NARRATIVE REVIEW ARTICLE

Urine Electrolytes in the Intensive Care Unit: From Pathophysiology to Clinical Practice

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Assessment of urine concentrations of sodium, chloride, and potassium is a widely available, rapid, and low-cost diagnostic option for the management of critically ill patients. Urine electrolytes have long been suggested in the diagnostic workup of hypovolemia, kidney injury, and acid-base and electrolyte disturbances. However, due to the wide range of normal reference values and challenges in interpretation, their use is controversial. To clarify their potential role in managing critical patients, we reviewed existing evidence on the use of urine electrolytes for diagnostic and therapeutic evaluation and assessment in critical illness. This review will describe the normal physiology of water and electrolyte excretion, summarize the use of urine electrolytes in hypovolemia, acute kidney injury, acid-base, and electrolyte disorders, and suggest some practical flowcharts for the potential use of urine electrolytes in daily critical care practice. (Anesth Analg XXX;XXX:00–00)

GLOSSARY

π-GST = π-glutathione-S-transferase; **ADH** = antidiuretic hormone; **AG** = anion gap; **AKI** = acute kidney injury; **AKIN** = Acute Kidney Injury Network; **ANP** = atrial network peptide; **AUROC** = area under the receiver operating characteristic curve; **cAMP** = cyclic adenosine monophosphate; **CI** = confidence interval; **Cl** = chloride; **ClU** = urine chloride; **CONSORT** = Consolidated Standards of Reporting Trials; **CVP** = central venous pressure; **CysC** = cystatin C; **ECV** = effective circulating volume; **EFWC** = electrolyte-free water clearance; **eGFR** = estimated glomerular filtration rate; **FEK** = fractional excretion of potassium; **FENa** = fractional excretion of sodium; **FENGAL** = fractional excretion of NGAL; **FEUrate** = fractional excretion of urate; **FeUrea** = fractional excretion of urea; **F_{IO_2}** = fraction of inspired oxygen; **FWC** = free water clearance; **GFR** = glomerular filtration rate; **HGF** = hepatocyte growth factor; **HR** = heart rate; **ICU** = intensive care unit; **IL-18** = interleukin-18; **KIM** = kidney injury molecule; **L-FABP** = liver-type fatty acid binding protein; **MV** = mechanical ventilation; **NGAL** = neutrophil gelatinase–associated lipocalin; **P-AKI** = persistent acute kidney injury; **Pao_2** = partial pressure of oxygen; **ROC** = receiver operating characteristic; **RRT** = renal replacement therapy; **SBE** = standard base excess; **SCr** = serum creatinine; **SIADH** = syndrome of inappropriate antidiuretic hormone; **SID** = strong ion difference; **SIDa** = apparent strong ion difference; **SIDe** = effective strong ion difference; **SIDu** = urine strong ion difference; **SIG** = strong ion gap; **T-AKI** = transient acute kidney injury; **TTKG** = transtubular potassium gradients; **UCr** = urine creatinine; **UFurosemide** = urine furosemide; **UK** = urine potassium; **UNa** = urine sodium concentration; **UO** = urine output

The term "urine electrolytes" is generally used to indicate urine concentrations of sodium, potassium, and chloride. Assessment of urine electrolytes is infrequently performed in critically ill patients, in part because their value depends on the amount of electrolyte that is excreted by the kidney—a balance between glomerular filtration, tubular secretion, and reabsorption of water and solutes, which can vary significantly under different pathophysiological conditions.

The information provided by urine electrolytes may be of value when the patient acid-base, fluid, or electrolyte status is abnormal.[1] Existing literature is mixed regarding the clinical utility of urine electrolyte measurement, with older papers finding limitations[2] and more recent study suggesting potential value[3] in the diagnosis and management of hypovolemia, acute kidney injury (AKI), and acid-base and electrolyte disorders.

In this review, we summarize the physiology of urine electrolyte regulation and review existing data with respect to the utility of urine electrolyte measurement in hypovolemia, AKI, acid-base and electrolyte disorders in critically ill patients. In addition, we suggest a practical guide to the use of urine electrolytes in daily critical care practice. This article adheres to the applicable Consolidated Standards of Reporting Trials (CONSORT) guidelines.

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Accepted for publication May 18, 2020.

Funding: None.

The authors declare no conflicts of interest.

Reprints will not be available from the authors.

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DOI: 10.1213/ANE.0000000000004994

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NORMAL PHYSIOLOGY OF WATER AND ELECTROLYTE EXCRETION

The kidneys play a critical role in the control of extracellular fluid volume and osmolality. Figure 1 summarizes the renal handling of water and electrolytes.

A healthy kidney produces ≈180 L of ultrafiltrate per day; under physiological conditions, the glomerular capillary wall is relatively impermeable to large molecules, so that <1 g of protein per day is filtered (which can become more in the setting of glomerular diseases like diabetes). Besides proteins, the ultrafiltrate composition is similar to plasma. As the ultrafiltrate flows across the nephron, sodium is reabsorbed via co-transport with glucose, amino acids, and phosphate in the proximal early tubule, and is exchanged with chloride in the late proximal.[4,5] Potassium reabsorption occurs paracellularly via passive exchange for sodium in the distal tubules (hence, its secretion is enhanced by sodium reabsorption). Water reabsorption is also passive and follows the osmotic gradient between the surrounding tissue and the inner side of the tubule. The ultrafiltrate then passes through the loop of Henle, which is divided into 3 anatomical components with different transport and permeability characteristics. While the reabsorption of water reaches 90%–95% in the proximal tubule and the loop of Henle, the distal tubule and collecting ducts account for the last 5%–10% of reabsorption. Urine pH is controlled by hydrogen secretion and bicarbonate reabsorption. The distal tubule is impermeable to water, whereas the permeability of the collecting duct is controlled by the antidiuretic hormone (ADH).[6]

Water balance is regulated by the hypothalamus, which acts on the kidney via the neurohypophysis.[4] Hypothalamic osmoceptors sense plasma osmolality, and the neurohypophysis secretes ADH at a rate proportional to the osmolality (and hence, because sodium is the main determinant of plasma osmolality, to sodium concentration), when the osmotic threshold of 285 mOsm/kg is reached.[5] In addition, ADH is also secreted when a decrease in effective circulating volume (ECV) is detected by baroceptors.[7] The sensitivity of ADH secretion to osmolality is higher than to circulating volume because only a 1%–2% change in

