Predictors of mortality in a cohort of acute kidney injury patients

Preditores de mortalidade em uma coorte de pacientes com lesão renal aguda

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ABSTRACT

BACKGROUND AND OBJETIVE: Acute kidney injury is related to high in-hospital mortality. The use of furosemide has been a controversial point in the prevention and treatment of acute kidney injury. The objective of this study was to identify predictors of mortality in critically ill patients with acute kidney injury with emphasis on use of furosemide. **METHODS**: A prospective cohort of 108 patients with acute kidney injury admitted consecutively in a intensive care unit and evaluated until death or hospital discharge. The dependent variable was death from any cause. The independent variables were age, sex, race, serum creatinine, potassium, admission diagnosis, urine output, volume infused, the twelve variables of Acute Physiology and Chronic Health disease Classification System II and furosemide use. We performed logistic regression analysis to identify predictors of death. **RESULTS**: The mean age of patients was 65.74 years with a predominance of women of African descent. The overall mortality rate was 44.4%. In logistic regression analysis, predictors of mortality were: using furosemide, age in years and Glasgow come scale. **CONCLUSION**: Use of furosemide was a predictor of mortality in a cohort of patients with acute kidney injury. The role of furosemide in the treatment and prevention of acute kidney injury certainly needs to be better evaluated.

Keywords: Acute kidney injury/mortality; Furosemide/therapeutic use; Risk factors; Treatment outocome; Cohort studies

RESUMO

JUSTIFICATIVA E OBJETIVO: A lesão renal aguda está relacionada a alta mortalidade intra-hospitalar. O uso de furosemida tem sido um ponto controverso em seu tratamento e sua prevenção. O objetivo deste estudo foi identificar preditores de mortalidade em pacientes gravemente enfermos com lesão renal aguda com ênfase para uso de furosemida. **MÉTODOS**: Coorte prospectiva de 108 portadores de lesão renal aguda admitidos consecutivamente em uma unidade de terapia intensiva e avaliados até o óbito ou a alta hospitalar. A variável dependente foi óbito por qualquer causa. As variáveis independentes foram: idade, gênero, raça, creatinina sérica, potássio, as 12 variáveis do *Acute Physiology and Chronic Health Disease Classification System II (*APACHE II), diagnóstico na admissão, débito urinário, volume infundido e uso de furosemida. Realizou-se análise de regressão logística para identificar os preditores de óbito. **RESULTADOS**: A média de idade dos pacientes foi de 65,74 anos com predomínio de mulheres afrodescendentes. A taxa de mortalidade global foi de 44,4%. Na análise de regressão logística, os preditores de mortalidade foram: uso de furosemida, idade em anos e escala de coma de Glasgow. **CONCLUSÃO**: Uso de furosemida foi preditor de mortalidade em uma coorte de portadores de lesão renal aguda. Seu papel no tratamento e na prevenção de lesão renal aguda certamente necessita ser mais bem avaliado.

Descritores: Lesão renal aguda/mortalidade; Furosemida/uso terapeutico; Fatores de risco; Resultado do tratamento; Estudos de coortes

INTRODUCTION

Acute kidney injury (AKI) is a common complication of the critically ill, and an independent predictor of mortality in this population. The causes of AKI in this setting are diverse; although sepsis is considered the most common, cardiac failure is also a frequent precipitant of this syndrome[1].

As oliguria presents very often in AKI patients, volume overload is commonly managed with diuretics. Although some authors have found that furosemide use, mainly in high dosages, has been associated to higher mortality rates[2,3], a recent randomized, controlled study did not found difference in mortality[4].

Recently, Levi et al., have suggested that furosemide use is associated to higher odds of developing AKI in critically ill patients with sepsis and septic shock[5]. A meta-analysis performed by Ho and Sheridan[6], however, concluded that

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preventive furosemide administration does not improve the risk of dialysis or mortality. On the basis of these results, the recent KDIGO guidelines recommended not using furosemide to prevent AKI [7].

As the role of diuretics in AKI recovery and mortality remains debatable, we aimed to identify predictors of mortality in a cohort of AKI patients with emphasis on diuretic use.

METHODS

We conducted an observational, prospective cohort of critically ill patients admitted to a 24-bed surgical and clinical intensive care unit (ICU) from a tertiary hospital in northeastern Brazil. Patients older than eighteen years consecutively admitted from January, 2010 and January, 2011 were evaluated. We excluded patients with chronic renal failure stages 3 to 5, kidney transplant, those suspect of brain death within 24 hours of admission, ICU permanence of less than 24 hours and those with only one serum creatinine dosage. The protocol was approved by the hospital´s ethics committee, and all patients signed the informed consent.

