REVIEW ARTICLE

Acute kidney injury

Thiago Reis[1]

1. Clínica de Doenças Renais de Brasília – CDRB, Brasília - DF, Brasil.

http://dx.doi.org/10.1590/1806-9282.66.S1.68

KEYWORDS: *Acute kidney injury. Water balance. Critical Care. Renal replacement therapy. Furosemide.*

Acute kidney injury (AKI) is a set of syndromes defined by the abrupt decrease in glomerular filtration rate (GFR). An AKI episode is associated with negative short-term outcomes, such as hypervolemia, acid-base disorders, immune system dysfunction. In addition, there is higher mortality in individuals who have suffered an episode of AKI up to 10 years after the event when compared to the general population.[1]

The current classification of AKI, KDIGO AKI (Kidney Diseases Improving Global Outcomes Acute Kidney Injury)[2] comes from a laboratory criterion, the serum creatinine value, and a clinical criterion, urinary output. If there is a staging divergence between the criteria, the greatest prevails.[1]

Stage	Serum creatinine concentration	Diuresis
Diagnosis	• Increased 0.3 mg/dL in 48h, or • Increase 50% (1.5x) of the baseline creatinine	• < 0.5 mL/kg/h for 6 hours
Stage 1	• 50-99% (1.5 to 1.9x) of the baseline creatinine, or • Increased 0.3 mg/dL of the baseline creatinine	• < 0.5 mL/kg/h from 6 to 12 hours
Stage 2	• 100-199% (2.0 to 2.9x) of the baseline creatinine	• > 0.5 mL/kg/h per period of 12 hours
Stage 3	• 200% (3x) of the baseline creatinine, or • Increased creatinine 4.0 mg/dL, or • Renal Replacement Therapy, or • In patients younger than 18 years, reduction in GFR < 35 mL/min/1.73m^2	• < 0.3 mL/kg/h per period of 24 hours, or • Anuria per period 12 hours

The incidence of AKI varies depending on the age, adult vs. pediatric, and the patient's location within the hospital structure, intensive care unit (ICU) vs. infirmary. Worldwide, AKI characteristics (epidemiology, etiology, outcomes), contrast between developed vs. developing countries. Nevertheless, the presentations of AKI in urban centers are similar to those found in developed countries.[1]

KIDNEY ATTACK

In 2013, in order to highlight AKI, Ronco[3] coined the term "Kidney Attack", an analogy to "Heart Attack"/ acute coronary syndrome. Obviously, this term is not a formal nomenclature. In the publication, an additional criterion proposed for the classification of AKI is a marker of renal tubular injury, NGAL (neutrophil gelatinase-associated lipocalin)[3]. It is important to emphasize that creatinine is a marker of renal function, whereas NGAL is a marker of injury. In this analogy, increased creatinine would represent an ST-segment elevation. Whereas Increased NGAL would mean an increase in troponin levels. There are four possible scenarios:

1. Normal creatinine and NGAL → Absence of AKI.

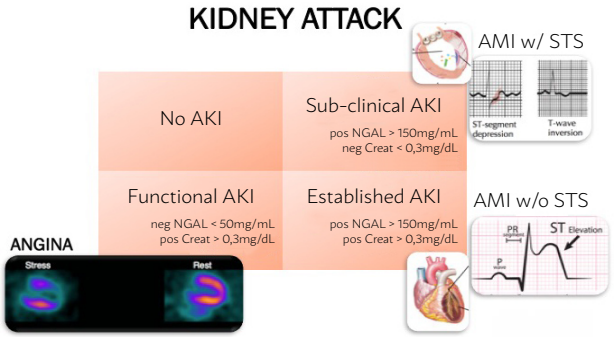
2. Increased creatinine and normal NGAL → functional AKI. Example: introduction of drugs that modify glomerular perfusion without causing a tubular lesion. Drugs commonly related: Angiotensin-converting