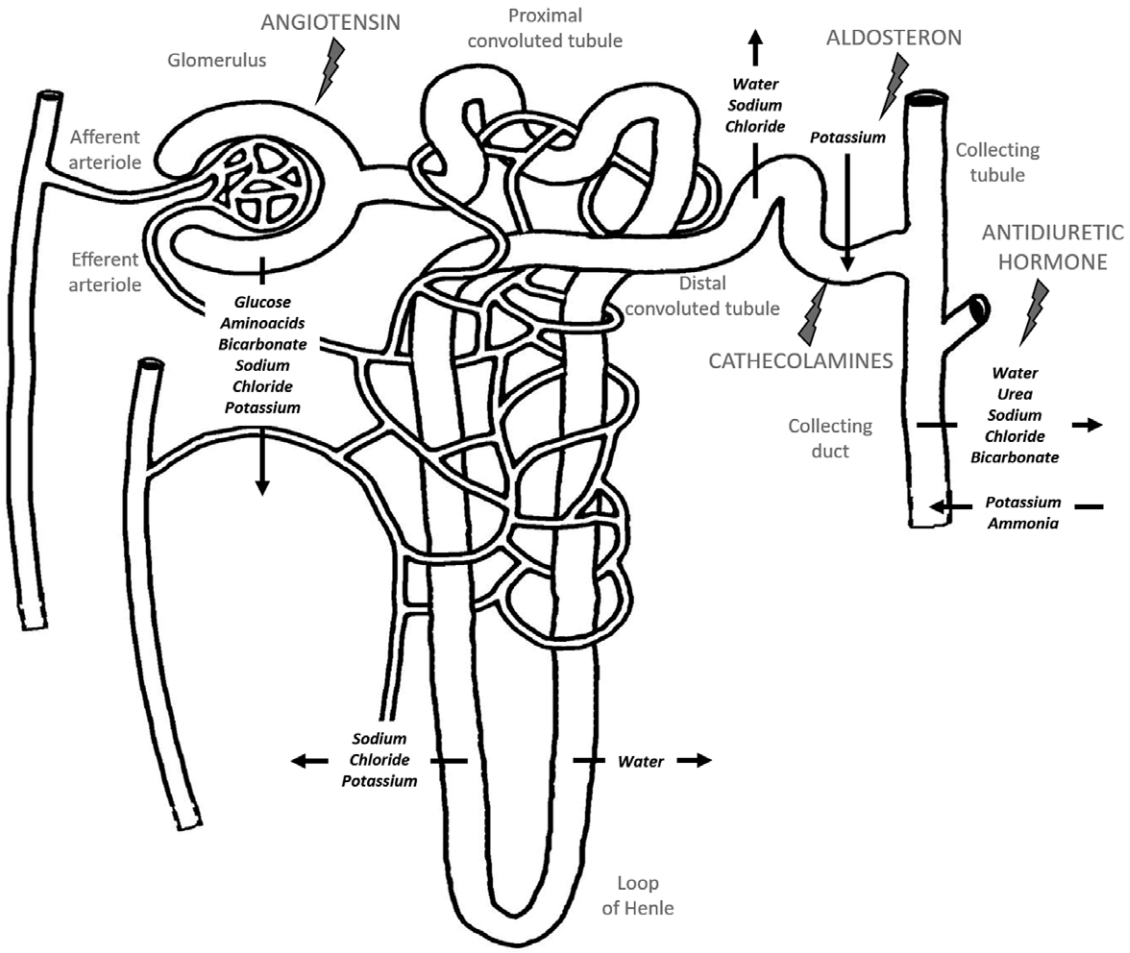

Figure 1. Renal handling of water and electrolytes. The different portions of the nephron are presented in lowercase, light gray; the black arrows indicate the directions (ie, filtration, secretion, or reabsorption) of the different molecules in the ultrafiltrate along their path in the nephron. The site of effect of the different hormones are depicted in uppercase, light grey.

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osmolality is required to induce osmotic secretion of ADH, whereas a change in circulating volume of >10% is normally needed to trigger nonosmotic secretion.[8] However, the hypovolemic trigger for ADH may override osmotic regulation, leading to water retention and hyponatremia in cases of severe loss of circulating blood volume. Further complicating the regulation of water balance are several nonosmotic, nonvolume triggers for ADH secretion, such as mechanical ventilation, drugs, infections, central nervous system diseases, malignant diseases, stress, or pain.[8,9] Once secreted, ADH binds to specific V2 renal receptors in the collecting ducts, increasing water permeability and resorption via a cyclic adenosine monophosphate (cAMP)–dependent mechanism. By inducing water resorption, ADH thus reduces plasma osmolality.

CLINICAL APPLICATIONS OF URINE ELECTROLYTES

In the following section, we will review the pathophysiology and the possible use of urine electrolytes in frequently encountered clinical circumstances. Each section will also include an illustrative clinical situation in which urine electrolytes may be used to clarify the diagnosis or treatment.

To identify relevant papers, a bibliographic search was conducted using the PubMed, Cochrane Library, Scopus, and Web of Science databases from inception to the cutoff date of September 1, 2019. We restricted our search to human studies published in English. To supplement the search, the reference list of every article was also manually screened to identify additional potentially eligible studies.

We used the following key words either alone or combined with appropriate Boolean operators, to conduct our search: "urine," "urinary," "electrolytes," "sodium," "potassium," "chloride," "critical care," "critically ill patients," "critical illness," "intensive care." A similar search was also performed using the PubMed MeSH thesaurus. The final search identified 106 studies. Two authors (M.U., P.F.) subsequently and independently screened the studies selected from the search strategy to identify potentially eligible studies, which then underwent full-text review. Every study was then classified into 1 of 4 categories: changes in effective circulating blood volume, AKI, acid-base abnormalities, and serum electrolyte disturbances.

Table 1 reports the characteristics and results of the clinical studies on the use of urine electrolytes for changes in effective circulating blood volume and AKI in critically ill patients; Table 2 reports the characteristics and results of the clinical studies on the use of urine electrolytes for acid-base abnormalities and serum electrolyte disturbances.

Changes in Effective Circulating Blood Volume

Sodium is the primary extracellular cation and the main determinant of tonicity (and hence, extracellular fluid volume).[38] Under normal conditions, sodium excretion and intake are matched. However, in critical illness, extracellular fluid volume and organ perfusion are often uncoupled and the ECV has been used to describe the part of the intravascular volume that affects organ perfusion.[39]

Whenever the ECV is reduced, both the sympathetic nervous system and the renin-angiotensin-aldosterone system[40] are activated. Both pathways increase systemic vascular resistance with the aim of attenuating the arterial underfilling. An avid sodium retention state then develops in the kidneys, decreasing urine sodium concentration (UNa) and increasing potassium excretion. In contrast, ECV expansion and increased atrial stretch induce the release of atrial natriuretic peptide, whose effects oppose those of the renin-angiotensin-aldosterone axis.[41]

UNa and the urine sodium/urine potassium (UK) ratio may then be considered an indirect measure of volume status.[3] As an example, a 2018 report on children with nephrotic syndrome suggests that a UK > UNa is an accurate indicator of hypovolemia.[11] However, the response to reduced ECV is complicated by the nonosmotic release of ADH in low cardiac output states,[8] or in vasodilatory conditions such as cirrhosis or sepsis.[42,43] These states lead to water retention, potentially increasing UNa independent of circulating volume.[44] Moreover, inflammation and oxidative stress may activate the renin-angiotensin-aldosterone system and induce sodium retention and affect UNa independent of global renal perfusion.[45] An osmotic diuresis or acute tubular necrosis may also prevent the kidney from reabsorbing sodium despite a decreased ECV, rendering the UNa inaccurate.[38]

To account for the effect of water reabsorption on the relationship between UNa and volume status, the fractional excretion of sodium (FENa) has been used:

$$\text{FENa} = \frac{S_{Cr} \cdot U_{Na}}{U_{Cr} \cdot S_{Na}} \cdot 100,$$

where S_{Cr} is serum creatinine, S_{Na} is serum sodium, and U_{Cr} is urine creatinine.

FENa is ≈1% in euvolemic, healthy subjects, and a normal kidney should respond to arterial underfilling with a FENa <1%.[44]

Evidence supporting the use of urine electrolytes for assessment of volume status in critically ill patients has been mixed. A 2016 study of normotensive, oliguric intensive care unit (ICU) patients found that neither UNa nor FENa predicted cardiac fluid responsiveness after a fluid challenge. The authors concluded that urinary biomarkers are not reliable

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Table 1. Clinical Studies Regarding the Use of Urine Electrolytes for Changes in Effective Circulating Blood Volume and AKI

