Effectiveness of liposomal amphotericin B in patients admitted to the ICU on renal replacement therapy

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ABSTRACT

Introduction. This study was designed to compare the effectiveness of liposomal amphotericin B (L-AmB) in ICU patients with and without renal replacement therapy (RRT).

Methods. Observational, retrospective, comparative and multicenter study conducted in critically ill patients treated with L-AmB for 3 or more days, divided into two cohorts depending on the use of RRT before or within the first 48 hours after starting L-AmB. Clinical and microbiological response at the end of treatment was evaluated.

Results. A total of 158 patients met the inclusion criteria, 36 (22.8%) of which required RRT during the ICU stay. Patients with RRT as compared with those without RRT showed a higher APACHE II score on admission (21.4 *vs* 18.4, $P = 0.041$), greater systemic response against infection ($P = 0.047$) and higher need of supportive techniques ($P = 0.002$). In both groups, main reasons for the use of L-AmB were broad spectrum and hemodynamic instability. A higher daily dose of L-AmB was used in the RRT group (4.30 *vs* 3.84 mg/kg, $P = 0.030$) without differences in the total cumulative dose or treatment duration. There were no differences in the clinical response (61.1% vs 56.6%, $P = 0.953$) or microbiological eradication rate (74.1% *vs* 64.6%, $P = 0.382$). In patients with proven invasive fungal infection, satisfactory clinical response was obtained in 74.1% and microbiological eradication 85.7%.

Conclusions. Although the study sample is small, this study shows that L-AmB is effective in critically ill patients admitted to the ICU requiring RRT.

Key words: Renal replacement therapy, ICU, liposomal amphotericin B, Clinical efficacy, Microbiological efficacy.

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Efectividad de anfotericina B liposomal en pacientes ingresados en UCI con técnicas de reemplazo renal

RESUMEN

Introducción. Comparar la efectividad de anfotericina B liposomal (L-AmB) en pacientes ingresados en UCI con o sin técnicas de reemplazo renal (TRR).

Métodos. Estudio observacional, retrospectivo, comparativo y multicéntrico realizado en pacientes críticos que han sido tratados con L-AmB durante 3 o más días diferenciándose dos cohortes en función de utilizar TRR (o no) antes o en las primeras 48 horas después de iniciar L-AmB. Se ha evaluado la respuesta clínica y microbiológica al final del tratamiento.

Resultados. Un total de 158 (22,8%) pacientes cumplían los criterios de inclusión, 36 (22,8%) de los cuales precisaron de TRR. Los pacientes con TRR tuvieron mayor APACHE II a su ingreso (21,4 *vs* 18,4; P=0,041), mayor respuesta sistémica a la infección (P=0,047) y mayor necesidad de técnicas de apoyo (P=0,002). No se han observado diferencias en los motivos para indicar L-AmB, predominando la amplitud del espectro y la inestabilidad hemodinámica. La dosis diaria de L-AmB fue mayor en el grupo de TRR (4,30 *vs* 3,84 mg/kg, P=0,030) sin cambios en la duración ni en la dosis total acumulada. No se observaron diferencias en la respuesta clínica satisfactoria (61,1% vs 56,6%, P=0,953) ni en la respuesta microbiológica con erradicación en 74,1 y 64,6% (P=0,382). En pacientes con infección fúngica invasiva la respuesta clínica fue satisfactoria en un 74,1% de los pacientes y hubo erradicación microbiológia en el 85,7%.

Conclusiones. Aunque se trata de una muestra pequeña, se demuestra que L-AmB es efectiva en pacientes críticos ingresados en la UCI que requieren TRR.

Palabras clave: Técnicas de Reemplazo Renal, ICU, Anfotericina B liposomal, Eficacia clínica, Eficacia microbiológica.

INTRODUCTION

The prescription of different formulations of amphotericin B in critically ill patients has decreased in recent years coinciding with the introduction of echinocandins in the market[1]. Liposomal amphotericin B (L-AmB) is the formulation of amphotericin B mostly used at the present time in the Intensive Care Units (ICUs) in Spain. In our country, two retrospective multicenter studies of the use of L-AmB in critically ill patients that have provide information on the profile of patients treated with this agent, indications of treatment, dosage and especially data of the effectiveness and tolerability of L-AmB even in the subgroup of patients with altered renal function at the time of starting the administration of the drug[2,3].

