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REVIEW PAPER

Urine biochemistry assessment in critically ill patients: controversies and future perspectives

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Abstract In the past, urine biochemistry was a major tool in acute kidney injury (AKI) management. Classic papers published some decades ago established the values of the urine indices which were thought to distinguish "pre-renal" (functional) AKI attributed to low renal perfusion and "renal" (structural) AKI attributed to acute tubular necrosis (ATN). However, there were a lot of drawbacks and limitations in these studies and some recent articles have questioned the utility of measuring urine electrolytes especially because they do not seem to adequately inform about renal perfusion nor AKI duration (transient vs. persistent). At the same time, the "pre-renal" paradigm has been consistently criticized because hypoperfusion followed by ischemia and ATN does not seem to explain most of the AKI developing in critically ill patients and distinct AKI durations do not seem to be clearly related to different pathophysiological mechanisms or histopathological findings. In this new context, other possible roles for urine biochemistry have emerged. Some studies have suggested standardized changes in the urine electrolyte composition preceding increases in serum creatinine independently of AKI subsequent duration, which might actually be due to intra-renal microcirculatory changes and activation of sodium-retaining mechanisms even in the absence of impaired global renal blood flow. In the present review, the points of controversy regarding urine biochemistry assessment were evaluated as well as future perspectives for its role in AKI monitoring. An alternative approach for the interpretation of measured urine electrolytes is proposed which needs further larger studies to be validated and incorporated in daily ICU practice.

Keywords Urine biochemistry · Acute kidney injury · Critically ill patients · Monitoring · Urine electrolytes · Fractional excretion · Review

1 Introduction

Measurement of urine electrolytes is a classic tool in acute kidney injury (AKI) management. For many years, its main utility was to distinguish a functional renal impairment ("pre-renal AKI"), generally associated with low renal perfusion, and a structural renal impairment ("renal AKI"), in which there is tubular damage leading to an inability to properly reabsorb electrolytes, including sodium. Based upon this idea, urine sodium (NaU) and its fractional excretion (FENa) were major parameters to define the best approach to oliguria and increasing levels of serum creatinine (sCr) [1, 2]. The studies that proposed NaU [3] and FENa [4] as useful tools in AKI were published many decades ago and they established the values that are used until now to separate the "pre-renal" from the "renal" AKI. Classically, NaU values below 20 mEq/L and a FENa <1 % indicate that there is no structural damage to the kidneys and a NaU above 40 mEq/L and a FENa value above 1–3 % sign for the presence of acute tubular necrosis (ATN) [2–4]. Of note, these studies [3, 4] included a very small number of patients with a very increased mean value of blood urea nitrogen and sCr, suggesting that only patients with severe AKI were included.

Along the years, our knowledge of the AKI pathophysiology has significantly improved, especially in the context of

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critical illness. Some old paradigms have been broken, including: (a) low perfusion and ischemia as predominant causes of renal impairment [5, 6]; (b) ATN as the histopathological finding in persistent AKI [7, 8], among others. It has been demonstrated that decreasing NaU and FENa values may be present in parallel with increasing renal blood flow in experimental sepsis [9, 10] a fact that challenged the "pre-renal" paradigm and the major reason for questioning the utility of urine tests in ICU practice [6, 11–13]. It seems inappropriate to consider low NaU and FENa as unequivocal synonyms of renal hypoperfusion and their use as guides to fluid therapy is no longer widely recommended [6, 14], especially in critically ill patients with sepsis. On the other hand, these low values may be a result of derangements inside the kidneys including microcirculatory impairment, which is one of the main focus of recent AKI pathophysiological studies [15–17]. In the present review, we discuss the controversies of urine biochemistry assessment and interpretation in critically ill patients, future perspectives for its use and propose an alternative approach to urine biochemistry data that could be of value in AKI monitoring.

