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REVIEW ARTICLE

Role of diuretics and lipid formulations in the prevention of amphotericin B-induced nephrotoxicity

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Abstract
Purpose To collect available clinical data to define the role of diuretics and lipid formulations in the prevention of amphotericin B (AmB)-induced nephrotoxicity (AIN) in human populations.
Method A literature search was performed in the following databases: Scopus, Medline, Embase, Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews.
Results and conclusion Co-administration of mannitol failed to show any clinically significant benefit in preventing AIN. Potassium-sparing diuretics, such as amiloride and spironolactone, have been shown to have beneficial effects as an alternative or adjunct to oral/-parenteral potassium supplements in preventing hypokalemia due to AmB. Lipid-based formulations of AmB are clinically effective and safe in preventing AIN. However, due to their high cost and limited accessibility, these formulations are generally used as second-line antifungal therapy in cases of conventional AmB refractoriness and/or intolerance or pre-existing renal dysfunction. The potential effects of other nephroprotective agents, such as N-acetylcysteine, AIN merit further considerations and investigations.

Keywords Amphotericin · Nephrotoxicity · Prevention

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Introduction

Amphotericin B (AmB) is a polyene antibiotic that was first isolated from *Streptomyces nodosus* in 1955. It has remained a mainstay of antifungal therapy for disseminated, serious, and life-threatening mycotic infections despite the introduction of newer antifungal agents [1] and its association with wide variety of acute and chronic adverse reactions that can limit its use. Nephrotoxicity is the most clinically significant adverse reaction of AmB, and up to 80 % patients receiving AmB have been found to develop some degree of reversible renal impairment within the first 2 weeks of treatment [2–5].

The exact pathophysiology of AmB-induced nephrotoxicity (AIN) has not been fully elucidated, but several probable mechanisms have been suggested. Direct vasoconstriction of systemic blood vessels as well as afferent arterioles by AmB itself or its deoxycholate moiety could cause an acute reduction in renal blood flow and glomerular filtration rate (GFR) within minutes after intravenous administration of this antibiotic. The reduction in GFR following AmB administration may not only be due to direct renal vasoconstriction, but also partly mediated by the tubule–glomerular feedback system. Increase in the permeability of the distal tubule can also enhance passive distal potassium as well as magnesium diffusion and, consequently, results in hypokalemia and hypomagnesemia, respectively [1, 6, 7].

Clinical manifestations of AIN include renal insufficiency, such as increases in serum creatinine level, urinary potassium wasting and hypokalemia (frequency 75–90 %), urinary magnesium wasting and hypomagnesemia (frequency 15.3–48.9 %), metabolic acidosis due to type 1 (distal) tubular acidosis, and polyuria due to nephrogenic diabetes insipidus [1, 8, 9]. Hypokalemia and hypomagnesemia itself can cause serious complications such as metabolic complications, rhabdomyolysis, and life-threatening arrhythmias [10].

Risk factors for AIN include male sex, high average daily dose of AmB (>35 mg/day), high cumulative dose of AmB (>2–5 g), hypovolemia, co-administration of diuretics, concomitant use of nephrotoxic agents (such as aminoglycosides, cyclosporine) or corticosteroids, and baseline renal dysfunction [1, 7].

Given the high incidence of AIN and its subsequent clinical and economical complications, such as prolonged length of hospital stay, increment of total treatment costs, and mortality [11], numerous experimental and clinical studies have been performed within the past 4 decades to explore effective interventions for preventing or minimizing the nephrotoxic impacts of AmB. Current clinical data clearly demonstrate that salt loading can prevent or alleviate AIN. The effects of this approach and prolongation of the duration of AmB infusion in the prevention of AIN have been critically reviewed by us recently [12]. The aim of the present literature review is to collect available clinical data specifically related to the actual role of diuretics and lipid formulations in the prevention of AIN in human populations.

Methods

A literature search was performed in the relevant databases, including Scopus, Medline, Embase, Cochrane Central Register of Controlled Trials, and Cochrane Database Systematic Reviews. The key words used were "amphotericin (B) and nephrotoxicity", "amphotericin (B) and renal failure", "amphotericin (B) and renal damage", "amphotericin (B) and renal dysfunction", and "amphotericin (B) and renal impairment". Literature searches using the above terms yielded more than 250 abstracts. The search was further limited by adding the search terms "lipid formulations", "lipid-based formulations", "intravenous lipid emulsion", "Intralipid", "loop diuretics", "thiazide diuretics", "osmotic diuretics", or "potassium sparing diuretics". Randomized clinical trials, prospective or retrospective human studies, case series, and case reports were included in this review. Regarding lipid-based formulations of AmB, only head-to-head clinical trials comparing clinical efficacy and renal safety of different lipid formulations of AmB with conventional AmB, as well as different lipid formulations of AmB with each other, have been included. No time limitation was considered in this review. Non-English language articles, congress abstracts, and in vitro and experimental studies were not eligible for inclusion. Based on these inclusion and exclusion criteria, we included 38 articles in this review.

Results

Osmotic and potassium-sparing diuretics

Mannitol As an osmotic diuretic, mannitol primarily acts at the proximal tubule and loop of Henle by driving water from intracellular compartments. Mannitol can flush out intratubular casts and diminish the backleak of the filtrate into the interstitial space. It can also act as a free radical scavenger, preserve mitochondrial function, and improve renal blood flow [13, 14]. In dogs, mannitol has been found to exert protective effects against GFR reduction induced by AmB, probably through the reduction of renal blood flow secondary to AmB-induced renal vasoconstriction [15]. In 1976, Rosch et al. reported beneficial effects of co-administered mannitol (25 g over 4 h, three times a week) in the prevention of AIN in a female patient with candidiasis–polyendocrinopathy syndrome. These authors proposed that mannitol probably exerts its protective effects via increasing the renal blood flow and GFR [16]. Hellebusch et al. [15], in their study on dogs, failed to show any significant difference in serum and urine levels of AmB in dogs treated with and without mannitol, thus indicating that the beneficial effects of AmB may not be due to an increase in the renal clearance of AmB and, consequently, to decreases in its serum level. According to the results of a case report, mannitol may be valuable as an adjunct therapy with AmB in patients with mild to moderate renal impairment [16]. In a case series published in 1975, Olivero et al. demonstrated the successful use of mannitol (12.5 g before and after each course of infusion) in four renal transplant recipients who received AmB for systemic fungal infections. No significant change in blood urea nitrogen (BUN) or serum creatinine (Scr) after AmB treatment was detected, but the patients did develop a mild metabolic acidosis, suggesting that mannitol could only prevent AmB-induced azotaemia, which is a vasomotor phenomenon, but not renal acidosis, which might be the consequence of the tubular toxicity of AmB. These authors proposed that patients receiving AmB should receive mannitol along with bicarbonate to fully protect the kidney from both mechanisms of renal injury by AmB, including vasoconstriction and direct tubular toxicity [17]. The first and only prospective, double-blind, controlled clinical trial that has evaluated the capacity of mannitol in reducing AIN was conducted by Bullock et al. [18]. Eleven patients with systemic fungal infections treated with AmB (1.0 mg/kg on alternate days) were randomly assigned to the control (n=6) and mannitol treatment groups (n=5). The control group received AmB alone. Mannitol at a dose of 1.0 g/kg was added to AmB solution in 5 % dextrose in water and infused over 4 h. The decrease in creatinine clearance (CrCl) and urinary concentrating ability following AmB administration was comparable both groups. The

failure of mannitol to diminish AIN could be partially due to the inadequacy of administered mannitol dose (1 g/kg) [18]. However, 1 g/kg of mannitol was about twice the dose used in the experimental study [15] as well as the case series [17]. Furthermore, an increase in mannitol dosage might result in several complications, such as dehydration, hyponatremia, and hypokalemia. In conclusion, these findings suggest that mannitol might not be effective in preventing either functional or histological manifestations of AIN [18].

Several animal and anecdotal human studies have been demonstrated the beneficial effects of mannitol in preventing and treating of acute kidney injury [13]. The results of an experimental study as well as a randomized clinical trial suggested that mannitol may attenuate cisplatin nephrotoxicity by reducing the concentration of platinum in the urine [19, 20]. However, significant adverse effects can be associated with mannitol, such as volume depletion or hypernatremia. The administration of very high doses of mannitol to patients with marked renal dysfunction can result in hyperosmolality, volume expansion, hyperkalemia, and metabolic acidosis [14]. Furthermore, the sample size of the only controlled clinical trial on mannitol efficacy in reducing AIN is too small (n=11). Therefore, the study is likely too underpowered to detect a clinically significant difference [18]. Despite the above-mentioned drawbacks, mannitol is commonly used for preventing and treating acute kidney injury in certain clinical settings, including the perioperative (cardiac, vascular surgery, biliary surgery) period, post transplantation, and rhabdomyolysis [14]. The combined use of mannitol with low-dose dopamine and/or sodium bicarbonate might be clinically effective in preventing AIN, although this has not been evaluated in clinical studies.

