302) multi-center, randomized, double-blind trial that demonstrated a decrease in transfusion requirements in patients who received a dose of 40,000 units of intravenous EPO administered subcutaneously once a week. In this study, the percentage of patients who received a blood transfusion was 50% in the group who received EPO compared with 60% in the group who received placebo; Kaplan-Meyer curves showed this separation to be noticeable as early as 1 week after randomization. These differences were maintained regardless of age, severity scores, type of ICU (trauma, surgical, or medical), and baseline hemoglobin level. Differences in 28-day mortality, length of ICU stay, and duration of mechanical ventilation were not statistically significant. An intriguing series of trends was noted with respect to secondary endpoints, such as the rate of ICU readmission (9.8% EPO versus 13.3% placebo, $P = 0.07$), need for reintubation (16.6% EPO versus 20.5% placebo, $P = 0.17$), or need for first intubation (20.8% EPO versus 24.4% placebo, $P = 0.32$). Overall, this large study indicated that the use of moderately high doses of EPO in critically ill patients is safe and results in fewer transfusion requirements. The trends in improvement in some clinical outcome measures cannot be accepted as absolute, but certainly warrant further studies, especially those that focus on specific subsets of high-risk patients, such as those who have heart failure, myocardial infarction, respiratory failure, and ARF.

Chronic renal failure is associated with depressed EPO levels and EPO therapy has been the cornerstone of the treatment of anemia of renal disease for more than a decade. Similar declines in EPO levels occur rapidly in patients who have ARF [56]. Despite this, EPO administration in the setting of ARF had been

discouraged until recently because of the EPO resistance that is induced by many of the mediators of the systemic inflammatory response syndrome, especially interleukin-1,interferon-γ, tumor necrosis factor-α and transforming growth factor (TGF)-β [51,57]. Data such as those discussed in the previous paragraph have raised hopes that patients who have ARF may benefit from the use of higher-dose EPO to overcome the state of resistance. We are not aware of any studies that have addressed this approach in ARF. Conversely, there are interesting data in animals that suggest that EPO rapidly corrects anemia and improves survival in ischemic ARF [58] and is associated with faster renal recovery following cisplatinum administration [59], which is believed to be the result of its trophic effects on renal tubular epithelium. In view of the above, we have taken a more liberal approach to EPO administration in patients who have ARF, primarily with the goal of decreasing transfusion requirements, while awaiting further data on costs, morbidity, and mortality.

Specific therapeutic interventions in established acute renal failure

Many strategies have been used in the attempt to limit the progression of ARF or to avert the need for dialysis in patients who have ARF. Unfortunately, no single approach has been successful in achieving this goal, including diuretics (loop, mannitol), dopamine, atrial natriuretic peptide, insulin-like growth factor 1, growth hormone, thyroxine, calcium channel blockers, oxygen-free radical scavengers, xanthine oxidase inhibition (allopurinol), methylxanthines (aminophylline), and different nutritional approaches with essential and nonessential amino acid supplementation [60–62]. Of these, two deserve specific discussion, diuretics, because of their frequent use, and dopamine, because of its common misuse.

Diuretics

Loop diuretics, alone, or in combination with thiazides, are often used in an attempt to convert oliguric ARF into nonoliguric ARF. An increase in urine output has been uniformly observed across multiple studies that used varying doses of loop diuretics in ARF; however, this effect has not been associated with any beneficial results, such as faster recovery of renal function or improved mortality (see references [61,63–66]). A recent multi-center, retrospective cohort study of patients in the ICU who had ARF concluded that the use of any diuretic was associated with a 77% increased odds of death and nonrecovery of renal function (36% increased risk ratio when alternate analyses were used); this observation was independent of interactions between diuretic use and urine output [67]. The study does not allow causal inferences, and no mechanism is clearly apparent for these observations. Dialysis was delayed by 1 to 2 days in the group that received diuretics; it is possible that more aggressive supportive therapy was delayed while awaiting the effects of the diuretic. The increased mortality was found in patients who were not responsive to the diuretics. In summary, diuretics should continue to be used in an attempt to increase urine output in oliguric patients only after careful correction of the volume status; the trial should be short in duration (a good idea of response can be obtained in 4 to 6 hours) and must not cause a delay in the institution of renal replacement therapies [68].

Renal-dose dopamine

The infusion of nonpressor doses of dopamine (DA) (0.5–3.0 μg/kg/minute) was used for a long time in an attempt to improve renal function in ARF. Observed effects include an increase in renal blood flow and a short-lived diuretic activity [69]. Marked interindividual variations in plasma levels of DA and lack of predictability in the response to exogenous DA among critically ill patients may occur because of decreased plasma clearance, particularly in patients who have renal failure [70]. This may lead to effects that would be ordinarily seen with higher-dose ranges and result in complications, including hypokalemia, hypophosphatemia, decreased respiratory drive, tachyarrhythmias, myocardial or gut ischemia, and impaired T-cell function [71].

Several studies have analyzed the use of renal-dose DA in the prevention and treatment of multiple clinical conditions that are related to ARF. This intervention does not improve hard endpoints, such as mortality, time to recovery of renal function, or need for dialysis (see references [69,72,73]). In a randomized, double-blind trial in 328 patients who had early renal dysfunction (oliguria of 4 hours duration or an elevation in serum creatinine) in the setting of the systemic inflammatory response syndrome, DA had no effect on the severity of renal failure (peak serum creatinine 245 μmol/L DA versus 249 μmol/L placebo), need for dialysis (22% DA versus 25% placebo), or overall in-hospital mortality (43% DA versus 40% placebo) [73]. A meta-analysis of published studies through 2000, which included 17 randomized trials in 854 patients, had similar findings [72]. In conclusion, renal-dose DA may be used as a diuretic agent in ARF if synergistic diuretic schemes are needed, but there is no support for its use in the treatment of ARF. Cognizance of the variable physiologic results that

may be achieved is paramount to avoid potentially severe side effects.

