Title
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Journal
Cancer, 116(17)

ISSN
0008-543X

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Publication Date
2010-09-01

DOI
10.1002/cncr.25306

Original Article

Predictors and Outcome of Acute Kidney Injury in Patients With Acute Myelogenous Leukemia or High-Risk Myelodysplastic Syndrome

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BACKGROUND: Acute kidney injury (AKIis a common complication in the treatment of patients with acute myelogenous leukemia (AML) or high-risk myelodysplastic syndrome (HR-MDS), but, to the authors' knowledge, its clinical relevance has not been detailed to date. The objective of the current study was to identify the incidence, predictors, and outcome for AKI in patients with AML and HR-MDS. **METHODS:** Data were analyzed from 537 patients with AML or HR-MDS undergoing induction chemotherapy from 1999 to 2007. Predictors for AKI were identified by logistic regression. Eight-week mortality of patients was estimated by the Kaplan-Meier method stratified by the RIFLE criteria, a novel multilevel classification system for AKI based on the percent rise in serum creatinine from baseline (Risk, >50%; Injury, >100%; and Failure, >200% or requiring dialysis). **RESULTS:** A total of 187 patients (36%) developed AKI. Significant independent risk factors for AKI included the following: age ≥55 years (odds ratio [OR], 1.8), mechanical ventilation (OR, 16), use of vancomycin (OR, 2.3), diuretics (OR, 3.0), amphotericin B lipid formulation (OR, 2.7), vasopressors (OR, 4.9), leukopenia (OR, 1.9), hypoalbuminemia (OR, 1.4), and use of non-fludarabine–based chemotherapy (OR, 2.7). The 8-week mortality rates were 3.8%, 13.6%, 19.6%, and 61.7% for the non-RIFLE, Risk, Injury, and Failure categories, respectively. Patients requiring dialysis (8%) had a median survival of 33 days. Survival of patients who achieved complete remission was favorable, regardless of degree of AKI. **CONCLUSIONS:** The RIFLE classification for AKI appears to have prognostic utility in predicting mortality in patients with AML or HR-MDS. Relatively mild elevations in creatinine are associated with higher mortality. Strategies to avoid nephrotoxic drugs or fluid overload may be of benefit. ***Cancer*** **2010;116:4063–8.** © *2010 American Cancer Society.*

KEYWORDS: acute kidney failure, acute myeloid leukemia, myelodysplastic syndrome, dialysis, logistic models.

Over the past several years, important advances have occurred in the treatment and supportive care of patients with hematologic malignancies. However, acute kidney injury (AKI) remains a common complication. The development of AKI can limit further cancer treatment, increase the toxicity of chemotherapy and reduce its delivery, and exclude patients from clinical trials. Recognized causes of AKI include tumor lysis syndrome, acute tubular necrosis from medications or sepsis, volume depletion, and direct leukemic infiltration. AKI is a negative prognostic factor for overall survival,[1,2] and the need for hemodialysis is associated with a poor prognosis.[3,4]

Elevation in serum creatinine has traditionally been used as a marker of AKI. However, patients with cancer often have decreased creatinine production secondary to cachexia, which may limit the sensitivity of creatinine as a marker of kidney injury. Other variables including total body volume, ethnicity, medications, and protein intake may also affect serum creatinine independent of renal function. Therefore, using an arbitrary level of serum creatinine as a marker of AKI (ie, >1.5 or 2.0 mg/dL) may not be adequate. Greater than 35 different definitions of AKI have been used in the literature, which has made cross-comparisons between studies difficult.

