

## CASE REPORT

# Early diagnosis of acute kidney injury in a critically ill patient using a combination of blood and urinary physicochemical parameters

Alexandre Toledo Maciel, Marcelo Park

Instituto Central do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, Intensive Care Unit, Department of Medical Emergencies, São Paulo, SP/Brazil.

Email: toledomaciel2003@yahoo.com.br

Tel.: 55 11 9343-0960

## INTRODUCTION

Acute kidney injury (AKI) is common among critically ill patients. Because it is associated with high rates of morbidity and mortality, efforts are being made to identify AKI early to increase the likelihood of successful intervention. Serum creatinine, the primary parameter used to diagnose AKI, is universally considered a late marker.

One of the major problems associated with AKI is acid-base disturbance. The physicochemical approach proposed by Stewart (1) is increasingly recognized as useful in managing complex acid-base disturbances. In this case, we demonstrate that, during the development of AKI, evolutive alterations in physicochemical serum and urinary variables are easily measured and may reliably precede increases in creatinine. These parameters may thus aid in the early diagnosis of AKI.

## CASE DESCRIPTION

A 45-year-old male was admitted to our intensive care unit (ICU) from the ward, where he was concluding antibiotic treatment for a urinary tract infection and being treated with oral anticoagulants for antiphospholipid syndrome. On the day of ICU admission (day 0), the patient was found unconscious on the floor of the ward. A cranial CT scan revealed an acute subdural hematoma. The patient was immediately transferred to the ICU and intubated. The anticoagulant was reversed with vitamin K and plasma. Soon after, the patient was transferred to the operating room, where the hematoma was drained and an intracranial pressure (ICP) monitoring device was installed. After the surgery, the patient returned to the ICU. Because of his elevated ICP, the patient was kept sedated with thiopental. Norepinephrine was infused to maintain an adequate cerebral-perfusion pressure. Initial exams after surgery (day 1) revealed normal blood urea nitrogen (BUN) and creatinine levels and increased levels of serum  $\text{Na}^+$  and  $\text{Cl}^-$  (Table 1). Blood gas analysis revealed a mild non-anion gap metabolic acidosis. A simultaneous spot sample of urine also revealed

high levels of  $\text{Na}^+$  (NaU) and  $\text{Cl}^-$  (CIU) as well as a high urinary strong ion difference ( $\text{SIDu} = [\text{Na}^+] + [\text{K}^+] - [\text{Cl}^-]$ ). By day 2, BUN and creatinine levels had decreased slightly. Urine output over the previous 24 h had been normal. Serum and urine levels of  $\text{Na}^+$  and  $\text{Cl}^-$  remained elevated, and the SIDu remained high, but the blood gas analysis was normal. The ICP was controlled; thiopental was replaced by dexmedetomidine, and the dose of norepinephrine was reduced. By day 3, BUN and creatinine levels had increased only minimally. Urine output had decreased over the previous 24 h but did not fall below the normal range (Table 1). Serum  $\text{Na}^+$  and  $\text{Cl}^-$  levels were evolutive similar, while NaU and CIU levels remained high. A significant increase in SIDu was observed, which resulted from increases in NaU and  $\text{K}^+$  (KU) levels and decreases in CIU levels (Figure 1). Sedation was stopped, but norepinephrine was still necessary to maintain the patient's mean blood pressure above 65 mmHg. C-reactive protein levels and the degree of leukocytosis increased daily, and cultures were collected. On day 4, the patient developed tachycardia, and urinary flow continued to decrease, while norepinephrine levels increased to maintain the mean blood pressure. There was no fever. Treatment with broad-spectrum antibiotics was initiated empirically. During this time, creatinine levels had not increased, but the BUN level increased slowly each day to levels that did not exceed the normal range. Serum phosphate and unmeasured anions (Table 1) also increased daily. Serum  $\text{Na}^+$  and  $\text{Cl}^-$  were still high, but NaU and CIU levels decreased; KU levels increased daily from day 2 onward. On day 5, the patient developed clear oliguria, although the creatinine measurements performed at the beginning of the day were normal. The BUN level continued to increase. An abrupt decrease in NaU and CIU levels occurred in parallel with the increases in KU levels. The SIDu decreased but remained very high. On day 6, the patient developed fever, severe metabolic acidosis, and refractory shock with overt multiple-organ failure. NaU and CIU levels fell further, but the KU and SIDu levels remained high. The patient's creatinine levels increased abruptly, and the nephrology team indicated the need for continuous renal-replacement therapy; however, the patient died before therapy could be initiated. None of the cultures collected revealed the presence of an infectious agent.

## DISCUSSION

The case described above is a common example of AKI (possibly septic in origin), and it demonstrates that creatinine

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No potential conflict of interest was reported.