CORRESPONDING AUTHOR: Thiago Reis
E-mail: thiagoreisnefro@gmail.com

enzyme inhibitors (Enalapril); angiotensin 2 receptor blockers (Losartan), calcineurin inhibitors (Tacrolimus); Gliflozins, sodium-glucose co-transporter type 2 inhibitors (Empagliflozin). Clinical situations such as Parathyroidectomy.[4] The parathyroid hormone has vasodilating action in the afferent arteriole of the glomeruli. Its sudden reduction causes a decrease in glomerular perfusion, a decrease in the glomerular filtration rate, increase of serum creatinine, without causing a tubular lesion.[4] Both the pharmacological and clinical causes would be equivalent to positive myocardial perfusion scintigraphy.[3]

3. Normal creatinine and increased NGAL → subclinical AKI. Example: AKI induced by intravenous iodine contrast with an increase of less than 0.3 mg/dL in serum creatinine. It would be equivalent to an acute myocardial infarction (AMI) without ST-segment elevation.

4. Increased creatinine and NGAL → established AKI. AMI with ST-segment elevation.[3]



FLUID BALANCE

The arbitrary definition of positive fluid balance would be an increase of more than 5% of the body mass related to the accumulation of fluids.[5] In these patients, there is a greater propensity to deleterious effects on multiple systems.

Central nervous system → Cognitive deficit, delirium.

Cardiovascular → Conduction disorders, decreased inotropism, diastolic dysfunction.

Respiratory → Reduction of gas exchange, decreased pulmonary compliance.

Hepatic → Cholestasis, reduced protein production.

Digestive → Malabsorption syndrome, paralytic ileus.

Skin and soft tissue → Cicatrization deficit, wound infections, pressure injuries.

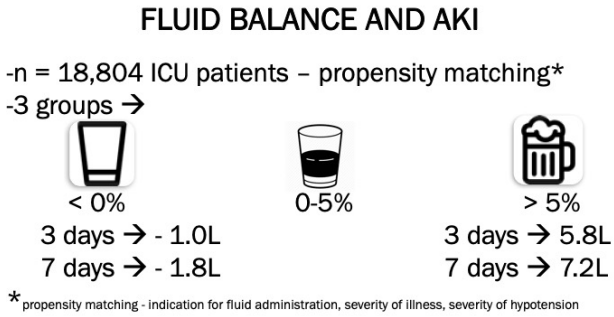
Renal → Increased interstitial pressure, reduced renal perfusion, retention of water and sodium, uremia. Due to the low compliance of the renal capsule, the interstitial edema leads to renal compartmental syndrome.[5]

In 2017, Balakumar et al.[6] published a retrospective study that included 18,804 patients admitted to an ICU. They were divided into three groups. The primary outcomes were mortality and recovery of renal function. The fluid balances on the third and seventh-day post-admission were analyzed. In one group, the fluid balance was negative. In the other group, the balance was positive, but less than 5%. In the last group, the balance was positive, exceeding 5% of the body mass. The individuals in the last group, when compared with the other two, showed a higher incidence of AKI, oliguria, length of hospital stay, and need for RRT, in addition to lower recovery of renal function and increased mortality after one year.[6]

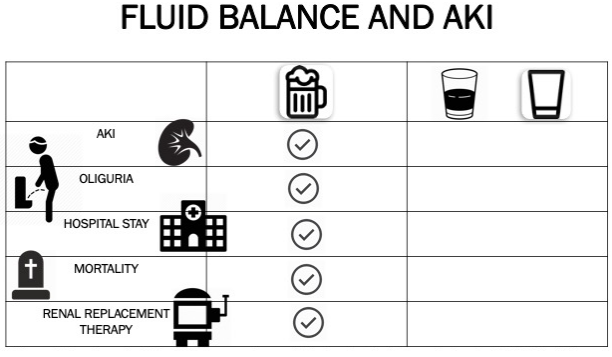
CHANGE OF PARADIGMS

In 2018, Ricci et al.[7] published an article with 10 incorrect concepts commonly spread on Nephrointensivism. Some to know:

1. Acute tubular necrosis is the predominant histologic finding in AKI → FALSE. In patients admitted to



Adapted from Balakumar et al.[6]



Adapted from Balakumar et al.[6]

the ICU with AKI who underwent kidney biopsy, the finding of acute tubular necrosis was only focal. This is because, in various etiologies of AKI, mechanisms other than renal ischemia have been found.

