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 Liposomal Amphotericin B  
 in the ICU

## Impact of liposomal amphotericin B on renal function in critically ill patients with renal function impairment

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### ABSTRACT

**Objective:** To assess the tolerability of liposomal amphotericin B (L-AmB) in critically ill patients with elevated serum creatinine concentrations (Cr) (> 1.5 mg/dL) at starting L-AmB therapy.

**Methods:** Retrospective, multicenter, comparative study of two cohorts of critically ill patients treated with L-AmB during 3 or more days, the difference between them was the level of Cr at the beginning of treatment. A cutoff value of Cr of 1.5 mg/dL was established. Patients undergoing extrarenal deuration procedures before or 48 hours after starting L-AmB were excluded. The primary endpoint was the difference between Cr values at the end of treatment as compared with Cr at starting L-AmB. Secondary endpoints were treatment-related withdrawals, need of extrarenal deuration techniques, and treatment-related severe adverse events. Demographic data, underlying illness, indication of L-AmB therapy, concomitant risk factors of nephrotoxicity, and vital status at ICU and hospital discharge were recorded.

**Results:** A total of 122 patients admitted to 26 ICUs (16 with Cr > 1.5 g/dL; 106 with normal Cr levels) were recruited. Main reasons for the use of L-AmB in both groups were the broad spectrum of the drug and the presence of hemodynamic instability. L-AmB was administered as first-line treatment in 68.8% of patients with elevated Cr and in 52.8% with normal Cr. The APACHE II score on ICU admission was 25 in patients with elevated Cr and 17 in those with normal Cr values ( $p < 0.001$ ). Duration of treatment with L-AmB was 16 and 12 days in patients with elevated and normal Cr values, respectively, with a mean dose of 3.5 vs 3.9 mg/kg/day. The use of concomi-

tant nephrotoxic drugs, mortality rate, and ICU and hospital length of stay were similar in both cohorts. In patients with renal function impairment at the initiation of L-AmB treatment, an absolute decrease of  $C_f-C_i$  of 1.08 mg/dL was observed ( $P < 0.001$ ). A decrease of Cr levels to normal limits was observed in 50% of the patients; in 37.5% of patients there was a decrease but normal levels were not achieved, whereas a Cr increased occurred in only one (6.25%) patient. None of the patients required withdrawal of L-AmB or use of extrarenal deuration procedures. Treatment-related severe adverse events were not reported.

**Conclusions:** In critically ill patients with impaired renal function, the impact of L-AmB on renal function was minimal. L-AmB can be used for the treatment of fungal infections in critically ill patients independently of renal function at the initiation of treatment.

**Key words:** Liposomal amphotericin B, critically ill patient, ICU, tolerability, nephrotoxicity.

### Impacto de anfotericina B liposomal en la función renal en pacientes críticos con la función renal deteriorada

#### RESUMEN

**Objetivo:** Evaluar la tolerabilidad de anfotericina B liposomal (L-AmB) en pacientes críticos con concentraciones elevadas de creatinina sérica (Cr) (> 1,5 mg/dL) al inicio del tratamiento con L-AmB.

**Métodos:** Estudio retrospectivo, multicéntrico y comparativo de dos cohortes de pacientes críticos tratados con L-AmB durante tres o más días, que se diferenciaban según el nivel de creatinina al inicio del tratamiento. Se estableció como punto de corte un valor de Cr de 1,5 mg/dL. Se excluyeron los pacientes con técnicas de deuración extrarrenal antes o 48 horas

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después del inicio de L-AmB. La variable principal fue la diferencia entre el valor de creatinina al final comparado con el inicio de tratamiento con L-AmB. Otros parámetros secundarios fueron: abandonos relacionados con el tratamiento, necesidad de técnicas de depuración extrarrenal (TDE) y acontecimientos adversos graves (AAG) relacionados con el tratamiento. Se recogieron datos demográficos, enfermedad subyacente, motivo de prescripción, factores concomitantes de riesgo de nefrotoxicidad y estado vital al alta de UCI y del hospital.