2 Urine biochemistry reappraisal: is the old "pre-renal" paradigm still applicable to the critically ill?

Most recent studies evaluating urine biochemistry in critically ill patients had the purpose to test its accuracy in predicting AKI duration and severity [18–23], which is expected to have therapeutic and prognostic relevance. The reasoning for these studies is strongly linked to the old paradigm of hypoperfusion and ATN as sequential stages of AKI development. Some of these studies failed to find any utility of urine biochemistry assessment [20, 21, 24] which suggests that the behavior of urine electrolytes is not usually different between transient and persistent AKI development. Since it is not well established that distinct AKI durations (transient vs. persistent) are closely related to distinct underlying pathophysiological mechanisms (functional vs. structural) [25], similar patterns of urine biochemistry independently of AKI duration [26–28] suggest a common pathway for most AKI developing in the ICU. In a new paradigm, persistent AKI could be viewed as a more severe and lasting presentation of transient AKI [25, 29].

3 Is the failure of urine biochemistry as a monitoring tool just a matter of time and frequency of assessment?

Although much effort has been made to use urine tests as diagnostic indexes in AKI patients with disappointing results, very few studies (with only very small samples) have measured urine electrolytes *before* AKI has been diagnosed. Previous clinical [26–29] and experimental [30] studies suggested that biochemical changes in urine precede that of the serum in AKI development. AKI recovery is also followed by reversal of the urine biochemical changes [26, 27, 31], suggesting a tight relationship between urine biochemistry and renal function.

In addition, urine electrolytes and indices were frequently assessed as a single measurement in most studies [3, 4, 11, 21, 32]. Nonetheless, NaU may still decrease as a result of decreases in glomerular filtration rate (GFR) and avid tubular sodium reabsorption along with parallel increases in sCr (Fig. 1a) [26, 27]. Thus, the "pre-renal" and ATN paradigms make the correct interpretation of urine indices difficult to achieve. The slopes of the descending NaU curve and ascending sCr curve are variable and depend on the severity/velocity of GFR impairment and simultaneous tubular damage, allowing a wide range of combinations of NaU and sCr values (Fig. 1b) [33].

Fast changes in NaU values may occur in response to systemic hemodynamic variations [34]. Based on this, some authors proposed a quasi-continuous monitoring of urine electrolytes as a way to monitor kidney function especially in unstable situations [34]. It is possible that fast variations in NaU values are a result of oscillations in GFR so that a single assessment of its value is usually inappropriate. Frequent evaluation of NaU value may be relevant in conditions such as post-cardiac surgery [27, 28] or after kidney transplantation [35] in which abrupt decreases in GFR may be expected. In these situations, urine electrolytes measurement repeatedly in spot samples seems more adequate and clinically feasible than a 24-h collected urine because the latter would reveal the total and the mean sodium excretion but not a punctual nor a close sequential evaluation of the kidney function, which is expected to allow more well-timed interventions when appropriate [34]. Sequential evaluation of urine electrolytes concentration before and after a specific intervention (for instance, different types of diuretic administration) was also found to help in the understanding of pathophysiological phenomena [36] as well as in defining prognosis [37].

4 Is there a role for 24-h urine electrolytes assessment in critically ill patients?

24-h urine collections are usually used to calculate creatinine clearance (CrCl), one of the methods to estimate GFR. However, in the critical care setting, variations in GFR along the day preclude CrCl (even when measured in shorter periods) to be accurate as well as estimating