The impact of renal replacement therapy (RRT), either intermittent or continuous RRT procedures, on the effectiveness of L-AmB has been poorly assessed. The techniques of RRT are increasingly being used in critically ill patients for different reasons, such as renal insufficiency, acidosis, hypovolemia, etc. Based on data of the ENVIN-HELICS registry[4], about 6% of patients admitted for more than 24 hours in the ICU underwent RRT. Although studies have been published in the literature regarding changes of pharmacokinetic parameters of different antifungal agents in relation to the use of RRT[5-9], there are a few data on the effectiveness of L-AmB were given to critically ill patients requiring RRT.

The present study is a subanalysis of patients included in the registry of the use of L-AmB in the ICU[2], the objective of which was to assess the clinical characteristics and outcome of patients treated simultaneously with L-AmB and RRT during their ICU stay, and to determine whether there were differences in the effectiveness of L-AmB as compared with patients who did not require RRT.

MATERIALS AND METHODS

Design. This was a nationwide, observational, multicenter and retrospective cohort study of patients treated in the ICU with L-AmB between September 2008 and December 2009. The study cohort included patients (adults or children) admitted to the ICU or resuscitation unit for any reason or indication, who required simultaneously any RRT, intermittent or continuous, prior to or within the first 48 hours of starting treatment with L-AmB. Data of these patients were compared patients admitted to the participating ICUs during the same period of time, treated with L-AmB during 3 days or more who did not require RRT. The study was approved by the Ethics Committee of the participating centers. Written informed consent was obtained from each patient before enrollment in the study.

Case report form. A case report form (CRF) was completed for each patient, whose variables including their definitions have been recently published[2]. All data were obtained by review of the medical records. Indications of L-AmB treatment and need of RRT were not previously protocolized, so that decisions taken by the physicians in charge of the patients. Infections treated with L-AmB were classified as proven, probable, possible or clinical suspicion of infection, and reasons for using L-AmB as one or more of the following: spectrum of activity, site of infection, hemodynamic instability, adherence to national or international therapeutic guidelines, implementation of local protocols, consultant's opinion, isolation of a filamentous fungi, intolerance to other antifungal agents and intolerance to the oral route. In each case, dates of start and end of treatment were recorded as well as reasons of stopping treatment, cumulative dose, change of doses during treatment and reasons for change. Techniques of RRT, days of use and reason(s) for use were also recorded.

Definition of dependent variables. Clinical response was evaluated as cure, improvement, stable or failure. Clinical response was considered satisfactory in case of improvement or cure. Microbiological response was classified as eradication, persistence and missed follow-up. Clinical and microbiological assessments were performed at the end of L-AmB treatment and in all patients included (intention-to-treat) independently of whether infections were classified as proven, probable, possible or clinical suspicion of infection.

Sample size and statistical analysis. The sample size for this exploratory observational study was based on a criterion of

Table 1 Details of RRT procedures and days of use

	Intermittent venovenous hemodialysis	Continuous venovenous hemofiltration	Continuous venovenous hemodiafiltration
Patients, no. (%)	5 (13.9)	13 (36.1)	11 (30.6)
Filter surface, m^2, mean ± SD	1.88 ± 0.45	1.29 ± 0.15	0.92 ± 0.27
Blood flow, mL/min, mean ± SD	325 ± 28.9	190 ± 26.5	123.9 ± 52.8
Treatment flow, mL/kg/h, mean ± SD		32.8 ± 4.3	46.8 ± 65.1
Duration procedure, daily hours, mean ± SD	3 ± 0	24 ± 0	24 ± 0
Duration procedure, total days, mean ± SD	26.6 ± 36.0	10.4 ± 8.5	43.8 ± 11

Table 2 Clinical characteristics of patients treated with L-AmB with and without RRT