2. The main cause of septic AKI is the reduction of renal perfusion → FALSE. On the contrary, in septic AKI, there is an increase in renal perfusion. However, changes occur in the renal microcirculation (shunts), with lower perfusion of the glomeruli despite a higher global renal perfusion. This phenomenon is corroborated by the low incidence of the histological finding of acute tubular necrosis in septic AKI.

3. Fluid challenge is always indicated in oliguric patients → FALSE. In several scenarios, oliguric patients do not present a volemic deficit. An emblematic example is patients with right ventricular failure. They are usually patients with increased central venous pressure. Consequently, there is an increase in renal venous pressure, which is transmitted to the kidney, causing renal congestion. If these patients are oliguric, fluid challenge will be harmful, because it will increase the pressure in the renal veins.

4. An mean arterial pressure of 65 mmHg is the main target in patients with AKI → FALSE. This is an analogy to the perfusion of the central nervous system. This perfusion results from the difference between the mean systolic arterial pressure and intracranial pressure since the skull has insignificant compliance. The renal perfusion pressure would be the difference between the mean systolic arterial pressure and the central venous pressure, extrapolating that the latter represents the renal intracavitary pressure. This analogy is made due to the low compliance of the renal capsule. However, there are no studies that define a target pressure for renal perfusion. It is also noteworthy that in patients who were previously hypertensive with septic shock, a target of 80 to 85 mmHg is related to a reduction in mortality.

5. The return to baseline creatinine pre-AKI means a full recovery of renal function → FALSE. After an episode of AKI, there are always irreversible lesions of some glomeruli and nephrons, so there is always a sequel. What happens is that the creatinine can return to the baseline value for two reasons. The first, the reduction of lean body mass/sarcopenia after admission to the ICU. In this situation, the generation of creatinine would be smaller. The second reason is the use of the renal functional reserve. It is known that there is adaptive renal capacity, and, faced with AKI episodes, the capacity of filtration of the remaining glomeruli is enhanced at the expense of the renal functional reserve.

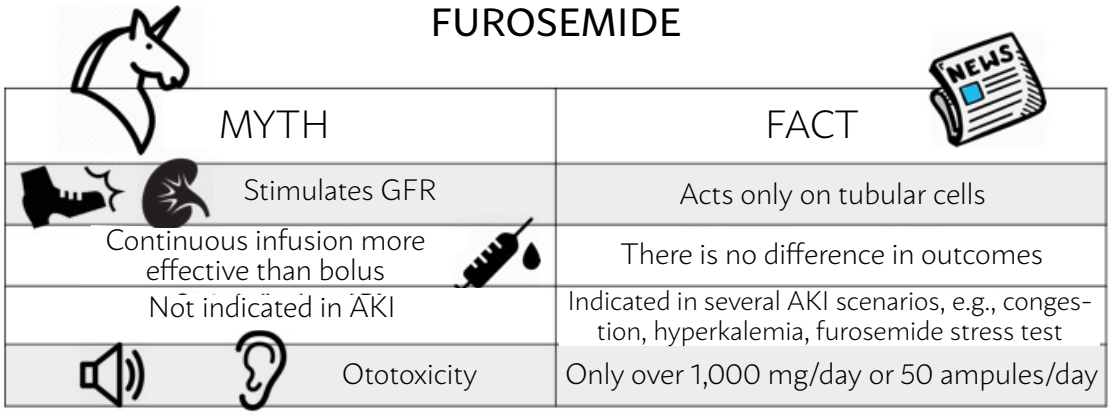
6. The Right Internal Jugular Vein is the best access for hemodialysis → FALSE. Current evidence shows that both femoral veins present similar rates of infection related to the catheter and patency of the catheter, except in obese patients with a body mass index above 30 kg/m^2, among whom the rates of catheter colonization and infection are higher.[7-9] In addition, catheters in the right jugular vein, there is an indication to place the tip of the device within the right atrium and not in the transition between the superior vena cava and the right atrium. In a study comparing these two positions, catheters with the tip in the atrium were related to a higher rate of patency of the hemodialysis filter, and there were not a higher rate of arrhythmias, right atrium perforation nor cardiac tamponade.[10]