AKI was diagnosed and staged accordingly to the *Risk, Injury, Failure, Loss and End-stage renal disease:* (RIFLE) criteria[8-10]; sepsis/septic shock were diagnosed in accordance to current guidelines[11].

Data were collected on a daily basis, from ICU admission to hospital discharge or death. Dependent variable was death of any cause. Independent variables were: age, sex, race, origin

Table 1. Clinical and demographic characteristics of 108 acute kidney injury (AKI) patients according to septic AKI etiology

Variables	AKI patients (n=108)	AKI with sepse/ septic shock (n=50)	AKI without sepse/ septic shock (n=58)	ʊ p value
Age (years)	65,74±17,26	64,82±20,92	66,53±13,48	0,62
Gender				0,51
Female	59 (54,6%)	29(58%)	30 (51,7%)	
Male	49 (45,4%)	21(42%)	28 (48,3)	
Ethnicity				0,47
Afrodescendent	83 (76,9%)	40(80%)	43 (74,1%)	
Non-afrodescendent	25 (23,1%)	10(20%)	15 (25,9%)	
RIFLE category				<0,01
Risk	43(39,8%)	10(20%)	33 (56,9%)	
Injury	35(32,4%)	20(40%)	15 (25,9%)	
Failure	30 (27,8%)	20(40%)	10 (17,2%)	
APACHE II	18 (11)	21 (12)	15,5 (9)	<0,01
Patient Origin				<0,01
Surgical Center	28 (26,2%)	8 (16%)	20 (34,5%)	
Clinicalwards	38 (35,5%)	23 (46%)	15 (25,9%)	
Emergencyroom	23 (21,5%)	11 (22%)	12 (20,7%)	
Otherhospitals	11 (10,3%)	8 (16%)	04 (6,9%)	
Hemodynamic Unit	07 (6,5%)	–	07(12,1%)	
SerumCreatinine (mg/dL)	1,40±0,88	1,41±0,87	1,39±0,90	0,87
¥ K+ (mEq/L)	4,20±1,59	4,19±1,49	4,21±1,68	0,97
Fluid balance (mL)	1383(1950)	2153(2117)	884 (1559)	<0,01
Heart failure/Cardiogenicshock	46 (42,6%)	10 (20%)	36 (62,1%)	<0,01
Temperature	35,82±2,90	35,64±4,22	35,95±0,63	0,64
§ MAP mmHg	90,38±23,62	89,43±24,10	91,19±23,39	0,70
¶ HR	88,79±24,37	100±26,43	79,14±17,54	<0,01
ϒ RR	20,5±6,42	22,54±7,63	18,74±4,53	<0,01
₮ PaO2/FiO2	298,03(204,74)	251,43 (201,58)	305,20 (139,20)	0,05
Ψ pH	7,37±0,09	7,34±0,11	7,40±0,06	<0,01
Ƶ Na+ (mEq/L)	140,84±0,94	139,82±6,18	141,72±5,13	0,08
Hematocrit %	32,52±6,64	31,08±6,86	33,76±6,24	0,03
WBC (mm^3)	12.550 (9275)	15.800 (13.300)	10.800 (6.950)	<0,01
Glasgow Coma Scale	11±3,25	9,98±3,42	11,94±2,80	<0,01

Continuous variables are expressed as mean±standard deviation. ₮ PaO2/FIO2: WBC (White Blood Cells); APACHE II and Fluid balance are expressed as median (IQR). Categorical variables are expressed as percentages and valid N absolute. ¶ HR: heart rate (bpm); ϒ RR: respiratory rate (bpm), Σ PH: hydrogen potential; Z serum Na +: sódio (mEq/L); § MAP: mean arterial pressure (mmHg); ¥ serum K +: potassium (mEq/L). ʊ p value for comparison between AKI with and without sepse/septic shock.

(from emergency, surgical or clinical units), serum creatinine, potassium, urine sediment, *Acute Physiology and Chronic Health Disease Classification System II (*APACHE II) score, diagnosis (trauma, heart failure, sepsis or septic shock). The twelve physiological variables from the APACHE II score were recorded within 24 hours of ICU admission. We also recorded data on urine output, volume infusion, medications (vasoactive drugs, antibiotics, contrast agents and other nephrotoxic drugs), mean arterial pressure and mechanical ventilation. Furosemide use and total doses were recorded.