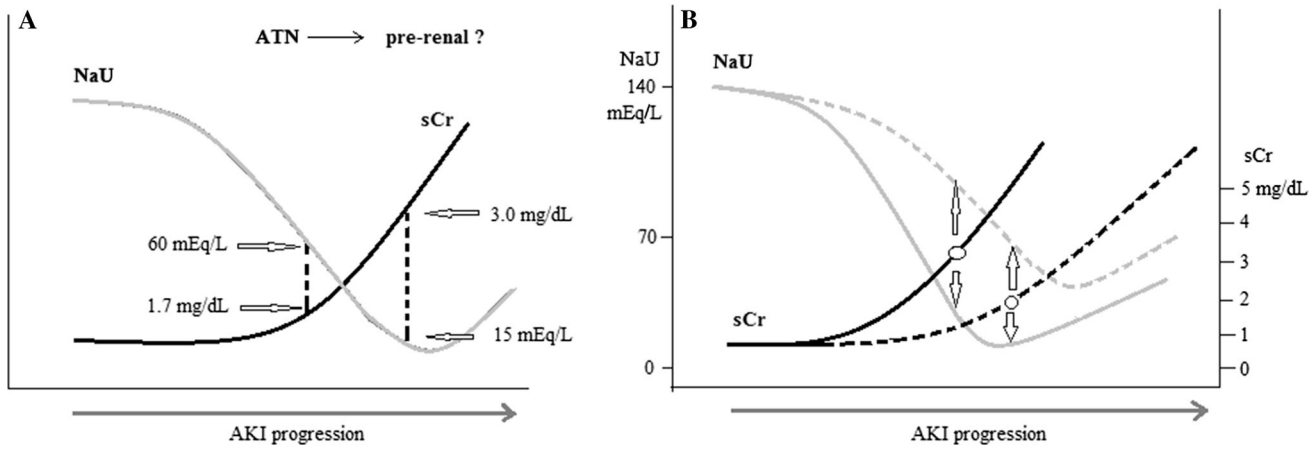

Fig. 1 Sequential simultaneous evaluation of serum creatinine (sCr) and urine sodium (NaU) in the course of acute kidney injury (AKI) development in critically ill patients. **a** Theoretical example of the inconsistency of the traditional interpretation of NaU and sCr values in the "pre-renal" paradigm. Values compatible with acute tubular necrosis (ATN) may precede the values compatible with "pre-renal" AKI. **b** Variability in the slopes of the descending NaU and ascending sCr curves leading to many possible combinations of their values according to distinct combinations of decreases in glomerular filtration rate and impaired tubular handling of sodium

equations [38]. 24-h urine sodium excretion is usually used to estimate daily salt intake and it seems particularly useful in hypertension management studies. Interestingly, the 24-h urine sodium excretion and the sodium balance were infrequently explored in ICU patients. Sodium overload is very common and thought to be related to increased sodium infusion (fluid challenge, maintenance fluids, drugs dilution) [39] in combination with a reduced capacity to excrete sodium especially in the setting of AKI [26]. A positive sodium balance may be even more detrimental than a positive fluid balance [40]. Unfortunately, much more attention is paid to fluid balance and it is common practice to neglect urine electrolyte composition [41]. Notably, fluid balance may not predict sodium balance in critically ill patients [42]. Hence, it seems that 24-h urine collection has a role in calculating total electrolyte excretion and may help to prevent the side effects of electrolyte overload in multiple organs [43]. In addition, it helps in the understanding of many acid–base and fluid/electrolyte imbalances including hypervolemic hypernatremia [43–45], a frequent but difficult situation to manage in the critically ill.

5 The early phase of AKI development as an avid urea and sodium-retaining state

The avidity for sodium retention is a frequent marker of early AKI development [10, 18, 19, 26, 46]. In this situation, both sodium and urea are avidly reabsorbed mainly in the proximal tubules. This is followed by decreases in the fractional excretions of both sodium (FENa) and urea (FEUr). Such intense sodium and urea retention was proposed to begin earlier than increases in sCr [26], being an alert sign that the kidneys are under some kind of stress not necessarily related to hypoperfusion, as already highlighted by Vaz [47] in septic patients many years ago. With AKI progression, we may observe a "U"-shaped behavior of both NaU [26] and FENa [18]. This could be due to severe impairment in global tubular sodium reabsorption in late AKI stages leading to increases in FENa and NaU (Fig. 2).

Tubular injury is an early and heterogeneous process in AKI development, not affecting all tubules together [8, 48]. Experimental studies have demonstrated down-regulation of sodium and chloride channels in renal tubules [49, 50] but healthy nephrons may compensate in terms of sodium and chloride retention those already jeopardized. This is in agreement with studies using urine microscopy [48] or biomarkers to demonstrate tubular damage (e.g., NGAL) [29] which reported low NaU and FENa even in this context.

6 Are we really monitoring the renal artery perfusion when measuring urine electrolytes in sepsis?

In the hyperemic AKI of the systemic inflammatory response syndrome (SIRS) and sepsis, a dissociation occurs between macro and microcirculation. A normal or high blood flow at the level of the renal artery does not imply in adequate blood flow inside the glomerulus [51]. This could be due to vasoconstriction in the afferent arteriole, and/or intra-renal shunting [52]. In addition, it is possible to have a high glomerular blood flow but a low glomerular filtration pressure as in cases that there is vasodilatation of both afferent and efferent arterioles but predominantly in the

