

## Comparison of effects of amphotericin B deoxycholate infused over 4 or 24 hours: randomised controlled trial

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### Abstract

**Objective** To test the hypothesis that amphotericin B deoxycholate is less toxic when given by continuous infusion than by conventional rapid infusion.

**Design** Randomised, controlled, non-blinded, single centre study.

**Setting** University hospital providing tertiary clinical care.

**Patients** 80 mostly neutropenic patients with refractory fever and suspected or proved invasive fungal infections.

**Intervention** Patients were randomised to receive 0.97 mg/kg amphotericin B by continuous infusion over 24 hours or 0.95 mg/kg by rapid infusion over four hours.

**Main outcome measures** Patients were evaluated for side effects related to infusion, nephrotoxicity, and mortality up to three months after treatment. Analysis was on an intention to treat basis.

**Results** Patients in the continuous infusion group had fewer side effects and significantly reduced nephrotoxicity than those in the rapid infusion group. Overall mortality was higher during treatment and after three months' follow up in the rapid infusion than in the continuous infusion group.

**Conclusion** Continuous infusions of amphotericin B reduce nephrotoxicity and side effects related to infusion without increasing mortality.

### Introduction

Amphotericin B deoxycholate has remained the mainstay of treatment for life threatening fungal infections in immunocompromised patients because of its broad fungicidal activity and cheapness. Treatment with amphotericin B, however, is associated with acute reactions related to infusion and dose dependent nephrotoxicity. It is recommended that amphotericin B is infused slowly over two to six hours, based on the assumption that the severity and frequency of toxic reactions increase during more rapid infusions.<sup>1-4</sup>

Incorporation of amphotericin B into liposomal formulations reduces its toxicity, but the reasons for this are unclear.<sup>5-11</sup> As liposomes do not specifically target fungal cells it would seem that the reduction in toxicity, at least in part, depends on a slower delivery of amphotericin B to tissues. The question as to whether a slower delivery of amphotericin B from lipid formu-

lations might be reproduced by a slow infusion rate therefore arises. The hypothesis that a continuous infusion of amphotericin B results in reduced toxicity has not been addressed yet in a prospective study. We therefore conducted a randomised, controlled, and open trial to compare the toxicity of amphotericin B given as a continuous infusion with a conventional rapid regimen over four hours.

### Patients and methods

#### *Inclusion and exclusion criteria and treatment*

All consecutive patients at our tertiary referral centre for adult internal medicine (Zurich University Hospital), including those at the medical intensive care unit, were considered eligible for entry to the study, providing their doctors had decided to start treatment with amphotericin B. Exclusion criteria were a baseline serum creatinine concentration in excess of 300  $\mu\text{mol/l}$  or systemic treatment with amphotericin B within the past seven days.

Patients received either a continuous (24 hours) or a rapid (four hours) infusion of amphotericin B. The drug was given in 500 ml of 5% glucose without any additives through a separate intravenous line. To take into account clinical practice patterns, doctors were free to adjust the drug dose during the study if necessary.

Drugs to prevent chills or fever were prohibited on day 1 of entry to the study.<sup>12</sup> To reduce nephrotoxicity from amphotericin B all patients received infusions of saline as standard care.<sup>13-15</sup> The protocol gave no other restrictions on the use of any concomitant treatment.

#### *Outcome measures*

Chills, rigors, and vomiting were monitored prospectively. Each patient completed a standardised questionnaire daily until the end of the study and was interviewed regularly. We also evaluated nursing charts for any other adverse reaction. Temperature was measured at least three times daily. Fever was defined as a core temperature of at least 39.3°C (core temperature readings are 1°C above the peripheral temperature readings). The concentrations of C reactive protein were determined every 24 hours during the first three days and at least every other day thereafter.