Characteristics	Patients with RRT (n = 36)	Patients without RRT (n = 122)	P value
Age, years			
Mean ± SD	47.7 ± 23.1	48.8 ± 23.8	0.790
Median (range)	52.5 (33-68)	54.5 (33-68)	
Sex, no. (%)			
Men	26 (72.2)	75 (61.5)	0.238
Women	10 (27.8)	47 (38.5)	
Weight, kg, mean ± SD	66.0 ± 28.2	63.0 ± 28.7	0.569
Body mass index, kg/m2, mean ± SD	23.8 ± 6.6	24.8 ± 6.4	0.406
APACHE II score			
Mean ± SD	21.4 ± 8.8	18.5 ± 7.0	0.041
Median (range)	22.0 (7-47)	18 (4-39)	
ICU stay, days			
Mean ± SD	45.1 ± 54.1	44.3 ± 51.6	0.917
Median (range)	28 (5-288)	29 (2-353)	
Hospital stay, days			
Mean ± SD	75.4 ± 87.3	80.1 ± 67.7	0.719
Median (range)	48 (17-464)	57.5 (7-367)	
Underlying illness, no. (%)			
Medical	18 (51.0)	72 (59.0)	0.573
Surgical	16 (44.4)	38 (31.1)	
Trauma	1 (2.8)	6 (4.9)	
Burns	1 (2.8)	4 (3.3)	
Systemic response, no. (%)			
Severe sepsis/septic shock	29 (80.6)	76 (62.8)	0.047
Neutropenia	1 (2.8)	16 (13.2)	0.080

Percentages are calculated according to the total number of events in each category.

feasibility for performing a study of these characteristics and was not based on considerations of statistical power. Descriptive statistics are presented with continuous variables expressed as mean, standard deviation (± SD) and ranges (minimum and maximum values), and categorical variables as frequencies and percentages. Two subgroups of patients depending on the use or not of RRT. The cohorts of patients with and without RRT at the initiation of L-AmB treatment were compared using the chi-square (CHI^2) test for categorical variables and the Student's *t* test for continuous variables. Statistical significance was set at $P < 0.05$.

RESULTS

A total of 158 patients treated with L-AmB for at least 3 days, 36 (22.8%) of which required RRT were included in the study. These patients were recruited from 27 ICUs, 13 (48.1%) of which included one or more patients undergoing RRT during their ICU stay. Details of RRT procedures and days of use are shown in table 1. Continuous renal replacement procedures were the most frequent, continuous venovenous hemofiltration in 13 (36.1%) patients and continuous venovenous hemodiafiltration in 11 (30.6%). Intermittent hemodialysis (5 patients) and peritoneal dialysis (1 patient) were less frequent. Ten patients underwent various RRT procedures consecutively. Reasons for the use of RRT included high serum level of urea nitrogen in 17 (47.2%) cases, accumulation of fluid in 15 (41.7%), metabolic acidosis in 8 (22.2%), multiorgan dysfunction in 2 (5.6%) and rhabdomyolysis due to hyperammonemia and acute pulmonary edema in 1. Reasons for the indication of RRT were not recorded in 11 cases.

Table 3 **Comorbidities of patients treated with L-AmB with and without RRT**

	Patients with RRT (n = 36)	Patients without RRT (n = 122)	P value
Comorbidities, no. (%)			
Immunosuppression	10 (27.8)	26 (21.3)	0,150
Chronic bronchitis (COPD)	7 (19.4)	17 (13.9)	0.681
HIV infection	4 (11.1)	8 (6.6)	0.751
Chronic renal insufficiency	2 (1.9)	5 (4.1)	0.541
Congestive heart failure	7 (6.6)	10 (8.2)	0.862
Diabetes mellitus	11 (10.4)	17 (13.9)	0.762
Radiation therapy	0	8 (6.6)	0.220
Hematological malignancy	15 (14.2)	18 (14.8)	0.940
Solid tumor	14 (13.2)	19 (15.6)	0.755
Liver cirrhosis	1 (2.8)	4 (3.3)	0.863
Bone marrow transplantation	0 (0)	2 (1.6)	0.620
Solid organ transplantation	3 (8.3)	7 (5.7)	0.587
Chemotherapy	2 (5.6)	21 (17.2)	0.081
Comorbidities per patient			0.844
0	11 (30.6)	41 (33.6)	
1 to 3	21 (58.3)	71 (58.2)	
4 to 6	4 (11.1)	10 (8.2)	
Supportive techniques, no. (%)			
Arterial catheter	34 (94.4)	86 (70.5)	0.003
Central venous catheter	36 (100)	117 (95.9)	0.574
Mechanical ventilation	35 (97.2)	93 (76.2)	0.003
Antibiotic therapy	33 (91.7)	102 (83.6)	0.290
Corticosteroids	14 (38.9)	43 (35.3)	0.697
Total parenteral nutrition	28 (77.8)	60 (49.2)	0.002
Urethral catheter	35(97.2)	110 (90.2)	0.321
Surgery on admission	13 (36.1)	41 (33.6)	0.733
Supportive techniques per patient, no.			0.002
0	0 (0)	1 (0.8)	
1 to 3	0 (0)	10 (8.2)	
4 to 6	7 (19.4)	54 (44.3)	
> 6	29 (80.6)	57 (46.7	