Setting	Author	Design	Parameters	Main Remarks
Reduced ECV	Legrand et al[10]	Prospective multicenter observational study (n = 54)	UO <0.5 mL/kg/h for 3 consecutive hours. UNa and FENa	UNa (37 ± 38 vs 25 ± 75 mmol/L; *P* = .44) and FENa (2.27 ± 2.5 vs 2.15% ± 5.0%; *P* = .94) were not statistically different between those who did and those who did not respond to the fluid challenge. Areas under the ROC curves were 0.51 and 0.56 for UNa and FENa. FeUrea had an AUROC of 0.70 for fluid responders.
	Keenswijk et al[11]	Prospective study (n = 44)	44 nephrotic children versus control group (36 children). Renal perfusion and GFR UK/UK + UNa	Urinary potassium to the sum of urinary potassium plus sodium ratio can accurately detect hypovolemia in nephrotic syndrome and thus identify those children who would probably respond to albumin infusion.
AKI	Caironi et al[12]	Case series (n = 3)	Quasicontinuous analysis of urine pH, sodium, chloride, potassium and ammonium levels	For each analytic parameter, the accuracy of measurements obtained was acceptable as compared with those of the reference techniques. In case 1, urine analysis revealed increased urinary sodium and chloride excretion strictly in parallel with mean arterial pressure, and increased ammonium excretion which was associated with moderate hypercapnia. Case 2 showed increases in urine pH and sodium and chloride levels following awakening after sedation suspension. In case 3, urine analysis revealed an impairment of renal concentrative power, which was associated with hypovolemia.
	Kaplan and Kohn[13]	Observational (n = 6) and retrospective study (n = 87)	FENa and FeUrea versus volume status	FEUr has been shown to be affected by volume status. low FEUr (≤35%) was found to be a sensitive index to renal perfusion, despite the prior administration of furosemide.
	Maciel[14]	Observational study (n = 108)	SIDu, UNa, ClU, SIG	AKI development was characterized in blood by increased values of phosphate and unmeasured anions (SIG), decreased albumin, and in urine by decreased values of UNa, ClU as well as high SIDu. These alterations began to occur before AKI diagnosis, and they reverted in transient AKI but remained in persistent AKI. UNa, ClU, and albumin decreased, and phosphate, SIG, and SIDu increased with AKI severity progression. UNa and ClU values increased again when AKIN stage 3 was reached.
	Maciel et al[15]	Observational study (n = 168)	FEK at admission and 2 d later	Fractional excretion of potassium was significantly higher in persistent AKI compared to transient AKI on the day of AKI diagnosis (24.8% vs 13.8%). The fractional excretion of potassium was fairly accurate in predicting persistent AKI
	Belcher et al[16]	Multicenter, prospective cohort study (n=36)	NGAL, IL-18, KIM-1, L-FABP, albumin, FENa	NGAL, IL-18, KIM-1, L-FABP, and albumin differed between etiologies of AKI and were significantly higher in patients with acute tubular necrosis. FENa was lowest in patients with hepatorenal syndrome.
	Nejat et al[17]	Observational study (n = 529)	Urinary biomarkers of injury (CysC, NGAL, γ-glutamyl transpeptidase, IL-18, and KIM-1) at 0, 12, and 24 h following ICU admission	Biomarker concentrations significantly and progressively increased with the duration of AKI. After restricting the AKI recovery within the 48 h cohort to prerenal AKI, this increase remained significant. The median concentration of KIM-1, CysC, and IL-18 were significantly greater in prerenal AKI compared with no AKI, whereas NGAL and γ-glutamyl transpeptidase concentrations were not significant.
	Maciel et al[18]	Prospective study (n = 50)	Urinary Na, Cl, and SID	Urine Na and Cl were lower and urine SID was higher on day 1 in patients who developed AKI among both survivors and nonsurvivors. Survivors had a progressive improvement in metabolic acid-base profile because of increases in the plasma strong ion difference and decreases in weak acids. In nonsurvivors, acid-base parameters did not significantly change during follow-up.
	Maciel et al[19]	Retrospective analysis of prospectively collected data (n = 29)	Patients after cardiac surgery who had 6 values of sCr measured within the first 48 h after surgery and concomitant spot urine samples for urine biochemistry	Most AKI patients had a SCr increase 6–12 h after surgery. When comparing the sequential alterations of blood and urinary parameters among patients with no AKI, transient and persistent AKI, the authors found that most of them were similar among groups, differing only in magnitude and duration
	Wlodzimirow et al[20]	Observational study (n = 150)	FeU	The diagnostic performance for FeU to discriminate T-AKI from P-AKI on the day of AKI was poor. The diagnostic performance of FeU to predict AKI 1 and 2 d before AKI was poor as well. FeU does not seem to be helpful in differentiating T- from P-AKI in critically ill patients and it is a poor predictor of AKI

(*Continued*)

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Table 1. Continued

Setting	Author	Design	Parameters	Main Remarks
	Koyner et al[21]	Prospective study cardiac surgery (n = 123)	Urinary NGAL, CysC, KIM-1, HGF, π-GST, α-GST, and FENa and FeU measured at baseline, postoperatively, and at the time of the initial clinical diagnosis of AKI	Preoperative KIM-1 and α-GST were able to predict the future development of stage 1 and stage 3 AKI. Urine CysC at ICU admission best detected early stage 1 AKI; the 6-h ICU NGAL best detected early stage 3 AKI. π-GST best predicted the progression to stage 3 AKI at the time of creatinine increase
	Pépin et al[22]	Prospective study (n = 99)	FeU versus FENa	Sensitivity and specificity of FeU were 48% and 75% in patients not administered diuretics and 79% and 33% in patients administered diuretics. Sensitivity and specificity of FENa were 78% and 75% in patients not administered diuretics and 58% and 81% in those administered diuretics. Receiver operating characteristic curves did not identify a better diagnostic cutoff value for FeU or FENa.
	Horpacsy et al[23]	Observational study after kidney transplantation	Urinary enzyme activity and sodium concentration of kidney transplant patients	The increase in the activity of enzymes is one of the earliest signs of tubular damage following rejection. The decrease in UNa points also to rejection episodes. Despite the unspecificity of both variables, their continuous determination and combined analysis of the results could improve the differential diagnosis of rejection after transplantation and might give important information about the pathogenesis of the graft damage
	Moviat et al[24]	Observational study (n = 65 mixed ICU patients)	The apparent and effective SID, strong ion gap, and urinary simplified strong ion difference (urine SID)	Creatinine concentrations were positively and significantly (P < .001) associated with urine SID values, adjusted for pH levels. Urine simplified SID were inversely and significantly (P < .001) related to pH.
	Singh et al[25]	Observational study (n = 52 acute decompensated heart failure patients)	Serum and urine sodium, UCr, and UFurosemide levels on a spot sample after treatment with continuous intravenous furosemide, and followed clinical and renal variables	Comparable correlations between UNa:UFurosemide ratio as well as UNa and FENa with 24-h net urine output (r = 0.52–0.64, all P < .01) and 24-h weight loss (r = 0.44–0.56, all P < .01). FENa (but not UNa or UNa:UFurosemide) were influenced by eGFR.
	Espinel[26]	Observational study (n = 17)	FENa in oliguric patients	Patients with prerenal azotemia had FENa<1, whereas acute tubular necrosis had FENa>3
	Carvounis et al[27]	Observational study (n = 102)	FENa and FEUrea	FENa was low in the patients with untreated prerenal AKI. FEUrea was essentially identical in the 2 prerenal groups (27.9% ± 2.4% vs 24.5% ± 2.3%), and very different from the FEUrea found in acute tubular necrosis (58.6% ± 3.6%, P < .0001). Whereas 92% of the patients with prerenal AKI had FENa<1%, only 48% of those patients with prerenal and diuretic therapy had such a low FENa. By contrast, 89% of this latter group had a FEUrea <35%.
	Vanmassenhove et al[28]	Observational study (n = 107)	FENa, FEUrea, and FENGAL at admission, 4 and 24 h were determined	FENa <1% and FEUrea <35% was present in 77.3% and 63.2% of patients. Urinary NGAL was higher in those with high versus low fractional sodium excretion, but this was only in patients with transient or intrinsic AKI and not in patients without AKI. The negative predictive value for either intrinsic AKI or not restoring diuresis in patients with FENa >0.36% and FEUrea >31.5% was 92% and 94.5%.
	Maciel and Vitorio[29]	Observational study (n = 168 AKI)	Urine sodium, chloride, and SIDu	AKI development was characterized in blood by increased values of phosphate and unmeasured anions (SIG), decreased albumin, and in urine by decreased UNa, chloride as well as high SIDu.
	Maciel et al[18]	Observational study (n = 50)	UNa, UK, CIU, and UCr, the SIDu, SBE, SIDa, SIDe, SIG and FENa	Urine chloride and sodium were lower and SIDu was higher on day 1 in patients who developed AKI, both in survivors and nonsurvivors. Survivors had a progressive improvement in metabolic acid-base profile because of increases in the plasma SID and decreases in weak acids.
	Kannapiran et al[30]	Observational study (n = 928)	SCr, GFR	29.1% had renal dysfunction on the basis of eGFR (<60 mL/min/1.73 m^2). With SCr, only 162 (17.5%) patients had abnormal renal function (>1.5 mg/dL) and SCr values misrepresented 11.6% patients with impaired kidney function.