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DOI: 10.1002/cncr.25306, **Received:** October 7, 2009; **Revised:** February 3, 2010; **Accepted:** February 9, 2010, **Published online** May 28, 2010 in Wiley InterScience (www.interscience.wiley.com)

What may be a more accurate measure of kidney injury is a classification system based on percent rise in serum creatinine *relative* to baseline. One such model is the RIFLE classification, which defines 3 levels of AKI: Risk (>50% rise in serum creatinine), Injury (>100% rise in serum creatinine), and Failure (>200% rise in serum creatinine).[5] The prognostic value of the RIFLE classification has been validated in numerous studies, but to the best of our knowledge has not been evaluated in patients with acute leukemia. No recent studies have examined the incidence, risk factors, and outcomes of AKI in patients with acute leukemia. The objective of this analysis is to estimate the incidence of AKI in patients with acute myelogenous leukemia (AML) or high-risk myelodysplastic syndrome (HR-MDS) undergoing induction chemotherapy and to evaluate the risk factors for AKI.

MATERIALS AND METHODS

The study included all patients aged ≥16 years with AML or HR-MDS (bone marrow with >10% blasts) who underwent induction chemotherapy in the Department of Leukemia at The University of Texas M. D. Anderson Cancer Center from 1999 through 2007. Patients with a baseline serum creatinine >1.5 mg/dL were excluded from the analysis. The protocol was approved by the Institutional Review Board. Institutional databases used included the Protocol Data Management System, Enterprise Information Warehouse, and the Department of Pharmacy databases. The data were incorporated into a single spreadsheet using Excel 12.2 for Mac (Microsoft, Seattle, Wash).

Statistical Analysis

Descriptive data were presented as medians with interquartile ranges for continuous variables and as absolute numbers with percentages for categorical variables. Correlated data were assessed by correlation coefficients, and no variables were significantly correlated >0.6. Baseline demographic and clinical data were analyzed in a multivariate logistic regression model using the backward stepwise selection method. The primary endpoint for logistic regression was AKI defined as at least a 50% rise in serum creatinine relative to baseline during induction chemotherapy. Overall model fit was assessed by the likelihood ratio test. Ten-fold cross-validation deleting one-tenth of observations was used to test model robustness, with area under the receiver operating characteristic (AUROC) curve calculated to assess the predictive ability of the model. A similarly cross-validated Hosmer-Lemeshow chi-square statistic was used to assess calibration. Model specification and linearity of predictor variables were tested and found to be intact. For survival analysis, AKI was further defined by the RIFLE criteria into degrees of severity of kidney injury: Risk (>50% rise in serum creatinine), Injury (>100% rise in serum creatinine), and Failure (>200% rise in serum creatinine). Patients who required dialysis were automatically classified into the RIFLE-Failure category, regardless of the percent rise in creatinine. Mortality at 8 weeks was assessed for patients with and without AKI as defined by the RIFLE criteria by the Kaplan-Meier method. Survival curves were stratified by disease response (complete remission [CR] vs no CR). Patients were censored at death or last known follow-up, as determined by the clinical record. A 2-tailed P value <.05 was considered statistically significant. No patients were excluded from the analysis because of missing data. Statistical analysis was performed with Stata 10 for Macintosh (StataCorp, College Station, Tex).

RESULTS

The patient characteristics are presented in Table 1. The median age was 56 years (range, 17-84 years). Nearly all the patients (98%) received high-dose cytarabine (HD-AC) -containing regimens as induction chemotherapy. Approximately 60% of the patients achieved CR, and 4.5% achieved CR with persistent thrombocytopenia. The median time to CR was 30 days (range, 18-144 days).

AKI, defined as a 50% rise in serum creatinine, developed in 187 patients (36%). The median time to the development of AKI was 18 days (range, 2-95 days). All factors were found to be significant predictors of AKI on univariate analysis except gender, ethnicity, underlying disease, and baseline platelet count. Using backward stepwise logistic regression, variables that remained significant predictors of AKI in the adjusted model were as follows: age ≥55 years; mechanical ventilation; vasopressors; low white blood cell count (WBC); hypoalbuminemia; non-fludarabine–based regimens; and the use of intravenous (iv) diuretics, vancomycin, and amphotericin B lipid formulation. Factors that were no longer found to be significant in the multivariate model were aminoglycosides, underlying disease, Zubrod performance status, infection at the start of chemotherapy, iv contrast, and baseline bilirubin level. Although not statistically significant, gender was kept in the final model as it was believed to be clinically relevant. The model was determined to be statistically robust and appropriately calibrated (Table 2).