Amiloride Amiloride has both potassium- and magnesium-sparing effects. By directly blocking the epithelial sodium channels located in the distal convoluted tubule of the kidney, amiloride increases urinary excretion of sodium and bicarbonate while decreasing urinary potassium excretion. It also inhibits sodium absorption from the distal colon. Therefore, theoretically, the use of amiloride to prevent or reduce hypokalemia and hypomagnesemia due to AmB seems rational [10]. This theory was first assessed by Smith et al. [21] in a prospective, controlled, clinical trial. Twenty neutropenic patients with various hematological disorders receiving AmB 0.5 mg/kg/day were randomized to the control (n=10) and amiloride treatment groups (n=10). Amiloride 5.0 mg was given orally twice daily, 1 h before initiating AmB infusion and 5 h after completion of the AmB infusion. The plasma potassium level was significantly higher in the amiloride treatment group (P<0.01), while urinary potassium loss as well as daily potassium supplementation was significantly higher in the control group (P<0.01). Hypomagnesemia requiring correction with intravenous magnesium supplementation developed in two versus one patient receiving AmB alone and AmB + amiloride, respectively. Interestingly, no clinically significant adverse reaction was observed in the amiloride treatment group [21]. A retrospective study in 19 oncology and bone marrow transplant patients receiving AmB (≥0.3 mg/kg/day) for suspected or documented fungal infections showed that mean serum potassium level in the 5 days following amiloride initiation was significantly higher than that in the 5 days preceding starting amiloride (P=0.002). Total potassium intake and amount of potassium supplement requirement were higher in the 5 days preceding amiloride treatment than in the 5 days following the initiation of amiloride treatment; however, these differences did not reach the level of statistical significance. In addition, no statistically significant differences were seen in the serum level of magnesium, total magnesium intake, and amount of magnesium supplement requirement before and after amiloride administration [22].

Spironolactone Unlike amiloride, spironolactone exerts its potassium-sparing activity by competitively inhibiting the binding of aldosterone to its receptors in the late distal tubule and collecting duct of the kidney [23]. Ural et al. [24] conducted a prospective, randomized, controlled clinical trial to evaluate the ability of spironolactone in preventing hypokalemia and reducing potassium requirements in 26 neutropenic patients with various hematological disorders on an AmB treatment regimen. Patients were randomly assigned into two equally sized groups of AmB alone or AmB concomitant with spironolactone (100 mg orally twice a day). The plasma potassium level was significantly higher in the group receiving spironolactone (P=0.0027). Potassium supplementation as well as urinary losses of potassium were significantly higher in patients treated with AmB alone than in those receiving AmB together with spironolactone (P=0.0223 and P=0.0402, respectively). No clinically significant adverse reaction was observed in the group receiving spironolactone [24].

The results of these studies primarily suggest the clinical efficacy and safety of potassium-sparing diuretics, including spironolactone (100 mg orally, twice daily) and amiloride (5 mg orally, twice daily), in preventing hypokalemia due to AmB [21, 22, 24]. However, the relatively small sample size appears to considerably limit the statistical power of these studies. Correction of the concomitant hypomagnesemia could also be helpful in the prevention or treatment of AmB-induced hypokalemia [8]. Regular monitoring of potassium serum level during AmB treatment is highly recommended [10]. There is no conclusive guideline for preventing and monitoring hypomagnesemia due to medications, such as AmB. Preventative approaches include oral

or parenteral supplementation, combination of these two approaches, or potassium-sparing diuretics, such as amiloride or spironolactone. Based on a review of more than published 100 cases of AmB-associated hypomagnesemia and at least one report of AmB-related hypomagnesemia with moderate to severe clinical manifestations, Atsmon et al. categorized hypomagnesemia due to AmB as clinically significant and suggested the frequent monitoring of magnesium level during AmB therapy as well as the consideration of preventive treatments [8].

Preparing conventional amB in intravenous lipid emulsion

Intralipid is an emulsion of soybean oil, egg yolk phosphatidylcholine, and glycerol that is used as a source of calories and essential fatty acids (linolenic acid and linoleic acid) for patients requiring parenteral nutrition [25]. Because of the high cost of Intralipid and limited accessibility to new lipid formulations of AmB, many efforts have been made to develop less nephrotoxic formulations of AmB which are also less expensive, stable, safe, and easily prepared. An experimental study in 1988 demonstrated that an AmB emulsion in Intralipid 20 % reduced nephrotoxicity (polyuria and urinary potassium loss) without altering its efficacy in treating systemic murine candidiasis [26]. Following the publication of this report, several clinical studies in different settings were performed in the attempt to show similar findings in humans (table 1).

Neutropenic patients

Moreau et al. were the first researchers to design a prospective, randomized study to compare the nephrotoxicity of AmB in 5 % dextrose with that of Intralipid 20 % in neutropenic patients. The incidence of renal toxicity was significantly lower in the group receiving AmB in Intralipid 20 % than in that receiving AmB in 5 % dextrose (2/16 vs. 9/16, respectively; $P<0.05$). Due to lower rate of nephrotoxicity, the mean duration of AmB administration in the AmB/Intralipid 20 % group was higher than that in the AmB/5 % dextrose group (18 vs. 11 days, respectively) [27]. Similar to the results of Moreau et al., a research group in Spain reported that compared with AmB in dextrose 5 %, AmB in Intralipid 20 % vehicle in neutropenic patients with hematological malignancies was associated with a statistically significant lower Scr ($P=0.047$), serum urea ($P=0.023$), and comparable antifungal efficacy [28]. In a small study in 14 neutropenic patients receiving AmB diluted in Intralipid 20 % for the treatment of candidemia, Scr remained within the normal range, the decrease in CrCl was mild, and no dose reduction of AmB due to nephrotoxicity was required during treatment [29]. Another prospective, randomized, non blinded study in 51 neutropenic cancer patients with pneumonia or fever of unknown origin was conducted by Schöffski et al. [30]. The patients received AmB dissolved in 5 % dextrose or Intralipid 20 %. The cumulative potassium requirement was significantly lower in patients receiving AmB in Intralipid 20 % than in those receiving AmB in 5 % dextrose (1,194 vs. 1,750 mmol, respectively; $P=0.037$); however, the incidence of hypokalemia was not statistically different in the two groups. Furthermore, no statistically significant differences were found between the groups in terms of Scr and BUN levels, CrCl, and dialysis requirement. Pulmonary events, including respiratory pain, pleuritis, fibrosis, and adult respiratory distress syndrome, occurred more frequently in patients receiving AmB in Intralipid 20 % ($P=0.029$). This was the first time that such pulmonary events had been reported in this context. Due to the sudden and transient nature of these symptoms, performing specific pulmonary function tests, bronchoscopy, or biopsy was not feasible to confirm these pulmonary events. However, the temporal relation between the infusion of AmB in Intralipid, the development of pulmonary events, and the rapid resolution of the pulmonary events upon discontinuation of the infusion all suggest a causal association. The authors attributed the pulmonary toxicity to several probable phenomena, including rapid infusion of Intralipid, fat overload syndrome (pulmonary events related to repeated infusions of concentrated soya bean oil preparations), or chemical incompatibility between Intralipid and AmB which can cause the precipitation and formation of AmB particles that may occlude the pulmonary artery [30].