7. In anuric patients, the suspension of the dialysis should be associated with volemic expansion and initiation or increase in the dose of diuretics (furosemide) → FALSE. The most important parameter for the weaning of renal replacement therapy should be the spontaneous increased of diuresis above 400 mL in 24 hours for patients who are not on diuretics. For patients on diuretics, diuresis exceeding 1000 mL in 24 hours is an indicator of renal recovery. When the urinary output in 24 hours is greater than this value, the suspension of dialysis can be considered.[11]

In 2019, Joannnidis et al.[12] published an editorial about myths related to furosemide. Some to know:

1. Furosemide promotes an increase in renal function → FALSE. The renal function is given by the glomerular filtration rate. Furosemide does not increase the glomerular filtration rate. Its action occurs in the lumen of the renal tubules. In summary, it promotes lower reabsorption of water in the glomerular ultrafiltrate, leading to an increase of diuresis.

2. Infusion by continuous infusion pump is more effective than bolus infusion → FALSE. Based on the current scientific evidence, there is no indication to prescribe furosemide in continuous infusion since there is no change in outcomes with this strategy. In addition, the cost of using an infusion pump may be up to R$ 1,000.00 per day. This is an unjustifiable cost for therapy with no added benefits.



Adapted from Joannidis et al.[12]

3. Furosemide should be stopped if there is a progressive increase of creatinine → FALSE. In situations of renal venous congestion/renal compartment syndrome, such as Cardiorenal Syndrome, even with daily increases in creatinine, there is an indication to maintain furosemide if the patient still has residual diuresis. In these situations, diuresis forced by furosemide and other measures that favor a negative fluid balance, such as extracorporeal ultrafiltration, low sodium diet, fluid restriction, are beneficial for the reversal of fluid overload status. In the same way, even if the patient is undergoing renal replacement therapy/hemodialysis, it is advisable to use furosemide to control the fluid balance.

4. In AKI, there is a contraindication to Furosemide → FALSE. In situations such as hypervolemia, hyperkalemia, and for the furosemide stress test, the use of this diuretic is encouraged.

5. Ototoxicity → FALSE. Only doses above 1,000 mg/day in adults have an ototoxic potential. The commercial presentation available on the national market is a 20 mg vial. Thus, only a dose exceeding 50 vial/day would put the patient at risk of cochlear lesion.[2]

PREVENTION

In 2017, Joannidis et al.[13] published guidelines on the prevention of AKI. The recommendations are classified according to the subjective level (1-Strongly recommended, 2-Weakly recommended) and to the evidence strength (A-high, B-moderate, C-low, D-very low). Some positions are noteworthy:

1. Volume expansion → Use of hypotonic solutions such as Ringer's lactate instead of 0.9% saline solution (2C).

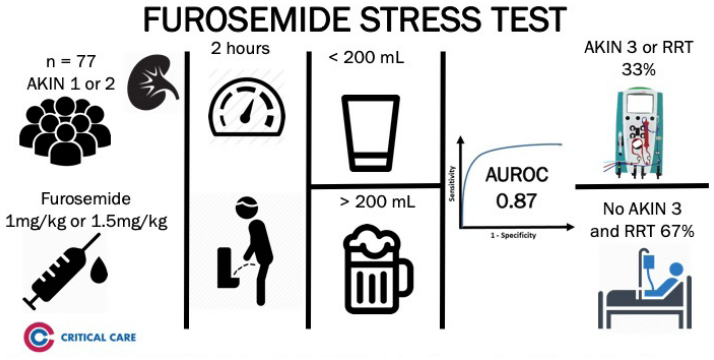
2. Use of loop diuretics (furosemide) to avoid/minimize positive fluid balance (2D).

3. Target mean arterial blood pressure → In previously hypertensive patients who evolve with septic shock, the target is 80-85 mmHg (1C).