By further defining AKI by the RIFLE criteria, we classified 15%, 10%, and 11% of patients into the RIFLE-Risk, Injury, and Failure categories, respectively (Table 3). The median elevation in creatinine from baseline was 0.6 mg/dL, 1.0 mg/dL, and 2.1 mg/dL, respectively. We found that 64% of patients did not develop AKI, and the 8-week mortality of these patients was 4%. In comparison, there was a stepwise increase in mortality at 8 weeks for patients with higher degrees of renal injury: 13.6%, 19.6%, and 61.7% for the RIFLE-Risk, -Injury, and -Failure categories, respectively ($P < .001$ compared with non-AKI category). When stratified by disease response, the effect of AKI on mortality was predominantly observed in patients who did not achieve CR (Fig. 1).

Table 1. Patient Characteristics

Characteristic	Value
Median age (range), y	56 (17-84)
Gender, no. (%)	
Male	281 (52)
Female	256 (48)
Race, no. (%)	
Caucasian	427 (80)
African American	38 (13)
Other	72 (7)
Mechanical ventilation, no. (%)[a]	43 (8)
Vasopressors, no. (%)[a]	41 (8)
Diuretics, no. (%)[a]	315 (59)
Vancomycin, no. (%)[a]	281 (52)
Amphotericin B, no. (%)[a]	234 (44)
Aminoglycosides, no. (%)[a]	38 (7)
Intravenous contrast, no. (%)[a]	85 (16)
Underlying disease	
AML, no. (%)	473 (88)
HR-MDS, no. (%)	64 (12)
Zubrod performance status, no. (%)	
0-2	523 (97)
3-4	14 (3)
Presence of infection at initiation of chemotherapy, no. (%)	69 (13)
Median baseline platelet count (range), k/uL	50 (4-676)
Median baseline WBC count (range), k/uL	5.3 (0.3-248.4)
Median baseline albumin (range), gm/dL	3.3 (1.7-5.3)
Median baseline bilirubin (range), mg/dL	0.6 (0.1-4.7)
Chemotherapy	
Fludarabine + HD-AC, no. (%)	92 (17)
Clofarabine + HD-AC, no. (%)	56 (10)
Cyclophosphamide + topotecan + HD-AC, no. (%)	46 (9)
Daunorubicin + HD-AC, no. (%)	86 (16)
Idarubicin + HD-AC, no. (%)	248 (46)
Miscellaneous regimen, no. (%)	9 (1.7)

AML indicates acute myelogenous leukemia; HR-MDS, high-risk myelodysplastic syndrome; WBC, white blood cell count; HD-AC, high-dose cytarabine.
[a] Included if patient received therapy at anytime from induction to date of maximum creatinine.

Table 2. Univariate and Multivariate Logistic Regression for Predictors of AKI

	Univariate Analysis	Multivariate Analysis		
	P	OR	95% CI	*P*
Age ≥55 y	<.001	1.8	1.1-2.8	.012
Male vs female	.42	0.9	0.6-1.4	.59
Black vs white	.28			
Cytogenetics				
Favorable vs normal	.001			
Unfavorable vs normal	.001			
Other vs white	.39			
Mechanical ventilation	<.001	16	3-75	<.001
Vasopressors	<.001	4.9	1.3-19	.021
Intravenous diuretics	<.001	3.0	1.8-4.8	<.001
Vancomycin	<.001	2.3	1.4-3.9	.002
Amphotericin B	<.001	2.7	1.6-4.4	<.001
Aminoglycosides	.027			
HR-MDS vs AML	.091			
Zubrod performance status (3-4 vs 0-2)	.003			
Infection	<.001			
Intravenous contrast	.002			
Platelet count	.69			
WBC	.002	1.9	1.1-3.4	.028
Albumin	<.001	0.7	0.5-0.99	.049
Bilirubin	.001			
Non-fludarabine-based regimen	<.001	2.7	1.3-5.5	.008

AKI indicates acute kidney injury; OR, odds ratio; 95% CI, 95% confidence interval; HR-MDS, high-risk myelodysplastic syndrome; AML, acute myelogenous leukemia; WBC, white blood cell count.