Abbreviations: π-GST, π-glutathione-S-transferase; AKI, acute kidney injury; AKIN, Acute Kidney Injury Network; AUROC, area under the receiver operating characteristic; CIU, urine chloride; CysC, cystatin C; ECV, effective circulating volume; eGFR, estimated glomerular filtration rate; FEK, fractional excretion of potassium; FENa, fractional excretion of sodium; FENGAL, fractional excretion of NGAL; FeUrea, fractional excretion of urea; GFR, glomerular filtration rate; HGF, hepatocyte growth factor; ICU, intensive care unit; IL-18, interleukin-18; KIM-1, kidney injury molecule-1; L-FABP, liver-type fatty acid binding protein; NGAL, neutrophil gelatinase–associated lipocalin; P-AKI, persistent acute kidney injury; ROC, receiver operating characteristic; SBE, standard base excess; SCr, serum creatinine; SID, strong ion difference; SIDa, apparent strong ion difference; SIDe, effective strong ion difference; SIDu, urine strong ion difference; SIG, strong ion gap; T-AKI, transient acute kidney injury; UCr, urine creatinine; UFurosemide, urine furosemide; UK, urine potassium; UNa, urine sodium concentration; UO, urine output.

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Table 2. Clinical Studies Regarding the Use of Urine Electrolytes Changes for Acid-Base Abnormalities and Serum Electrolyte Disturbances

Setting	Author	Design	Parameters	Main Remarks
Acid-base disorders	Balsorano et al[31]	Observational study (n = 143)	Urine SID	Urine SID significantly differed between patients with persistent or transient AKI, with rising values from controls to persistent AKI groups (16.4 [12], 30 [24], and 47.3 [21.5] mEq/L, respectively, $P < .001$)
	Masevicius et al[32]	Prospective observational study (n = 98)	Urine SID, AG	12% had negative SIDu and 88% had positive SIDu compared with patients with positive SIDu those with negative SIDu had higher bicarbonate (20 ± 2 vs 18 ± 3 mmol/L), base excess (−5 ± 2 vs -7 ± 2 mmol/L), anion gap (21 ± 5 vs 17 ± 4 mmol/L), Δ[AG] − Δ[HCO(3)(−)] (1 ± 5 vs −3 ± 3 mmol/L), and lower chloride (105 ± 5 vs 111 ± 3 mmol/L).
	Masevicius et al[33]	Observational study (n = 148 postoperative)	Plasma Cl, urine SID	Multiple linear regression analysis showed that the Cl on admission and [SID] urine were independent predictors of the variation in Cl 24 h later.
	Zazzeron et al[34]	Retrospective observational study (n = 39)	Urinary output, pH, Na+, K+, Cl^- and NH4+ concentrations measured every 10 min for 3–8 h. Urinary AG, electrolyte excretion rate, Fe, and time constant of urinary [Na+] variation (τNa+) Furosemide administration	After furosemide administration, urinary [Cl−] decreased less rapidly than [Na+]. During the first 2 h, difference between FeCl− and FeNa+ increased. In patients receiving multiple administrations, arterial pH, base excess and SID increased, because of a decrease in plasmatic [Cl−].
Electrolyte disorders	Shepshelovich et al[35]	Retrospective study (n = 555)	SIADH	Long-term survival was determined primarily by SIADH etiology rather than hyponatremia severity, with hazard ratios for death of up to 7.31 (95% CI, 4.93–10.82, $P < .001$) for patients with malignancy-associated SIADH as compared with patients with idiopathic SIADH. Hyponatremia grade at short-term follow-up was also predictive for long-term survival (HR 1.42 per grade, 95% CI, 1.21–1.66, $P < .001$).
	Burns and Ho[36]	Prospective cohort study (n = 50)	FEK, CrCl at admission and after 7 d	FEK correlated linearly with CrCl and had a moderate ability to predict subsequent AKI (n = 19 [31%]; AUROC 0.747, 95% CI, 0.620—0.850; $P = .001$), especially in patients without prior exposure to furosemide within 24 h
	Bihari et al[37]	Prospective, observational study (n = 50)	Daily Na and fluid input and output, biochemistry, hemodynamic variables, oxygenation, steroid, and vasopressor use	A positive sodium balance was associated with a reduction in the next day Pao_2/Fio_2 ratio ($\rho = -0.36$; $P = .001$) and an increased length of MV (linear regression analysis; $P < .01$).

Abbreviations: AG, anion gap; AKI, acute kidney injury; AUROC, area under the receiver operating characteristic; CI, confidence interval; Cl, chloride; FEK, fractional excretion of potassium; Fio_2, fraction of inspired oxygen; HR, heart rate; MV, mechanical ventilation; Pao_2, partial pressure of oxygen; SIADH, syndrome of inappropriate antidiuretic hormone; SID, strong ion difference; SIDu, urine strong ion difference.

predictors of fluid responsiveness in oliguric normotensive ICU patients.[10] This result may be due to the difference between a reduced ECV and position on the cardiac function curve.

Figure 2 summarizes the pathways activated in response to reduced and increased ECV and the resulting urine electrolyte profile.

In summary, UNa and FENa may be clinical indicators of volume status. A low UNa (ie, <40 mEq/L or lower than UK) may indicate that both the kidneys are under a sodium-retaining stimulus and suggests a diagnosis of hypovolemia. However, many limitations reduce the diagnostic yield of UNa: its value is not independent on the serum sodium concentration; some types of renal failure may increase UNa, such as in early sepsis, interstitial nephritis, severe ischemic nephropathy, radiocontrast administration, or hemolysis and rhabdomyolysis. Moreover, the concomitant use of diuretics or drugs such as dopamine and aminoglycosides, or the presence of an osmotic diuresis may increase the value of UNa independent of volume status. Eventually, ADH secretion independent of volume status, such as in low output or vasodilatory states, may alter UNa levels.

Clinical Case. A patient has been admitted to the ICU for 1 week after an initial diagnosis of septic shock in pneumonia. His blood pressure is 145/65 mm Hg, heart rate (HR) 85 bpm, and central venous pressure (CVP) 12 mm Hg; kidney and liver function are normal, and the clinical examination shows peripheral edema. A spot urine sample shows a UNa of 11 and a UK of 36 mEq/L. This patient has probably less effective circulating blood volume than a patient with

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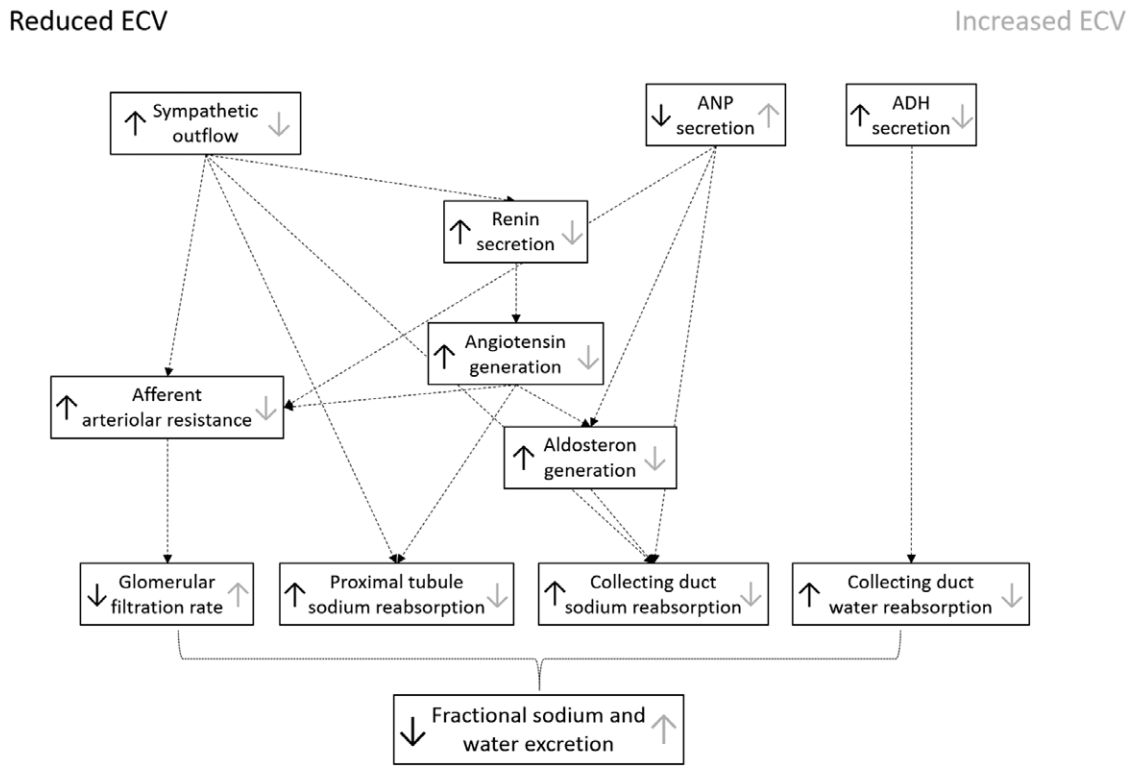