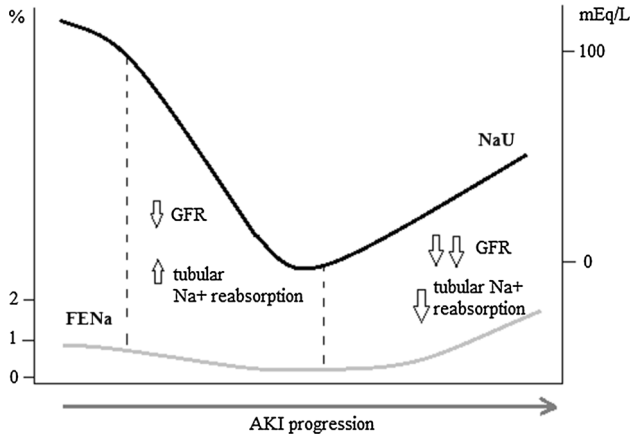

Fig. 2 Simultaneous changes in the fractional excretion of sodium (FENa) and urine sodium (NaU) during AKI development. The early phase of AKI is characterized by decreases in both NaU and FENa due to lower glomerular filtration and activation of sodium-retaining mechanisms. Significant changes in NaU are usually accompanied by only subtle absolute changes in FENa since normal values of FENa are usually very low even in healthy conditions. In the late phases of AKI, there is an increase in NaU and FENa due to the global loss of tubular capacity to retain sodium

efferent arteriole, reducing the pressure inside the glomerulus [52]. All these hypotheses exist to explain a reduced GFR even with normal or increased blood flow to the kidneys. Whatever of these is present, the result would be activation of sodium-retaining mechanisms, similar to cases of renal hypoperfusion (hypovolemia, low cardiac output, etc.). This is why the term "pre-renal" is flawed [12]: the alterations might actually be "renal", involving the renal microcirculation.

7 Dissociation between urine electrolytes and histopathological findings in AKI

As mentioned above, functional and structural kidney impairments seem to occur at the same time with variable severities. Markers of tubular injury are present in cases of clinical "pre-renal" and transient AKI [18, 19, 29] and signs of functional impairment may still be present even with evidence of structural damage [48]. This is the possible reason why traditional cut-off values of NaU and FENa fail in distinguishing functional and structural AKI. In other words, decreases in GFR and tubular damage are frequently simultaneous, not sequential processes. Even when the primary insult to the kidneys is tubular damage ("structural"), it is invariably followed by reductions in GFR ("functional") mediated by tubuloglomerular feedback [17, 53]. Since glomerular filtration is the cornerstone of kidney function and the main source of sodium to the tubules, decreases in GFR would generally result in reduced NaU, independently of the histopathological nature of the AKI.

8 Lack of NaU reference range in the critical care setting

Although very low NaU values (<10 mEq/L) may be found in healthy persons on a regular sodium-restricted diet [1], such low values in critically ill patients may be an alert sign for some threat to normal kidney function, even in patients with normal sCr [26]. These patients frequently have a high sodium intake from multiple sources [39] so that higher NaU values were usually expected for this population. Severe hepatic (hepatorenal) [54], cardiac (cardiorenal) [55] or even renal impairment itself [26] may manifest with very low NaU values. All these situations have in common extremely activated sympathetic nervous and renin-angiotensin systems. Miller et al. [3] proposed, in a small sample of patients, a NaU value higher than 40 mEq/L as a marker of ATN in oliguric patients. Unfortunately, no data reporting the NaU values of the patients without AKI was mentioned. Masevicius et al. [56] reported a mean NaU value of 104 mEq/L in healthy volunteers. Recent data of critically ill patients that have not developed AKI have shown that these patients consistently had higher values of NaU, particularly in the two subsequent days after ICU admission [26]. A NaU value higher