Table 3. Kaplan-Meier Estimates of 8-Week Mortality by RIFLE Category

	Initial Cr[a]	Maximum Cr[a]	No. of Patients (%)	8-Week Mortality	95% CI
No AKI	0.9	1.0	345 (64)	3.8%	2.2-6.4%
RIFLE–Risk	0.9	1.5	81 (15)	13.6%	7.8-23%
RIFLE–Injury	0.8	1.8	51 (10)	19.6%	11-33%
RIFLE-Failure	0.9	3.0	60 (11)	61.7%	50-74%

RIFLE indicates a classification system that defines 3 levels of acute kidney injury (AKI): Risk (>50% rise in serum creatinine), Injury (>100% rise in serum creatinine), and Failure (>200% rise in serum creatinine); Cr, serum creatinine; 95% CI, 95% confidence interval.
[a] Median values.

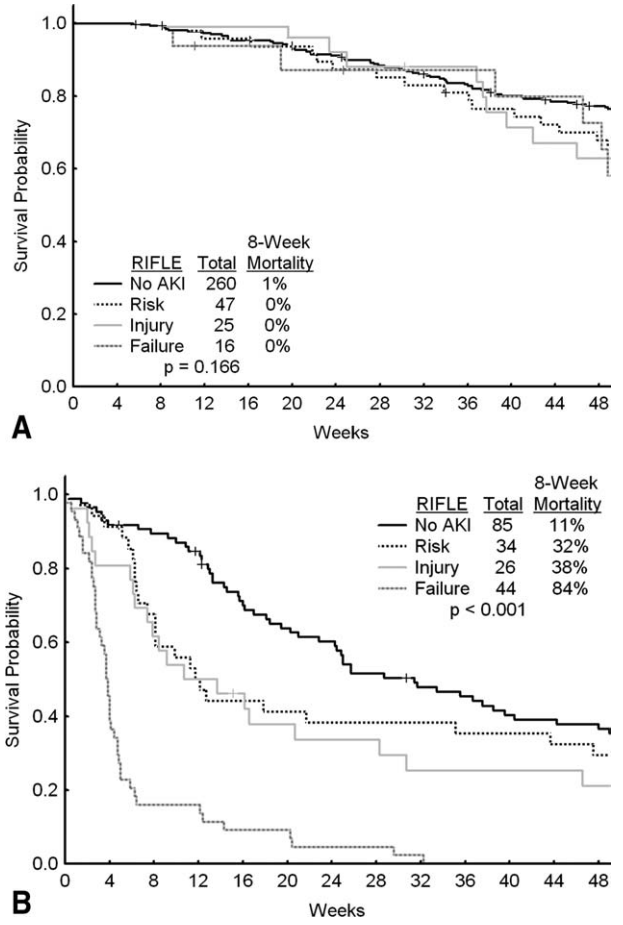

Figure 1. Kaplan-Meier estimates of patient survival stratified by disease response: (A) complete disease remission and (B) no complete remission. RIFLE indicates a classification system that defines 3 levels of acute kidney injury (AKI): Risk (>50% rise in serum creatinine), Injury (>100% rise in serum creatinine), and Failure (>200% rise in serum creatinine).

Dialysis was required in 8% of patients (43 of 537 patients). Survival of patients who required dialysis was poor, with a median survival of 33 days. Among the RIFLE-Failure category, the 8-week mortality was similar between patients who required dialysis and those who did not (60% vs 65%, respectively; $P = .7$).