**Table 1 - Traditional renal and physicochemical parameters in the evolution of AKI.**

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6
BUN (mg/dL)	15	10	13	17	27	47
Creatinine (mg/dL) <sup>Ω</sup>	0.89	0.76	0.90	0.87	0.95	2.14
SIDa (mEq/L) * <sup>Ω</sup>	34.5	37.1	39.5	39.8	38.4	40.0
SIDu (mEq/L) #	48	51	145	160	108	106
SIG (mEq/L) * <sup>Ω</sup>	1.7	2.6	4.5	7.0	9.1	14.2
Lactate (mEq/L) <sup>Ω</sup>	0.9	2.1	3.1	2.6	3.2	6.4
Phosphate (mg/dL) <sup>Ω</sup>	3.0	1.8	2.1	3.1	3.8	5.5
FeNa (%)	1.5	4.7	1.8	0.9	0.1	0.1
FeCl (%)	1.9	5.2	1.6	0.7	0.3	0.2
FeK (%)	17.2	19.4	17.6	15.3	25.1	39.6
Preceding 24-h diuresis (mL)	---	2440	1100	920	840	225

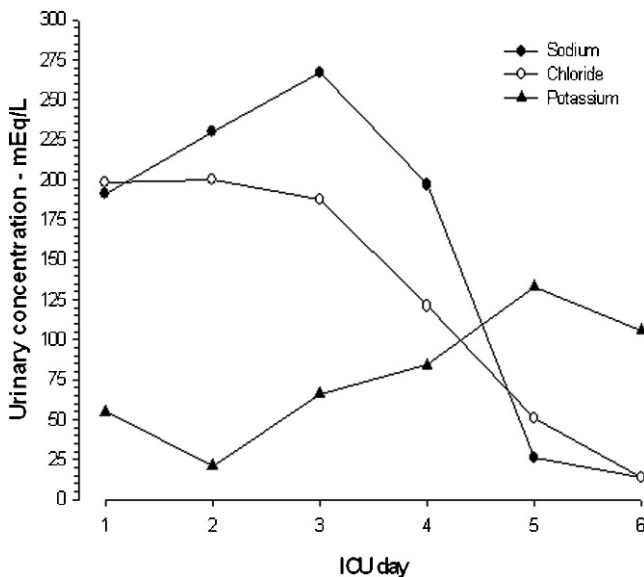
AKI: acute kidney injury; BUN: blood urea nitrogen; SIDa: apparent strong ion difference; SIDu: urinary strong ion difference; SIG: strong ion gap (unmeasured anions); FeNa, FeCl, and FeK: fractional excretion of sodium, chloride and potassium, respectively.

<sup>Ω</sup> measured in blood.

\*SIDa and SIG were calculated as previously reported (see reference 3).

# SIDu was calculated as follows: urinary [Na<sup>+</sup>] + [K<sup>+</sup>] - [Cl<sup>-</sup>].

is a late diagnostic marker. In this case, increases in creatinine occurred simultaneously with overt multiple-organ failure, which limited the likelihood of effective intervention. Using the Acute Kidney Injury Network criteria (2), AKI diagnosis in this patient was possible on day 4 by considering urine output (AKIN stage 1 – data not shown). A delayed diagnosis of AKI stage 2 was possible only on day 6 using the creatinine criteria, and AKI stage 3 could be diagnosed using urine-output criteria on day 5. Interestingly, other variables exhibited daily trends that suggested that AKI was developing before the major changes in creatinine levels occurred. First, relative decreases in urinary flow should be taken into



**Figure 1 - Daily changes in electrolyte levels in spot urine samples.**

account; in this case, daily decreases in urine output might have suggested AKI as early as day 2, although the levels remained within a “normal” range (>0.5 ml/kg/h). Daily simultaneous increases in BUN, unmeasured anions, and phosphate levels, even within the normal range, could also be useful in the diagnosis of a progressive impairment in renal function. It has been previously demonstrated that hyperphosphatemia and an increased concentration of unmeasured anions account for metabolic acidosis in AKI (3). Furthermore, a persistently high SIDu (well above plasmatic SID; Table 1) would not be expected in hyperchloremic acidosis, which is usually present after major crystalloid infusion, as occurred during surgery. It has also been previously suggested that high levels of SIDu are associated with renal failure in metabolic acidosis (4). Finally, abrupt decreases in NaU, ClU, and their respective fractional excretions, occurring in parallel with increases in KU and its fractional excretion between days 4 and 6, might also signal severe renal hemodynamic compromise with exacerbated activity of the sympathetic and angiotensin system (a “pre-renal” pattern of AKI). These changes were probably part of a systemic inflammatory response, with microcirculatory impairment that, if left untreated, would lead to multiple-organ failure and death. This “pre-renal” pattern of AKI has been previously shown in experimental hyperdynamic sepsis (5). Cardiac output was not measured in this patient, but successive positive fluid balances argue against hypovolemia as the main cause of the urinary findings.

In conclusion, the daily evaluation of changes in simple parameters such as consistent increases in serum phosphate levels, unmeasured anions, and KU, with decreases in NaU and ClU and a persistently high SIDu, could facilitate the early diagnosis of renal impairment before major decreases in urine output or increases in creatinine are observed. Even small alterations in these parameters might be a warning sign of ongoing renal and perhaps systemic hemodynamic impairment.

**AUTHOR CONTRIBUTIONS**

Maciel AT provided care to the patient, collected and analyzed the data, and wrote the manuscript. Park M provided care to the patient and collected the data.

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