**Resultados:** Se reclutaron 122 pacientes en 26 UCI (Cr > 1,5 g/dL, n= 16; Cr normal, n= 106). Los motivos principales por los que se indicó L-AmB en ambos grupos fueron el amplio espectro y la presencia de inestabilidad hemodinámica. Se administró como tratamiento de 1ª línea en el 68,8% de los pacientes con Cr elevada y en el 52,8% con Cr normal. La puntuación APACHE II al ingreso en UCI fue 25 en pacientes con Cr elevada y 17 en aquellos con Cr normal ( $p < 0,001$ ). La duración del tratamiento con L-AmB fue 16 y 12 días en pacientes con Cr elevada y normal y una dosis media de 3,5 vs 3,9 mg/kg/día. El uso concomitante de otros fármacos nefrotóxicos, la tasa de mortalidad, y la estancia en UCI y hospitalaria fueron similares en ambas cohortes. En los pacientes con función renal alterada al inicio de L-AmB se observó una reducción absoluta de  $C_r - C_i$  de 1,08 mg/dl ( $P < 0,001$ ). La Cr bajó a valores normales en el 50% de los pacientes, descendió pero sin llegar a valores normales en el 37,5% y sólo se elevó en 1 (6,25%) paciente. En ningún paciente se suspendió L-AmB por nefrotoxicidad ni se precisaron técnicas de depuración extrarrenal. No se reportaron AAG relacionados con el tratamiento.

**Conclusiones:** El tratamiento con L-AmB en pacientes críticos con función renal deteriorada tuvo un impacto mínimo en la función renal. L-AmB puede utilizarse para el tratamiento de infecciones fúngicas en pacientes críticos independientemente de la función renal al inicio del tratamiento.

**Palabras clave:** Anfotericina B liposomal, paciente crítico, UCI, tolerabilidad, nefrotoxicidad

## INTRODUCTION

The administration of amphotericin B deoxycholate has been traditionally related to the appearance of nephrotoxicity, so that it has been recommended to avoid its prescription in patients with altered renal function or in those with a higher risk of renal dysfunction (such as, elderly patients, concomitant use of other nephrotoxic drugs or patients with hemodynamic instability)<sup>1</sup>.

The development of lipid formulations of amphotericin B has been accompanied by a large number of published studies assessing the ability of each formulation to cause renal toxicity and in comparison with conventional amphotericin B in different models of patients and infections<sup>2-11</sup>. Although a decrease of nephrotoxicity has been observed with the use of all lipid formulations, a more marked decrease has been associated with the use liposomal amphotericin B (L-AmB)<sup>10,11</sup>. Despite these findings, some clinical guidelines recommend physicians

in charge of critically ill patients admitted to Services of Intensive Care Units (ICUs) the use of other antifungals not associated with this adverse event, such as fluconazole or candins, in cases of altered renal function<sup>12,13</sup>.

Recently, a multicenter pharmacoepidemiological study carried out in 33 Spanish ICUs that included all critically ill patients treated with L-AmB over a period of 12 months has been published<sup>14</sup>. A subanalysis of 49 patients with serum creatinine (Cr) values > 1.5 mg/dL at the beginning of treatment with L-AmB showed a significant decrease of mean Cr levels at the end of treatment as compared with pre-treatment values<sup>15</sup>. Therefore, the present study was designed to confirm previous data of the use of L-AmB in patients with renal function impairment at initiation of antifungal treatment.

## MATERIALS AND METHODS

**Design.** This was a nationwide multicenter, observational and retrospective cohort study of patients treated in the ICU with L-AmB between September 2008 to December 2009. Cases were defined as patients (adults or children) admitted to the ICU or resuscitation unit treated with L-AmB during 3 days or more days for any reason or indication, who at the beginning of treatment showed serum Cr levels > 1,5 mg/dL, and controls were patients with normal renal function at the time of starting treatment. Patients undergoing extrarenal depuration procedures before or 48 hours after starting L-AmB were excluded.

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, in which the following data were recorded: demographic variables (age, sex, weight, height); dates of admission to the hospital and to the ICU, and dates of discharge from the ICU and from the hospital; vital status on hospital discharge (alive or dead); underlying conditions (diabetes mellitus, hematological neoplasm, chronic renal insufficiency, chronic obstructive pulmonary disease [COPD], human immunodeficiency virus (HIV) infection, transplant recipient, solid neoplasm); classification of the main diagnosis (medical, surgical, trauma, coronary, hematological); risk factors associated with hospitalization (vascular catheter, urinary catheter, mechanical ventilation, total parenteral nutrition, treatment with steroids, use of antimicrobials > 7 days, extrarenal depuration procedures, urgent surgery, chemotherapy, immunosuppression); presence of neutropenia (absolute neutrophil count < 500/mm<sup>3</sup>); and severity level on ICU admission calculated by the APACHE II score system<sup>16</sup>. Data on previous antifungal treatment included dose, duration of treatment, and reason of withdrawal (adverse reaction, treatment failure, and other).