Timing of initiation of dialysis

There is no consensus about the best time to initiate dialysis in ARF. In many cases, there is a strong clinical indication, such as refractory volume overload, hyperkalemia, metabolic acidosis, or clinical uremia (severe symptoms, neurotoxicity, pericarditis). In others, however, the decision to commence dialysis is based mostly on the prevailing serum urea nitrogen (SUN) and creatinine, although these are incomplete markers of renal function. Older prospective studies still guide our practice of not delaying dialysis after the SUN is higher than 100 mg/dL [74,75], but these studies were performed at times of completely different technologies to deliver medical care and dialysis. The only recent study that evaluated this issue was restricted to continuous replacement techniques in trauma patients [76]. In this retrospective study, mortality was lower (61%) in those who started dialysis earlier (SUN < 60 mg/dL, mean 43 mg/dL) than in those who started dialysis later (SUN>60 mg/dL, mean 95 mg/dL, mortality 80%, $P = 0.004$). The trend certainly justifies the earlier initiation of dialysis, but the exact cut-off points are still undetermined.

Choice of dialysis modality

Several options for renal replacement are available, including predominantly diffusive methods (conventional hemodialysis [HD], continuous venovenous hemodialysis [CVVHD], slow low-efficiency dialysis [SLED]), predominantly convective methods (continuous venovenous hemofiltration [CVVH]), and combined diffusive-convective methods (continuous venovenous hemodiafiltration [CVVHDF], acute peritoneal dialysis [PD]). Continuous arteriovenous hemofiltration has been replaced by the pump-driven venovenous modalities and is rarely used today. Table 3 presents a summary of specifications and advantages and disadvantages of each technique.

Conventional HD is extensively used, although the use of continuous (CVVH, CVVHD, CVVHDF) or semicontinuous modalities (SLED) has increased in the ICU setting in this country, especially in tertiary centers [77,78]. This is mostly due to the ability of continuous modalities to provide greater hemodynamic stability than conventional HD [79–81]. Furthermore, continuous renal replacement therapy (CRRT) modalities provide better solute control and provide an ''infinite volume space'' so that control of volume status in patients who have large obligatory intake is made much easier. There are no current data to substantiate an advantage of CRRT over HD. In the largest, prospective, randomized study that included 166 subjects, patients who were assigned to CRRT had higher ICU and hospital mortality, but there was an unequal randomization of patients who had liver failure (43% versus 29%) and higher Acute Physiology and Chronic Health Evaluation (APACHE) III scores (96.4 versus 87.7) to this group [82]. After adjusting for these differences in a multiple regression model, mortality differences were no longer observed. In addition, patients who had hypotension were not randomized, a group in which CRRT is of greater value, which further limited the interpretation of the data.

Two meta-analyses published last year reached different conclusions about the outcomes of CRRT compared with HD, because the pool of studies and exclusion criteria were slightly different. The first one showed a trend toward better results with CRRT after adjustment for study quality and severity of illness (relative risk of death with CRRT 0.72 [0.60–0.87]), although the investigators were careful to acknowledge the limitations in methodology of available studies, which did not allow their analysis to stand as strong evidence favoring CRRT over HD [83]. In contradistinction, the other meta-analysis concluded that the differences in mortality (relative risk of death with HD 0.96 [0.85–1.08]) and loss of renal function (relative risk of renal death with HD 1.02 [0.89–1.17]) were not significant [84]. No studies have compared outcomes with SLED with CRRT or HD. These studies epitomize the difficulties in interpreting this literature. They also underscore the fact that there is no evidence to support the use of one modality over the other. Mindful of these limitations, Box 1 lists clinical situations in which CRRT is favored (anecdotally) as the preferred dialysis modality by most practicing nephrologists in the management of ARF. These ''indications'' have to do with CRRT's ability to remove fluid with greater hemodynamic stability, its greater ability to provide solute control, and its minimization of intracranial pressure changes that are related to dialysis [85]. CRRT has also been used in the management of several clinical syndromes (heart failure, acute respiratory distress syndrome, sepsis, liver failure) despite the absence of significant renal dysfunction. The evidence to date does not support such practices.

PD is an often forgotten technique that may be useful in selected patients, especially those who have heart failure. A major limitation is the requirement of an intact peritoneum, which is often a problem in the surgical ICU setting. Additionally, a recent random-

Table 3
Specific characteristics of different renal replacement modalities

Modality	Urea clearance L/d (L/wk)	Volume control	Comments
Conventional HD	43–48 (129–288)[a]	Limited by hemodynamic instability. It is difficult to remove more than 1-L/h even in patients who do not have impaired hemodynamics.	Pro: widely available. Good solute control, which can become excellent with the use of daily HD. Con: limited hemodynamic stability. Often difficult to perform without anticoagulation. Requires central venous access.
CRRT		Excellent hemodynamic stability because of continuous nature. Allows for removal of large volumes of fluid per hour (up to 1–2-L/h) while matching intake, thereby leading to neutral fluid balance. In volume overloaded patients, removal of 50–100 mL/h can be achieved even in hemodynamically unstable patients who require vasopressors.	Pro: excellent solute and volume control (''infinite space''). Hemodynamic stability. Con: not widely available, labor intensive, expensive. Requires prolonged anticoagulation (except in coagulopathic patients). Central venous access needed.
CVVH	24–34 (168–238)[b]		
CVVHD	34–43 (238–301)		
CVVHDF	52–55 (364–385)		
SLED	14–22 (98–154)[c]	Excellent hemodynamic profile if duration is long enough to allow low ultrafiltration rates to match intake (<200–300 mL/h).	Pro: less labor intensive than CRRT while providing similar solute and volume control. Con: not widely available. Requires anticoagulation and central venous access.
PD	12–29 (84–203)[b]	Hemodynamically stable and potentially good volume control, although ultrafiltration is of limited predictability.	Pro: widely available. Technically simple. No anticoagulation required. Con: requires intact peritoneum (a frequent problem in the SICU). High volumes may impair pulmonary mechanics.