Percentages are calculated according to the total number of events in each category.

Demographic characteristics and underlying illnesses of patients with and without RRT are shown in table 2. Patients in the RRT cohort showed a higher APACHE II score (21.4 *vs* 18.5, $P = 0.041$) and systemic response to infection (severe sepsis or septic shock 80.6% *vs* 18.5%, $P = 0.047$), whereas de percentage of patients with neutropenia was less frequent (2.8% *vs* 13.2%, $P = 0.08$). Differences in the duration of ICU stay or hospital stay were not found.

Comorbidities and supportive measures are summarized in table 3. There no statistically significant differences between

Table 4 Reasons for the use of L-AmB in critically ill patients with and without RRT

	Patients with RRT (n = 36)	Patients without RRT (n = 122)	P value
Reasons to prescribe L-AmB, no. (%)			
Broad spectrum of activity	23 (63.9)	75 (62.0)	0.836
Localization of infection	8 (22.2)	38 (31.4)	0.288
Intolerance to the oral route	2 (5.6)	4 (3.3)	0.621
Hemodynamic instability	27 (75.0)	71 (58.2)	0.076
Hospital protocol	4 (11.1)	11 (9.1)	0.749
Intolerance to other antifungals	1 (2.8)	6 (5.0)	1.000
Adherence to clinical guidelines	14 (38.9)	48 (39.7)	0.933
Consultant's opinion	4 (11.1)	25 (20.7)	0.195
Resistant species	2 (5.6)	11 (9.1)	0.538
Classification of infection, no. (%)			
Proven	14 (38.9)	39 (32.8)	
Probable	6 (16.7)	13 (10.9)	0.534
Possible	6 (16.7)	20 (16.8)	
Empirical	10 (27.8)	47 (39.5)	

Percentages are calculated according to the total number of events in each category.

patients with and without RRT, except for the use of chemotherapy which was less frequent in the RRT cohort (5.6% *vs* 17.2%, $P = 0.081$). Most patients with RRT also required six or more supportive measures. Also, the use of arterial catheter (94.4% *vs* 70.5%, $P = 0.003$), mechanical ventilation (97.2% *vs* 76.2%, $P = 0.003$) and parenteral nutrition (77.8% *vs* 49.2%, $P = 0.002$) was more frequent in patients with RRT.

As shown in table 4, hemodynamic instability was the most frequent reason for the use of L-AmB in patients undergoing RRT (75% *vs* 58.2%, $P = 0.076$). Other reasons were the spectrum of activity of L-AmB (63.9%) and adherence to clinical guidelines (38.9%). Significant differences in the use of L-AmB according to the degree certainty of infection (proven, probable, possible or suspicion) between both cohorts were not observed. In the group of patients with RRT, one or more fungi were identified in 27 (75%) occasions, which were candidemias in 5. Biological samples in which fungi were isolated as well as the most frequent genus and species are shown in Table 5. Isolates from respiratory samples (bronchial aspirates), blood and biopsy samples of different tissues were the most frequent. *Candida* spp., in particular *Candida albicans* and *Candida glabrata*, and different *Aspergillus* spp. predominated.

No differences were found in the duration of treatment with L-AmB between the two subgroups, although both daily doses (4.30 mg/kg *vs* 3.94 mg/kg, $P = 0.030$) and percentage of patients treated with daily doses higher than 4 mg/kg (52.8% *vs* 36.1%, $P = 0.033$) were greater among patients in the RRT cohort (table 6). Differences in the use of L-AmB therapy as rescue medication or first-choice agent were not found either.