Patients with malignancy

Caillot et al. [31] performed a single-center, randomized, open, controlled trial comparing clinical tolerance and nephrotoxicity of AmB diluted in 5 % dextrose with AmB diluted in Intralipid 20 % in 42 patients with hematological malignancies. Along with daily monitoring of Scr and electrolytes, the authors determined trough and peak concentrations of AmB during the first 5 days of treatment. Both Scr and the decrease in CrCl were significantly lower in the AmB/Intralipid-treated group than in the AmB/5 % dextrose-treated group ($P=0.0001$ and $P=0.025$, respectively). In terms of potassium requirement, no statistically significant difference was found between the two groups. Significantly more patients in the AmB/5 % dextrose group required magnesium supplementation than in the AmB/Intralipid 20 % group (8/12 vs. 2/11 patients, respectively; $P=0.02$). Unlike peak concentrations, trough concentrations of AmB were significantly higher in the AmB/5 % dextrose-treated group than in the AmB/ Intralipid-treated group ($P=0.01$). Duration of survival and rate of death were not different between the two groups [31]. Another non-

Table 1 Clinical studies published to date that have evaluated renal safety of amphotericin B prepared in intravenous lipid emulsion

Reference	Study design	Underlying disease (number of patients)	Antifungal indication	AmB dose (mg/kg/day)	Method of preparation	Concentration of AmB prepared in Intralipid (mg/mL)	Duration of infusion (h)	Nephrotoxicity definition	Main results
Moreau et al. 1992 [27]	Prospective, randomized, controlled	Hematological malignancies (32)	Fever of unknown origin	0.7–1.0	First dissolved in 5 % dextrose (10 mg with 1 mL) and then mixed with 250 mL of Intralipid 20 %	0.16–0.32	4.0	100 % increase in Scr from the baseline value	The incidence of renal toxicity was significantly lower in the group receiving AmB in Intralipid 20 %
Pascual et al. 1995 [28]	Prospective, randomized, controlled	Hematological malignancies (20)	Proven or suspected fungal infections	Not mentioned in the abstract	Not mentioned in the abstract	1.0	1.0	Not mentioned in the abstract	Infusion of AmB in Intralipid 20 % vehicle was associated with statistically significant lower Scr and serum urea levels
Caillot et al. 1993 [29]	Prospective (without dextrose group)	Hematological malignancies (14)	Candidemia	0.73–1.55	Directly diluted in Intralipid 20 %	1–2	8 (1 mg/mL) 2 (2 mg/mL)	No specific definition	Scr remained within the normal range, decrease in CrCl was mild, and no dose reduction of AmB due to nephrotoxicity was required
Schöffski et al. 1998 [30]	Prospective, randomized, controlled	Hematological or non-hematological malignancies (51)	Fever of unknown origin or pneumonia	0.75	First dissolved in 5 % dextrose (10 mg with 1 mL) and then mixed with 250 mL of Intralipid 20 %	0.19 (Mean)	1–4	No specific definition	No statistically significant differences in Scr, BUN, CrCl, and the rate of dialysis-requiring between two groups
Caillot et al. 1994 [31]	Prospective, randomized, controlled	Hematological malignancies (42)	Fever of unknown origin, documented fungal infection, or non-documented pneumonia	1.0–1.1	Directly diluted in Intralipid 20 %	0.002	2.0	No specific definition	Scr as well as the decrease in CrCl was significantly lower in the AmB in Intralipid-treated group
Nucci et al. 1999 [32]	Multi-centric, prospective, randomized, controlled	Hematological or non-hematological malignancies (61)	Empirical antifungal therapy, documented systemic fungal infections, or secondary prophylaxis	1.0–1.5	First dissolved in 10 mL distilled water and then mixed with Intralipid 10 % (1 mg with 4 mL) or 20 % (1 mg with 2 mL)	0.5 (Intralipid 20 %) 0.25 (Intralipid 10 %)	1.0	≥50 % decrease in CrCl or at least a 0.5-mg/dL increase in Scr from the baseline levels	No statistically significant difference in the rate of nephrotoxicity between 2 groups
Nath et al. 1999 [33]	Single-center, Prospective, randomized, controlled	Hematological or non-hematological malignancies (82)	Fever of u nknown origin	1.0	First dissolved in distilled water and then mixed with Intralipid 20 % (≤40 mg with 100 ml and >40–50 with 250 mL)	0.4 (Maximum)	2.0	No specific definition	No statistically significant difference in Scr and plasma urea concentration changes between 2 groups
Chavanet et al. 1992 [35]	Prospective, randomized, controlled	HIV positive (22)	Oral candidiasis	1.0	Directly diluted in Intralipid 20 %	2.0	1.0	No specific definition	The daily as well as mean increase in Scr from baseline were significantly lower in patients treated with AmB in Intralipid 20 %
Chavanet et al. 1997 [36]	Prospective, randomized, controlled	HIV positive (42)	Oral candidiasis	1, 2, or 3	Directly diluted in Intralipid 20 % (50 mg with 25 ml and >50 mg with 50 mL)	2.0	0.5 mg/kg/h	Scr of≥1.8 mg/dl	The cumulative probability of renal impairment for the highest dose of 3 mg/kg/day was significantly lower than that of 1 mg/kg/day AmB in 5 % dextrose

Table 1 (continued)

Reference	Study design	Underlying disease (number of patients)	Antifungal indication	AmB dose (mg/kg/day)	Method of preparation	Concentration of AmB prepared in Intralipid (mg/mL)	Duration of infusion (h)	Nephrotoxicity definition	Main results
Joly et al. 1996 [37]	Prospective, randomized, controlled	AIDS (90)	Cryptococcal meningitis	0.7–1	Directly diluted in Intralipid 20 % (first, 50 mg with 10 mL and then, reach the final 125 mL)	0.4	2.0	No specific definition	Scr changes from baseline values were significantly higher in patients treated with AmB in Intralipid 20 %
Sorkine et al. 1996 [38]	Prospective, randomized, controlled	Critically illness (60)	Confirmed or suspected candida infection	1.0	Diluted in 250 mL Intralipid 20 %	Not mentioned	3.0	Increase of Scr of >0.3 mg/dL/day or a decrease of CrCl of ≤50 % from baseline values	Nephrotoxicity was occurred less frequently in the AmB in Intralipid 20 % group
Barquist et al. 1999 [39]	Prospective, randomized, controlled	Critically illness (27)	Confirmed fungal infections	1.0	First dissolved in 10 mL diluent and then, mixed with 100 mL of Intralipid 20 %	1.0 (Maximum)	2–3	No specific definition	Residual fraction of CrCl was significantly higher in the patients received AmB in Intralipid 20 %
Thakur 1994 [40]	Prospective, randomized, controlled	Kala-azar (22)	Visceral leishmaniasis unresponsive to sodium stibogluconate and pentamidine	0.05–1.0	First dissolved in 10 mL distilled water and then mixed with Intralipid 10 %	Not mentioned	2.0	No specific definition	No statistically significant differences in Scr between the 2 groups
Sundar et al. 2008 [41]	Open label, non-comparative	Kala-azar (45)	Visceral leishmaniasis unresponsive to sodium stibogluconate	9, 12, or 15 at days 0 and 7	Commercially pre mixed formulation with lipid emulsion (containing egg lecithin, soybean oil, and glycerin)	1.0	15 min (test dose) 2.5 mg/kg/h (remaining dose)	National Cancer Institute (NCI) Common Toxicity Criteria	Pre-mixed formulation of AmB with lipid emulsion was effective as well as safe and no nephrotoxicity or other organ toxicity was observed
Sundar et al. 2009 [42]	Prospective, open-label	Kala-azar (60)	Visceral leishmaniasis unresponsive to antileishmanial drugs other than AmB	15 (total dose) as a single bolus or 2 divided doses on days 1 and 3	Commercially pre mixed formulation with lipid emulsion (containing egg lecithin, soybean oil, and glycerin)	1.0	15 min (test dose) 4.0 (remaining dose)	NCI Common Toxicity Criteria	Pre-mixed formulation of AmB with lipid emulsion was effective as well as safe and no nephrotoxicity was observed
Salama et al. 1997 [43]	Pilot, crossover	Immunocompromised (10)	Systemic candidal infection	1.0	First dissolved in 10 mL distilled water and then mixed with 100 mL Intralipid 20 %	0.5	2.0	≥50 % decrease in calculated CrCl from the baseline values	AmB in Intralipid 20 % vehicle significantly increased CrCl in immunocompromised patients experienced decline in CrCl

HIV, Human-immunodeficiency virus; AIDS, acquired immunodeficiency syndrome; AmB, Amphotericin B; Scr, serum creatinine; BUN, blood urea nitrogen; CrCl, creatinine clearance

blinded, randomized trial in cancer patients demonstrated that nephrotoxicity in patients receiving AmB diluted in Intralipid 10 % did not differ significantly from those receiving the drug diluted in 5 % dextrose (21 vs. 32 %, respectively; P=0.44). Interestingly, hypokalemia occurred less frequently in the group treated with AmB diluted in Intralipid 10 % (21 vs. 58 %; P=0.004) [32]. Nath et al. [33] were the first research group to compare the pharmacokinetics and toxicities of AmB (1.0 mg/kg/day) in Intralipid 20 % to those of AmB in 5 % dextrose in a prospective, randomized, open-label, controlled, clinical trial in children with malignant disease. The AmB concentration was determined from samples collected on the first day of the treatment. The mean, maximum concentration, and area under the curve (AUC) from 0 to 24 h of AmB in the AmB/Intralipid 20 % group were significantly lower than those in the group receiving AmB in 5 % dextrose. In contrast, the volume of distribution at steady-state (V_{SS}) as well as the clearance of AmB were significantly higher in the AmB/Intralipid 20 %-treated group. There was no significant difference in Scr and plasma urea concentration changes nor in potassium requirement between the two groups. The authors ascribed the differences in the pharmacokinetic parameters of AmB in the two groups to variation in the particle size of AmB in 5 % dextrose and Intralipid 20 % and/or Intralipid competition with lipoproteins for binding to AmB molecules [33]. Another study reported that the particle size of AmB in lipid emulsion was several times greater than that in dextrose solutions, probably due to a greater degree of self-association of AmB molecules in lipid emulsion vehicle [34]. Increased particle size could account for the increased uptake of AmB by the reticuloendothelial system (liver, spleen, and lung), V_{SS}, and clearance of AmB prepared in Intralipid 20 %. On the other hand, Intralipid competition with lipoproteins for binding to AmB increases the unbound fraction of the drug. The authors of this study concluded that AmB in lipid emulsion offered no significant advantage compared to the common preparation of AmB in dextrose in terms of the prevention and treatment of fungal infections in children with malignant disease [33].