Abbreviations: CRRT, continuous renal replacement therapy; CVVH, continuous venovenous hemofiltration; CVVHD, continuous venovenous hemodialysis; CVVHDF, continuous venovenous hemodialfiltration; HD, hemodialysis; PD, peritoneal dialysis; SICU, surgical ICU; SLED, slow low efficiency hemodialysis.

[a] Lower weekly estimate assumes HD for 4 h/d, 3 days a week. Upper estimate assumes HD for 4 h/d, 6 days a week.

[b] Estimates assume therapy lasting approximately 24h/d. Variation in clearance is predicated upon ultrafiltration prescription in CRRT and frequency of exchanges in PD.

[c] Lower and upper estimates refer to daily SLED for 8 h/d and 12 h/d, respectively.

Box 1. Indications for continuous renal replacement modalities when combined with the occurrence of acute renal failure

- Hypotension/hemodynamic instability
- Severe volume overload or heart failure
- Excessive obligatory intake
- Hypercatabolic states or inability to meet nutritional requirements because of volume overload or excessive azotemia
- Severe sepsis
- Increased intracranial pressure (liver failure, encephalitis, neurosurgical postoperative period)
- Acute respiratory distress syndrome
- Severe hypercalcemia, hyperphosphatemia, rhabdomyolysis, or tumor lysis syndrome in which conventional hemodialysis is unable to match the release of solutes into the circulation

ized, prospective study in 70 patients who had ARF due to severe falciparum malaria or sepsis of different etiologies showed that high-dose PD (70 L/d, 30-minute dwell times) resulted in less optimal solute control and greater mortality (47% versus 17%, $P = 0.005$) compared with CVVH (25 L/day) [86]. Thus, further data are needed to assess the value of PD in other groups, such as patients who have heart failure. Its use in sepsis seems unwarranted, at least in comparison with a CRRT modality.

Dialysis dose: more is better

Separate from the issue of delivering dialysis through a continuous or intermittent modality is the issue of dialysis dose. In this matter, two important prospective, randomized studies have been published in the past 2 years that demonstrated the impact of higher dialysis dose on the mortality of patients who had ARF. The first study compared three doses of hemofiltration (20 mL/kg/day, 35 mL/kg/day, and 45 mL/kg/day adjusted by changes in pump blood flow rate) in 425 patients who had ARF [87]. Individuals who were randomized to the "low" hemofiltration group had a significantly higher mortality than the other two groups (59%, 43%, and 42%, respectively, $P < 0.0001$ for both comparisons) after multiple adjustments for relevant factors such as age, sex, cause of ARF, presence of sepsis, SUN at initiation of CRRT, and APACHE II scores [87]. A subanalysis of the 52 patients who had sepsis showed improved survival in the highest ultrafiltration group. This study demonstrated that patients who have ARF and are undergoing CVVH should receive an ultrafiltration dose of at least 35 mL/kg/hour; patients who have sepsis may benefit from even higher ultrafiltration rates.

The second study compared two doses of conventional HD in 160 patients who had ARF (daily HD for 4 hours each session versus 4 hours every other day) [88]. Patients who were randomized to daily HD had a significantly lower mortality rate 2 weeks after the last HD session (28% versus 46%, $P = 0.01$) and had faster recovery from ARF (9 days versus 16 days, $P = 0.001$), which seemed most likely related to a much lower incidence of episodes of intradialytic hypotension (5% versus 25% of sessions). In addition, daily HD was associated with a lower incidence of oliguria after initiation of dialysis and the development of clinical complications, such as respiratory failure, delirium, and gastrointestinal bleeding. These studies indicate that patients who have ARF who receive higher dialysis doses have better outcomes, regardless of the modality used.

Value of continuous renal replacement in modulating the inflammatory response in critical illness

One of the often discussed values of CRRT modalities is the elimination of inflammatory mediators of the systemic inflammatory response syndrome (SIRS) [89,90]. The available literature in animals and uncontrolled studies in man is extensive and has shown variable results [91]. The removal of such mediators is dependent on several factors that are related to the inflammatory mediator (molecular size, sieving coefficient, elimination half-life, volume of distribution) and the dialysis apparatus (type of membrane, frequency of exchange, amount of ultrafiltration) [92]. Furthermore, proinflammatory and anti-inflammatory substances would be removed during hemofiltration. A mathematical model that accounts for these factors predicted that available conventional CRRT techniques are not capable of effectively decreasing the concentration of relevant mediators of SIRS [92]. In agreement with these calculations are the data from prospective trials on the use of ultrafiltration in patients who have SIRS. In the best study performed to date, Cole et al [93] tested the value of 48 hours of isovolemic CVVH (2 L/hour) in 24 patients who had early sepsis without renal failure. No difference was noted in the progression of multiple organ dysfunction, oxygenation, or vasopressor requirements in the group who received CVVH compared with the group who received usual supportive care without hemofiltration. In another prospective study, Bauer et al [94] evaluated

the role of lower rate CVVH (0.5 L/hour) in preventing the development of multiple organ failure following trauma in 24 patients who had injury severity scores that were higher than 27 [94]. There were no clinically relevant differences between the group who received CVVH and the control group with respect to organ failure scores or systemic hemodynamics [94]. Another study used plasmafiltration, a different approach to the removal of inflammatory mediators that uses a combination of hemofiltration, hemoadsorption, and plasma exchange, in 30 patients who had the sepsis syndrome [95]. Although the acute phase response mediators had their concentration decreased by the procedure, there were no differences in clinical outcomes between the group that underwent plasmafiltration and the control group [95]. In summary, available techniques to perform CRRT are limited in their ability to promote effective changes in inflammatory mediators of SIRS and there is no evidence that such interventions improve outcomes in patients who have SIRS. New developments, such as novel combinations of hemofiltration and adsorption [96] or the use of higher volume hemofiltration [97], not yet supported by most commercially available CRRT machines, may lead to improved outcomes in such patients.