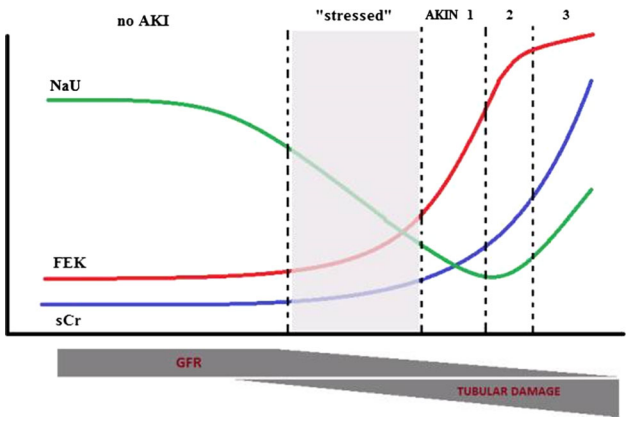

Fig. 3 Summary of the Imed Group hypothesis for the course of serum creatinine (sCr), urine sodium (NaU) and fractional excretion of potassium (FEK) during acute kidney injury (AKI) development in most critically ill patients. Normal renal function of these patients is usually characterized by low sCr, low FEK (<10 %) and high NaU (>100–140 mEq/L). Before sCr-based AKI diagnosis occurs, there is a significant decrease in NaU and increases in FEK, probably due to activated sodium-retaining mechanisms—the so-called "stressed" kidneys. It is noteworthy that tubular damage may also be happening but only in AKIN stage 3 it seems to jeopardize global sodium reabsorption. *AKIN* acute kidney injury network *GFR* glomerular filtration rate

than 140 mEq/L (equivalent to normal serum sodium) was found to be almost exclusive of patients with normal sCr, even when diuretics were administered [33]. Hence, this cut-off value was suggested to be a truly high NaU that may be useful as a specific marker of normal or at least improving renal function [33]. Since NaU may have a wide range of values, relative changes in its value are also very important in NaU interpretation. Significant decreases occurring in a short period of time have a great chance to be epiphenomena of significant decreases in GFR particularly in the presence of stable or high sodium infusion.

9 Is there any role for fractional excretions monitoring in AKI?

Only two fractional excretions were largely studied in critically ill patients: FENa and FEUr. Current use of FENa and FEUr in the AKI management remains a matter of controversy. Most recent studies [20, 21, 24, 57] were not able to find a consistent role for their measurement and to date there is no precise indication for their assessment. However, some authors [18] argue that FENa and FEUr are useful in sepsis and proposed a lower cut-off value for improving the diagnostic ability of these parameters (0.36 and 31.5 %, respectively). Due to the frequent use of diuretics in the ICU, jeopardizing FENa interpretation, FEUr has gained more focus as a possible relevant parameter in AKI although with variable results [20–24, 57, 58]. The fractional excretion of potassium (FEK), which is a quite less studied parameter, seems to increase in AKI development [59–62] and decrease in AKI recovery [62] which is supposed to occur due to a negative correlation with GFR. Decreases in GFR are frequently followed by activation of the renin-angiotensin-aldosterone system which stimulates sodium reabsorption in the distal and collecting tubules in exchange for potassium, increasing its secretion and, consequently, FEK. This physiological mechanism also helps to maintain potassium homeostasis even in the presence of low potassium filtration, usually preventing life-threatening hiperkalemia until very low levels of GFR (<15 mL/min/1.73 m^2) [63].

Normal FEK values are considered to be around 8 ± 2 % [64], which are similar to critically ill patients with no-AKI but significantly different from those with pAKI [62]. A potential advantage of FEK over FENa is that the latter has a low range of variation in avid sodium retaining states, decreasing its value to near zero, an absolute variation of only 1 % in relation to normal values (Fig. 2). FEK, on the contrary, may simultaneously increase its value many fold (for instance, from 10 to 50 %), making the variation more evident for monitoring purposes. Although preliminary results are promising, larger clinical studies are necessary in order to evaluate if there is a role for FEK in AKI monitoring.

It is also important to emphasize the mathematical coupling between fractional excretions and sCr so that very low or very high values of sCr have a tendency to influence the fractional excretion values in a possible "non-physiological" way.

10 Specific situations with potential for urine biochemistry utility

There are some situations in which measurement of urine electrolytes could be of particular relevance.

10.1 Immediately after ICU admission in patients who have normal sCr and information regarding urine output is not yet available

In these patients, a spot urine sample would probably help in distinguishing cases with a higher risk of AKI. For example, a patient admitted with a sCr of 0.8 mg/dL, a NaU value of 15 mEq/L and a FEK value of 25 % is probably at higher risk than a patient admitted with the same sCr but with a NaU value of 150 mEq/L and a FEK value of 7 % (Fig. 3).