Serum creatinine concentrations were measured daily during treatment. To obtain a variable for nephrotoxicity independent of age and body mass, we

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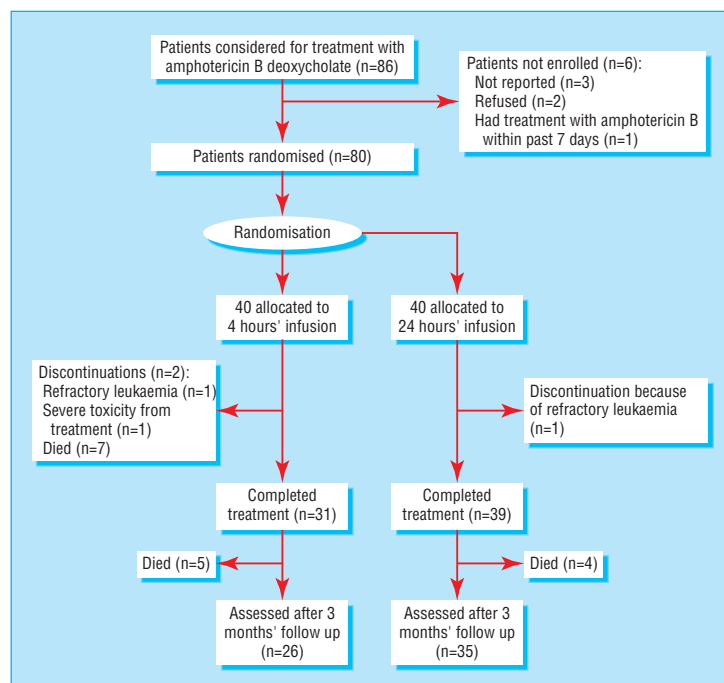


Fig 1 Trial profile

used a model of calculated creatinine clearance based on lean body mass.<sup>16 17</sup> This model predicts accurately the change in creatinine clearance from serum creatinine values. It works equally for patients with either stable or unstable renal function. Creatinine clearance per lean body mass may be calculated according to the formula  $Cl_{LBM} = E/S + [600 \times (S_1 - S_2) / (T \times S)]$ , where S is the mean of two serum creatinine values  $S_1$  and  $S_2$ , T is the time interval between  $S_1$  and  $S_2$ , and E corresponds to an age dependent urinary creatinine excretion rate in mg/min/50 kg lean body mass.<sup>17</sup>

Electrolytes, pH, and venous bicarbonate concentrations were measured every other day. Hypokalaemia was defined as a serum potassium concentration less

than 2.5 mmol/l and hypomagnesaemia as a serum magnesium concentration less than 0.5 mmol/l, regardless of any enteral or parenteral substitution. Efficacy was monitored for overall mortality, mortality due to invasive fungal infections, and breakthrough fungaemia during treatment.

Statistics and study ethics

Analysis was on an intention to treat basis. The design of our trial was based on a prior power calculation for the calculated serum creatinine clearance at the end of treatment. The possible difference between the study arms was estimated from a retrospective analysis of patients receiving amphotericin B at our centre. We planned to randomise 40 patients to each arm so as to achieve a power of 90% for the detection of an effect size of  $[difference]/[standard\ deviation] = 0.8$  when applying a two sided t test at the 5% level. For the calculated creatinine clearance, this corresponds to a difference of at least 20 ml/min between the treatments, assuming a standard deviation of 25 ml/min within each group.

We present continuous data as the median (range), which were evaluated using the Mann-Whitney U test. The effect of treatment was reported as the difference of medians between study groups. We calculated the differences of medians with the Hodge-Lehmann estimator and the confidence intervals of median differences with the exact distribution of the Mann-Whitney test statistic.<sup>18</sup> We present dichotomous data as the number of patients, analysed with Fisher's exact test. We report the effect of amphotericin B treatment for dichotomous data as relative risk. Confidence intervals for relative risks were obtained as described previously.<sup>19</sup> We considered differences for which  $P < 0.05$  significant.

Study ethics—Our study was approved by the institutional ethics committee of Zurich University Hospital. We obtained written consent from all patients at enrolment.

Assignment

The initial dosage for amphotericin B was chosen before randomisation by the doctors in charge, who were not members of the study team. Eligible patients were then randomised in blocks of 10 by sealed envelope. Treatment started immediately after randomisation.

Results

Patient flow and follow up

Figure 1 shows the flow of patients through the trial. Patients were followed up three months after completion of treatment or when treatment was discontinued for any reason.