4. Statins to prevent AKI in the postoperative period of cardiac surgery → contraindicated for ineffectiveness (1A).

MANAGEMENT

In 2013, Chawla et al.[14] published a manuscript about the usefulness of furosemide as a prognostic tool in the AKI, the Furosemide Stress Test. They performed a retrospective analysis of 77 individuals with AKI KDIGO 1 and 2. Patients who were already on furosemide received a dose of 1.5 mg/kg of furosemide via bolus. Patients who were not on the medication received 1.0 mg/kg via bolus. They used 200 mL as the cutoff point of diuresis 2 hours after the administration of furosemide. They were able to anticipate the outcomes of progression to KDIGO 3 and/or need



Adapted from Chawla et al.[14]

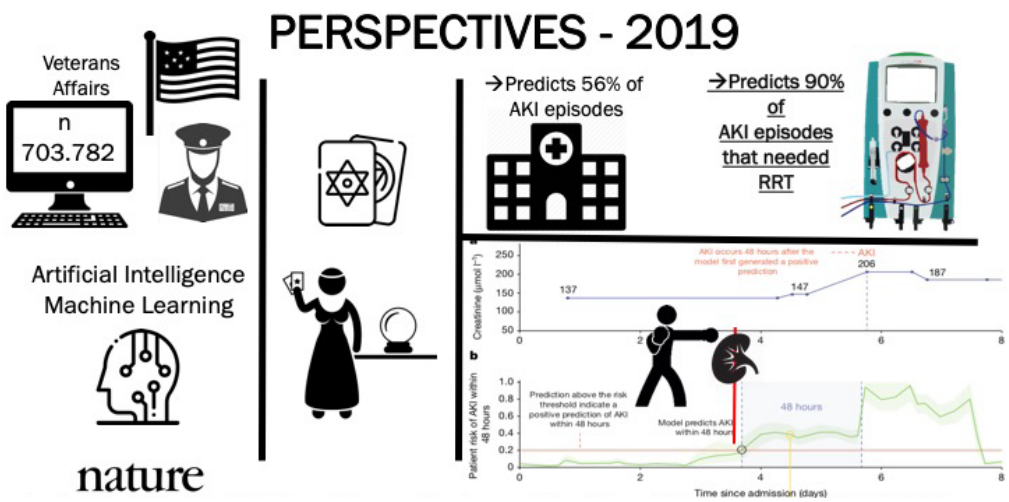
SCAMP - Standardized Clinical Assessment and Management Plan				
Complete on Day 1				
Site of Nephrology Evaluation:	□ Room	□ ICU		
Nephrology Evaluation was (timing): □ Early		□ On time	□ Late	
AKIN Etiology: □ Sepsis	□ Hypotension	□ Iodinated contrast	□ Glomerulonephritis	□ Nephrotoxin
□ Pre-renal	□ Tubulointerstitial nephritis	□ Rhabdomyolysis	□ Thrombotic microangiopathy	
□ Hepatorenal Sy.	□ Cardiorenal Sy.	□ Hemolysis	□ Vasculitis	
□ Post-renal/Obstructive	□ Other:			
KDIGO: DI	□ 2	□ 3		
DIAGNOSIS HYPOTHESIS:				
HISTORY:				
□ DRC 5D				
ETIOLOGY	START OF RRT (year):	ACCESS:	DRY WEIGHT:	RESIDUAL: GAIN:
SEROLOGIC TESTS:	HD PRESCRIPTION:	CLINICAL:	NEPHROLOGIST	
What is your estimate of in-hospital mortality of the patient? SAPS II -->				
□ Unlikely (<25%)	□ Possible (25-74%)	□ Very Likely (75-94%)	□ Almost certain (>95%)	
Do you consider initiating RRT?				
□ YES (proceed to the next question)		□ **NO: (Move on to indications for RRT start)->**		
Would RRT be a futile measure?				
□ **NO: (move on to indications for RRT start)->**				
□ YES, because:				
□ Base disease severity:				
□ Metastatic cancer				
□ Irreversible acidosis (10 mmol/L)				
□ Irreversible sepsis (3 vasopressors, SBP < 90 mmHg, presence of infection)				
□ Irreversible neurological damage				
□ Other:				
Even so, will you initiate RRT?				
□ YES, because:			□ NO:	
□ Request from the ICU team	□ Decision of the family		□ Prior choice of the patient	
□ No time for discussion			□ Other:	