Selected issues in acid-base disorders

The value of the anion gap in the ICU

The serum anion gap (AG) (AG = [Na] – [Cl + HCO_3]) is a useful tool in the evaluation of acid-base disorders and its estimation is routine practice in the care of patients in the ICU. Fig. 1 outlines the causes of an abnormal anion gap and illustrates the importance of considering the alternative definition of anion gap (ie, the difference between unmeasured anions and unmeasured cations). This alternative definition often makes the thinking process about the differential diagnosis more straightforward.

Previous data had established the value of the anion gap in defining the causes of metabolic acidosis, especially the presence of an organic acidosis. In a landmark study, Gabow et al [98] provided guidelines for the individualized approach to acidosis on the basis of the AG, as well as the prevalent serum bicarbonate, as can be summarized below:

When the AG is greater than 30 mmol/L, an organic acidosis (lactic acidosis, ketoacidosis, toxic ingestions) is uniformly present, regardless of pH or serum bicarbonate, and should be aggressively sought.

If acidosis is present (defined as serum bicarbonate <20 mmol/L), an AG that is greater than 25 mmol/L is highly predictive of organic acidosis or renal failure.

If severe acidosis is present (defined as serum bicarbonate <8 mmol/L), an AG that is greater than 20 is virtually diagnostic of an organic acidosis.

These data are probably still applicable, but an important caveat needs to be mentioned. Since the collection of the data of Gabow et al, significant developments have occurred in the instruments that are used for electrolyte measurements. Of greatest

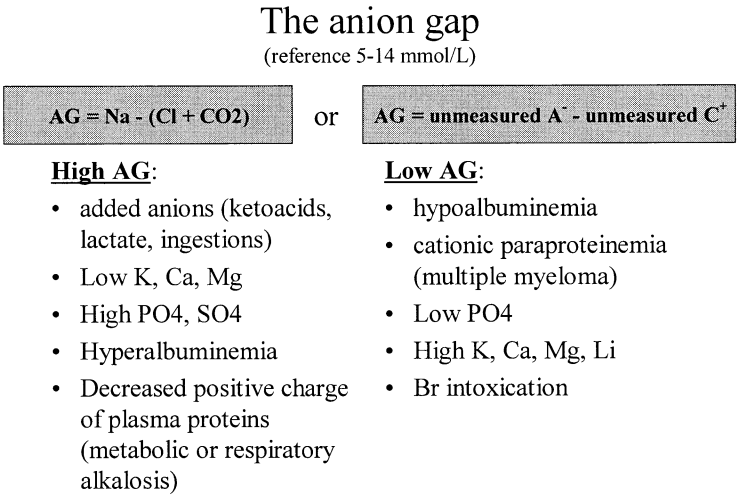

Fig. 1. Causes of an abnormal anion gap. GI, gastrointestinal.

significance has been the widespread use of ion-specific probes, which uniformly provide higher serum chloride levels [99,100]. As a result, the reference levels for the AG have decreased and current accepted levels of normality vary between 5 and 14 mmol/L [99]; these are substantially lower than the previously acknowledged normal value of 12 to 16 mmol/L. Accordingly, we must adapt our interpretation of AG levels; a reasonable, although anecdotal, approach is to decrease the thresholds by about 5 mmol/L.

Two other valuable factors are often overlooked in the assessment of the AG in the ICU. The first factor is the need to account for the degree of hypoalbuminemia, which may cause a false underestimation of the AG. Taking this conversion into account leads to a sevenfold increase in the detection of a high AG (>22 mmol/L) in patients in the ICU [101]. Several approaches have been devised to make the adjustment practical [102] and mathematical [103]. Using the Figge formula [103], the adjustment is as follows:

$$\text{Adjusted AG} = \text{observed AG} + [0.25 \times (4 - \text{observed albumin})]$$

The second factor is the use of the measured, not corrected, serum sodium when calculating the anion gap in the setting of hyperglycemia [104]. Because glucose is electrically inert, no correction should be made because the measured serum sodium, although low due to displacement (“transpositional hyponatremia”), accurately reflects the sodium activity of serum, and, therefore, its strong ion force. Using the corrected serum sodium will spuriously overestimate the AG.

The use of sodium bicarbonate in the treatment of organic acidoses

A long-standing controversy in critical care is the use of sodium bicarbonate in the treatment of organic acidoses (lactic acidosis, ketoacidosis). Proponents of therapy argue that severe acidemia is harmful in its own right, mostly as a result of cardiovascular toxicity, and that increasing the pH with bicarbonate improves this defect [105,106]. The evidence to support such contentions is lacking [105,107]; bicarbonate therapy, when excessive, as it often is in the setting of severe acidemia or during cardiopulmonary resuscitation (CPR), can be associated with several adverse results, such as volume overload, postrecovery alkalosis, hypernatremia, hyperosmolality, ionized hypocalcemia, and possible worsening of intracellular acidosis [106]. A systematic review of the literature concluded that the available evidence did not support the use of bicarbonate during CPR or hypoxic lactic acidosis [107]. Such conclusions were drawn based on physiologic data that showed that the deleterious cardiovascular effects of acidemia were due to tissue pCO_2, not serum bicarbonate or pH, and the fact that several human studies showed deleterious effects on physiologic endpoints, whereas no study had shown a survival advantage [107]. Thus, bicarbonate therapy seems to have no role in the management of such patients. Treatment lies in the correction of the underlying problem; restoration of an effective circulation will rapidly restore bicarbonate levels and pH. If the circulation cannot be restored, bicarbonate will not alter the final outcome.