Human immunodeficency virus-infected patients

Chavanet et al. [35] were the first researchers to perform a non-blind, randomized, controlled trial comparing the tolerance, efficacy, and pharmokinetics of AmB prepared in Intralipid 20 % with that of 5 % dextrose in human immunodeficiency virus (HIV). Twenty-two HIV-positive patients with oral candidiasis were randomly divided in two equally sized groups based on treatment with AmB dissolved in 5 % dextrose or Amb in Intralipid 20 %. Both the daily and mean increase in Scr from baseline were significantly higher in patients treated with AmB dissolved in 5 % dextrose than in patients treated with AmB dissolved in Intralipid 20 %. Unlike the AmB/Intralipid 20 % group, a significant decrease in serum magnesium concentrations was observed in patients treated with AmB dissolved in 5 % dextrose. No significant variation in potassium or sodium values was detected in both groups [35]. In terms of pharmacokinetic parameters, these results are similar to those of Nath et al. [33]. The oral candidiasis score was similarly reduced in both groups, confirming the notion that egg lecithins as one of the major components of fat emulsions do not adversely affect the bioactivity of AmB. The authors concluded that the renal tolerance of AmB is dramatically improved, with no alteration in its clinical efficacy in the treatment of oral candidiasis, in HIV patients when the drug is prepared in Intralipid 20 % [35].

In continuation of this study, the same research group performed another trial in HIV patients with azole-resistant oral candidiasis to evaluate the therapeutic range of escalating doses of AmB in fat emulsion and compare these with an AmB dose of 1.0 mg/kg/day in 5 % dextrose. In addition to this 1.0 mg/kg/day dose, doses of 2.0 and 3.0 mg/kg/day of AmB in Intralipid 20 % were also administered. In contrast to the 3.0 mg/kg/day dose of AmB, no statistically significant differences in the increase in Scr were detected between patients receiving 1.0 and 2.0 mg/kg/day AmB in Intralipid 20 % (P=0.72). Interestingly, the cumulative probability of renal impairment for the highest dose (3.0 mg/kg/day) was significantly lower than that of the lowest dose (1.0 mg/kg/day AmB) in 5 % dextrose (22 vs. 54 %, respectively; P=0.05). The clinical efficacy of AmB in Intralipid 20 % increased significantly with increases in AmB dose (P=0.06). The results of this study suggest that the preparation of AmB in Intralipid 20 % allows higher dosages of AmB to given, up to 3.0 mg/kg/day, to treat refractory fungal infections in HIV patients, without any concern about increasing nephrotoxicity [36]. The only study to date which has demonstrated the higher nephrotoxicity of AmB in a fat emulsion other than 5 % dextrose was conducted by Joly et al. in 90 patients with acquired immunodeficiency syndrome (AIDS) who had developed cryptococcal meningitis [37]. The percentage of patients with increased levels of Scr was significantly higher in the Intralipid/AmB group than in the AmB/dextrose group on day 28 of treatment (P<0.001). Furthermore, Scr changes from baseline values were significantly higher in the Intralipid/AmB group (P=0.012). The mycological as well as clinical outcomes and mortality rate were comparable in the two groups [37].

Critically ill patients

Two randomized, prospective studies specifically compared the efficacy and safety of AmB in Intralipid 20 % with AmB

in 5 % dextrose in intensive care unit (ICU) patients. In the first study [38], 60 critically ill patients in a medical–surgical ICU with unexplained fever unresponsive to antimicrobial agents were allocated to two equally sized treatment groups—AmB in 5 % dextrose or Intralipid 20 %—for the treatment of confirmed or suspected candidal infection. Daily sodium and potassium supplementations to maintain their respective normal serum levels were significantly higher in the AmB/5 % dextrose group than in the AmB/Intralipid 20 % group. Furthermore, moderate hypomagnesemia was observed more frequently in patients receiving AmB in 5 % dextrose ($P<0.02$). Nephrotoxicity occurred less frequently in the AmB/Intralipid 20 % group than in the AmB/5 % dextrose group (20 vs. 66.7 %, respectively; $P<0.0002$). Survival to discharge from the ICU as well as clinical response to treatment did not differ significantly in both groups. Shortly before this study was published, Barquist et al. had started a similar investigation in critically ill patients in a surgical ICU. In contrast to the former study, AmB was used at lower dosage (0.5 vs. 1.0 mg/kg/day) in the 5 % dextrose arm of Barquist et al.'s trial because the authors believed that a lower dose of AmB in 5 % dextrose is associated with less nephrotoxicity. Furthermore, AmB in the first investigation was used empirically to treat confirmed or suspected Candida infection; however, all patients in the Barquist et al. survey had positive fungal cultures of the peritoneum, sputum, and/or blood. The residual fraction of CrCl, calculated by dividing the final CrCl by the initial CrCl, was significantly higher in patients receiving AmB in Intralipid 20 % ($P=0.038$). Dyspnea was not noted in any patient in the group receiving AmB in Intralipid 20 %. The criteria of treatment efficacy, such as length of hospital or ICU stay, days on the mechanical ventilator, and days of vasopressor requirement, did not differ significantly between the two groups [39].

Visceral leishmaniasis (Kala-azar) patients

In a short report by Thakur, AmB prepared in Intralipid 10 % failed to show any significant benefit compared to AmB prepared in 5 % dextrose in terms of increases in Scr level in adult patients with uncomplicated kala-azar unresponsive to sodium stibogluconate and pentamidine. The author justified this finding by the lower concentration of lipids in Intralipid 10 % compared to Intralipid 20 % used in other studies to prepare AmB [40]. In two open label, non-comparative studies by Sundar et al., different regimens of the pre-formulated AmB in lipid emulsion, up to total dose of 15 mg/kg, was clinically effective as well as safe in the treatment of Indian visceral leishmaniasis, and no nephrotoxicity or other organ toxicity was observed during the treatment [41, 42].

Other populations

In an interesting pilot crossover trial in ten immunocompromised patients with systemic candidal infection, AmB in dextrose was first infused, followed by a switch from AmB in dextrose to AmB in Intralipid 20 % during the treatment course ($n=6$) or at the onset of nephrotoxicity ($n=4$). The mean total dose as well as duration of AmB treatment were non-significantly higher in the patients receiving AmB in Intralipid 20 % than in those receiving AmB in dextrose. The mean ± standard deviation (SD) of CrCl dropped by 23.5±9.2 mL/min during the administration of AmB in dextrose; in contrast, during AmB in Intralipid 20 % therapy, the mean ± SD of CrCl increased by 10.7±7.7 mL/min ($P=0.026$). This is the first study to clearly describe that the administration of AmB in Intralipid vehicle significantly increased CrCl in immunocompromised patients who experienced a decline in CrCl following the administration of AmB in conventional dextrose vehicle [43].

The administration of AmB in fat emulsion has been shown to reduce its nephrotoxicity in eight of 15 studies published to date [27, 28, 31, 35, 36, 38, 39, 43]. Four trials reported no significant difference [30, 32, 33, 40] while in one trial, nephrotoxicity was higher in the group receiving AmB in Intralipid [37]. In the remaining two studies, including one case report, renal function was not assessed [44], and in three clinical trials, patients receiving AmB in fat emulsion maintained their renal function—but these studies had no control group [29, 41, 42]. These variations in the results could be justified by differences in the sample size, definition of nephrotoxicity, risk factors of AmB nephrotoxicity, concentration of AmB in fat emulsion, formulation (preparation) procedure, and clinical settings. Interestingly, the results of a recently published meta-analysis which compared the rates of nephrotoxicity among patients receiving AmB in fat emulsion versus those among patients receiving liposomal AmB demonstrated that both lipid formulations reduced the risk of AIN by a similar degree in comparison to conventional AmB. However, as stated by the authors, this result must be interpreted with caution due to the limitations of the meta-analysis, such as the indirect comparison of nephrotoxicity of these two formulations of AmB and considerable heterogeneity and differences in the methodological quality of the studies in terms of both AmB dose as well as the definition of nephrotoxicity. These authors emphasized the need to perform head-to-head clinical trials that directly compare AmB in fat emulsion with liposomal AmB in terms of both efficacy and safety[45].