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,

**Tabla 1** Cinical characteristics of patients treated with L-AmB according to renal function at the initiation of treatment

Characteristics	Creatinine $\leq$ 1.5 mg/dL (n = 106)	Creatinine > 1.5 mg/dL (n = 16)	P value
Age, years			0.002
Mean $\pm$ SD	45 $\pm$ 26	65.6 $\pm$ 9.1	
Median (range)	52.0 (0-85)	68.5 (68.5-79.0)	
Sex, no. (%)			0.022
Men	61 (57.6)	14 (87.5)	
Women	45 (42.5)	2 (12.5)	
APACHE II score			< 0.0001
Mean $\pm$ SD	17.4 $\pm$ 6.3	24.9 $\pm$ 7.8	
Median (range)	18.0 (4-33)	23 (10-31)	
ICU stay, days			0.208
Mean $\pm$ SD	43.3 (53.1)	50.7 (41.1)	
Median (range)	26 (2-353)	38.5 (5-152)	
Hospital stay, days			0.624
Mean $\pm$ SD	81.5 $\pm$ 69.9	69.9 $\pm$ 49.00	
Median (range)	59 (7-367)	50 (26-178)	
Underlying diseases, no. (%)			0.995
Medical	47 (44.3)	9 (56.3)	
Surgical	28 (26.4)	4 (25.0)	
Hematological	14 (13.2)	0	
Trauma	5 (4.7)	1 (6.3)	
Transplantation	5 (4.7)	0	
Burns	4 (3.8)	0	
Other	3 (2.8)	2 (12.5)	
Systemic response, no. (%)			0.093
Severe sepsis/ septic shock	65 (59.4)	13 (81.3)	

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

implementation of local protocols, consultant's opinion, isolation of a filamentous fungus, intolerance to other antifungal agents, and intolerance of the oral route. In each case, dates of start and end of treatment were recorded as well as reasons of stopping treatment, daily dose, cumulative dose, change of doses during treatment and reasons for change.

Tolerability was assessed by recording daily serum Cr concentrations and the presence of infusion-related severe reactions (fever, chills, muscle pain, erythrodermia, headache, nausea) as well as any other treatment-related adverse event.

All data were obtained by review of the medical records. Indications of L-AmB treatment were not previously protocolized, so that physicians in charge of the patients were free to choose this agent.

**Study endpoints.** The primary endpoint was the difference in the mean serum Cr level at the end of L-AmB treatment as compared with baseline (pre-treatment) level ( $Cr_f$  -  $Cr_i$ ). The serum Cr level corresponding to the nearest date to the end of treatment was taken as the final value ( $Cr_f$ ). In patients undergoing extrarenal deuration techniques during L-AmB treatment,  $Cr_f$  was the last value recorded before starting the extrarenal deuration procedure. Secondary endpoints were the percentage of change as compared with the initial value, withdrawals due to nephrotoxicity, need to start extrarenal deuration techniques during treatment with L-AmB, and treatment-related severe adverse events.

**Statistical analysis.** The sample size for this exploratory observational study was based on a criterion of feasibility for perform-