Patients who have nonhypoxic (type B) lactic acidosis may represent a separate problem. These conditions are associated with preserved tissue perfusion; the only option for patient survival is maintenance of a pH that is compatible with life (>7.0–7.1) until the underlying defect in oxidative phosphorylation has resolved. Under nucleoside analog reverse transcriptase (NRTI)–induced lactic acidosis, the use of alkali therapy with dialytic support will allow this to happen in many cases.

Available data in ketoacidosis do not support the use of bicarbonate. In agreement with previous studies, a recently published, large, retrospective study in patients who had diabetic ketoacidosis demonstrated no difference in correction of acidemia in patients who received bicarbonate compared with those who did not, despite similar baseline characteristics [108]. The only significant difference between the two groups was a much higher requirement for potassium supplementation in the group who received bicarbonate (366 $\pm$ 74 mmol versus 188 $\pm$ 109 mmol) to maintain the same degree of kalemia [108]. Therefore, bicarbonate’s only role in the treatment of ketoacidosis is in the correction of the “nongap, nonketoacidosis” metabolic acidosis which may develop as a result of loss of ketoacids in urine or excessive chloride-containing fluid replacement (dilutional acidosis). These processes often develop after the first 24 hours of therapy and it is reasonable to address them if pH remains lower than 7.3 after resolution of the ketoacidosis component.

Nucleoside analog reverse transcriptase–induced lactic acidosis in patients who are HIV-positive

NRTIs are used as part of highly active antiretroviral therapy in patients who are HIV-positive. A syndrome of hepatic steatosis with lactic acidosis has been well described in patients who were taking NRTIs and seems to be related to NRTI-induced mitochondrial toxicity [109,110]. Risk factors include female

sex, overweight, underlying liver disease (especially coexisting hepatitis B or C), and exposure to stavudine and didanosine [109].

It was recently recognized that there is a broad spectrum of presentation of hyperlactatemia during NRTI therapy that ranges from mild asymptomatic hyperlactatemia, to moderate symptomatic hyperlactatemia without acidosis (usually with associated hepatic steatosis), to severe lactic acidosis [109]. The asymptomatic presentation remains stable over time [111] and does not require therapy. The symptomatic forms are marked by gastrointestinal symptoms, mostly related to the liver injury. Patients present with nausea, vomiting, anorexia, abdominal pain, distension, and tender hepatomegaly [109]. The intermediate phenotype of symptomatic hyperlactatemia without acidosis is marked by a slow normalization of serum lactate following discontinuation of the drugs, which allows for cautious rechallenge with another NRTI, especially abacavir, under close follow-up [109].

Severe lactic acidosis with hepatic steatosis is an ominous clinical syndrome with a mortality rate of more than 50% [110]. Fortunately, this condition is rare and occurs with an incidence of 1.3 to 8.3 cases per 1000 person-years [109]. Time on therapy varies widely, 1–36 months, and there is no apparent relationship to the stage of HIV disease [110]. Patients present with acidemia and markedly elevated lactate levels (median 10–15 mmol/L); there is a particularly brisk increase in mortality when lactate levels are greater than 15 mmol/L at presentation [110]. Treatment of this syndrome is supportive; bicarbonate therapy may be used as a temporizing measure, although it often requires concomitant dialysis [109,110]. In our experience, a continuous modality is required to maintain adequate volume control (create "space" for the large amounts of bicarbonate required) and acceptable control of acidemia until the defect has normalized, which may take as little as 1 week or as long as 6 months [110]. Supportive use of certain cofactors to increase lactate disposition, such as thiamine, riboflavin, coenzyme Q, L-carnitine, and dichloroacetate has been widely reported in the literature (see references [109,110,112]), although there are no controlled studies to support their use. Given the innocuous nature of most of these cofactors, it is reasonable to use them when treating these severely ill patients.

Approach to ethylene glycol and methanol intoxications

Toxic alcohol ingestions, although rare, have classic presentations and ominous clinical consequences if not diagnosed promptly [113]. Of greatest relevance are ethylene glycol and methanol poisonings, which present with a high anion gap, high osmolar gap metabolic acidosis. Suspicion of these ingestions should always be raised in patients who present with otherwise unexplained acidosis with a high anion gap. In such cases, calculation of the osmolar gap (measured serum osmolality [Osm] − calculated serum Osm), where calculated Osm = 2Na + SUN/2.8 + glucose/18 + ethanol/4.3 is essential in providing a clue to the diagnosis. If the osmolar gap is greater than 10, and, particularly, if greater than 20, it is highly likely that an ingestion has occurred and empiric initiation of therapy is indicated [114]. Early diagnosis and initiation of therapy are important markers of improved outcomes in these patients, and such differences are measured in hours [115–117].

The value of analyzing the osmolar gap lies in its widespread availability and its direct relationship to serum levels of the intoxicants, because these levels are not readily available in most clinical laboratories. The reader should be familiar with the concept that a serum concentration of 100 mg/dL of an alcohol will result in different degrees of elevation of the osmolar gap, because this is dependent on the size of the molecules. A 100 mg/dL will thus result in the following osmolar contributions:

Ethanol 22 mOsm/L (not a cause of acidosis, but a common coingestion)
Methanol 34 mOsm/L
Ethylene glycol 17 mOsm/L
Isopropanol 17 mOsm/L (not a cause of acidosis, but an occasional coingestion).

In ethylene glycol and methanol poisoning, toxicity is not inflicted by these alcohols but by their metabolites through the action of hepatic alcohol dehydrogenase (primarily glycolate with ethylene glycol and formate with methanol). Thus, the cornerstones of therapy include blocking further metabolism (alcohol dehydrogenase inhibition, thiamine, folate, pyridoxine), treating the acidemia (bicarbonate), and removing the agent and toxic metabolites (forced diuresis, hemodialysis) [114].