Possible advantages of the AmB–fat emulsion combination are convenience in preparing the admixture, availability of its components, including AmB and fat emulsion

(Intralipid), and the low cost of the combination compared to lipid-based formulations of AmB. This last point was noted in several of the relevant studies discussed above. For example, in 1996, Barquist et al. [39] declared that the cost of 250 mL of Intralipid 20 % at their institution was $12.50 while AmB in 5 % dextrose was $10.00 per 50-mL dose. They suggested that AmB in fat emulsion might be used as an alternative for the expensive lipid-based formulations of AmB in countries where the healthcare budget is limited [39]. However, there are several drawbacks to the use of AmB in fat emulsion in clinical practice. First, the stability of AmB in lipid emulsions has been a concern. Several studies have demonstrated that AmB may undergo creaming at room temperature as little as 4 h after mixing with the fat emulsion [46, 47]. It has also been reported that the amount as well as the size of the non-dissolved particles (especially those >10 μm) increase considerably upon preparation of AmB in fat emulsion compared to 5 % dextrose [34]. Analysis of the particles and precipitates being formed in the fat emulsion vehicle confirmed their identity as AmB. It has been hypothesized that the desoxycholic acid excipient in the C-AmB (conventional AmB), which is an anion, interacts with the positively charged choline groups of the egg yolk component of the fat emulsion. This would result in insufficient surfactant so that the solubility of AmB molecules in the aqueous solution could not be maintained [48]. Particles can be removed by using an in-line filter, but this might reduce the antifungal efficacy of AmB [32]. Second, were AmB precipitates to be administered to patients, they may lodge the blood vessels and cause pulmonary embolism. Schöffski et al. reported pulmonary events in patients receiving AmB in Intralipid; however, due to the sudden and transient nature of these symptoms, it was not practical to perform further examinations, such as computed tomography angiography, to confirm the presence of pulmonary embolism. To date, documented and confirmed pulmonary embolisms due to the infusion of AmB in lipid emulsions have not been reported in the literature [30]. Third, methods of preparation of AmB in fat emulsion, storage, administration conditions, and optimal concentration of AmB have not yet been standardized. Fourth, giving a patient fat emulsion is not without risk. Few cases of cholestasis and thrombocytopenia have been reported from patients receiving fat emulsions. According to the monograph of the drug, the administration of intravenous fat emulsion is contraindicated in certain conditions, including pathologic hyperlipidemia, lipoid nephrosis, and acute pancreatitis in the presence of hyperlipidemia/hypertriglyceridemia. Furthermore, fat emulsion products contain aluminum, which may reach toxic levels with prolonged use if renal function is impaired or immature, specifically in premature neonates [49]. Finally, it is worth noting that the administration of AmB prepared in fat emulsion is not currently approved by the Food and Drug Administration. However, in India, which is a hyperendemic area for visceral leishmaniasis and where novel lipid formulations of AmB are unaffordable for most patients, a commercial standardized product of preformed AmB with lipid emulsion is manufactured by a local company (Bharat Serum and Vaccines Limited, Mumbai, India) with low cost (about US $10.00 per 50 mg vial) [42].

Administration of lipid-based formulations of AmB

Attempts to eliminate deoxycholate detergent from C-AmB by constructing the AmB methyl ester or *N*-**D**-ornithyl AmB methyl ester failed because of the more significant neurotoxicity (damage to white matter) of the former derivative of AmB and the inadequate in vivo antifungal activity of the latter (about one-eight of the parent drug) [50, 51]. Research on lipid-associated formulations of therapeutic agents, such as AmB, began in the 1970s [52]. Such formulations were developed to enhance the therapeutic index of the parent compound while preserving their pharmacological activity [53]. It was hypothesized that lipid-associated formulations would allow the parent compound to be captured by the reticuloendothelial system and to be easily delivered to the site of infection [54]. Furthermore, the deoxycholate moiety of C-AmB, an agent used to increase the solubility of AmB in aqueous solution, may itself be nephrotoxic [1, 6, 7]. Currently, there are three commercially available lipid formulations of AmB. AmB lipid complex (ABLC; trade name of Abelcet®), AmB colloidal dispersion (ABCD; trade names of Amphocil® or Amphotec®), and liposomal AmB (L-AmB; trade name of Ambisome®) [55]. Several mechanisms have been suggested to explain the reduced nephrotoxicity of lipid formulations of AmB compared to C-AmB: (1) selective transfer of AmB to fungal rather than mammalian cell membranes; this would reduce the levels of AmB in the kidney; (2) preferential binding of L-AmB to high-density lipoproteins, as compared with C-AmB, which is bound to low-density lipoproteins. Low numbers of high-density lipoprotein receptors in renal tubular cells minimize AmB access to the kidney [56–60]. In the following section, head-to-head clinical trials comparing the clinical efficacy and renal safety of different lipid formulations of AmB with C-AmB as well as lipid formulations of AmB with each other are briefly discussed. These studies are also summarized in Table 2.

L-AmB versus C-AmB

Prentice et al. were the first researchers to conduct a large, multicenter, randomized trial in 438 neutropenic patients with fever of unknown origin (134 adults, 204 children). The patients were randomly assigned to two treatment

Table 2 Summary of clinical studies which have compared lipid-based formulations of amphotericin B with each other or with conventional amphotericin B

Reference	Study design	Underlying disease	Antifungal indication	Compared agents	Dose (mg/kg/day)	Number of patients in each group	Nephrotoxicity definition	Main results
Prentice et al. 1997 [61]	Multicenter, prospective, randomized, controlled	Hematological or non-hematological malignancies	Fever of unknown origin or confirmed fungal infection	L-AmB vs. C-AmB	L-AmB: 1 or 3 C-AmB: 1	L-AmB: n=236 C-AmB: n=102	≥100 % in the baseline Scr value	L-AmB at 1 or 3 mg/kg/day is significantly less nephrotoxic along with equivalent or superior clinical efficacy than C-AmB
Leenders et al. 1998 [62]	Prospective, randomized, controlled	Hematological or non-hematological malignancies	Documented or suspected invasive fungal infections	L-AmB vs. C-AmB	L-AmB: 5 C-AmB: 1	L-AmB: n=32 C-AmB: n=34	No specific definition	High-dose L-AmB (5 mg/kg/day) is superior to C-AmB regarding efficacy and safety
Walsh et al. 1999 [63]	Multicenter, prospective, randomized, controlled	Hematological or non-hematological malignancies	Persistent neutropenic fever	L-AmB vs. C-AmB	L-AmB: 3 C-AmB: 0.6	L-AmB: n=343 C-AmB: n=344	Doubling or tripling of the baseline Scr or peak Scr values >3 mg/dl	L-AmB is an appropriate alternative to C-AmB due to similar rates of successful treatment along with preserving renal function
Johnson et al. 2002 [64]	Multicenter, prospective, randomized, controlled	AIDS	Induction therapy of moderate to severe disseminated histoplasmosis	L-AmB vs. C-AmB	L-AmB: 3 C-AmB: 0.7	L-AmB: n=51 C-AmB: n=22	≥100 % increase in the baseline Scr value	L-AmB has superior clinical efficacy and lower nephrotoxicity compared to C-AmB
Sharkey et al. 1996 [65]	Multicenter, prospective, randomized, controlled	AIDS	Treatment of cryptococcal meningitis	ABLC vs. C-AmB	ABLC: 1.2–5 C-AmB: 0.7–1.2	ABLC: n=38 C-AmB: n=17	No specific definition	ABLC can be used as an effective and less nephrotoxic alternative to C-AmB
Subira et al. 2004 [68]	Multicenter, prospective, randomized, controlled	Hematological malignancies	Fever of unknown origin	ABLC vs. C-AmB	ABLC: 1 C-AmB: 0.6	ABLC: n=49 C-AmB: n=56	Increase in Scr >1.5 mg/dL or an increase of >2-fold baseline value	Low-dose ABLC provides similar efficacy with less nephrotoxicity than C-AmB
White et al. 1997 [54]	Multicenter, retrospective, unblinded	Hematological or non-hematological malignancies	Proven or probable aspergillosis	ABCD vs. C-AmB	ABCD: 0.5–8 C-AmB: 0.1–1.4	ABCD: n=82 C-AmB: n=261	≥100 % increase in the baseline Scr, an increase in the Scr of at least 1 mg/dL, or a 50 % decrease in the calculated CrCl	ABCD was associated with higher response rates, lower mortality rates, and renal safety than C-AmB
White et al. 1998 [53]	Multicenter, prospective, randomized, controlled	Hematological malignancies	Persistent neutropenic fever	ABCD vs. C-AmB	ABCD: 4 C-AmB: 0.8	ABCD: n=101 c-AmB: n=95	≥100 % increase in the baseline Scr, an increase in the Scr of at least 1 mg/dL, or a 50 % decrease in the calculated CrCl	ABCD appeared to be as effective as C-AmB along with less nephrotoxicity
Malani et al. 2005 [69]	Retrospective medical record review	Various underlying diseases	Definite, probable, or possible fungal infection, empiric therapy, or prophylaxis	Lipid-based formulations vs. C-AmB	C-AmB: 0.7±0.3 L-AmB: 4±1 ABLC: 4.5±0.9 ABCD: 4±1 (mean±SD)	Not determined	100 % increase or at least a 1 mg/dL increase in the baseline Scr	Lipid formulations of AmB failed to demonstrate protection against nephrotoxicity compared to C-AmB
Ullmann et al. 2006 [70]	Multicenter, prospective, observational	Various underlying diseases (Immunocompromised)	Proven, probable, possible, or suspected invasive fungal infection	Lipid-based formulations vs. C-AmB	C-AmB: 0.7±0.3 L-AmB: 2.6±0.8 ABLC: 3.7±1.1 ABCD: 2.7±0.5 (mean ± SD)	C-AmB: n=259 L-AmB: n=112 ABLC or ABCD: n=47	≥50 % increase in Scr in the baseline value	Nephrotoxicity, length of hospital stay, and mortality were less frequent with lipid formulations of AmB compared to C-AmB
Clark et al. 1998 [71]	Single center, retrospective	Hematological malignancies	Proven or suspected fungal infection	L-AmB vs. ABLC	L-AmB: 0.7–4 ABLC: 1.9–5.8	L-AmB: n=32 ABLC: n=36	No specific definition	No statistically significant differences in clinical efficacy and renal toxicity between L-AmB and ABLC