Statistical analysis

Descriptive statistics were used to summarize the data. Categorical variables were expressed as percentages and continuous variables as mean±standard deviation or median and interquartile range (IQR), depending upon the shape of the distribution of frequencies (Gaussian versus non-Gaussian). Comparisons between two groups were performed using the Pearson Chi-square or Fisher´s Exact test for categorical variables or the Student's t or Mann-Whitney U tests for continuous variables. Variables that showed an association with the outcome characterized by a p value<0.10 on these tests were selected for the multivariable analysis. We performed a backward stepwise multivariable model to identify independent predictors of death; p values<0.05 in the final multivariable model were considered statistically significant. Model fit was assessed with the Hosmer-Lemeshow goodness-of-fit test; all calculations were performed using the statistical software package SPSS 17.0 for Windows (SPSS Inc. Chicago. IL).

We searched for interactions in the multivariate logistic regression model for death. Correlation among maximum serum creatinine, total doses and duration of furosemide use was examined by using Spearman. P values<0.05 in the final analyses were considered statistically significant.

This project was approved by the Ethics Committee of the Hospital Santo Antonio on 03/07/2012; report number: 49340.

Table 2. Clinical and demographic characteristics of 108 acute kidney injury (AKI) patients according to the outcome (death *versus* no death)

Variables	Death (N=48)	No death(N=60)	ʊ p value
Age (years)	70,83±15,60	61,67±17,57	<0,01
Gender			0,76
Female	21 (43,75%)	28 (46,67%)	
Male	27 (56,25%)	32 (53,33%)	
Ethnicity			0,18
Afrodescendent	34 (70,83%)	49 (81,67%)	
Non-afrodescendent	14 (29,17%)	11 (18,33%)	
RIFLE category			
Risk	9 (18,75%)	34 (56,67%)	<0,01
Injury	18 (27,5%)	17 (35,42%)	0,21
Failure	21 (43,75%)	9 (18,75%)	<0,01
APACHE II	24 (8,75)	15 (7)	<0,01
SerumCreatinine (mg/dL)	1,50±0,79	1,32±0,95	0,27
¥ K+ (mEq/L)	4,23±1,15	4,18±1,87	0,87
Fluid balance(ml)	2.153 (2.059,75)	846 (1.436)	<0,01
Sepsis/septic shock	33 (68,75%)	17 (35,42%)	<0,01
Use of furosemide	38 (79,17%)	33(55%)	<0,01
Dose of venous furosemide (mg/day)	51,18±30,89	35,63±20,96	<0,01
Use of vasoactive drugs	19 (39,58%)	16 (26,67%)	0,15
Temperature	36,25±0,82	35,48±3,80	0,17
§ MAP mmHg	89,32±23,03	91,22±24,24	0,68
¶ HR	89,42±17,20	88,30±28,95	0,80
ϒ RR	21,20±6,46	19,93±6,38	0,30
₮ PaO2/FiO2	289,58 (219,43)	295 (171,67)	0,71
Ψ pH	7,35±0,10	7,39±0,08	<0,01
Ƶ Na+ (mEq/L)	140,98±6,77	140,73±4,71	0,83
Hematocrit %	32,74±7,36	32,34±6,05	0,76
Glasgow Coma Scale	8,98±2,81	12,66±2,59	<0,01
WBC (mm^3)	14.850(13.125)	11.600(8.100)	0,02

Continuous variables are expressed as mean±standard deviation. ₮ PaO 2 / FIO 2: WBC (White blood Cells); APACHE II and Fluid balance are expressed as median (IQR). Categorical variables are expressed as percentages and valid N absolute. ¶ HR: heart rate (bpm); ϒ RR: respiratory rate (bpm); Σ PH: hydrogen potential, Z serum Na +: sódio (mEq/L); § MAP: mean arterial pressure (mmHg); ¥ serum K +: potassium (mEq/L). ʊ p value for comparison between death versus no death.

RESULTS

We followed 108 patients, with a mean age of 65.74±17.26 years; women and patients from African descent were more prevalent (Table 1). The overall mortality rate was 44.4% (48/108 patients); in the group with sepsis/septic shock, there was 68% of mortality (33/50 patients) and in the non-sepsis/septic shock group, 32% (18/58 patients). Median APACHE II score for the entire cohort was 18.