DISCUSSION

To the best of our knowledge, the current study is the largest reported study of patients with hematologic malignancies who develop AKI published to date. We found that AKI, defined as a 50% rise in creatinine from baseline, was present in 36% of patients with AML and HR-MDS undergoing induction chemotherapy. We also determined that patients with mild renal injury (RIFLE-Risk category) had a significantly higher mortality rate than patients without AKI, although the effect of AKI on mortality was noted mainly in patients who did not achieve CR. We also identified several predictors of AKI: age >55 years; mechanical ventilation; vasopressors; low WBC; hypoalbuminemia; use of vancomycin, diuretics, and amphotericin B lipid formulations; and use of non-fludarabine–based chemotherapy. In our analysis, patients who achieved CR had a favorable outcome regardless whether renal failure was present. This is not unexpected considering that the same clinical features that predict for the development of renal failure are associated with the probability of achieving CR. These features include age and type of chemotherapy. However, the probability of achieving CR was significantly lower for patients who developed renal failure (41%) compared with those without renal failure (71%; $P < .001$). Thus, CR is still the most important predictor of long-term survival. The survival of patients who required dialysis after induction chemotherapy was extremely poor.

The findings in the current study are in agreement with other studies examining the utility of the RIFLE classification system as a prognostic model for AKI. Lopes et al found a similar stepwise decrease in overall survival with worsening RIFLE class in patients undergoing stem cell transplantation.[6] Several studies in patients without cancer have demonstrated a similar relation between RIFLE class and mortality among patients in the intensive care unit (ICU) after cardiac surgery, with burn injury, and after liver transplantation.[7-11] To the best of our knowledge, the current study is the first to report the utility of the RIFLE criteria in patients with acute leukemia. By using the RIFLE criteria, we have emphasized that relatively mild elevation in creatinine as small as 0.6 mg/dL (RIFLE-Risk category) were associated with a significantly higher mortality rate.

The current study findings are also consistent with prior studies of AKI in patients with hematologic malignancies. As in our present study, age, sepsis, and nephrotoxic drugs have been previously reported to be predictors of AKI.[2,12] In contrast with the results of Munker et al, we did not find male gender to be a significant risk factor.[13] Others have reported an incidence of AKI in 15% to 40% of patients with acute leukemia,[13,14] which is lower than the incidence of 36% reported in the current study. However, a more conservative definition for AKI was used in these studies, such as doubling of serum creatinine or an absolute value >3.4 mg/dL. The incidence of AKI in these studies, when defined by the RIFLE criteria, was

likely higher than reported. Benoit et al found that critically ill patients with hematologic malignancies who were receiving dialysis had a higher incidence of ICU stays and hospitalizations and higher 6-month mortality rates compared with patients without hematologic malignancies.[15] Further studies have reported a 84% to 96% hospital mortality rate in patients with hematologic malignancies who required dialysis.[3,4,15] In comparison, the lower mortality of patients in the current study (60% at 8 weeks) may be reflective of improvements in renal replacement therapy, critical care, and leukemia treatment.

The findings of the current study highlight the potential benefit of avoiding nephrotoxic drugs. Several alternatives to amphotericin, which have less renal toxicity, have recently become available, such as the echinocandin class of antifungal drugs. These newer antifungal drugs should help decrease the incidence of AKI. Vancomycin use was also found to be a strong predictor of AKI in the current study, which may reflect residual confounding but may also suggest a direct causal effect, because vancomycin nephrotoxicity has been described in several studies.[16-20] In addition, dosing guidelines for the treatment of methicillin-resistant *Staphylococcus aureus* calling for higher trough levels (15-20 mg/L) have required increased doses of vancomycin, which may increase nephrotoxicity.[21] Others have reported that vancomycin doses >4 g/day[19] and serum trough levels >15 mg/L[20] were associated with AKI. However, to the best of our knowledge, a physiologic basis for direct injury has yet to be delineated. It is possible that the use of alternative drugs such as linezolid or daptomycin may also reduce the incidence of AKI in this setting.

There was a strong correlation noted between mechanical ventilation and diuretics with AKI in the current study. Many patients with acute leukemia develop acute lung injury secondary to infectious etiologies. However, mechanical ventilation and diuretic use may also reflect fluid overload secondary to aggressive hydration during induction chemotherapy. A positive cumulative fluid balance has been associated with increased mortality in other clinical settings such as acute lung injury, sepsis, and stem cell transplantation.[22-27] Several studies have demonstrated a physiologic relation between acute lung injury and AKI by means of systemic cytokine release.[28,29] A conservative fluid management strategy or fluid removal by ultrafiltration may limit a positive cumulative fluid balance, and thereby prevent the need for mechanical ventilation and diuretics. Whether this also indirectly decreases the incidence of AKI is of interest.