Analysis

Patients—Overall, 86 consecutive patients received amphotericin B during the study period. Most of them were severely neutropenic, with haematological neoplasias. Of these patients, only three had not been reported to the study team. One patient was not eligible because of amphotericin B treatment within the past seven days, and two did not give their consent. We

Table 1 Dosages of amphotericin B deoxycholate and characteristics of patients receiving rapid (four hours) and continuous (24 hours) infusions of the drug. Values are numbers (percentages) of patients unless stated otherwise

	Infusion rate	
	Rapid (n=40)	Continuous (n=40)
Median age (range)	46 (20-75)	47 (17-74)
Median (range) No of days of treatment	12 (3-51)	16 (3-89)
Median (range) maximum daily dose (mg/kg)	0.95 (0.4-1.2)	0.96 (0.5-1.5)
Median (range) cumulative dose (mg/kg)	10.8 (2.1-42.7)	14.3 (1.8-89.0)
Male	22	27
Diagnosis:		
Acute myeloid leukaemia	29 (73)	25 (63)
Acute lymphatic leukaemia	4 (10)	5 (13)
Lymphoma	4 (10)	5 (13)
Solid tumour	2 (5)	2 (5)
HIV	0	2 (5)
Others	1 (3)	1 (3)
Neutropenia (<500/ $\mu$ l)	36 (90)	37 (93)
Concurrent treatment:		
Aminoglycosides	18 (45)	22 (55)
Vancomycin	10 (25)	11 (28)
Diuretics	18 (45)	16 (40)
Granulocyte colony stimulating factor	13 (33)	18 (45)

enrolled 80 patients. The study population also included patients with moderately impaired renal function (baseline serum creatinine concentration less than 300  $\mu\text{mol/l}$ ). The groups did not differ significantly with regard to treatment with aminoglycosides, vancomycin, diuretics, and granulocyte colony stimulating factor. No patient received cyclosporin (table 1). At enrolment the two groups did not differ significantly regarding number of patients with refractory fever and probable and proved fungal infections (table 2).

**Dosage and dose reductions**—Overall duration of treatment and cumulative and daily doses did not differ significantly between the groups. There was a non-significant trend towards longer duration of treatment and higher cumulative doses in the continuous infusion group. We observed significantly more dose reductions or infusion interruptions due to side effects in the rapid infusion group (table 3).

**Side effects**—The major side effects related to infusion were chills, fever, and vomiting. They occurred mainly during the first three days of treatment. We also observed flushing reactions, rashes, and headaches. Patients receiving continuous infusions had fewer side effects. We found significantly more patients with fever in the rapid infusion group during the first 24 hours after treatment had started (fig 2). For those who had fever at the beginning of treatment there was also a significant difference in the mean time to defervescence (table 3). The concentrations of C reactive protein did not differ between the two groups at entry to the study, but there was a significant increase in the rapid infusion group 24 and 48 hours after the start of treatment. Concentrations gradually decreased from baseline levels in the continuous infusion group (fig 3). Reflecting the reduced frequency of side effects in the continuous infusion group, these patients were less likely to receive drugs directed against febrile reactions or chills after the first treatment day (table 3).

**Nephrotoxicity**—The serum creatinine concentration or calculated creatinine clearance did not differ between the two groups at baseline. Comparing the ratio of peak serum creatinine to baseline creatinine

**Table 2** Indications for treatment with amphotericin B deoxycholate, by rapid (four hours) or continuous (24 hours) infusion. Values are numbers (percentages) of patients

	Infusion rate	
	Rapid (n=40)	Continuous (n=40)
Refractory fever	18 (45)	12 (30)
Possible fungal infection	12 (30)	8 (20)
Probable fungal infection	10 (25)	17 (43)
Proved fungal infection	0	3* (8)

\* Cryptococcosis (two patients), pulmonary aspergillosis (one).

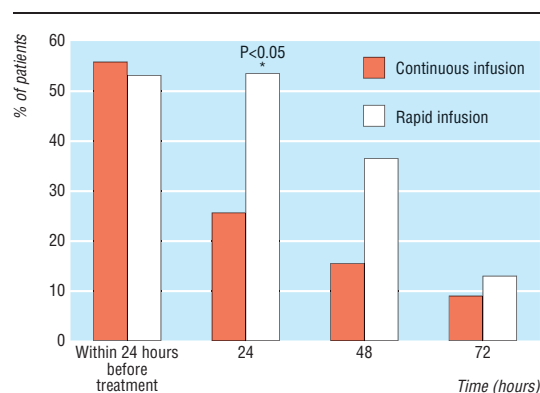
**Table 3** Infusion related side effects and drugs to suppress febrile reactions in patients receiving rapid (four hours) or continuous (24 hours) infusions of amphotericin B deoxycholate. Values are numbers (percentages) of patients unless stated otherwise