We also analyzed the subgroups of sepsis/septic shock (n=50) and non-sepsis/septic shock (n=58) (Table 1). Most patients in this latter group had heart failure or cardiogenic shock diagnosis (47 patients – 43.51%); the other diagnoses in this subgroup were elective surgery (28 patients – 25.93%) and urgency surgery (9 patients – 8.33%). RIFLE I and F were more prevalent in the group of sepsis/septic shock (40% in both) than in the group of non-sepsis/septic shock (25.9% and 17.2%, respectively, p<0.001). Patients in the first group had, also, a higher respiratory and heart rates, leucocyte count, fluid balance and APACHE II score; Glasgow Coma Scale was lower in this group (Table 1).

In the univariate logistic regression model for mortality in the entire cohort, were selected for the multivariate model the following variables: Glasgow Coma Scale, APACHE II, fluid balance, ph, leucometry, sepsis/septic shock, RIFLE F, furosemide use, dose of intravenous furosemide and age (Table 2). In the multivariate logistic regression model for mortality age in years, Glasgow Coma Scale and use of furosemide remained in the final model as independent predictors for death (Table 3).

Table 3. Predictors of intrahospitalar mortality in 108 acute kidney injury patients

Variables	Adjusted odds ratio	Valor de p
Age (years)	1,04	0,04
Sepsis/Septic Shock	1,22	0,78
RIFLE category:Failure	2,93	0,17
Use of furosemide	4,98	0,04
Dose of intravenous furosemide	1,00	0,66
APACHE II	1,03	0,65
Glasglow Coma Scale	0,66	0,01
Fluid balance	1,00	0,26
ph	0,19	0,60
Leucometry	1,00	0,64

We searched for iterations in the multivariate logistic regression model for mortality; however, none attained statistical significance.

We found a moderate correlation between higher serum creatinine and furosemide doses (Spearman's rho=0.40; p=0.01). There was also moderate correlation between duration of furosemide treatment and the higher serum creatinine (Spearman's rho=0.37; p=0.02).

DISCUSSION

Although the mortality rate in the AKI critically ill patients varies widely in the literature, this probably reflects differences in AKI severity, definition and populational characteristics. Also, the use of the creatinine or urine RIFLE criteria results in different incidence and mortality rates. However, the majority of studies report an average mortality rate close to 50%[12-14]. In this work we found an overall mortality rate of 44.4%; we attribute to a higher percent of RIFLE R (40%) and I (30%) the lower mortality rate compared to previous reports, as we had milder AKI cases[8].

We found a high percent of septic etiology of AKI; indeed, sepsis is nowadays considered the main cause of AKI in the ICU setting. Also, the second most common AKI etiology in this cohort, heart failure and cardiogenic shock, is an AKI precipitant commonly reported in the literature; another feature in our cohort is the advanced mean age of the patients[15]. According to racial distribution of our population, there was a majority of african descents (76.9%)[16].

In the multivariate analysis for mortality, we found as independent predictors: age, furosemide use and Glasgow Coma Scale (Table 3). Age, septic etiology of AKI, RIFLE F, need for dialysis and extra-renal organ failure has been described as risk factors for mortality in critically ill AKI patients[17-22]. Metha et al., previously reported furosemide as predictor of mortality in a cohort of AKI patients; possible explanations for the associations observed include a direct toxic effect of diuretics, or untoward effects secondary to delaying initiation of dialysis[2].

Nowadays, it is considered that early fluid administration can help preventing or minimizing AKI[23]. However, recent observational studies found that excessive fluid overload may have a negative influence on kidney function and mortality[24-26]. In our cohort, we found higher fluid balance in the septic group; probably this is due to sepsis treatment. In accordance with the literature, the fluid balance was higher in the group of non-survivors (Table 2).

The literature reports that furosemide use also predicts a worse prognosis in patients with heart failure; this association is probably explained by the continuous stimulation of the renine-angiotensine system[3]. Aldosterone is also important in the pathophysiology of heart failure, as it promotes retention of sodium, the loss of magnesium and potassium, sympathetic activation and myocardial and vascular fibrosis, potentially contributing to a higher risk of sudden death in these patients.

The ESCAPE study suggested that intravenous furosemide dosage, specially above 300mg/day, is associated to higher in-hospital mortality and six-month re-admission rate in heart failure patients, even when adjusted for confounding factors[3]. In our analyses, we found a moderate correlation between furosemide dose and higher serum creatinine.