The clinical response was satisfactory in 61.1% of patients with RRT and in 56.6% of those who did not require RRT but differences were not statistically significant (table 7). In patients with RRT and proven infection, satisfactory clinical response was achieved in 78.6% of cases. In patients with microbiological fungal isolates (n = 27), eradication was documented in 20 (74.1%) reaching 85.7% in those patients with proven infection.

The ICU mortality rate was 36.1% (n = 13) in patients who required RRT and 36.9% (n = 45) in those without RRT. Cumulative hospital mortality in both groups was 38.9% and 42.6%, respectively.

DISCUSSION

A total of 23% of patients who received L-AmB during their stay in the participating ICUs underwent RRT concomitantly. As far as we are aware, this finding has not been previously reported in the literature. The clinical and microbiological response to the use of L-AmB in patients with RRT has been similar to that observed in L-AmB-treated patients without RRT. Also, differences between both groups in ICU and hospital mortality rates were not observed.

The use RRT has increased in recent years in critically ill patients admitted to the ICU especially continuous RRT. Al-

Table 5 Localization of samples and fungal species identified in critically ill patients treated with L-AmB with and without RRT

	Patients with RRT (n = 36)	Patients without RRT (n = 122)	P value
Localization of samples, no. (%)			
Bronchial aspirates	17 (47.2)	35 (34.7)	0.182
Blood	5		
Catheter	4 (11.1)	6 (5.9)	0.455
Urine	6		
Peritoneal exudate (direct)	4 (11.1)	5 (5.0)	0.242
Tissue biopsy	1 (2.8)	2 (2.0)	1.000
Pharynx	3 (8.3)	11 (10.9)	
Other	11 (30.6)	41 (40.6)	0.287
Species of fungi, no. (%)			
Candida albicans	8 (22.2)	40 (39.6)	0.061
Candida glabrata	6 (16.7)	13 (12.9)	0.581
Candida parapsilosis	5 (13.9)	16 (15.8)	0.800
Candida tropicalis	2 (5.6)	10 (9.9)	0.732
Candida dubliniensis	1 (2.8))	0 (0.0)	0.263
Aspergillus fumigatus	2 (5.6)	6 (5.9)	1.000
Aspergillus flavus	1 (2.8)	1 (1.0)	0.458
Aspergillus niger	1 (2.8)	0 (0.0)	0.263
Mucor	1 (2.8)	0 (0.0)	0.263
Histoplasma capsulatum	1 (2.8)	0 (0.0)	0.263
Paracoccidiodes brasilensis	1 (2.8)	1 (1.0)	0.458

Percentages are calculated according to the total number of events in each category.

though the reason for using RRT is to substitute the renal function in cases of acute renal insufficiency (uremia, metabolic acidosis), it is increasingly common the use of RRT for treating other clinical conditions, such as anasarca, electrolyte disbalance, acute intoxications, acute pulmonary edema and even severe sepsis. While the use of RRT may affect plasma concentrations of azoles[5,7], the administration of candins[8,9] or polyenes[6,10] are associated with minimal changes, so that monitorization of plasma concentrations or dosage changes are not necessary. In patients with RRT differences in the selection of L-AmB as rescue treatment or first-line treatment were not observed. Reasons for the selection of L-AmB were mainly the broad spectrum of activity and severity of the patients, particularly the presence of hemodynamic instability. Comparative studies in this patient model reported in the literature are lacking but different case reports in patients with renal failure and/or need of RRT treated with L-AmB as recue treatment have shown favourable results[11,12].

Patients included in the present study in which treatment with L-AmB was indicated, had a severity level higher to the mean severity of patients admitted to the ICU. The median APACHE II score was 18 and 22 for each subgroup, which is much higher than that of patients admitted to the Spanish ICUs in 2009[13]. The study population included patients with numerous comorbidities, most of them with solid tumor or haematological malignancies under oncological treatment in whom fungal infections were diagnosed in the context of a severe immunosuppression. The present findings support that in this model of patient, the selection of L-AmB is a therapeutic option that should be considered, with acceptable clinical and microbiological response independently of the presence of acute or chronic renal insufficiency or treatment with RRT.

Fungi identified as the causative pathogens of infections treated with L-AmB in patients requiring RRT were similar than those isolated in the comparator group. There was a predominance of *Candida* spp. followed by *Aspergillus* spp., being less frequent and/or exceptional other species, such as *Mucor*, *Histoplasma capsulatum* or *Paracoccidiodes brasilensis*. These findings are consistent with data reported in most epidemiological studies of fungal infections in critically ill patients[14,15].

