

## **AMPHOTERICIN B FOR THE TREATMENT OF SYSTEMIC FUNGAL INFECTIONS: A META-ANALYSIS OF CONVENTIONAL VERSUS LIPID FORMULATIONS**

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**BACKGROUND:** While it has been postulated that lipid formulations of amphotericin B (AmB) may offer improved tolerability and efficacy over conventional amphotericin B, this remains to be established.

**OBJECTIVES:** To determine if lipid AmB formulations are superior to conventional AmB for the treatment of suspected or documented systemic fungal infections. To sub-analyse whether individual lipid formulations are superior to conventional AmB.

**METHODS:** Medline, Cochrane Library, Embase, and IPA were searched for randomized comparative trials of any language. Unpublished data were obtained from authors, manufacturers, and the United States Food and Drug Administration CDER database. The primary outcome of interest was all-cause mortality. Secondary outcomes included treatment failure, nephrotoxicity, hypokalemia, and infusion reactions. Each outcome was analysed for lipid formulations, in aggregate, versus conventional amphotericin B, and for individual lipid formulations versus conventional amphotericin B. Jadad scores were used to assess trial quality. Data were extracted and odds ratios with 95% confidence intervals were calculated using the random or fixed effects model according to presence or absence of heterogeneity, respectively.

**RESULTS:** Eighteen studies met the inclusion criteria. Four different lipid formulations of AmB were identified: liposomal AmB, AmB lipid complex (ABLc), AmB colloidal dispersion (ABCD), and AmB in Intralipid suspension. Patients enrolled in these trials had documented or suspected systemic fungal infections and included those with febrile neutropenia, AIDS, or those in an intensive care unit. Compared to conventional AmB deoxycholate, the lipid group was associated with an OR of 0.76 [95% CI, 0.59-0.98] for mortality, 0.84 [95% CI 0.70-1.00] for treatment failure, 0.38 [95% CI, 0.32-0.46] for nephrotoxicity, 0.61 [95% CI, 0.48-0.79] for hypokalemia, and 0.39 [95% CI, 0.32-0.47] for infusion reactions. Sub-analyses comparing individual lipid formulations with conventional AmB demonstrated that only liposomal AmB significantly reduced mortality (OR 0.63 [95% CI, 0.44-0.90]). Liposomal AmB also significantly reduced nephrotoxicity (OR 0.39 [95% CI, 0.30-0.51]), hypokalemia (OR 0.59 [95% CI, 0.44-0.78]), and infusion reactions (OR 0.22 [95% CI, 0.17-0.28]). Sub-analyses also indicated that the ABLc formulation was associated with significantly less nephrotoxicity compared to the conventional formulation (OR 0.49 [95% CI, 0.29-0.82]).

Sub-analyses of ABCD versus conventional AmB showed that there was a significant reduction in nephrotoxicity (OR 0.28 [95% CI, 0.17-0.44]), but a significant increase in infusion reactions (OR 2.35 [95% CI, 1.52-3.64]). Sub-analyses of Intralipid preparations showed a significant reduction in nephrotoxicity (OR 0.42 [95% CI, 0.23-0.76]) and infusion reactions (OR 0.27 [95%CI, 0.17-0.43]) compared with conventional AmB.