Table 2 (continued)

Reference	Study design	Underlying disease	Antifungal indication	Compared agents	Dose (mg/kg/day)	Number of patients in each group	Nephrotoxicity definition	Main results
Wingard et al. 2000 [72]	Multicenter, prospective, randomized, controlled	Hematological or non-hematological malignancies	Neutropenic fever	L-AmB vs. ABLC	L-AmB: 3 or 5 ABLC: 5	L-AmB 3: *n*=85 L-AmB 5: *n*=81 ABLC: *n*=78	≥100 % increase in the baseline Scr value	L-AmB at a dose of 3 or 5 mg/kg/day presented a superior renal safety profile in comparison with ABLC at a dose of 5 mg/kg/day
Fleming et al. 2001 [73]	Prospective, randomized, controlled	Leukemia	Suspected or documented fungal infections	L-AmB vs. ABLC	L-AmB: 3-5 ABLC: 3-5	L-AmB: n=39 ABLC: n=43	>50 % increase in the baseline Scr value	Similar clinical efficacy and renal safety between L-AmB and ABLC
Cannon et al. 2001 [74]	Prospective and retrospective	Malignancy or other underlying diseases	Documented fungal infections or neutropenic fever	L-AmB vs. ABLC	L-AmB: 4 ABLC: 5 (mean)	L-AmB: *n*=21 ABLC: *n*=46	≥100 % increase in the baseline Scr value	No statistically significant differences in clinical efficacy and renal toxicity between L-AmB and ABLC
Mattiuzzi et al. 2003 [75]	Single center, prospective, randomized, historical control	Acute myelogenous leukemia or high-risk myelodysplastic syndrome undergoing induction chemotherapy	Prophylaxis of invasive fungal infections	L-AmB vs. ABLC	L-AmB: 3 three times weekly ABLC: 2.5 three times weekly	L-AmB: *n*=70 ABLC: *n*=131	NCI Common Toxicity Criteria	Comparable clinical efficacy and renal safety between L-AmB and ABLC
Hachem et al. 2008 [76]	Single center, retrospective	Hematological malignancies	Probable or proven invasive aspergillosis	L-AmB vs. ABLC	L-AmB: 5–10 ABLC: 5–10	L-AmB: *n*=106 ABLC: *n*=52	≥100 % increase in the baseline Scr value	Comparable clinical efficacy between L-AmB and ABLC with less nephrotoxicity between L-AmB in the primary therapy setting

C-AmB, Conventional amphotericin B; L-AmB, liposomal amphotericin B; ABLC, amphotericin B lipid complex; ABCD, amphotericin B colloidal dispersion; Scr, serum creatinine; CrCl, Creatinine clearance

groups receiving C-AmB (1.0 mg/kg/day) or L-AmB (1.0 or 3.0 mg/kg/day), respectively. The incidence of nephrotoxicity was significantly less in the L-AmB group than in the C-AmB group ($P<0.01$). In addition, time to development of nephrotoxicity was significantly longer in both subgroups of the L-AmB arm than in the C-AmB group ($P<0.01$). In contrast to C-AmB, the incidence of nephrotoxicity in the L-AmB arm was influenced significantly by the concomitant use of nephrotoxic drugs (platinum derivatives, aminoglycosides, vancomycin, and cyclosporine A. Of the eight patients switched from C-AmB to L-AmB, seven had a subsequent decrease or stabilization of their Scr. The rate of hypokalemia was significantly lower in the L-AmB than in the C-AmB group ($P<0.01$). The prescription of potassium supplements or potassium-sparing diuretics was significantly lower in patients receiving L-AmB. Compared to L-AmB at the dose of 1.0 mg/kg/day, the success rate was significantly higher in L-AmB at 3.0 mg/kg/day than C-AmB ($P=0.03$). Although L-AmB-associated adverse reactions were dose dependent, the incidence as well as severity of L-AmB toxicities, such as nephrotoxicity, at the dose of 3.0 mg/kg/day was still below that reported for C-AmB at the dose of 1.0 mg/kg/day. This study provided evidence that liposomal AmB at doses of 1.0 or 3.0 mg/kg/day was significantly less nephrotoxic than C-AmB in neutropenic children and adult patients with fever of unknown origin but with equivalent or superior efficacy [61]. In another randomized multicenter study published 1 year later, Leenders et al. [62] demonstrated the superior clinical efficacy of L-AmB over C-AmB in the treatment of invasive fungal infections in 66 neutropenic patients. These authors also observed a significantly more favorable profile of renal function in L-AmB-treated patients. In this regard, for example, significantly more patients treated with C-AmB had a >100 % increase in their baseline Scr level (40 vs. 12 %; $P<0.001$). Furthermore, significantly more patients receiving C-AmB required a dose reduction or temporarily drug therapy discontinuation due to increased Scr levels (18 vs. 2 patients; $P<0.001$) [62]. In line with the results of the Leenders et al. study, a comparison of C-AmB with L-AmB as an empirical antifungal treatment for 687 patients with persistent fever and neutropenia demonstrated that L-AmB is an appropriate alternative to C-AmB due to similar rates of successful treatment along with preservation of renal function. In this study, significantly fewer patients receiving L-AmB developed nephrotoxicity ($P<0.001$). Moreover, compared with patients receiving C-AmB, the incidence of hypokalemia was significantly lower in patients receiving L-AmB. There was also a non-significant trend toward a reduction in the rate of hypomagnesemia in the L-AmB treated group ($P=0.12$) [63]. Finally, in a randomized, double-blind, multicenter clinical trial, Johnson et al. compared the safety and efficacy of L-AmB with C-AmB for the induction therapy of moderate to severe disseminated histoplasmosis in 81 patients with AIDS. The overall clinical efficacy of induction therapy was significantly higher in patients treated with L-AmB than in recipients of C-AmB (88 vs. 64 %, respectively; $P=0.014$). The mortality rate was significantly lower in the L-AmB group than in the C-AmB group ($P=0.04$). Patients receiving L-AmB developed significantly less nephrotoxicity than those given C-AmB (9 vs. 37 %, respectively; $P=0.003$). These results suggest the superior clinical efficacy and lower nephrotoxicity of L-AmB compared to C-AmB in the induction therapy of disseminated histoplasmosis in patients with AIDS [64].