Figure 2. Pathways activated in response to reduced and increased effective circulating volume and the resulting urine electrolyte profile. The figure describes a practical approach in evaluating the effective circulating volume in 2 different scenarios commonly encountered at the bedside, that is, a reduced effective circulating volume (the effects of which are indicated by the black arrows) or an increased effective circulating volume (indicated by light grey arrows). ADH indicates antidiuretic hormone; ANP, atrial natriuretic peptide; ECV, effective circulating volume; GFR, glomerular filtration rate.

similar hemodynamic parameters but with a UNa of 150 and a UK of 12 mEq/L, and is less likely to benefit from diuretic administration should the attending physician want to treat the edema.

Acute Kidney Injury

AKI has traditionally been classified into prerenal, intrinsic, and postrenal forms according to the presumptive site of injury; however, this classification is often clinically ineffective due to the difficulty in assessing its reversibility.[45,46] To focus on the mechanism of prerenal AKI, some articles have suggested that the term transient AKI may be used instead to describe a dynamic process which can progress to persistent AKI.[47] This section will address the potential use of urine electrolytes to assess for prerenal AKI due to compromised renal perfusion and use a "transient-persistent" AKI classification for clarity.

Unlike persistent AKI due to renal tubular damage or dysfunction, transient AKI[48] is caused by compromised renal perfusion.[49,50] In transient AKI, intense renal vasoconstriction, together with increased aldosterone levels, leads to tubular sodium reabsorption and decreased UNa. Although both UNa and FENa have been used to identify transient AKI, FENa is considered more sensitive[26,51] because it is not affected by altered serum sodium concentrations.[38] However, progression toward a persistent AKI may increase sodium excretion and render FENa inaccurate. In general, UNa <20 mmol/L and FENa <1% are associated with transient AKI, whereas in persistent AKI, UNa is generally >40 mmol/L and FENa is >1%. The effectiveness of FENa in the diagnosis of AKI is unclear. A 2011 observational multicenter study found a 63% sensitivity and 54% specificity for the diagnosis of transient AKI[52]; a 2013 study of 244 patients likewise found that although urinary indices 24 hours after admission performed slightly better than those at admission in differentiating the 2 conditions, they were not sufficiently reliable to be clinically relevant.[53]

The main limitation with FENa is that several nontransient causes of AKI may produce a FENa <1% such as hepatorenal or cardiorenal syndromes, early sepsis, interstitial nephritis, severe ischemic nephropathy, or AKI from radiocontrast media or either hemolysis or rhabdomyolysis.[54] Conversely, FENa may be >1% when AKI occurs in patients with chronic kidney disease or any cause of sodium wasting, such as the effect of diuretic therapy. Moreover, in addition to diuretics, other drugs may increase the FENa independently of volume status such as nesiritide, aminoglycosides, dopamine, calcitonin, cisplatin, caffeine, ethanol, and calcineurin inhibitors such as cyclosporine A and

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tacrolimus.[55] As with UNa, FENa may particularly be unreliable in patients who are not oliguric.

Because fast changes in UNa occur in response to systemic hemodynamic variations, the quasicontinuous monitoring of urine electrolytes has been suggested as a more effective approach to monitoring kidney function.[12] Studies conducted after cardiac surgery[56] or kidney transplantation[57] have suggested that frequent urine electrolyte measurements were effective in the evaluation of kidney function. FENa measurements are more effective when assessed in oliguric patients AKI.[58]

Because urea reabsorption may be less dependent on diuretic therapy than sodium, fractional excretion of urea (FEUrea) has been studied as a potential substitute. In a 1992 study, a FEUrea <35% was a sensitive marker of renal perfusion despite the prior administration of furosemide.[13] The measurement of the FEUrea may thus be useful in patients with AKI, with the FEUrea being 50%–65% in persistent and usually <35% in transient status.[22,27] However, a 2014 study on 150 critically ill patients found that FEUrea was a poor predictor of the reversibility of kidney injury,[20] as did a multicentre 2011 study.[52] In summary, although still controversial, most evidence suggests that FEUrea is more accurate than FENa in patients receiving diuretics, but that neither reliably distinguishes transient from persistent AKI. Limitations in the use of FeUrea include osmotic diuresis such as with mannitol use, where impaired proximal tubular reabsorption of salt and water causes an increase in FEUrea even in hypoperfusion states.[59] High protein diet or states with excessive catabolism may also elevate FEUrea independent of renal status. A 2002 study found a 90% sensitivity and 96% specificity for (FeUrea) <35% in identifying transient AKI,[27] but only a 48% sensitivity in the presence of diuretics. Two 2013 reviews of experimental and human urinary findings in septic AKI also highlight the paucity and limitations of the available evidence.[60,61] Moreover, these urinary biochemical findings may not predict the kidney response to hemodynamic optimization. It is possible that a conventional 1% cutoff for FENa may not be valid in some conditions. A 2013 study of 107 septic patients found that FENa was <1% in >75% of patients, but that the combination of a FENa >0.36% and a FEUrea <31.5% was associated with persistent AKI, whereas a combined FENa >0.36% and FEUrea >31.5% was strongly predictive of transient AKI.[28] Low UNa values in AKI may also be a sign of renal microcirculatory stress.[14] In patients with heart failure, Singh et al[25] observed an association between lower UNa and greater likelihood of worsening renal function and poorer adverse clinical outcomes.

On the other hand, high UNa values are generally more difficult to interpret because a normal range is not well established. In a 2010 prospective study of 123 adults undergoing cardiac surgery, Koyner et al[21] observed that although novel urinary biomarkers such as neutrophil gelatinase–associated lipocalin (NGAL), cystatin C (CysC), kidney injury molecule-1 (KIM-1) predicted the future development of stage 1 or progression to stage 3 AKI, traditional tools such as FENa and FEUrea did not. In a 2012 study in 489 critically ill patients clinically diagnosed with transient AKI, several novel biomarkers of injury correlated poorly with the absolute FENa.[17] More recently, a 2015 study in 77 critically ill patients with stage 1 AKI compared the performance of FENa, urine and plasma NGAL, urine albumin-to-creatinine ratio, urinary interleukin-18 (IL-18), and KIM-1, for the prediction of progressive AKI, need for renal replacement therapy (RRT), and inpatient mortality.[62] While 2-hour urine output after a furosemide stress-test outperformed biochemical biomarkers, the FENa performed worse than newer markers for almost every outcome. The differential diagnosis of AKI in patients with coexisting liver disease, in which the underlying cause may be transient, persistent, or due to hepatorenal syndrome, is another challenge. In a 2014 multicenter, prospective cohort study of 188 patients with cirrhosis and AKI,[16] only novel biomarkers such as NGAL, KIM-1, IL-18 (and not FENa) effectively differentiated between transient and persistent AKI and only FENa was significantly different in patients with hepatorenal syndrome, being on average <0.1%. The authors noted how the intense sodium avidity characteristic of hepatorenal syndrome may be identifiable with FENa, and suggest a reappraisal of this marker in patients with AKI and cirrhosis.