The most relevant development in recent years has occurred in the area of alcohol dehydrogenase inhibition. The classic approach had been the use of ethanol, but this treatment was fraught with several difficulties, such as sedation, need for frequent monitoring of blood levels, and possible hepatotoxicity and hypoglycemia with prolonged infusions (see references [113,117–119]). The development and clinical testing of fomepizole resulted in the availability of a drug that is easy to use and has few side effects and need for

monitoring. This inhibitor of alcohol dehydrogenase is effective in treating ethylene glycol and methanol intoxications with an excellent safety profile, twice daily dosing, and no need for drug level monitoring [115–118]. It has thus replaced ethanol as the agent of choice in the management of these toxic ingestions.

The guidelines for initiation of hemodialysis in these intoxications are still not clear. Classic recommendations were to use dialysis when serum levels were greater than 50 mg/dL (osmolar gap >9 mOsm/L for ethylene glycol, >17 mOsm/L for methanol) or in the presence of severe or refractory acidemia or ARF [116,117]. Prospective data showed that patients who do not have symptoms (decreased mentation or cardiovascular collapse with ethylene glycol or methanol, visual changes with methanol), acidemia, or renal failure do well without dialysis despite serum levels that are greater than 50 mg/dL [115–117]. This approach relies on the use of aggressive hydration, urinary alkalinization, and forced diuresis (eg, with mannitol) to remove the toxins. Unfortunately, no comparative data exist on treatment with or without dialysis; until such data are available, we believe that hemodialysis should be offered routinely to patients who have serum levels that are greater than 50 mg/dL.

Management of chloride-unresponsive metabolic alkalosis in the ICU

Metabolic alkalosis is a common abnormality in hospitalized patients and in the ICU. When abnormal arterial blood gases (ABGs) are analyzed, up to 51% of samples have metabolic alkalosis as the principal disorder [120], although other studies showed respiratory alkalosis to be much more common [121]. When severe metabolic alkalosis (pH>7.6) is present, especially if accompanied by the added alkalemic effect of respiratory alkalosis, in-hospital mortality is increased and may reach 48.5% [121], mostly as a result of a combination of central nervous system (CNS) depression and cardiac arrhythmias [122].

Metabolic alkalosis can be generated and maintained by a host of factors as outlined in Table 4, which uses the general groupings of chloride-responsive alkalosis (volume related) and chloride-resistant alkalosis. In addition to the history and examination, a valuable test to differentiate between the two types is the measurement of urinary chloride on a spot urine sample. This test provides diagnostic information with direct therapeutic implications; most patients who have chloride-responsive alkalosis will respond promptly to interventions that replete volume and chloride concentrations, such as saline with or without potassium replacement, which is often needed.

Table 4
Causes of metabolic alkalosis according to the urinary chloride level

Low urine Cl (<25 mmol/L)	High urine Cl (>40 mmol/L)
Vomiting, nasogastric suctioning	Mineralocorticoids, glucocorticoids
Diuretics (late)	Diuretics (early)
Posthypercapnia	Alkali load
Cystic fibrosis	Severe hypokalemia
Low Cl diet	Bartter's, Gitelman's syndrome
Refeeding	

A common and often challenging problem in the ICU is the treatment of chloride-resistant alkalosis in patients who are receiving high doses of corticosteroids and diuretics during mechanical ventilation. These patients develop alkalosis that may impair their weaning in addition to the increased mortality risk [123]. Because these patients are resistant to potassium repletion and volume replacement is often contraindicated, few options exist for treatment. The most precise method is the infusion of hydrochloric acid, but this requires special protocols, the use of central venous access [122], and is often met with resistance by the nursing staff. Similarly, the use of precursors of hydrochloric acid, such as ammonium chloride or arginine hydrochloride, can be complicated by encephalopathy in liver disease (ammonium chloride) or hyperkalemia (arginine hydrochloride) [122]. A safe and effective approach is to use acetazolamide, a carbonic anhydrase inhibitor with potent bicarbonaturic effects. A recent prospective, randomized, double-blind study in ventilated patients in the ICU showed that a single dose of acetazolamide, 500 mg IV decreased serum bicarbonate by about 6 mmol/L after 24 hours, an effect that was indistinguishable from a dose of 250 mg, every 6 hours for 24 hours [123]. In our experience, acetazolamide is safe and effective in these patients, although fastidious replacement of potassium must take place because of its potent kaliuretic effect.

Patients who have renal failure may represent a particularly difficult problem when they develop refractory alkalosis, a rare complication that can occur in the setting of excessive gastric drainage or multiple transfusions [124,125]. In such cases, patients may be refractory to acid replacement; dialysis with a low bicarbonate bath may be the only therapeutic option [124,125]. In some extreme cases in anuric patients, bicarbonate-free continuous hemodialysis/hemofiltration may be necessary to correct the alkalemia until the

underlying problem is corrected (Lee et al, unpublished observations).

Selected issues in electrolyte disorders

New causes and novel approaches to hyponatremia

The classic approach to hyponatremia involves an initial determination of volume status, which will often provide a clue to the diagnosis. In patients who have a volume depletion, the usual cause is a volume-mediated increase in vasopressin secretion that leads to water retention. Patients who have increases in extracellular volume develop hyponatremia because of a maladaptive increase in vasopressin secretion that is a result of the development of an ineffective plasma volume, along with decreases in renal perfusion that lead to impaired renal function, and, thereby, decreased renal water excretion. Common causes include decompensated heart failure, nephrosis, cirrhosis, pregnancy, and renal failure (acute or chronic) [126]. Euvolemic hyponatremia can be seen in states of compulsive water intake (especially if accompanied by limited solute intake), thiazide diuretics, adrenal insufficiency, hypothyroidism, and in the syndrome of inappropriate vasopressin release (SIADH).