ABLC versus C-AmB

Sharkey et al. [65] performed a, randomized, open label multicenter trial to evaluate the safety and efficacy of ABLC with C-AmB in the treatment of AIDS-associated cryptococcal meningitis. Fifty-five patients were randomly assigned to the ABLC- or C-AmB-treated groups. Patients receiving ABLC were divided into three subgroups based on treatment regimen: 1.2 mg/kg/day for weeks 1 and 2 followed by 2.5 mg/kg three times weekly for weeks 3–6 (Cohort I); 2.5 mg/kg/day for weeks 1 and 2 followed by 5 mg/kg three times weekly for weeks 3–6 (Cohort II); 5 mg/kg/day for weeks 1 and 2 followed by 5 mg/kg three times weekly for weeks 3–6 (Cohort III). No statistically significant differences were detected in the clinical, mycological, and overall responses between any two groups. However, the rate of mycological failure in Cohort III was higher than that in the C-AmB group which received≥12 doses of the medication (42 vs 14 %, respectively; $P=0.09$). The mean increment in Scr from baseline values in the C-AmB group was significantly higher than that in patients who received ABLC at weeks 2 and 3 of treatment (0.7–mg/dL in C-AmB group vs. −0.2 to −0.25 mg/dL in Cohort I and 0.35–0.45 mg/dL in Cohort III; $P<0.05$ for each comparison). The authors discussed the possibility that higher rates of mycological failure in the ABLC group might not be attributable to the lower penetration of lipid-based formulations of AmB into the brain through the blood–brain barrier [65]. In line with their statement, a number of experimental and clinical studies have demonstrated the efficacy of AmB lipid-based formulations, including ABLC and L-AmB, in the treatment of cryptococcal meningitis [66, 67]. Another randomized, controlled trial compared the efficacy and safety of low-dose ABLC with c-AmB as empirical antifungal treatment of neutropenic fever in 105 adult patients with hematological malignancies. The ABLC group of patients had a significantly lower incidence of nephrotoxicity than the C-AmB group (8 vs. 32 %, respectively; $P=0.003$). Hypokalemia was observed less frequently in the ABLC than the C-AmB group (12 vs. 32 %, respectively; $P=$

0.01). In accordance with the data of Sharkey et al. the results of this study suggest that low-dose ABLC provides a similar efficacy as C-AmB but with less nephrotoxicity [68].

ABCD versus C-AmB

In 2 consecutive years, White et al. published two trials comparing ABCD with C-AmB [53, 54]. In the first trial, they compared retrospectively 82 patients with proven or probable aspergillosis who were treated with ABCD to 261 patients with aspergillosis who were treated with C-AmB. The response rate was significantly higher among ABCD recipient than among C-AmB recipients (48.8 vs. 23.4 %, respectively; $P<0.001$). Furthermore, the mortality rate was significantly lower in the ABCD group than in the C-AmB group (50 vs. 71.6 %, respectively; $P<0.001$). Also, nephrotoxicity developed less frequently in the ABCD group than in the C-AmB group (8.2 vs. 43.1 %, respectively; $P<0.001$). Despite these favorable features of ABCD compared to C-AmB, the authors believed that they were unable to draw any rational conclusion regarding the superiority ABCD to C-AmB as first line treatment of aspergillosis due to limitations of the study, such as its retrospective and unblinded design, insufficient daily dose of C-AmB, and better management and monitoring of ABCD recipients [54]. The second survey was a prospective, randomized, double-blinded trial performed in patients with neutropenia and persistent fever. The patients received fixed doses of C-AmB or ABCD. In contrast to the first study, the rate of successful response was comparable between the two treatment groups. The favorable renal safety profile of ABCD compared to C-AmB (incidence and time to onset) was similar to that of these authors' first survey. The absolute and percentage decrease in the serum potassium level from baseline to the end of therapy was significantly greater for the C-AmB group than for the ABCD group ($P=0.012$ and $P=0.005$, respectively). These data suggest that ABCD appears to be as effective as C-AmB in the empirical treatment of patients with neutropenia and fever and that it is associated with less nephrotoxicity [53].

Lipid-based formulations versus C-AmB

In a retrospective analysis of medical records of 105 patients who received AmB, Malani et al. [69] evaluated the types and frequencies of adverse events associated with a community-based AmB treatment in an outpatient clinic at a tertiary care center in the USA. Patients received AmB from a homecare provider. No statistically significant differences in the rate and time to onset of nephrotoxicity and in electrolyte abnormalities were observed between recipients of the various formulations of AmB (lipid-based and conventional). The failure of lipid formulations of AmB to demonstrate protection against nephrotoxicity could be partially explained by the fact that about 30 % of C-AmB courses were given to children, a group with a low risk of nephrotoxicity. In turn, lipid formulations of AmB were preferentially administered to patients at higher risk for AIN [69]. Another prospective, observational study was performed in 418 adult immunocompromised patients treated with different formulations of AmB in 20 medical centers in four European countries [70]. Patients received AmB for treatment of proven invasive fungal infections or empirical antifungal therapy. Worsening of renal function was observed in 91 of 259 (35.14 %) patients who received C-AmB and in 11 of 159 (6.92 %) recipients of lipid formulations of AmB. The choice of AmB formulation for initial use [odds ratio (OR) 0.12, 95 % confidence interval 0.06–0.22, $P<0.001$ for L-AmB] was identified as one of the significant predictors for the development of AmB nephrotoxicity. In addition, renal toxicity was the leading cause of switching from C-AmB to lipid formulations of AmB [70].

ABLC versus L-AmB

All head-to-head clinical trials that have compared ABLC with L-AmB were performed in the setting of hematological or non-hematological malignancies. The first of these series was published in 1998 [71]. This was a single-center retrospective study in 59 adult patients with hematological malignancies who received AmB for confirmed or strongly suspected fungal infections between October 1992 and January 1997. No statistically significant difference in the overall outcome, mortality rate, median Scr level at the start and cessation of treatment, and electrolyte abnormalities were observed between patients who received ABLC and those given L-AmB. Due to the retrospective design of the study, the authors suggested performing prospective, randomized, comparative trials to definitively differentiate the clinical efficacy as well as the renal toxicity of ABLC from L-AmB [71]. Soon after this first study was completed, Wingard et al. [72] commenced a randomized, double-blind trial at 18 centers in the USA in October 1997 to compare the safety of L-AmB (3.0 or 5.0 mg/kg/day) with ABLC (5.0 mg/kg/day) in the empirical treatment of febrile neutropenic patients with different malignancies. Nephrotoxicity developed less frequently among the L-AmB recipients compared to those receiving ABLC ($P<0.001$). There was no statistically significant difference in nephrotoxicity rate between the two subgroups of the L-AmB arm (3.0 and 5.0 mg/kg/day). Unlike L-AmB at a dose of 3.0 mg/kg/day, significantly fewer patients receiving 5.0 mg/kg/day of L-AmB compared to recipients of ABLC had a peak Scr of >3.0 mg/dL (1.2 vs. 12.8 %, respectively; $P<0.01$). Therapeutic success was similar in all three groups. These data

demonstrate the superior renal safety profile of L-AmB at dose of 3.0 or 5.0 mg/kg/day in comparison with ABLC at dose of 5.0 mg/kg/day in the empirical treatment of febrile neutropenia in malignant patients [72]. Fleming et al. [73] were the first researchers to compare ABLC with L-AmB in the treatment of suspected or documented fungal infections specifically in patients with leukemia. The overall response and nephrotoxicity rates did not differ significantly between the two groups (P=0.15 and P=0.26, respectively). Furthermore, significant nephrotoxicity requiring cessations of treatment, dialysis, or increases in Scr to >3 mg/dL were comparable between ABLC and L-AmB groups. The results of this study suggest that ABLC and L-AmB are equally effective in the treatment of suspected or documented fungal infections in leukemia patients and that they have a similar profile of severe renal toxicity [73]. A prospective and retrospective analysis was performed in the University of Illinois at Chicago Medical Center to compare the efficacy and nephrotoxicity of ABLC with L-AmB [74]. The study cohort comprised 67 patients who were prescribed ABLC or L-AmB for more than 3 days. The rate of nephrotoxicity or overall response did not differ significantly between the two groups. The authors explained the comparable nephrotoxicity associated with ABLC and L-AmB by the small sample size, concomitant use of nephrotoxic agents (such as vancomycin, acyclovir, and tacrolimus), heterogeneity of the study population (oncology patients had a significantly lower baseline Scr than all other treated patients, P=0.008), and the lack of an evaluation of the possible effects of salt loading. The authors concluded that economic issues continue to be the major determinant for the selection of lipid-based formulations of AmB until further trials could differentiate clinically significant differences in the safety or efficacy profile of ABLC from L-AmB [74]. Similar results were obtained in an investigation involving patients with acute myelogenous leukemia or high-risk myelodysplastic syndrome undergoing induction chemotherapy who received ABLC or L-AmB as prophylaxis of invasive fungal infections [75]. Hachem et al. [76], in a retrospective study, were the first researchers to compare the efficacy and safety of ABLC with L-AmB as either primary or salvage treatment in hematological malignancy patients with probable or proven invasive aspergillosis. Response rates were comparable between the patients of either group. As primary antifungal therapy, L-AmB was associated with less nephrotoxicity than ABLC (2.8 vs. 21.2 %, respectively; P< 0.001). However, as salvage therapy, this difference was not statistically significant (5.9 vs. 10 %, respectively; P= 0.67). The result of this study, namely, a higher rate of nephrotoxicity in ABLC recipients than L-AmB recipients when both formulations were used as primary therapy, is in accordance with those of Wingard et al. [72]. The authors presumed that this lack of difference in the nephrotoxicity rate of ABLC with L-AmB in the salvage therapy group might be due to advanced stages of underlying disease and concomitant therapy with various medications, including nephrotoxic or non-nephrotoxic drugs [76].