**Tabla 2** Comorbidities in patients treated with L-AmB according to renal function at the initiation of treatment

	Creatinine $\leq$ 1.5 mg/dL (n = 106)	Creatinine > 1.5 mg/dL (n = 16)	P value
Comorbid conditions, no. (%)			
Immunosuppression	24 (10.4)	2 (12.5)	0.518
COPD	10 (9.4)	7 (43.8)	0.002
HIV infection	8 (7.6)	0	0.595
Renal insufficiency	2 (1.9)	3 (18.9)	0.016
Congestive heart failure	7 (6.6)	3 (18.9)	0.125
Diabetes mellitus	11 (10.4)	6 (37.5)	0.010
Radiation therapy	7 (6.6)	1 (6.3)	1.000
Hematological neoplasm	15 (14.2)	3 (18.9)	0.705
Solid tumor	14 (13.2)	5 (31.3)	0.130
Liver cirrhosis	3 (2.8)	1 (6.3)	0.434
Bone marrow transplantation	2 (1.9)	0	1.000
Solid organ transplantation	6 (5.7)	1 (6.3)	1.000
Chemotherapy	16 (15.1)	5 (31.3)	0.150
Comorbid conditions/patient			0.012
0	39 (36.8)	2 (12.5)	
1 to 3	61 (57.6)	10 (62.5)	
4 to 6	6 (5.7)	4 (25.5)	
Supportive measures, no. (%)			
Arterial catheter	72 (67.9)	14 (87.5)	0.148
Central venous catheter	101 (95.3)	16 (100)	1.000
Mechanical ventilation	79 (74.5)	14 (87.5)	0.354
Antibiotics	91 (85.6)	11 (68.8)	0.138
Steroids	40 (37.7)	3 (18.8)	0.138
Total parenteral nutrition	51 (48.1)	9 (56.3)	0.544
Urinary catheter	94 (88.7)	16 (100)	0.363
Surgery on admission	37 (34.9)	9 (25.0)	0.434

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

ing 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 ( $\pm$  SD) or median and ranges (minimum and maximum values), and categorical variables as frequencies and percentages. The cohorts of patients with serum Cr > 1.5 mg/dL and serum Cr  $\leq$  1.5 mg/dL at the initiation of L-AmB treatment were compared using the chi-square test for qualitative variables and the Student's *t* test for quantitative variables. Statistical significance was set at  $P < 0.05$ .

## RESULTS

A total of 122 patients admitted to 26 ICUs were recruited

(23 cases per participating ICU, minimum 1 case and maximum 23 cases). The cohort of patients with serum Cr > 1.5 mg/dL at the beginning of L-AmB treatment included 16 patients, and the cohort of patients with serum Cr  $\leq$  1.5 mg/dL the remaining 106 patients.

**Patient characteristics and infections.** Table 1 shows the baseline characteristics of the patients in each cohort. Patients with renal function impairment at starting L-AmB treatment were significantly older, with a higher proportion of males, and higher level of severity on ICU admission (APACHE II score  $24.9 \pm 7.8$  vs  $17.4 \pm 6.3$ ,  $P < 0.0001$ ) as compared with those with normal renal function. Both groups showed a prolonged length of ICU stay and hospital stay but signifi-

**Tabla 3** Reasons for the use of L-AmB in the study patients according to renal function at the initiation of treatment

	Creatinine $\leq$ 1.5 mg/dL (n = 106)	Creatinine $>$ 1.5 mg/dL (n = 16)
Reasons for L-AmB treatment, no. (%)		
Localization of infection	34 (32.1)	4 (25.0)
Intolerance to the oral route	4 (3.8)	0
Hemodynamic instability	61 (57.6)	10 (62.5)
Hospital protocol	11 (10.4)	0
Intolerance to other antifungals	6 (5.7)	0
Adherence to clinical guidelines	35 (33.0)	5 (31.3)
ICU	25 (23.6)	4 (25.0)
Other specialties	10 (9.4)	1 (6.3)
Broad spectrum of activity	64 (60.4)	11 (68.8)
Consultant's opinion	24 (22.6)	1 (6.3)
Resistant species	9 (8.5)	2 (12.5)
Suspicious of filamentous fungi	16 (15.1)	1 (6.3)
Classification of infection, no. (%)		
Proven	32 (30.2)	7 (43.8)
Probable	11 (10.4)	1 (6.3)
Possible	19 (17.9)	2 (12.5)

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

cant differences were not observed. Underlying conditions and supportive measures required in the study patients are detailed in table 2. In the cohort of patients with renal function impairment, the number of patients with COPD, diabetes, and chronic renal failure was significantly higher than in the cohort of patients with normal renal function. Also, a higher mean number of comorbidities per patient was also present (2.3 vs 1.2,  $P = 0.006$ ).