INDICATIONS FOR START OF RENAL REPLACEMENT THERAPY

	Emergency	Urgency	Not urgent
A-E-I-O-U			
Acidosis	□ pH < 7.20	□ pH 7.20-7.30	□ pH > 7.30
Electrolytes	□ K > 6.5 or abnormal ECG	□ K 6.0 - 6.5	□ K < 6.0
Ingestion:	□ Toxin:		
Overloaded/Hypervolemia	□ Severe anasarca □ IRpA FiO2 >70% □ Diuresis < 100mL/ 24h	□ Edema 2+ to 3 + □ FiO2 50-70% □ Diuresis 100-500mL/ 24h	□ Edema 1 + □ No edema
Uremia	□ Uremic symptoms □ Neurological abnormality	□ Urea 130- 280	□ Urea < 130
SCAMP RECOMMENDS --->	□ 1 -> RRT	□ 3 -> RRT □ 1-2 -> No RRT	□ 4-> No RRT

SELECT the option that will be deployed -> (IT IS NOT NECESSARY TO JUSTIFY IF THE OPTION IS THE SAME RECOMMENDED BY SCAMP)

□ RRT	□ No RRT
Justification to start RRT if SCAMP recommends NOT STARTING RRT (complete only if there is a disagreement between the SCAMP RECOMMENDATION and the option that will be deployed)	**Justification to NOT start RRT if SCAMP recommends STARTING RRT (complete only if there is a disagreement between the SCAMP RECOMMENDATION and the option that will be deployed)**
□ Hypervolemia (relative seriousness)	□ could accelerate a death outcome
□ Predicted worsening of renal function	□ Is not relevant to the therapeutic objective
□ Hyperkalemia (not severe < 6.0)	□ Predicted improvement of renal function
□ Other:	because:
	□ Useless therapy/Base disease:
	□ Metastatic cancer
	□ Irreversible lactic acidosis
	□ Irreversible sepsis
	□ Irreversible neurological damage
	Other:
	□ Other:



Adapted from Tomašev et al.[16]

for renal replacement therapy with good accuracy. Individuals with diuresis less than 200 mL showed a tendency of evolution of the renal lesion. On the other hand, diuresis exceeding 200 mL had the contrary prognosis in relation to the progression of the renal lesion. The AUCROC (area under the curve receiving operating characteristic) was 0.87.

In an article published in 2017, Mendu et al.[15] presented an algorithm on decision-making in relation to the use of renal replacement therapy in patients with acute kidney injury, the protocol named by the acronym SCAMP (standardized clinical assessment and management plan). The SCAMP form is filled out with the data of the patient. At the end of the flow chart, there is a suggestion to start or not renal replacement therapy. However, there is no obligation to follow the protocol's suggestion. It is up to the physician alone to justify the conduct chosen if it is contrary to the SCAMP suggestion. In-hospital mortality and mortality at 60 days were the primary outcomes.

Patients whose nephrologists agreed with the protocol had lower in-hospital mortality (42 vs 63%; P<0.01) and 60-day mortality (46 vs 68%; P<0.01). However, this protective effect was only observed in patients whose predictive mortality at the first evaluation was below 50%.

PROSPECTS

In an article published in Nature magazine in 2019, the discriminatory power of prognosis of a multifactorial analysis via artificial intelligence was tested.[16] In a retrospective analysis of the Veteran Affairs records, with 703,782 individuals, by means of software with artificial intelligence, it was possible to discern, 48 hours in advance, 56% of the AKI episodes. The same tool can point out in 90% of the cases which AKI patients will require renal replacement therapy.

Note

The visual abstracts were created by this author; they were not taken from other sources.