The introduction of lipid formulations of AmB is considered to be a revolution in its use in the treatment of invasive fungal infections [7]. These lipid formulations were developed to minimize the toxicities associated with C-AmB, especially nephrotoxicity and infusion-related reactions, without compromising the antifungal efficacy of AmB [53]. More than 200 publications on lipid preparations of AmB have been published to date [77]. However, differences in the renal safety profile of various lipid formulations of AmB remain a subject of debate. An early meta-analysis by Johansen and Gotzsche in 2000 compared mortality, invasive fungal infection, and nephrotoxicity of lipid-based formulations of AmB with C-AmB in cancer patients with neutropenia [78]. These authors analyzed 12 clinical trials, including L-AmB versus C-AmB (3 trials), AmB in Intralipid versus C-AmB (6 trials), ABCD versus C-AmB (2 trials), and ABLC versus C-AmB (1 trial). Their analyses demonstrated that compared to C-AmB, lipid-based formulations of AmB were associated with a significant decrease in the incidence of nephrotoxicity as well as the tendency to decrease invasive fungal infections, but that they were not superior in reducing mortality. The authors concluded that although lipid formulations of AmB might be tolerated better than C-AmB, their high cost limits their routine use in most clinical settings. They also speculated that providing optimal conditions for C-AmB administration might mitigate the advantages of lipid formulations of AmB over C-AmB [78]. Two other meta-analyses of clinical efficacy and tolerability data from seven and 16 randomized clinical trials, respectively, both which compared lipid-based formulations of AmB with C-AmB, concluded that the former are associated with less nephrotoxicity and hypokalemia compared to C-AmB. However, partially due to controversial results and the homogeneity of the studies, these meta-analyses failed to show any significant difference in renal safety between the different lipid-based formulations of AmB [79, 80]. In a literature review of published data on the safety, efficacy, and cost-effectiveness of ABLC, Martino concluded that ABLC has a superior efficacy and tolerability profile compared to C-AmB. This author also declared that ABLC and L-AmB have a similar efficacy and risk of nephrotoxicity [81]. Moen et al. in a literature review of data from 1980 up to 2009 on L-AmB usage for the empirical treatment of febrile neutropenia or invasive fungal infections proposed that L-AmB is associated with fewer infusion-related adverse events and nephrotoxicity than C-AmB and ABLC [82]. Safdar et al. [83] conducted a meta-analysis on the data of eight studies on nephrotoxicity associated with ABLC and L-AmB in adult patients

receiving these lipid-based formulations of AmB. These meta-analyses demonstrate an increased probability of nephrotoxicity in patients receiving ABLC (n=588) compared with those treated with L-AmB (n=572) with a Cochran–Mantel–Haenszel OR and relative risk (RR) of 1.75 and 1.55, respectively. Interestingly, when the Wingard et al. study [72] (n=916) was excluded from these meta-analyses, the probability of nephrotoxicity did not differ significantly between patients treated with ABLC (n=510) versus L-AmB (n=406) (OR1.31, RR 1.24). With the exception of the subgroups that were included in Wingard et al. study, additional sub-analyses of data implicated other factors including study design (randomization), age (≥ 50 years), percentage of bone marrow transfusion recipients, and number of patients receiving concomitant nephrotoxic drugs, are not associated with higher rates of nephrotoxicity in patients receiving ABLC compared to L-AmB. Safdar et al. offer several explanations for the large difference in nephrotoxicity between ABLC and L-AmB reported in the Wingard et al. trial, including variations in the method of determining nephrotoxicity, duration of AmB treatment, and patient follow-up. Due to the probability that the pattern of nephrotoxicity of AmB lipid-based formulations is transitory, the time point of assessing nephrotoxicity (for example, 1 vs. 6 weeks) is a critical factor in determining the rate of nephrotoxicity. In conclusion, these authors suggest that ABLC or L-AmB can be given to immunocompromised patients for the treatment or prophylaxis of invasive fungal infections with comparable efficacy and safety [83]. Martino believed that the differences identified in the Wingard et al. trial can be attributed to the different pharmacokinetic and pharmacodynamic profiles of ABLC and L-AmB [81]. Compared to L-AmB, AmB is released from ABLC more rapidly, achieves a higher concentration in target organs, and is retained for longer duration in target organs [84, 85]. Apart from clinical efficacy and safety, the main drawback to the use of AmB lipid-based formulations compared to C-AmB in clinical practice is the high cost. L-AmB has the highest acquisition cost followed by ABLC. ABCD is the least expensive of currently available lipid-based formulations of AmB [81]. Taking overall costs into consideration, the authors of two studies suggest that ABLC is more cost-effective than C-AmB, L-AmB, and ABCD [86, 87]. Regarding the limitations of current studies assessing cost-effectiveness, such as relying only on assumptions and geographical bias, further well-designed and prospective pharmaco-economic analyses are warranted to clearly determine the place of each lipid-based formulation of AmB in antifungal treatment in humans. By that time, it will be reasonable to consider lipid-based formulations of AmB as second-line antifungal agents in patients who are unresponsive or intolerant to C-AmB or other systemic antifungals, have a history renal impairment, or developed AIN within the treatment regimen.

Future perspectives

Endogenous adenosine has been demonstrated to be a mediator of TGF [88]. Since TGF plays a major role in AIN [1, 6, 7], it has been hypothesized that adenosine receptor antagonists may attenuate AmB-induced TGF and, consequently, its nephrotoxicity. In two early experimental studies in rats and dogs, aminophylline as an adenosine receptor antagonist prevented acute renal vasoconstriction due to the intravenous infusion of AmB [89, 90]. In contrast to these findings, 1,3-dipropyl-8-(p-sulfophenyl) xanthine (DPSPX), an adenosine receptor antagonist with limited access to the intracellular space, has been found to be unable to abolish acute reduction of renal blood flow and glomerular function due to AmB infusion [91]. Fenoldopam, a selective D1 receptor agonist, and its prodrug SK&F R-105058 were found to produce a significant attenuation of AIN in dogs [92, 93]. In terms of the contribution of renal arteriolar vasoconstriction to the development of AIN, several experimental investigations in rats have demonstrated that unlike nifedipine, a dihydropyridine calcium channel blocker [94], verapamil and diltiazem, non-dihydropyridine calcium channel blockers, are able to ameliorate the AmB-induced rise in Scr level and decrease CrCl [95, 96]. According to an experimental study in rats, concomitant use of an antiapoptotic agent, insulin-like growth factor 1, prevented or significantly reduced apoptosis of renal cells as well as manifestations of AmB nephrotoxicity, including a decrease in weight gain and loss of renal concentrating ability [97]. N-acetylcysteine, a drug with vasodilating, antiapoptotic, and anti-oxidant features, has been found to diminish the nephrotoxicity of cisplatin [98], CsA [99], gentamicin [100], and radiographic-contrast agents [101]. The results of two experimental studies in rats have suggested that N-acetylcysteine can mitigate GFR reduction as well as renal tubular apoptosis caused by AmB [102, 103]. To our knowledge, the probable nephroprotective actions of none of the aforementioned agents have as yet been evaluated in clinical setting. All of these agents, especially N-acetylcysteine, have favorable safety profiles and if their efficacy in preventing AmB nephrotoxicity without altering its fungicidal activity could be documented by randomized, controlled, clinical, trials, they could be considered for clinical use.

Conclusion

Nephrotoxicity has been considered as the most clinically significant, costly, and dose-limiting adverse reaction of AmB. Among the various preventive modalities studied to date, saline loading and the use of lipid formulations of AmB have been clearly demonstrated to be clinically effective and safe in preventing AmB nephrotoxicity. ABLC or

L-AmB can be given as second-line therapy for empirical or maintenance treatment of fungal infections with comparable efficacy and safety. However, ABLC seems to be more cost-effective than L-AmB. Despite insufficient clinical evidence, potassium-sparing diuretics, such as amiloride and spironolactone, appears to be effective as an alternative or adjunct to oral/parenteral potassium supplements in preventing hypokalemia due to AmB. Other preventive approaches, such as the co-administration of mannitol and preparing AmB in lipid emulsions, are not currently recommended due to their lack of clinical efficacy or safety concerns. Co-administrations of potential nephroprotective agents, such as N-acetylcysteine, merit further consideration as potential preventive strategies against AIN.

Competing interests None.

Founding None.

Ethical Approval Not required.

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