**Reasons for the use of L-AmB.** Reasons for the administration of L-AmB are shown in table 3, with the broad spectrum of activity of L-AmB and the presence of hemodynamic instability as the most frequent reasons in both subgroups. Differences in the reasons for starting L-AmB at the initiation of treatment were not found. In all cases, treatment with L-AmB was prescribed because of suspicion of a fungal infection, which was microbiologically confirmed in 72 (59.1%) of the patients, being classified as proved fungal infection in 39 (32.0%), probable in 12 (9.8%), and possible in 21 (17.2%), without differences between the two cohorts.

**Characteristics of treatment.** L-AmB was administered as first-line treatment in 56 (52.8%) patients with normal serum Cr and in 11 (68.8%) patients with elevated serum Cr ( $P = NS$ ). In the remaining 55 patients, L-AmB was prescribed as rescue medication. Previous antifungal agents given to these patients are shown in table 4. Either in patients with impaired

renal function or in those with normal renal function, azoles were the most frequently used drugs (38/50 and 4/6). L-AmB was predominantly administered as a directed treatment in 58.5% and 62.5% ( $P = NS$ ) of patients in both groups. The mean duration of treatment was longer, but without significant differences, in patients with elevated serum Cr (16.2 vs 14.1 days). Differences in the mean daily dose of L-AmB were not observed, although total cumulative dose was higher in patients with serum Cr  $>$  1.5 mg/dL ( $P = 0.023$ ) (table 5). Initial doses were modified in 14.2% and 12.5% of patients with normal and altered renal function, respectively ( $P = NS$ ). In both cohorts, other potentially nephrotoxic drugs were also administered, particularly among patients with normal renal function (70.8% vs 50%,  $P = NS$ ).

**Tolerability.** Table 6 shows initial ( $Cr_i$ ), final ( $Cr_f$ ), and  $Cr_f - Cr_i$  differences in all patients, in patients with renal function impairment at starting L-AmB and in patients with normal renal function. Daily changes of mean serum Cr levels (mg/dL) according to serum Cr values at the initiation of L-AmB treatment ( $>$  or  $\leq$  1.5 mg/dL) are shown in figure 1.

In patients with renal function impairment at starting L-AmB treatment, serum Cr concentration showed a median decrease of 1.08 mg/dL (44.3%) as compared with baseline ( $P < 0.001$ ). In none of the patients, treatment with L-AmB was discontinued due to nephrotoxicity or required extrarenal depuration procedures. In half of the patients, serum  $Cr_f$  decreased to normal values and in 6 patients (37.5%), serum  $Cr_f$  decreased but without reaching normal limits. Serum  $Cr_f$  remained unchanged in one patient, and increased in only one case. This was a 57-year-old patient with history of diabetes, chronic renal insufficiency, COPD, solid organ transplantation recipient, diagnosed of solid organ neoplasm, and treated with another nephrotoxic drug. The patient was given L-AmB (daily dose 45 mg) and serum Cr increased from 1.8 mg% to 2.7 mg%, and he died after limitation of therapeutic effort.

In patients with normal renal function at the start of L-AmB treatment, an increase in serum  $Cr_f$  was observed in 13 patients (12.3%), 9 of whom received concomitant treatment with one or more nephrotoxic drugs. In these patients, a median increase of 0.07 mg/dL (14.9%) was observed as compared with serum  $Cr_i$  ( $P < 0.001$ ). Extrarenal depuration techniques were indicated in two patients (fluid accumulation and metabolic acidosis in one, and hypercalcemia in one).

**Outcome.** The overall ICU mortality rate and hospital mortality rate was 36.9% and 42.6%, respectively. Differences in mortality rates between patients with normal and impaired renal function at initiation of L-AmB treatment were not observed (hospital mortality rate 40.7% vs 56.3%,  $P = 0.237$ ).