	Infusion rate		P value	Relative risk (95% CI)
	Rapid (n=40)	Continuous (n=40)		
Reactions on day 1:				
Fever*	21 (53)	10 (25)	0.021	2.1 (1.1 to 3.9)
Chills or rigors	21 (53)	5 (13)	0.0003	4.2 (1.8 to 10)
Vomiting	14 (35)	4 (10)	0.009	3.5 (1.3 to 9.7)
Headache	4 (10)	0		
Others	1 (3)	0		
Overall reactions:				
Chills or rigors	25 (63)	8 (20)	0.0001	3.1 (1.6 to 6.1)
Vomiting	24 (60)	11 (28)	0.004	2.2 (1.2 to 3.8)
Headache	11 (28)	4 (10)		
Others	8 (20)	2 (5)		
Drugs after day 1:				
Meperidine	20 (50)	6 (15)	0.002	3.3 (1.5 to 7.4)
Steroids	18 (45)	3 (8)	0.0001	6 (1.9 to 19)
Acetaminophen	30 (75)	19 (48)	0.021	1.6 (1.1 to 2.3)
Dose reductions or infusion interruption	11 (28)	3 (8)	0.022	3.7 (1.1 to 12)
Median (range) defervescence† (days)	2 (1-10)	1 (1-4)	0.016	-1 (-2 to 0)‡

\* $>39.3^{\circ}\text{C}$  core temperature (corresponding to an axillary temperature of  $38.3^{\circ}\text{C}$ ).

†Fever within 24 hours before treatment was documented for 26 patients in the rapid infusion group and 22 patients in the continuous infusion group.

‡Median difference.



**Fig 2** Percentage of patients with fever during first days of treatment with amphotericin B

concentrations during and at the end of treatment, we found a significantly higher ratio in the rapid infusion group (table 4). The increase in serum creatinine concentration was reversible in all but two patients, both assigned to the rapid infusion group, within three months after treatment had been completed. Comparison of the calculated creatinine clearance ratios between both infusion groups illustrates a significantly less impaired creatinine clearance for patients with

## Definitions

### Refractory fever

Persistent fever for more than 72 hours despite antibiotics in patients who are neutropenic (less than 500 neutrophils/ $\mu\text{l}$ )

### Possible fungal infections

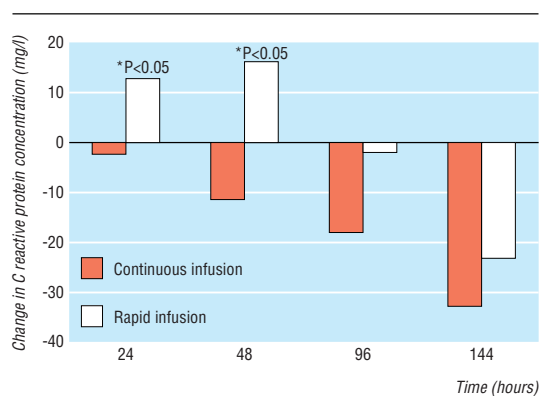
Persistent fever, neutropenia, chest symptoms, or the presence of pulmonary infiltrations on chest radiographs

### Probable fungal infections

Persistent fever or increased concentration of C reactive protein, neutropenia, and infiltrates characteristic of fungal pneumonia on a computed tomogram

### Proved fungal infections

Typical infiltrates on a computed tomogram and detection of moulds in bronchoalveolar lavage or bronchial secretions by culture and microscopy during neutropenia, or presence of pathogenic fungi in usually sterile sites



**Fig 3** C reactive protein (CRP) concentrations during treatment with amphotericin B compared with baseline levels, expressed as median of  $\Delta$ CRP ( $\Delta$ CRP=CRP-CRP<sub>baseline</sub>) in mg/l

continuous infusions during and at the end of treatment (table 4).

The proportion of patients who had hypokalaemia or hypomagnesaemia did not differ significantly between the two groups. Hypokalaemia was observed in 10 patients in the rapid infusion group and four patients in the continuous infusion group. Hypomagnesaemia occurred in 19 patients in the rapid infusion group and 17 patients in the continuous infusion group (table 4).

#### Efficacy

All seven deaths during treatment occurred in the rapid infusion group. Necropsy was carried out in six of these seven cases and severe pneumonia was found. Invasive fungi were proved in three cases; in one case *Pneumocystis carinii* was detected. In two patients no infection was found. Breakthrough fungaemia did not occur in any patient of either group (table 5).