Abbreviations

- AKI: acute kidney injury.
- GFR: glomerular filtration rate.
- KDIGO AKI: *Kidney Diseases Improving Global Outcomes Acute Kidney Injury.*
- RRT: renal replacement therapy.
- NGAL: *neutrophil gelatinase-associated lipocalin.*
- AMI: acute myocardial infarction.
- ICU: intensive care unit.

PALAVRAS CHAVE: *Lesão renal aguda. Balanço hídrico. Cuidados Críticos. Terapia de Substituição Renal. Furosemida.*

REFERENCES

1. Hoste EAJ, Kellum JA, Selby NM, Zarbock A, Palevsky PM, Bagshaw SM, et al. Global epidemiology and outcomes of acute kidney injury. Nat Rev Nephrol. 2018;14(10):607-25.
2. KDIGO. Section 2: AKI definition. Kidney Int Suppl. 2012;2(1):19-36.
3. Ronco C. Kidney attack: overdiagnosis of acute kidney injury or comprehensive definition of acute kidney syndromes? Blood Purif. 2013;36(2):65-8.
4. Parikh S, Nagaraja H, Agarwal A, Samavedi S, Von Visger J, Nori U, et al. Impact of post-kidney transplant parathyroidectomy on allograft function. Clin Transplant. 2013;27(3):397-402.
5. Prowle JR, Echeverri JE, Ligabo EV, Ronco C, Bellomo R. Fluid balance and acute kidney injury. Nat Rev Nephrol. 2010;6(2):107-15.
6. Balakumar V, Murugan R, Sileanu FE, Palevsky P, Clermont G, Kellum JA. Both positive and negative fluid balance may be associated with reduced long-term survival in the critically ill. Crit Care Med. 2017;45(8):e749-57.
7. Ricci Z, Romagnoli S, Ronco C. The 10 false beliefs in adult critical care nephrology. Intensive Care Med. 2018;44(8):1302-5.
8. Parienti JJ, Thirion M, Mégarbane B, Souweine B, Ouchikhe A, Polito A, et al; Members of the Cathedia Study Group. Femoral vs jugular venous catheterization and risk of nosocomial events in adults requiring acute renal replacement therapy: a randomized controlled trial. JAMA. 2008;299(20):2413-22.
9. Parienti JJ, Mégarbane B, Fischer MO, Lautrette A, Gazui N, Marin N, et al. Catheter dysfunction and dialysis performance according to vascular access among 736 critically ill adults requiring renal replacement therapy: a randomized controlled study. Crit Care Med. 2010;38(4):1118-25.
10. Morgan D, Ho K, Murray C, Davies H, Louw J. A randomized trial of catheters of different lengths to achieve right atrium versus superior vena cava placement for continuous renal replacement therapy. Am J Kidney Dis. 2012;60(2):272-9.
11. Klouche K, Gibney RTN, Forni LG. Can this patient be safely weaned from RRT? Intensive Care Med. 2018;44(5):639-42.
12. Joannidis M, Klein SJ, Ostermann M. 10 myths about frusemide. Intensive Care Med. 2019;45(4):545-8.
13. Joannidis M, Druml W, Forni LG, Groeneveld ABJ, Honore PM, Hoste E, et al. Prevention of acute kidney injury and protection of renal function in the intensive care unit: update 2017: expert opinion of the Working Group on Prevention, AKI section, European Society of Intensive Care Medicine. Intensive Care Med. 2017;43(6):730-49.
14. Chawla LS, Davison DL, Brasha-Mitchell E, Koyner JL, Arthur JM, Shaw AD, et al. Development and standardization of a furosemide stress test to predict the severity of acute kidney injury. Crit Care. 2013;17(5):R207.
15. Mendu ML, Ciociolo GR Jr, McLaughlin SR, Graham DA, Ghazinouri R, Parmar S, et al. A decision-making algorithm for initiation and discontinuation of RRT in severe AKI. Clin J Am Soc Nephrol. 2017;12(2):228-36.
16. Tomašev N, Glorot X, Rae JW, Zielinski M, Askham H, Saraiva A, et al. A clinically applicable approach to continuous prediction of future acute kidney injury. Nature. 2019;572(7767):116-9.