The role of the fractional excretion of potassium (FEK) has also been evaluated as a marker of AKI reversibility. Because potassium secretion is enhanced by sodium reabsorption, increases in the FEK, particularly as AKI evolves, may be effective surrogates for decreases in GFR. A 2014 study of 168 critically ill patients compared the diagnostic performance of FENa, FEUrea, and FEK at the day of AKI diagnosis in predicting AKI evolution.[15] Moreover, the authors found that FEK was higher in persistent than in transient AKI (on average, 24.8% vs 13.8%; $P < .001$) on the day of diagnosis of AKI, that it increased immediately before the development of AKI in both groups, but remained elevated in persistent AKI. When assessed by overall receiver operating characteristic curve, the diagnostic accuracy of FEK was higher than FENa and FEUrea, with a cutoff at 18.3% to predict AKI reversibility. A 2016 study of 112 surgical patients found that FEK was high in both groups at admission, but remained high in the subsequent days only in patients who developed AKI, with a cutoff of 6%

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having a 97% specificity for the prediction of persistent AKI.[57] In another prospective 2013 investigation, the sequential evaluation of urine biochemistry identified patterns in urine electrolytes that paralleled AKI duration and severity: decreased values of urine sodium and chloride, and high urinary strong ion differences (SIDs) occurred before the development of AKI, and returned to normal in transient AKI but remained altered in persistent AKI.[19]

Using a physicochemical approach based on the assessment of urine SID (ie, the difference between the sum of cations sodium and potassium, and anions such as chloride and lactate), Balsorano et al[31] used the urine SID as a marker of renal dysfunction in critically ill patients. A retrospective analysis of 143 patients admitted with transient or persistent AKI compared with a control group with normal renal function showed how urine SID significantly differed between groups, with rising values from controls to persistent AKI (16.4 vs 30 vs 47.3 mEq/L, respectively).

In summary, assessment of sodium, potassium, and creatinine in blood and urine may assist in identifying persistent from transient AKI. In the absence of the confounding effect of diuretics, myoglobinuria, glomerulonephritis, or contrast-induced nephropathy, a UNa <20 mmol/L, or a FENa <1%, as well as a FEK between 10% and 15% are highly suggestive of a transient AKI. When diuretics are used, a FEUrea <35% is predictive of a transient AKI.

Clinical Case. A patient presents with an acute increase in SCr to 1.8 mg/dL with a previous reduction in urine output of 0.3 mL/kg during the last 24 hours. In this situation, the finding of UNa 15 mEq/L, or a FENa 0.5%, as well as a FEK of 12% or a FEUrea of 25% is highly suggestive of a transient form of AKI, which may potentially be improved by fluid loading. The same patient with a UNa of 60 and FENA of 1.2%, or FEK of 22% and FEUrea 41% is more likely to have persistent AKI, and less likely to respond to volume loading.

Figure 3 presents a flow diagram for the approach to patients with AKI on the basis of urine electrolyte profile.

Acid-Base Abnormalities

Urine electrolytes may also be useful in analysis of acid-base homeostasis.[63] Classically, healthy kidneys excrete bicarbonate and a reduced ECV should lead to reabsorption of both sodium, and bicarbonate, leading to a metabolic alkalosis and a low urine concentration of chloride.[64] In contrast, bicarbonate reabsorption in the presence of a high urine chloride suggests potassium depletion. Elevated urine chloride levels in the presence of metabolic alkalosis may also indicate a steroid-dependent alkalosis such as hyperaldosteronism or Cushing syndrome. In addition to bicarbonate reabsorption, the kidney maintains acid-base status through regeneration of the bicarbonate consumed with titration of fixed acids (urine acidification), which involves the excretion of ammonium.[65] This picture is however complicated by the presence of several other buffer systems that play an important role in determining urine pH, such as citrate and phosphate.

Recently, several pieces of evidence ranging from bench studies to physiological investigations, to more and more powered clinical studies, have identified a small association between the administration of chloride-rich fluids and adverse outcomes,[66–69] leading some authors to suggest to abandon the practice of volume replacement with normal saline.[70] Given the association between serum chloride concentration, mortality, and incidence of AKI, a 2019 retrospective study in 170 critically ill found that urine chloride concentration was lower in nonsurvivors even on the day of ICU admission, while other urinary and serum electrolytes were not, and that lower urine chloride concentration was associated both with increased mortality and incidence of AKI.[71]

The urine SID may also facilitate acid-base analysis. As shown earlier, it is defined as the difference between measured strong cations and anions and can be calculated as follows:

$$\mathrm{SID} = \left(\left[\mathrm{Na^+}\right] + \left[\mathrm{K^+}\right] + \left[\mathrm{Ca_2^+}\right] + \left[\mathrm{Mg_2^+}\right]\right) - \left(\left[\mathrm{Cl^-}\right] + \left[\mathrm{Lactate^-}\right]\right),$$

where Na denotes sodium, K denotes potassium, Ca denotes calcium, Mg denotes magnesium, and Cl denotes chloride. Despite the theoretical importance of the assessment of urine SID for acid-base disturbances, only limited evidence is available in critically ill patients. In a 2013 study of postoperative patients admitted to the ICU, changes in chloride concentration were largely related to urine SID and chloride values at admission, and not to the characteristics of the infused fluids, suggesting that the renal ability to modify urine SID is a major mechanism to prevent the development of postoperative hyperchloremia.[33] A 2012 study of 65 critically ill patients found a significant association between urine SID and creatinine concentrations, while urine SID was inversely related to pH.[24] The authors concluded that in metabolic acidosis, impaired renal function was associated with greater urinary SIDs. A 2012 study performed daily spot urinary electrolyte measurements and found lower urine chloride and sodium and higher urine SID at ICU admission in patients who developed AKI and that urine SID was persistently higher in nonsurvivors.[18] A 2010 study of patients with metabolic acidosis observed that the vast majority of patients had an inappropriate renal compensatory response to

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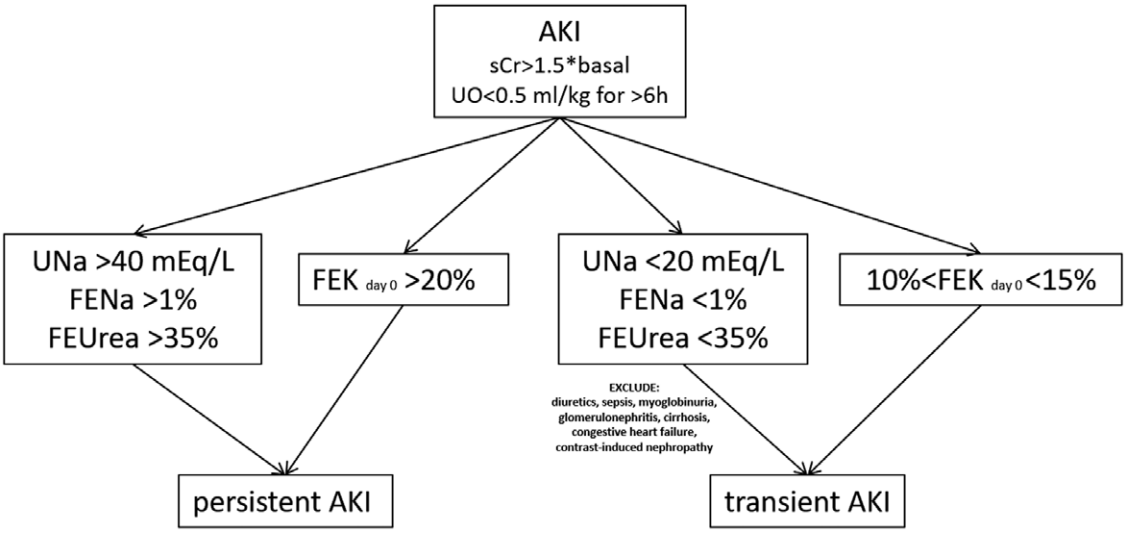