Treatment was discontinued in two patients assigned to rapid infusion: one because of refractory leukaemia and the other because of severe nephrotoxicity from treatment. Treatment was discontinued in one patient in the continuous infusion group because of refractory leukaemia. None of the patients with refractory disease showed invasive mycosis at necropsy.

After 3 months' follow up the two groups still differed with regard to death (table 5). All patients recovered from neutropenia, with the exception of those who died or where treatment had been discontinued.

## Discussion

Continuous infusions of amphotericin B are significantly better tolerated than rapid infusions. Similar advantages of continuous infusions could be sought for other toxic drugs—for example, antineoplastic agents. Continuous applications are, however, not feasible if high peak values are necessary for efficacy (that is, with aminoglycosides). The rapid infusion of amphotericin B over fewer hours has been adopted empirically in clinical practice. Despite a retrospective analysis suggesting fewer side effects from continuous infusions, no controlled trials have compared rapid and continuous infusions of amphotericin B.<sup>2</sup>

Our study was not blinded for practical reasons. Nevertheless, differences in toxicity between groups were evident regarding C reactive protein and creatinine concentrations, which were assessed at predetermined times and were not biased by the non-blinded study design. The reduction of side effects by continuous infusion of amphotericin B seems comparable to recent reports of liposomal amphotericin B (table 6),<sup>8</sup> despite higher daily and cumulative doses being given in our study. Amphotericin B triggers a proinflammatory response by activating different cytokines.<sup>20, 21</sup> Continuous infusions may be better tolerated because of delayed induction or release of such mediators, as reflected by differences in concentrations of C reactive protein and fever. We also observed a noticeable reduction of nephrotoxicity in the continuous infusion group. The mechanisms involved in amphotericin B nephrotoxicity are not yet fully understood.<sup>15</sup> They can be broken down into pre-tubular and tubular effects. Pre-tubular effects, which include mainly a decrease in renal blood flow and glomerular filtration rate, are clearly reduced in patients having continuous infusions, as suggested by only a small decrease in calculated creatinine clearance. No noticeable difference was found in tubular effects between the two groups. Hypokalaemia was

**Table 4** Nephrotoxicity in patients receiving rapid (four hours) or continuous (24 hours) infusion of amphotericin B deoxycholate. Values are median (range) unless stated otherwise

	Infusion rate		P value	Median difference (95% CI)
	Rapid (n=40)	Continuous (n=40)		
Serum creatinine concentration ( $\mu$ mol/l):				
Baseline serum creatinine	78 (51-128)	78 (54-165)		
Maximal creatinine:baseline	1.62 (0.94-3.42)	1.25 (0.91-2.53)	0.005	-0.26 (-0.49 to -0.08)
Creatinine at end of study:baseline	1.55 (0.79-3.42)	1.17 (0.46-2.26)	0.001	-0.32 (-0.53 to -0.13)
Calculated creatinine clearance*:				
Minimal clearance:baseline	0.62 (0.29-1.05)	0.80 (0.39-1.10)	0.013	0.12 (0.03 to 0.22)
Clearance at end of study:baseline	0.65 (0.29-1.26)	0.86 (0.44-1.91)	0.001	0.19 (0.09 to 0.29)
Electrolyte abnormalities:				
No (%) with hypokalaemia (<2.5 mmol/l)	10 (25)	4 (10)		
No (%) with hypernatraemia (>155 mmol/l)	3 (8)	2 (5)		
No (%) with hypomagnesaemia (<0.5 mmol/l)	19 (48)	17 (43)		
Venous bicarbonate concentration†				
Minimal bicarbonate:baseline	0.77 (0.44-1.00)	0.84 (0.59-1.37)	0.015	0.09 (0.02 to 0.17)

\*Creatinine clearance per 50 kg lean body mass calculated from serum creatinine concentrations.

†Data missing for eight (rapid infusion) and five (continuous infusion) patients.

non-significantly decreased and tubular acidosis significantly decreased in the continuous infusion group. These observations are comparable to those in patients treated with liposomal amphotericin B: Walsh et al<sup>8</sup> found no differences in the frequency of hypomagnesaemia between patients treated with liposomal amphotericin B and those receiving amphotericin B. In addition, they found only slight, although significant, differences in the frequency of hypokalaemia. Our study comprised only 80 patients. Nevertheless, hypokalaemia had been observed in 10 patients allocated to the rapid infusion arm compared with four patients in the continuous infusion group. Therefore, as with liposomal amphotericin B, a continuous infusion of amphotericin B primarily reduces pretubular toxicity.