The use of chemotherapy regimens including anthracyclines or topoisomerase I to II reactive agents was associated with an independently higher risk of AKI. Our experience to date has indicated that regimens containing fludarabine and cytarabine are perhaps less toxic than other regimens, an observation supported by this analysis. This regimen is gentler than others on the gastrointestinal mucosa, the disruption of which can lead to infection and a cascade of events that may result in AKI and other organ failures.

The current study incorporated a relatively large cohort of patients, likely to be representative of patients seen in current clinical practice. We included a statistically robust logistic regression model that was internally cross-validated. The predictive ability of the model was respectable as determined by relatively large AUROC curve.

This study has some limitations. First, it is retrospective in nature, and any conclusions should be interpreted as exploratory in nature. Second, we were limited by the data that were already collected in the database. As such, there may still be residual confounding, which we could not ascertain. For example, there were no data concerning uric acid levels, which may cause AKI in the setting of tumor lysis syndrome. However, the advent of rasburicase has made this less problematic, and perhaps not as relevant to current clinical practice. Lastly, we were unable to externally validate our findings in a separate data set. Other studies would be needed to corroborate our findings.

In summary, the RIFLE classification for AKI has utility for mortality risk stratification in patients with acute leukemia undergoing induction chemotherapy. However, patients who achieve CR generally have a good prognosis regardless of the degree of renal injury. We were able to identify several predictors for AKI, and less nephrotoxic therapies may decrease the incidence of AKI. Amphotericin and vancomycin are strong predictors of AKI, and alternative drugs may be a consideration in the treatment of infections. In addition, a more conservative fluid management approach may decrease the need for mechanical ventilation and diuretic use, which may indirectly prevent AKI. Prospective studies would be needed to determine whether these strategies will actually decrease the incidence of AKI.

CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

REFERENCES

1. Scott CS, Stark AN, Limbert HJ, Master PS, Head C, Roberts BE. Diagnostic and prognostic factors in acute monocytic leukaemia: an analysis of 51 cases. *Br J Haematol.* 1988;69: 247-252.