**Tabla 4** Antifungals previously used in patients treated with L-AmB as a rescue treatment according to renal function at the initiation of treatment

	Creatinine $\leq$ 1.5 mg/dL (n = 106)	Creatinine > 1.5 mg/dL (n = 16)
First-choice, no. (%)	56 (52.8)	11 (68.7)
Rescue treatment, no. (%)	50 (47.2)	5 (31.3)
Previous antifungals, no. (%)	66	6
Amphotericin lipid complex	1 (0.9)	1 (6.3)
Caspofungin	19 (17.9)	0
Fluconazole	18 (17.0)	3 (18.8)
Voriconazole	14 (14.2)	1 (6.3)
Itraconazole	5 (4.7)	0
Micafungin	1 (0.9)	0
Anidulafungin	2 (1.9)	1 (6.3)
Other	5 (4.7)	0

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

## DISCUSSION

Results of the present study confirm previous findings in a group of critically ill patients showing the low impact of the administration of L-AmB to patients with altered renal function at the initiation of treatment<sup>15</sup>. In this second study, in which confounding factors, such as the concomitant use of extrarenal deputation procedures were eliminated, also demonstrates an improvement of renal function parameters (expressed as the difference between final and initial serum Cr levels) in the majority of patients, independently of the use of other potentially nephrotoxic drugs. Also, none of the patients required starting extrarenal deputation techniques during L-AmB treatment because of nephrotoxicity nor treatment-related adverse events were recorded.

Similar results have been published by Walsh et al.<sup>17</sup> in a large series of patients treated with amphotericin B lipid complex in whom most indications included the use of this antifungal agent as rescue medication due to poor clinical response or the appearance of adverse events, in particular, renal failure secondary to treatment with amphotericin B deoxycholate. Mean creatinine values in patients with high concentrations at the beginning of treatment improved significantly at the end of treatment.

Different reasons have been argued to justify the lower toxicity of amphotericin lipid formulations as compared with amphotericin deoxycholate. Mehta et al.<sup>18</sup> have shown that the markedly improved therapeutic index of liposomal amphotericin B is largely due to a fundamental alteration in the ability of the drug to interact with mammalian cell membranes rather than to alterations in pharmacokinetics or drug distribution. However, Olsen et al.<sup>19</sup> suggested differences in the pharmaco-

kinetic distribution model of both antifungal drugs. While amphotericin B deoxycholate reaches the kidney in a very early phase, lipid formulations appear to be preferentially accumulated in organs of the reticuloendothelial system (liver, lung, spleen), which reduces plasma drug concentration and renal clearance. Janoff et al.<sup>20</sup> explained the lower renal toxicity of amphotericin B lipid formulations in relation to a process of degradation and release of amphotericin B at the cellular level, to which lipases and phospholipases not present in the glomerular cells or epithelial cells of the renal tubule are needed. Finally, Adler-Moore et al.<sup>21</sup> suggested that the lower toxicity of L-AmB would be related to a higher transitional temperature of its phospholipids compared with other lipid formulations, which would prevent the release of amphotericin B prior to reach the fungal cell. In fact, the final clinical result of the use of L-AmB is a lower renal toxicity, which was demonstrated in our observational study by restoration or improvement of renal function over the treatment period in patients with renal function impairment at the initiation of L-AmB administration.

Patients included in the cohort of renal function impairment at starting L-AmB treatment showed a higher level of severity than the cohort of patients with normal renal function but showed a lower severity level than the mean score of patients admitted to the ICU (ENVIN registry data)<sup>22</sup>. Patients with altered renal function were significantly older, with a higher percentage of males, and a higher number of comorbid diseases, in particular, diabetes, chronic renal failure, and COPD. The higher severity level assessed by the APACHE II score and recorded in these patients may be biased by a higher score related to the presence of renal failure and the age of the patients. Although systemic response of infection and hospital mortality were higher in patients with renal function impairment, differences were not statistically significant.

**Tabla 5** Characteristics of the administration of L-AmB in the study patients according to renal function at the initiation of treatment

	Creatinine $\leq$ 1.5 mg/dL (n = 106)	Creatinine $>$ 1.5 mg/dL (n = 16)	P value
Mode of administration, no. (%)			0.761
Empirical treatment	44 (41.5)	6 (37.5)	
Directed treatment	62 (58.5)	10 (62.5)	
Duration of treatment, days			0.250
Mean (SD)	14.1 (8.8)	16.2 (8.5)	
Median (range)	12 (3-46)	16 (6-33)	
Patients with $>$ 7 days of treatment, no. (%)	89 (84.0)	15 (93.8)	0.462
Daily dose, mg/kg			0.198
Mean (SD)	3.9 $\pm$ 1.1	3.5 $\pm$ 0.9	
Median (range)	4.0 (1.0-9.2)	3.3 (1.5-5.0)	
Patients with doses $>$ 4 mg/kg, no. (%)	41 (38.7)	3 (18.8)	0.116
Total daily dose, mg/kg			0.669
Mean (SD)	55.8 $\pm$ 41.2	57.8 $\pm$ 30.4	
Median (range)	42 (7-215)	52 (15-105)	
Total cumulative dose, mg			0.023
Mean (SD)	3.252 $\pm$ 3.109	5.097 $\pm$ 3.955	
Median (range)	2.415 (75-17.200)	3.535 (1.125-16.380)	
Change of doses, no. (%)	15 (14.2)	2 (12.5)	1.000
Reason for change, no. (%)			
Improvement	4 (26.3)	0	
Worsening	4 (26.3)	1 (50)	
Toxicity	0	1 (50)	
Other	7 (46.3)	0	