SIADH is the most common cause of hyponatremia in hospitalized patients [127]. The syndrome is characterized by clinical euvolemia, elevated urinary Na (>20 mmol/L), and inappropriately high urinary osmolality (>100 mOsm/kg) in the presence of hyponatremia. The use of the spot urine Na measurement is relevant in the confirmation of euvolemia because there is evidence that the clinical examination has poor sensitivity and specificity in the setting of hyponatremia when compared with the urine Na concentration [128]. SIADH can be caused by multiple mechanisms in critically ill patients, including [126]:

- Malignancies, especially of the lung and brain
- Primary brain disorders, especially acute psychoses and parenchymal or subarachnoid hemorrhages
- Acute pulmonary infections, respiratory failure and positive pressure mechanical ventilation This latter condition is somewhat controversial, since the mechanisms seem more related to changes in central pressures leading to an appropriate increase in vasopressin secretion and decreased renal blood flow, especially if associated with positive end-expiratory pressure [129,130]
- Postoperative pain and nausea
- Hypotonic postoperative fluid replacement or hypotonic irrigating solutions (sorbitol, glycine) used for transurethral prostate resections and hysteroscopies
- Drugs that are vasopressin analogs (desmopressin, oxytocin), enhance vasopressin release (nicotine, opiates, phenothiazines, tricyclic antidepressants, carbamazepine, vincristine), potentiate renal vasopressin activity (cyclophosphamide, NSAIDs), or act by unknown or combined mechanisms (haloperidol, selective serotonin reuptake inhibitors [SSRIs], ecstasy)

Two recently recognized causes of hyponatremia with SIADH features are SSRIs and ecstasy. SSRIs are the most commonly prescribed class of antidepressants and are associated with about five case of hyponatremia per 1000 elderly patients per year [131]; this may be higher in hospitalized psychiatric patients [132]. Cases usually occur within the first several weeks of therapy and may occur with any of the classic SSRIs (fluoxetine, sertraline, paroxetine, fluvoxamine) or venlafaxine [133,134]. Older age, female sex, and concomitant diuretic therapy are important predisposing factors [133]. Ecstasy (3,4-methylenedioxymethamphetamine) is now a frequently used recreational drug among the youth. These patients may be admitted to the ICU after presenting to the emergency room with confusion, seizures, hyperthermia and hyponatremia [135] after use of this drug in conjunction with large volumes of hypotonic fluids, as is often encouraged — incorrectly so — by other ecstasy users [136].

The treatment of hyponatremia is plagued by controversies. Untreated severe hyponatremia is marked by a risk of respiratory compromise and anoxic encephalopathy [137]. Excessively rapid correction of chronic hyponatremia may result in the osmotic demyelination syndrome; a reasonable approach consists of the elimination of offending mechanisms and water restriction in all patients and the use of hypertonic saline in judicious amounts in patients who have evidence of more severe CNS toxicity, such as seizures or coma [126]. In these patients, the rate of correction should be 1 to 2 mmol/L/hour for the first several hours; total correction should be no more than 12 mmol/L during the first day. Frequent monitoring of serum Na is essential to prevent overshoot, especially because anecdotal evidence shows that the use of hypotonic solutions to slow down or reverse the increase of serum Na is successful in averting neurologic damage from overcorrection [138]

Antagonists of the vasopressin-2 receptor have been developed and recently tested as therapy for hyponatremia [139]. These agents, also called aquaretics,

are effective in improving water balance and correcting serum sodium in hyponatremic patients who have heart failure, cirrhosis, or SIADH [140]. In a multicenter, dose-finding study, the nonpeptide VPA–985 rapidly and consistently increased water excretion and elevated serum sodium [140]. In fact, a correction rate that is too rapid (>8 mmol/L by day 2 of therapy) or overshooting to greater than 142 mmol/L demanded that a dose be withheld in 7 of the 33 patients who received the active drug. Thus, such an agent represents a powerful option to correct hyponatremia, but close observation is needed to avoid potentially detrimental overcorrection.

Hypernatremia: important "balance" in the quality of ICU care

The frequency of hypernatremia approaches 6% in patients in the ICU [141]; this frequency is disturbing because it occurs in the setting of daily measurements of serum chemistries and extremely tight monitoring of fluid prescription and balance. Previous data that included patients who were and were not in the ICU revealed that 85% of cases of hypernatremia developed during hospitalization and were due to inappropriate fluid prescription or lack of identification of the patient's limited access to free water [142]. In Polderman et al's study, the development of hypernatremia during the ICU stay was associated with greater mortality (32%) than the presence of hypernatremia on admission, which occurred in 9% of patients and was associated with a 20% mortality rate [141]. Thus, one could argue that hypernatremia that happens in front of our eyes is a prognostic indicator that reflects the quality of delivered care.

The development of hypernatremia in critically ill patients results from a combination of the lack of access to water and excessive loss of hypotonic fluids as outlined in Fig. 2. The evaluation of hypernatremia is straightforward; it is always associated with a net state of water deficiency regardless of extracellular volume status [143]. Some investigators have preferred the more descriptive terms "aquapenia" or "hypoaquemia" to describe this disorder. Accordingly, the management is focused on the correction of possible underlying mechanisms and replacement of water losses, with the understanding that replacement of previous and ongoing losses is necessary to correct serum osmolality.