Figure 3. A flow diagram for the approach to patients with AKI on the basis of urine electrolyte profile. Whenever a patient develops AKI, we suggest that both blood and urine are sampled for the assessment of sodium, potassium, urea, and creatinine. In the absence of the confounding effect of diuretics, myoglobinuria, glomerulonephritis, or contrast-induced nephropathy, the finding of UNa <20 mmol/L, or a FENa <1%, a FEUrea <35%, as well as a FEK between 10% and 15% are highly suggestive of a transient form of kidney injury; higher values are suggestive of a persistent form. AKI indicates acute kidney injury; FEK, fractional excretion of potassium; FENa, fractional excretion of sodium; FEUrea, fractional excretion of urea; sCr, serum creatinine; UNa, urine sodium concentration; UO, urine output.

the acid-base disturbance, as assessed by a positive urine SID and higher plasma chloride concentration, whereas patients with an adequate renal response were characterized by a negative urine SID and a positive difference between the increase in plasma anion gap and bicarbonate.[32]

In summary, urine electrolytes may help in prognosis when acid-base abnormalities are present. In the presence of a metabolic acidosis, if urine pH is acidic and SID is low or negative, a compensatory response of the kidney is present; if the opposite holds true, the kidney is not able to compensate and this is associated with a worse prognosis.

Clinical Case. A septic patient is admitted after massive volume resuscitation with an arterial pH of 7.25 and a base excess of −8. Assessment of plasma SID is 32 mEq/L, and an underlying hyperchloremic acidosis is identified (plasma chloride 120 mEq/L). A spot sample of urine electrolytes shows chloride level of 40 and sodium level of 80 mEq/Land a pH of 8. Kidney function should be strictly monitored because a persistent AKI should soon develop, given the relatively low urine chloride level.

Serum Electrolyte Disturbances

Sodium concentration is the ratio of the amount of sodium and the volume of the extracellular fluid in which it is diluted, and it does not represent an index of total body sodium. As discussed above, provided a preserved kidney function and no interfering drugs, UNa is a sensitive index of total body sodium.[38] Hyponatremia can only occur if the normal process of urine dilution and sodium retention is impaired, such as with the use of diuretics or in the presence of ADH, or if the amount of fluid intake exceeds the capacity of the kidneys to excrete free water.[72] Nonosmotic release of ADH may account for >95% of cases of hyponatremia.[73] Sodium concentrations may also increase as a result of the infusion of large amounts of concentrated salt solutions, or if aquaresis or osmotic diuresis lead to large and unreplaced losses of electrolyte-free water.[74]

Hyponatremia. Hyponatremia is generally classified on the basis of plasma tonicity, and, if hypotonic hyponatremia is present, the assessment of volume status allows the subsequent classification into hypovolemic, euvolemic, and hypervolemic hyponatremia.[75] Urine electrolytes, including measurement of urine osmolality and UNa, may facilitate this process.[76] The concepts of free water clearance (FWC) and electrolyte-free water clearance (EFWC) have been proposed to characterize and predict the effect of an abnormal rate of urinary free water excretion on serum sodium concentration. A positive FWC denotes an excess excretion of free water, and an increase in serum sodium concentration with urine production; on the contrary, a negative value indicates reabsorption of excess free water, and a decrease in sodium concentration with urine production. A negative (electrolyte) FWC in conjunction with serum hypotonicity indicates abnormal ADH-renal axis responses.[77] Determination of FWC is the most direct clinical method to measure the ability of the kidney to reabsorb or excrete water and can be used to describe

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the abnormal water homeostasis in simple quantitative terms.

FWC is calculated as follows[78]:

$$FWC = UO \cdot \left(1 - \frac{Osm_U}{Osm_P} \right),$$

where UO is urine output, Osm_U is urine osmolality, Osm_P is plasma osmolality.

EFWC has been suggested to be superior to the FWC to document the cause of a possible dysnatremia because it takes into account the fact that urea is an ineffective osmole, and is calculated as follows:[79]

$$EFWC = UO \cdot \left(1 - \frac{UNa + UK}{Na_P} \right),$$

where UNa is urine sodium, UK is urine potassium, and Na_p is plasma sodium concentration.

UNa and FENa may also have some efficacy in the diagnostic pathway for hyponatremia. As a rule-of-thumb, with hypovolemic hyponatremia, FENa is generally <1%. However, UNa may be unreliable in patients who are not oliguric or with diuretics. On the contrary, renal losses are associated with FENa >1%.[80] UNa may also help in distinguishing a syndrome of inappropriate antidiuretic hormone (SIADH) from ECV depletion. Values <20 mEq/L are generally associated with a response to fluid loading,[81] while SIADH is associated with elevated UNa. In a study of >500 patients with SIADH-dependent hyponatremia, the mean UNa was 72 mEq/L (range 30–251) and the median urine osmolality was 379 mOsm/kg.[35] In the critical care setting, traditional classifications of sodium disorders according to volume status are of little use because hypovolemia and normovolemia cannot be reliably separated,[81,82] and multiple causes are common. Indeed, a retrospective study on patients with hyponatremia and an inconclusive diagnosis between SIAD and hypovolemia showed that a UNa cutoff of 50 mEq/L identified the cause of hyponatremia with an 82% accuracy.[83]

The traditional approach to the hyponatremic patient has been based on volume status and sodium excretion. However, accurate assessment of volume is often difficult, and the excretion of sodium may be influenced by multiple factors. An alternative approach has been proposed, which is based on determination of fractional excretion of urate (FEUrate), that is, the percent of filtered urate that is excreted in urine. Urate is actively secreted and reabsorbed in the proximal tubule; a 1979 report noted that the coexistence of hypouricemia and hyponatremia differentiated SIADH from other causes of hyponatremia.[84] Subsequent studies found that FEUrate may be even more sensitive than uric acid concentration. Fenske et al[85] compared the diagnostic performance of several parameters to identify SIADH and found that FEUrate >12% had the highest sensitivity and specificity independent of diuretic use. More recently, a 2017 prospective multicentre observational study of 298 patients confirmed the same cutoff.[86] Imbriano et al[87] recently proposed an algorithm for the use of this index: FeUrate <4% is suggestive of reduced ECV, Addison disease or chronic heart, kidney or liver failure; values 4%–11% are indicative of psychogenic polydipsia, and values >11% are suggestive of SIADH.[87]

In summary, urine electrolytes may assist in the diagnosis of hyponatremia. After excluding pseudohyponatremia (due to hyperproteinemia or hyperlipidemia) and hypertonic hyponatremia (due to hyperglycemia), we suggest to assess both volume status and urine electrolytes. In case of hypovolemia, a sodium-retaining state is suggestive for extrarenal factors, such as third-spacing or gastroenteral losses. Alternatively, UNa >50 mEq/L or a FENa >1% indicate renal losses (such as a diuretic effect or a mineralocorticoid deficiency), or a cerebral salt wasting. If the patient is normovolemic, then hyponatremia is usually associated with elevated UNa and caused by SIADH, hypocortisolism, or hypothyroidism. If the patient is hypervolemic, the assessment of urine electrolytes allows the differentiation between renal failure and heart failure or cirrhosis. Figure 4 provides an algorithm for the evaluation of the patient with hyponatremia based on urine electrolytes.

Clinical Case. A patient has a progressive reduction in serum sodium to 128 mEq/L, with a serum osmolality of 260 mEq/L. The concomitant hemodynamic assessment shows normal blood pressure, 18 cm H_2O of central venous pressure, a reduction in urine output without signs of sepsis. A spot sample of urine electrolytes shows a low UNa of 12 mEq/L and FENa of 0.8%, suggesting a hypervolemic status, and leading to the administration of diuretics.

Hypokalemia. Increased potassium loss, the most common cause of hypokalemia, occurs mostly in patients on diuretics or with gastrointestinal diseases.[88] When volume depletion occurs, aldosterone secretion increases causing metabolic alkalosis by increasing bicarbonate reabsorption.