Decisions to prescribe L-AmB by physicians in charge of these patients (with and without renal function impairment) were mainly based on the greater spectrum of activity and the presence of signs of hemodynamic instability. Amphotericin B continues to be the antifungal drug with the broadest spectrum of activity against different species of molds and filamentous fungi and also with the most solid evidences in different population groups. However, toxicity associated with the use of this agent has been the reason for the substitution of amphotericin B deoxycholate by other less toxic antifungal families (azoles and candins) in therapeutic protocols and clinical guidelines. Although numerous studies have shown that L-AmB has a lower toxicity than amphotericin B deoxycholate and other lipid formulations while maintaining the spectrum of activity<sup>6,7,10,11</sup>, recommendations of the use of L-AmB in non-neutropenic critically ill patients in some guidelines are still limited, favoring fluconazole or candins due to their safety profile. However, the present findings based on observations from daily practice in patients admitted to the ICU demon-

strate that the use of L-AmB, not only did not produce renal toxicity in patients with normal renal function at the beginning of treatment, but also allowed normalization of serum Cr values in half of the patients with Cr  $>$  1.5 g/dL and improvement in another one-third.

Although in this study, a detailed analysis of infections responsible for the indication of L-AmB was not performed, it is remarkable that infection was only confirmed in 72 (59.1%) patients (by clinical and/or microbiological findings), and only in 39 (32.0%), infection was classified as proven, without differences between the two study cohorts. These data are in contrast to clinical trials in which proven or probable infections are usually included in the selection criteria. In clinical practice conditions of critically ill patients, antifungals are frequently used as rescue treatment for unclassified infections, in which there are reasonable doubts of the presence of filamentous fungi (*Aspergillus*, *Mucor*, *Fusarium* spp.) as causative pathogens of a process with unfavorable clinical course, although in some cases a definite diagnosis of fungal infection is not reached.

Table 6 Impact of the administration of L-AmB on serum creatinine (Cr) concentration at the end of treatment according to renal function at the initiation of treatment					
Patients	Creatinine initial (Cr <sub>i</sub> )	Creatinine final (Cr <sub>f</sub> )	Cr <sub>i</sub> -Cr <sub>f</sub> differences	Percentage of change	P value
All patients, n = 122					
Mean (SD)	0.92 (0.85)	0.96 (0.66)	0.03 (0.69)	33.29 (92.8)	<0.001
Median (IQR)	0.65 (0.43-1.11)	0.80 (0.50-1.30)	0.02 (-0.13-0.20)	5.37 (-20.0-43.6)	<0.001
Range	0.03-4.70	0.08-3.80	-2.55-1.85	-71.4-492.9	
Cr > 1.5 mg/dL, n=16					
Mean (SD)	2.71 (1.01)	1.69 (0.77)	-1.02 (1.00)	-32.85	0.035
Median (IQR)	2.40 (1.83-3.64)	1.50 (1.14-1.90)	-1.08 (-1.72- -0.16)	-44.34	0.035
Range	1.60-4.70	0.90-3.80	-2.55-0.90	-71.4 - 50.0	
Cr ≤1.5 mg/dL, n=106					
Mean (SD)	0.65 (0.35)	0.85 (0.57)	0.19 (0.46)	43.28 (94.9)	<0.001
Median (IQR)	0.60 (0.39-0.89)	0.69 (0.45-1.06)	0.07 (-0.07-0.27)	14.87 (-10.26-59.68)	<0.001
Range	0.03-1.50	0.08-2.50	-0.52-1.85	-64.7-492.9	

IQR: interquartile range (25th-75th percentile).