10.2 Patients admitted with a borderline sCr and unknown baseline sCr

A patient may be admitted with a sCr of 1.2 mg/dL and, without a known baseline sCr, it is difficult to know if this is a normal sCr or an elevated sCr. This sCr value may correspond to AKIN stage 2 [65] in a patient with a baseline sCr of 0.6 mg/dL. Values compatible with "stressed" kidneys (low NaU, high FEK) may suggest that there is a risk or presence of AKI even without a known baseline sCr. High NaU and low FEK in this context is more compatible with a normal or improving renal function.

10.3 Patients with a theoretically "normal" urine output

It is generally accepted that a urine output of 0.5 mL/kg/h is a good cut-off value for normality but in fact this is the *minimum* value considered normal. It is quite possible that AKI development begins well before with progressive decreases in urine output but still in a range considered normal [66]. The concept of "normal" urine output is hard to define because it depends on multiple variables including how much volume is being given to the patient, the patientś weight, how much fluid is being losing by other

ways (feces, sweat, drains), the degree of systemic inflammatory stress, etc. Additionally, urine has a role in acid–base homeostasis which depends on its electrolyte composition [67–69]. Hence, adequate urine output evaluation must involve both its volume and content [41].

10.4 Patients with a very low baseline sCr

Malnourished patients or patients with some muscular diseases may have very low baseline sCr (as low as 0.2 mg/dL). In these patients, even discrete elevations in sCr may represent severe decreases in GFR. Since the urine biochemical profile seems to alter before increases in sCr, measurement of urine electrolytes may be of particular relevance in this population.

10.5 Decreasing sCr due to hemodilution

It has been previously demonstrated that AKI diagnosis may be delayed or its degree may be underestimated due to sCr dilution secondary to positive fluid balances [70]. Significant and abrupt decreases in NaU or increases in FEK may sign for AKI progression even in the presence of a lower sCr.

11 Major limitations of the use of urine biochemistry

As the majority of the monitoring tools, urine biochemistry also has its limitations. Of course, the urine electrolyte concentration depends also on the amount of the electrolyte that is being given to the patient. Increases in sodium administration are expected to increase NaU as well as a sodium restriction is expected to reduce NaU. In addition, measurement of urine electrolytes is frequently used in the understanding of dyskalemias and dysnatremias so that patients with serum sodium or potassium out of their normal range may need a careful interpretation of their urine biochemistry. For instance, a patient may have a very increased FEK in spite of the absence of AKI due to primary hyperaldosteronism leading to hypokalemia. Nonetheless, this review focused mainly in patients in which electrolyte disturbances are primarily related to critical illness itself, not to previously acquired diseases.

Many factors may lead to variable and oscillating NaU values along the day. However, it has been reported that even a single spot NaU measurement once daily is capable in some circumstances to reliably help in AKI management [26, 46, 71, 72]. Another limitation is the frequent use of diuretics in the ICU. Diuretic use, usually loop diuretic, is a frequent cause of "artificial" increases in NaU [46, 57, 72] and fractional excretions of both sodium and potassium [73]. Nonetheless, the natriuretic response to furosemide has been demonstrated to have prognostic implications in heart failure [37].

Finally, perhaps one of the greatest limitations of urine biochemistry is its frequent incapacity to determine adequate fluid resuscitation. It is now clear that a low NaU or a low FENa is frequently found in critically ill patients without impaired renal perfusion. Consequently, low NaU may be compared to high serum lactate: both are usually bad signs in critically ill patients but the reason why they are altered is not mandatorily related to (macro)perfusion but may be related to microcirculatory impairment.

12 Conclusions

The utility of urine biochemistry assessment in AKI management remains controversial. If it is somehow useful, it is usually not in the way it was previously thought. Prediction of AKI duration and underlying histopathology seem not to be the questions to be answered measuring urine electrolytes in critically ill patients as previously suggested under the "pre-renal" paradigm. Future perspectives for its usefulness involve: (a) changes in urine electrolyte composition as markers of intra-renal microcirculatory changes which may precede increases in sCr independently of its subsequent duration; (b) 24-h urine collection in selected cases in order to perform rigorous electrolyte balance avoiding overload which carries a poor prognosis in AKI, perhaps even worse than fluid overload, and (c) improvement in the understanding of the genesis of acid–base and electrolyte derangements in blood, both very frequent among critically ill patients.

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

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