Detailed evaluation of potassium deficiency in the ICU

The evaluation of hypokalemia in patients in the ICU must start with an evaluation of the likely operative mechanism. Three basic mechanisms are responsible for hypokalemia: (1) decreased intake, (2) increased losses (gastrointestinal or renal), or (3) transcellular shifts. The patient's medical history can provide clues about the presence of gastrointestinal losses, and a detailed review of medications and other laboratory tests can identify causes of increased transcellular shifts, such as catecholamines (epinephrine, high-dose dopamine, β2-agonists), insulin, alkalemia, or the refeeding syndrome. A useful test to differentiate renal from extrarenal losses is the measurement of the urinary transtubular potassium (K) gradient (TTKG) [TTKG = (UK/PK)/(Uosm/Posm)]. In this test, the urinary concentration of K is adjusted for the degree of water abstraction that occurs at sites distal to

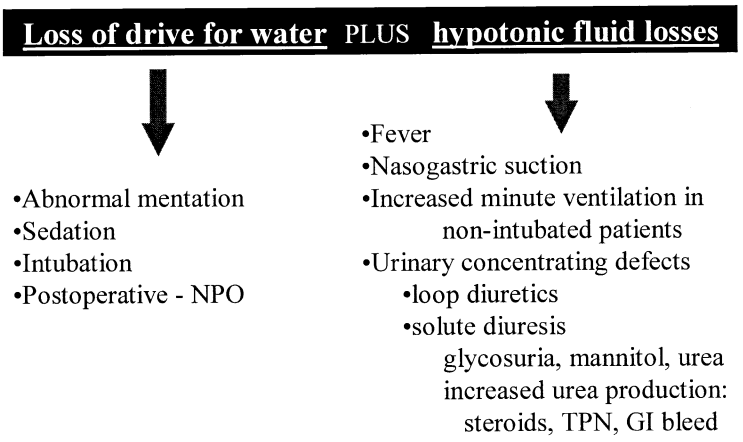

Fig. 2. Mechanisms of hypernatremia in the ICU. NPO, nothing per os; TPN, parenteral nutrition.

those of K regulation. In the setting of hypokalemia, the appropriate TTKG should be approximately 1.0 which indicates maximal conservation of K [144]. Patients who have hypokalemia and a TTKG that is greater than 4.0 have excessive renal losses, which are at least partly responsible for the negative K balance. Causes of K losses that are relevant to ICU patients include:

Renal: diuretics (thiazides, loop, acetazolamide, mannitol), glycosuria, chronic alcoholism, bicarbonate-containing intravenous solutions, postobstructive or post-ATN diuresis, amphotericin B, hypomagnesemia, excessive mineralocorticoid activity (volume depletion, heart failure, high-dose glucocorticoids)
Extrarenal: vomiting, nasogastric suction, diarrhea, pancreatic-biliary fistulas

The use of urinary electrolytes calculate the TTKG also allows for the determination of the average daily renal K losses, which can be estimated by multiplying the urinary K concentration by the total urine output for the 24-hour period. In patients who have severe hypokalemia or with cardiac toxicity that is related to the hypokalemia, rapid infusions of KCl, up to 40 mmol/h, are safe [145,146]. Because of its predominantly intracellular distribution, relatively small decreases in serum K levels can represent large changes in total body K stores [147]. In a systematic review of studies in which total body K was measured, Sterns et al [147] demonstrated that a serum K level of 3 mmol/L could represent a total K deficit of 200 to 400 mmol/70 kg body weight; this deficit was greater than 700 mmol/70 kg body weight when serum K reached 2 mmol/L [147]. The treating physician must take in to account this baseline deficit, as well as the pattern of ongoing losses when designing an effective replacement prescription.

Potassium-magnesium interactions in critical care

Potassium and magnesium deficiency are often coexistent in critically ill patients because many of the causes of hypokalemia are also causes of hypomagnesemia (diarrhea, diuretics, chronic alcoholism, postobstructive and post-ATN diuresis, and any state of aldosterone excess). Hypomagnesemia is a cause of hypokalemia in its own right, and it is well recognized that Mg replacement is necessary before successful K repletion can be accomplished [148]. The mechanisms for this interaction are not completely understood, but current evidence suggests that Mg leads to decreased ATP activity, thereby increasing the activity of ATP-inhibitable luminal K channels [149,150]. Only aggressive replacement of Mg will allow successful K repletion.

Important aspects of hypophosphatemia to the intensivist

Hypophosphatemia can be caused by multiple mechanisms in patients in the ICU, including factors that lead to transcellular shifts (respiratory alkalosis, dextrose therapy, insulin, refeeding, sepsis), decreased intestinal absorption (vitamin D deficiency, antacids) or prolonged decreased intake, and increased renal losses (osmotic diuretics, glycosuria, chronic alcoholism, hyperparathyroidism). Severe hypophosphatemia (< 1 mg/dL) promotes significant morbidity in patients in the ICU because of its effects on multiple

Table 5
Causes and mechanisms of severe hypophosphatemia (< 1 mg/dL)

Cause	Mechanisms
Alcohol withdrawal	Chronic depletion from renal losses
	Respiratory alkalosis (transcellular shifts)
	Dextrose infusions/refeeding (transcellular shifts)
Diabetic ketoacidosis	Urinary losses (osmotic diuresis)
	Insulin therapy (transcellular shifts)
Refeeding syndrome[a]	Transcellular shifts into liver/muscle
Acute respiratory alkalosis[b]	Transcellular shifts
Recovery/diuretic phase of severe burns	Transcellular shifts
	Respiratory alkalosis (transcellular shifts)
	Renal losses

[a] The refeeding syndrome may occur even after short fasting periods (< 5 days), and may occur with enteral as well as parenteral nutrition [155,156].

[b] The correction of chronic respiratory acidosis can also result in severe hypophosphatemia even in the absence of frankly alkalemic pH [157].

organ systems; the most relevant syndromes in which severe hypophosphatemia can occur are few and often have multiple operating mechanisms (Table 5). With special relevance to the intensivist, even moderate degrees of phosphate depletion leads to impaired diaphragmatic contractility and may impair weaning from mechanical ventilation [151,152] and severe hypophosphatemia is associated with impaired myocardial contractility [153,154]. Phosphate replacement rapidly corrects these abnormalities.

Summary

Renal and electrolyte problems are common in patients in the ICU. Several advances that occurred in the recent past have been incorporated in the diagnosis and management of these disorders and were reviewed in this article. Unfortunately, many important questions remain unanswered, especially in the area of ARF, where new therapies are anxiously awaited to make the transition from bench to bedside. Better studies are sorely needed to define the best approach to dialysis in patients who have ARF.

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