Table 6 Characteristics of L-AmB administration in critically ill patients with and without RRT

	Patients with RRT (n = 36)	Patients without RRT (n = 122)	P value
Rescue treatment, no. (%)	20 (55.6)	55 (45.1)	0.269
Previous antifungals, no. (%)			
Fluconazole	9 (25)	21 (17.2)	0.295
Caspofungin	9 (25)	19 (15.6)	0.193
Voriconazole	3 (8.3)	16 (13.1)	0.569
Anidulafungin	3 (8.3)	3 (2.4)	0.132
Itraconazole	1 (2.8)	5 (4.1)	1.000
Amphotericin lipid complex	1 (2.8)	2 (1.6)	0.542
Micafungin	0	1 (0.8)	1.000
Duration of treatment, days			
Mean ± SD	15,44 ± 8,9	14.4 ± 8,8	0.524
Median (range)	13.5 (4-42)	12 (3-46)	
Patients with > 7 days of treatment, no. (%)	32 (88.9)	104 (85.3)	0.579
Daily dose, mg/kg			
Mean ± SD	4,30 ± 1.13	3.84 ± 1,11	0.030
Median (range)	4.75 (2.8-7)	3.8 (1-9.2)	
Patients with doses > 4 mg/kg, no. (%)	19 (52.8)	44 (36.1)	0.033
Total daily dose, mg/kg			
Mean ± SD	69.0 ± 55.4	55.8 ± 39.8	0.112
Median (range)	56 (18-294)	45.0 (7-215)	
Total cumulative dose, mg			
Mean ± SD	4.332 ± 4.311	3.500 ± 3.277	0.212
Median (range)	2.898 (165-20.580)	2.640 (75-17.200)	
Change of doses, no. (%)	4 (11.1)	17 (13.9)	0.976
Reason for change, no. (%)			
Improvement	3 (42.9)	9 (37.5)	1.000
Worsening	2 (28.6)	5 (20.8)	
Toxicity	0	1 (4.2)	
Other	2 (28.6)	9 (37.5)	

Percentages are calculated according to the total number of events in each category.

The doses of L-AmB administered to patients in the RRT cohort where higher than doses given to patients without RRT. Patients in the RRT cohort received a dose of 4.3 mg/kg/day for more than 2 weeks with minimal dose changes during treatment. In these patients, however, it not possible to quantify the morbidity related to the use of L-AmB but in patients without RRT, the use of this drug had minimal effect on renal function even in those patients with altered renal function at the beginning of treatment, which confirms the excellent tolerability of L-AmB in these risk patients[3,16].

The main limitations of this study are related to the retrospective and multicenter design, although the participating physicians belong to a network of specialists in the diagnosis and treatment of infections in critically ill patients, which may minimize bias related to the diagnosis and assessment of the clinical response. However, the diagnosis of fungal infections is still challenging for clinicians despite consensus and recommendations published in recent years, and the limits between proven, probable or possible infection continue to be poorly defined.

Table 7 **Clinical and microbiological response to the use of L-AmB to critically ill patients with and without RRT**

	Patients with RRT (n = 36)	Patients without RRT (n = 122)	P value
Clinical response, no. (%)			
Satisfactory			
Cure	13 (36.1)	39 (32.0)	0.953
Improvement	9 (25.0)	30 (24.6)	
Stable	11 (30.6)	43 (35.3)	
Failure	3 (8.3)	10 (8.2)	
Microbiological response, no. (%)			
Eradication	20 (74.1)	62 (64.6)	0.382
Persistence	4 (14.8)	11 (11.4)	
Missed follow-up	3 (11.1)	23 (24.0)	

Percentages are calculated according to the total number of events in each category.

In summary, this study shows that an important number of patients treated with L-AmB are concomitantly undergoing any technique of RRT. The selection of this antifungal drug in this subgroup of patients is based on the wide spectrum of activity and the patient's severity of illness, being used indistinctly as first-choice agent or as rescue medication. In these patients, the use of L-AmB has been associated with an acceptable clinical and microbiological response similar to that observed in patients not requiring RRT.

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