The transtubular potassium gradient (TTKG), reflects the amount of potassium excreted,[89] can also be calculated as follows:

$$TTKG = \frac{U_K}{S_K} \quad \frac{U_{Osm}}{S_{Osm}},$$

where U_K is urine potassium, S_K is serum potassium, U_{Osm} is urine osmolality, and S_{Osm} is serum osmolality.

Values >4 are inappropriately high and indicate renal potassium wasting, whereas a TTKG <3 suggests

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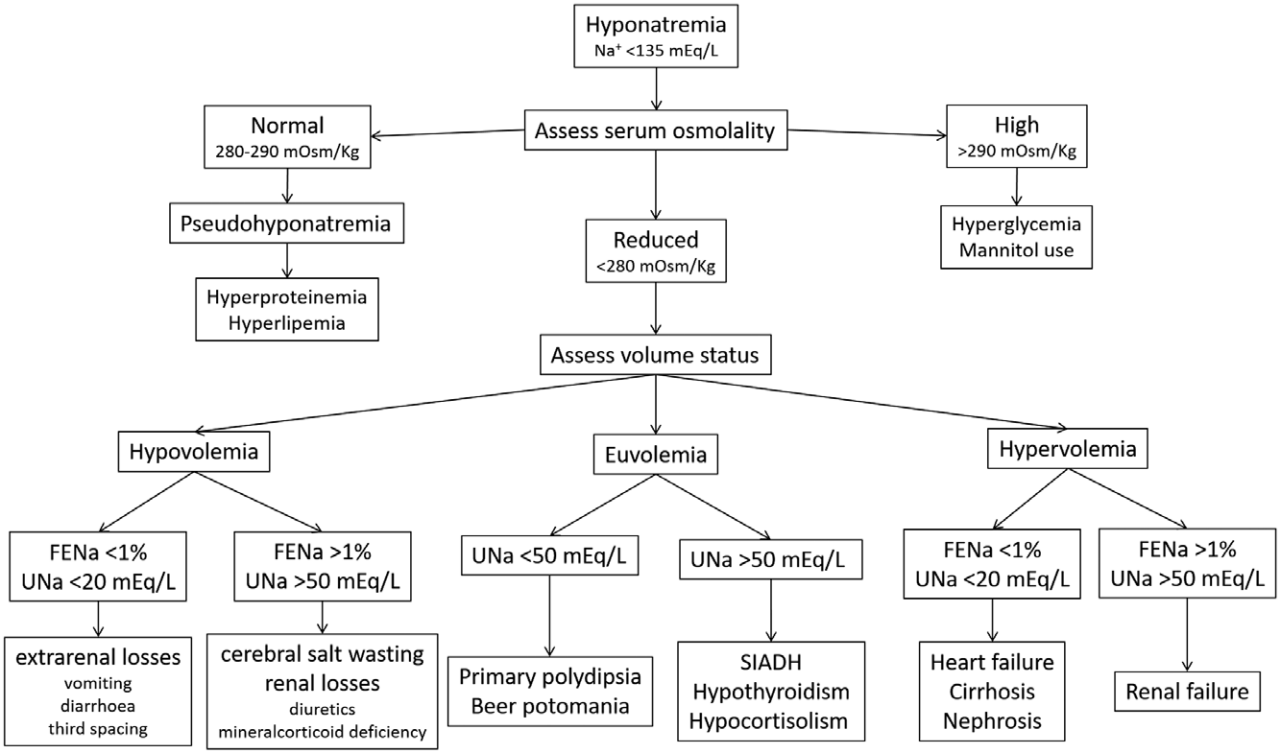

Figure 4. Algorithm for the evaluation of the patient with hyponatremia based on urine electrolytes. In all patients with hyponatremia, both a spot urine sample (for urine osmolality and sodium determination), as well as 24-h UNa excretion (for total sodium balance) should be collected as soon as possible and preferably before treatment. After excluding pseudohyponatremia and hypertonic hyponatremia, both the volume status and urine electrolytes should be assessed. In case of hypovolemia, a sodium-retaining state is suggestive for extrarenal factors, such as third-spacing or gastroenteral losses; on the other side, a UNa >50 mEq/L or a FENa >1% indicate renal losses (such as a diuretic effect or a mineralocorticoid deficiency), or a cerebral salt wasting. If the patient is normovolemic, then hyponatremia is usually associated with elevated UNa, and caused by SIADH, hypocortisolism, or hypothyroidism; if a low UNa is present, then primary polydipsia or beer-potomania syndrome should be considered. If the patient is hypervolemic, the assessment of urine electrolytes allows the differentiation between renal failure and heart failure or cirrhosis. FENa indicates fractional excretion of sodium; SIADH, syndrome of inappropriate antidiuretic hormone; UNa, urinary sodium.

extrarenal causes such as cellular shifts. The TTKG was developed with the aim of providing a semiquantitative analysis of the driving force to secrete potassium in the cortical collecting duct. However, the large quantity of urea reabsorbed daily[90] invalidates the assumption behind this index, making its physiological significance lower than expected. Moreover, the TTKG is unreliable if UNa is <25 mEq/L because low urine sodium limits potassium excretion. UK may also be useful in the workup of hypokalemia patient when volume depletion is not evident because potassium is excreted at a near-constant daily rate. A simpler approach to classify a disordered potassium homeostasis is the expected rate of excretion of potassium when the cause of the dyskalemia is nonrenal. Because creatinine is also excreted at a near-constant rate throughout the day, a spot sample ratio of UK-to-creatinine ratio can be used for this aim. A UK-to-creatinine ratio corrects for variations in urine volume; when this ratio is >13 mEq/g, renal potassium losses should be suspected. If the ratio is <13 mEq/g, hypokalemia is likely due to transcellular potassium shifts, gastrointestinal losses, diuretics, or poor intake.[18] Given the limitations of TTKG and its complex calculation, the simpler approach using only the urine concentration of potassium, and its ratio with urine creatinine, may be used instead. A recent study found that UK excretion is related to simultaneously calculated creatinine clearance and can predict AKI.[30]

Hyperkalemia. Factors associated with hyperkalemia include altered renal clearance, release from or transfer to the intracellular space.[27] Twenty-four–hour urinary potassium excretion is of limited utility in patients with persistent stable hyperkalemia because potassium excretion is related to its intake. The TTKG was previously used to assess the degree of aldosterone activity by estimating the potassium concentration in the cortical collecting tubule. However, as shown above, this index has some limitations. A simpler, yet still physiologically sound, approach to identify intracellular shift as the cause of the dyskalemia is the use of the UK-to-creatinine ratio. The expected ratio in a patient with hyperkalemia and a normal renal response is >200 mEq/g creatinine, while the

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opposite holds true when intracellular shifts are the underlying cause.

CONCLUSIONS

The diagnostic and prognostic information provided by urine electrolytes may have considerable value in providing an overview of disorders of circulating blood volume, AKI, acid-base, and electrolyte disturbances. Moreover, their wide availability, speed, and ease of measurement makes them ideal markers both in the acute phase and during the course of ICU stay. However, urine electrolytes should be paired with other clinical assessments because a wide range of values may still be compatible with a normal status. Even more complicated is the use of urine electrolytes in critically ill patients, for whom many factors such as pharmacological therapies, alterations to and from steady-state conditions, nutritional status, renal function, and the action of ADH often play an unappreciated role. Thus, urine chemistries cannot be interpreted in isolation but instead often require concurrent serum chemistries, including renal function and other key clinical pieces of information. However, even with these potential pitfalls, the assessment urine composition allows clinicians to shed potentially useful light on the often-complex pathophysiology of critical illness.

DISCLOSURES

Name: Michele Umbrello, MD.
Contribution: This author helped with the literature search, drafted the article, and read and approved the final manuscript.
Name: Paolo Formenti, MD.
Contribution: This author helped with the literature search, drafted the article, and read and approved the final manuscript.
Name: Davide Chiumello, MD.
Contribution: This author revised the article for important intellectual content and read and approved the final manuscript.
This manuscript was handled by: Avery Tung, MD, FCCM.

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