Despite being a prospective cohort, our work has several limitations. It is a single center study involving a relatively small number of patients; also, we found non-homogeneous groups. Altough our data points to an association between furosemide and mortality, studies with more homogeneous of septic and

non-septic patients, as well as with and without heart failure are welcomed to explore our findings in these subgroups.

CONCLUSION

In a cohort of 108 critically ill AKI patients, we found that age, use of furosemide and Glasgow Coma Scale were independent predictors of mortality; also, there was a moderate correlation between dosis, duration of furosemide treatment and the higher serum creatinine. In this scenario, our findings underscore the complex relationship between diuretic use and mortality in AKI; their role in treating and preventing AKI certainly needs better evaluation.

REFERENCES

1. Bagshaw SM, Laupland KB, Doing CJ, Mortis G, Fick GH, Mucenski M, et al. Prognosis for long-term survival and renal recovery in critically ill patients with severe acute renal failure: a population-based study. Crit Care Med. 2005;9:R700-R709.
2. Mehta RL, Pascual MT, Soroko S, Chertow GM. Diuretics, mortality and nonrecovery of renal function in acute renal failure. JAMA. 2002;288(20):2547-53.
3. Hasselblad V, Gattis Stough W, Shah MR, Lokhnygina Y, O'Connor CM, Califf RM, et al. Relation between dose of loop diuretics and outcomes in a heart failure population: results of the ESCAPE trial. Eur J Heart Fail. 2007;9(10):1064-9.
4. Cantarovich F, Rangoonwala B, Lorenz H, Verho M, Esnault VL. High-Dose Flurosemide in Acute Renal Failure Study Group. High-dose furosemide for established ARF: a prospective, randomized, double-blind, placebo controlled, multicenter trial. Am J Kidney Dis. 2004;44(3):402-9. Comment in: Am J Kidney Dis. 2005;45(4):786; autor reply 786-7.
5. Levi TM, Rocha MS, Almeida DN, Martins RT, Silva MG, Santana NC, et al. Furosemide is associated with acute kidney injury in critically ill patients. Braz J Med Biol Res. 2012;45(9):827-33.
6. Ho KM, Sheridan DJ. Meta-analysis of furosemide to prevent or treat acute renal failure. BMJ. 2006;333(7565):420. Comment in: BMJ. 2006; 333(7565):406-7.
7. KDIGO Clinical Practice Guideline for Acute Kidney Injury. Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. Kidney Int Suppl [Internet]. 2012 [cited 2013 Jun 21];2 (Suppl 1):1-138.Available from: http://www.kdigo.org/clinical_practice_guidelines/pdf/KDIGO%20AKI%20Guideline.pdf
8. Hoste EA, Clermont G, Kersten A, Venkataraman R, Angus DC, De Bacquer D, et al. RIFLE criteria for acute kidney injury are associated with hospital mortality in critically ill patients: a cohort analysis. Crit Care Med. 2006;10(3):R73.
9. Uchino S, Doig GS, Bellomo R, Morimatsu H, Morgera S, Schetz M, Tan I, Bouman C, Nacedo E, Gibney N, Tolwani A, Ronco C, Kellum JA; Beginning and Ending Supportive Therapy for the Kidney (B.E.S.T. Kidney) Investigators. Diuretics and mortality in acute renal failure. Crit Care Med. 2004;32(8):1669-77. Comment in: Crit Care Med. 2005;33(4):917; author reply 917; Crit Care Med. 2004;32(8):1794-5.
10. Mehta RL, Kellum JA, Shah SV, Molitoris BA, Ronco C, Warnock DG, Levi A; Acute Kidney Injury Network. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. Crit Care Med. 2007;11(2):R31. Comment in: Crit Care. 2008;12(4):423; author reply 423.
11. Dellinger RP, Levy MM, Carlet JM, Bion J, Parker MM, Jaeschke R, Reinhart K, Angus DC, Brun-Buisson C, Beale R, Calandra T, Dhainaut JF, Gerlach H, Harvey M, Marini JJ, Marshall J, Ranieri M, Ramsay G, Sevransky J, Thompson BT, Townsend S, Vender JS, Zimmerman JL, Vincent JL; International Surviving Sepsis Campaign Guidelines Committee; American Association of Critical-Care Nurses; American College of Chest Physicians; American College of Emergency Physicians; Canadian Critical Care Society; European Society of Clinical Microbiology and Infectious Diseases; European Society of Intensive Care Medicine; European Respiratory Society; International Sepsis Forum; Japanese Association for Acute Medicine; Japanese Society of Intensive Care Medicine; Society of Critical Care Medicine; Society of Hospital Medicine; Surgical Infection Society; World Federation of Societies of Intensive and Critical Care Medicine. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. Crit Care Med. 2008;36(1):296-327. Erratum in: Crit Care Med. 2008;36(4):1394-6.