Indications for amphotericin B in our study were proved fungal infections, probable fungal infections, possible fungal infections, and refractory fever during neutropenia. Given the high mortality of invasive mycoses after a delay in treatment, amphotericin B is often prescribed empirically. A definitive baseline diagnosis of invasive mycosis would require invasive diagnostic procedures that are seldom justified in neutropenic and thrombocytopenic patients. It is therefore scarcely ever possible to identify the true prevalence of invasive mycoses, although clinical and radiological criteria (computed tomography) allow some risk stratification. For patients surviving proved mycoses during aplasia it is also difficult to assess efficacy of treatment. For instance, progressive changes in computed tomograms of these patients may represent ongoing infection as well as host response after resolution of neutropenia.<sup>22</sup> In addition, recovery from neutropenia in itself results in healing of invasive mycoses. As criteria for efficacy we therefore chose mortality, mortality due to invasive fungal infections, and breakthrough fungaemia. Although our study population was small for assessment of efficacy, the outcome was encouraging for continuous infusion. We found a higher overall mortality during amphotericin B in the rapid infusion group. Mortality also remained significantly higher after three months' follow up. Despite a higher number of proved or probable fungal infections in the continuous infusion group, three patients died with proved fungal infections at necropsy in the rapid infusion group whereas none died in the continuous infusion group. Accordingly, the death rate in the rapid infusion

**Table 5** Mortality and frequency of invasive fungal infections in patients receiving rapid (four hours) or continuous (24 hours) infusions of amphotericin B deoxycholate. Values are numbers (percentages) of patients

	Infusion rate	
	Rapid (n=40)	Continuous (n=40)
Proved fungal infections	3* (8)	7† (18)
Breakthrough fungaemia	0	0
Mortality:		
During treatment‡	7 (18)	0
After 3 months' follow up§	12 (30)	4 (10)

\*Proved angioinvasive pulmonary mould infection with septated branching hyphae at necropsy.

†Cryptococcosis (two patients), systemic candidiasis (one), pulmonary aspergillosis (three), and pulmonary *Rhizopus pusillus* and *Aspergillus fumigatus* infection (one).

‡P=0.012, relative risk is infinity.

§P=0.048, relative risk (3.0, 95% confidence interval 1.1 to 8.5).

**Table 6** Nephrotoxicity from liposomal amphotericin B<sup>8</sup> and continuous infusions of amphotericin B deoxycholate (24 hours) compared with rapid (four hours) and continuous (24 hours) infusions of amphotericin B deoxycholate in present study. Values are numbers (percentages) of patients

	Walsh et al <sup>8</sup>		Infusion rate	
	Liposomal amphotericin B (n=343)	Amphotericin B deoxycholate (n=344)	Continuous (n=40)	Rapid (n=40)
Creatinine concentration during treatment:				
1.5 times baseline value	99 (29)	168 (49)	13 (33)	23 (58)
2.0 times baseline value	65 (19)	117 (34)	6 (15)	11 (28)
3.0 times baseline value	27 (8)	58 (17)	0	4 (10)
Hypokalaemia	24 (7)	41 (12)	4 (10)	10 (25)

### What is already known on this topic

Amphotericin B is the cornerstone for treatment of invasive fungal infections, especially in neutropenic patients

Its use is limited by general toxic reactions and nephrotoxicity

### What this study adds

By giving amphotericin B as a continuous infusion, both nephrotoxicity and infusion related toxicity can be lowered significantly without loss of efficacy

group was strongly influenced by the occurrence of invasive mycoses. Consequently, our data support the notion that a continuous infusion of amphotericin B may be at least as effective as daily infusions over four hours. We therefore recommend continuous infusions of amphotericin B, where practical, as an effective and well tolerated alternative to the usual rapid infusions.

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Contributors: UE was responsible for preparing, coordinating, performing, and analysing the clinical trial and is the principal author of the paper. BS was responsible for statistical design and analysis. AS had the original idea for the study and participated in designing the protocol and analysing the study data and is coauthor of the paper. UE and AS will act as guarantors for the paper.

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