2. Harris KP, Hattersley JM, Feehally J, Walls J. Acute renal failure associated with haematological malignancies: a review of 10 years experience. *Eur J Haematol.* 1991;47:119-122.
3. Lanore JJ, Brunet F, Pochard F, et al. Hemodialysis for acute renal failure in patients with hematologic malignancies. *Crit Care Med.* 1991;19:346-351.
4. Brunet F, Lanore JJ, Dhainaut JF, et al. Is intensive care justified for patients with haematological malignancies? *Intensive Care Med.* 1990;16:291-297.
5. Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P. Acute renal failure - definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. *Crit Care.* 2004; 8:R204-R212.
6. Lopes JA, Jorge S, Silva S, et al. An assessment of the RIFLE criteria for acute renal failure following myeloablative autologous and allogeneic haematopoietic cell transplantation. *Bone Marrow Transplant.* 2006;38:395.
7. Ostermann M, Chang RW. Acute kidney injury in the intensive care unit according to RIFLE. *Crit Care Med.* 2007; 35:1837-1843; quiz 1852.
8. Kuitunen A, Vento A, Suojaranta-Ylinen R, Pettila V. Acute renal failure after cardiac surgery: evaluation of the RIFLE classification. *Ann Thorac Surg.* 2006;81:542-546.
9. Coca SG, Bauling P, Schifftner T, Howard CS, Teitelbaum I, Parikh CR. Contribution of acute kidney injury toward morbidity and mortality in burns: a contemporary analysis. *Am J Kidney Dis.* 2007;49:517-523.
10. Guitard J, Cointault O, Kamar N, et al. Acute renal failure following liver transplantation with induction therapy. *Clin Nephrol.* 2006;65:103-112.
11. O'Riordan A, Wong V, McQuillan R, McCormick PA, Hegarty JE, Watson AJ. Acute renal disease, as defined by the RIFLE criteria, post-liver transplantation. *Am J Transplant.* 2007;7:168-176.
12. Eckman LN, Lynch EC. Acute renal failure in patients with acute leukemia. *South Med J.* 1978;71:382-385.
13. Munker R, Hill U, Jehn U, Kolb HJ, Schalhorn A. Renal complications in acute leukemias. *Haematologica.* 1998;83: 416-421.
14. Cordonnier C, Vernant JP, Brun B, et al. Acute promyelocytic leukemia in 57 previously untreated patients. *Cancer.* 1985;55:18-25.
15. Benoit DD, Hoste EA, Depuydt PO, et al. Outcome in critically ill medical patients treated with renal replacement therapy for acute renal failure: comparison between patients with and those without haematological malignancies. *Nephrol Dial Transplant.* 2005;20:552-558.
16. Wicklow BA, Ogborn MR, Gibson IW, Blydt-Hansen TD. Biopsy-proven acute tubular necrosis in a child attributed to vancomycin intoxication. *Pediatr Nephrol.* 2006;21:1194-1196.
17. Sokol H, Vigneau C, Maury E, Guidet B, Offenstadt G. Biopsy-proven anuric acute tubular necrosis associated with vancomycin and one dose of aminoside. *Nephrol Dial Transplant.* 2004;19:1921-1922.
18. Lodise TP, Patel N, Lomaestro BM, Rodvold KA, Drusano GL. Relationship between initial vancomycin concentration-time profile and nephrotoxicity among hospitalized patients. *Clin Infect Dis.* 2009;49:507-514.
19. Lodise TP, Lomaestro B, Graves J, Drusano GL. Larger vancomycin doses (at least four grams per day) are associated with an increased incidence of nephrotoxicity. *Antimicrob Agents Chemother.* 2008;52:1330-1336.
20. Jeffres MN, Isakow W, Doherty JA, Micek ST, Kollef MH. A retrospective analysis of possible renal toxicity associated with vancomycin in patients with health care-associated methicillin-resistant Staphylococcus aureus pneumonia. *Clin Ther.* 2007;29:1107-1115.
21. Mohr JF, Murray BE. Point: vancomycin is not obsolete for the treatment of infection caused by methicillin-resistant Staphylococcus aureus. *Clin Infect Dis.* 2007;44:1536-1542.
22. Wiedemann HP, Wheeler AP, Bernard GR, et al. Comparison of two fluid-management strategies in acute lung injury. *N Engl J Med.* 2006;354:2564-2575.
23. Sakr Y, Vincent JL, Reinhart K, et al. High tidal volume and positive fluid balance are associated with worse outcome in acute lung injury. *Chest.* 2005;128:3098-3108.
24. Payen D, de Pont AC, Sakr Y, Spies C, Reinhart K, Vincent JL. A positive fluid balance is associated with a worse outcome in patients with acute renal failure. *Crit Care.* 2008;12:R74.
25. Mehta RL. Fluid balance and acute kidney injury: the missing link for predicting adverse outcomes? *Nat Clin Pract Nephrol.* 2009;5:10-11.
26. Dickout WJ, Chan CK, Hyland RH, et al. Prevention of acute pulmonary edema after bone marrow transplantation. *Chest.* 1987;92:303-309.
27. Vincent JL, Sakr Y, Sprung CL, et al. Sepsis in European intensive care units: results of the SOAP study. *Crit Care Med.* 2006;34:344-353.
28. Paladino JD, Hotchkiss JR, Rabb H. Acute kidney injury and lung dysfunction: a paradigm for remote organ effects of kidney disease? *Microvasc Res.* 2009;77:8-12.
29. Rabb H, Wang Z, Nemoto T, Hotchkiss J, Yokota N, Soleimani M. Acute renal failure leads to dysregulation of lung salt and water channels. *Kidney Int.* 2003;63:600-606.