12. Liaño F, Junco E, Pascual J, Madero R, Verde E. The spectrum of acute renal failure in the intensive care unit compared with that seen in other settings. The Madrid Acute Renal Failure Study Group. Kidney Int Suppl. 1998;66:S16-24.
13. De Mendonça A, Vincent JL, Suter PM, Moreno R, Dearden NM, Antonelli M, et al. Acute renal failure in the ICU: risk factors and outcome evaluated by the SOFA score. Intensive Care Med. 2000;26(7):915-21.
14. Barretti P, Soares VA. Acute renal failure: clinical outcome and causes of death. Ren Fail. 1997;19(2):253-7.
15. Ali T, Khan I, Simpson W, Prescott G, Townend J**,** Smith W, et al. Incidence and outcomes in acute kidney injury: a comprehensive population-based study. J Am Soc Nephrol. 2007;18(4):1292-81298
16. Suarez-Kurtz G. Pharmacogenomics and the genetic diversity of the Brazilian population. Cad Saude Publica. 2009;25(8):1650-1.
17. Bagshaw SM, Uchino S, Bellomo R, Morimatsu H, Morgera S, Schetz M, Tan I, Bouman C, Macedo E, Gibney N, Tolwani A, Oudemans-van Straaten HN, Ronco C, Kellum JA; Beginning and Ending Supportive Therapy for the Kidney (BEST Kidney) Investigators. Septic acute kidney injury in critically ill patients: clinical characteristics and outcomes. Clin J Am Soc Nephrol. 2007;2(3):431-9.
18. Uchino S, Bellomo R, Goldsmith D, Bates S, Ronco C. An assessment of the RIFLE criteria for acute renal failure in hospitalized patients. Crit Care Med. 2006;34(7):1913-17. Comment in: Crit Care Med. 2006; 34(7):2016-7.
19. Bagshaw SM, George C, Bellomo R; ANZICS Database Management Committee. Early acute kidney injury and sepsis: a multicentre evaluation. Crit Care Med. 2008;12(2):R47.
20. Chertow GM, Soroko SH, Paganini EP, Cho KC, Himmelfarb J, Izikler TA, et al. Mortality after acute renal failure: Models for prognostic stratification and risk adjustment. Kidney Int. 2006;70(6)1120-6.
21. Ostermann M, Chang RW. Acute kidney injury in the intensive care unit according to RIFLE. Crit Care Med. 2007;35(8):1837-43. Comment in: Crit Care Med. 2007;35(11):2669; author reply 2669-70.
22. Lin CY, Chen YC, Tsai FC, Tian YC, Jenq CC, Fang JT, et al. RIFLE classification is predictive of short-term prognosis in critically ill patients with acute renal failure supported by extracorporeal membrane oxygenation. Nephrol Dial Transpl. 2006;21(10):2867-73.
23. Nadeau-Fredette AC, Bouchar J. Fluid management and use of diuretics in acute kidney injury. Adv Chronic Kidney Dis. 2013;20(1) 45-55.

24. Bouchard J, Soroko SB, Chertow GM, Himmelfarb J, Ikizler TA, Paganini EP, Mehta RL; Program to Improve Care in Acute Renal Disease (PICARD) Study Group. Fluid accumulation, survival and recovery of kidney function in critically ill patients with acute kidney injury. Kidney Int. 2009;76(4):422-7.
25. Payen D, de Pont AC, Sakr Y, Spies C, Reinhart K, Vicent JL; Sepsis Occurrence in Acutely III Patients (SOAP) Investigators. A positive fluid balance is associated with a worse outcome in patients with acute renal failure. Crit Care. 2008;12(3):R74. Comment in: Nat Clin Pract Nephrol. 2009;5(1):10-1; Crit Care. 2008;12(4):169.
26. Heung M, Wolfgram DF, Kommareddi M, Hu Y, Song PX, Ojo AO. Fluid overload at initiation of renal replacement therapy is associated with lack of renal recovery in patients with acute kidney injury. Nephrol Dial Transplant. 2012;27(3):956-61. Comment in: Nephrol Dial Transplant. 2011;26(12):4150; author reply 4150-1.