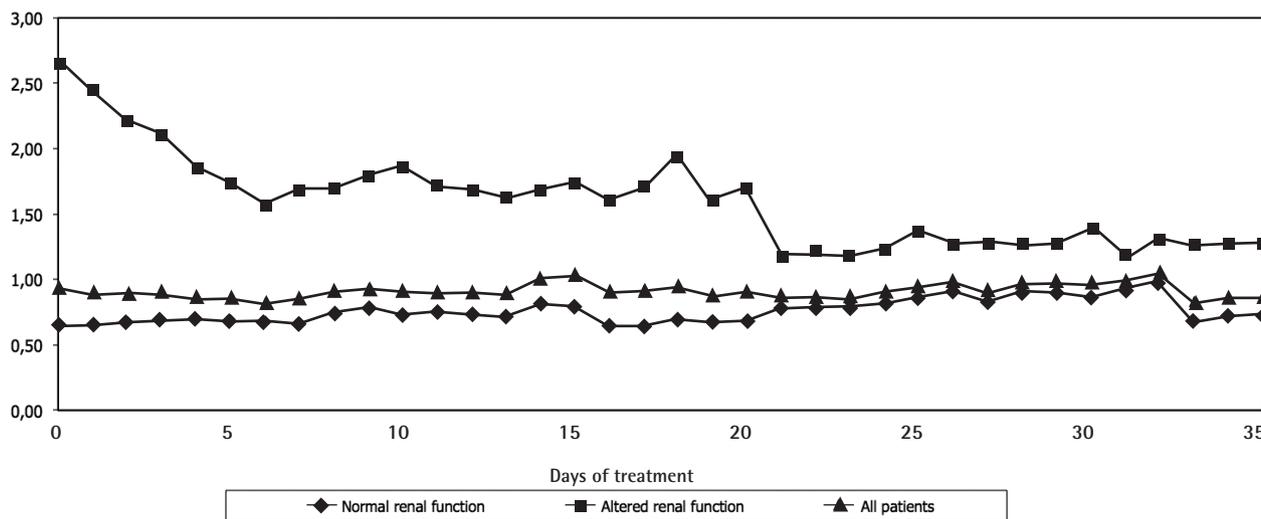


Figure 1 Mean serum creatinine levels (mg/dL) in patients treated with L-AmB according to serum creatinine level at the initiation of treatment (> 1.5 mg/dL or ≤ 1.5 mg/dL)

As opposed to the study of Walsh et al.<sup>17</sup>, in our series, L-AmB was administered as directed and first-line treatment in more than half of the patients, independently of the renal function. When L-AmB was indicated as rescue treatment (poor clinical course, toxicity), in most of the cases, was prescribed after the use of different azoles. In a previous study carried out by our group<sup>23</sup>, differences in clinical and microbiological responses between patients previously treated with

azoles and the remaining patients treated with L-AmB were not observed.

The presence of renal function impairment at the beginning of L-AmB treatment was not associated with a lower daily dose or a shorter duration of treatment. In fact, total cumulative dose was significantly higher in patients with impaired renal function. It is possible that the absence of differences in

the duration of treatment and daily doses may be due to the lack of toxicity recorded during the next days after the initiation of treatment.

Results of the present study should be interpreted according to limitations of retrospective and multicenter studies in relation to the variability of observers and the absence of study protocols and consensus on treatment approaches. In contrast, this is the second study carried out with the same objective with the participation of the majority of the same hospitals, which allowed standardize definitions. On the other hand, the primary endpoint to assess tolerability of L-AmB has been the difference between final and initial serum Cr level because calculation of creatinine clearance was not possible in all participating centers. The cutoff of 1.5 mg/dL to differentiate patients with impaired renal function was arbitrarily chosen and was the same used in the first study<sup>15</sup>.

In conclusion, treatment with L-AmB in critically ill patients with renal function impairment had a minimal impact on renal function as determined by serum Cr concentrations. These data suggest that L-AmB is a valuable option for the treatment of fungal infections in critically ill patients independently of renal function at the initiation of treatment.

## ACKNOWLEDGMENTS

The authors thank Marta Pulido, MD, for editing the manuscript and editorial assistance.

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