Nephrotoxicity of Different Formulations of Amphotericin B: Summarizing Evidence by Network Meta-analysis

To the Editor—The nephrotoxicity of amphotericin B (AmB) has long been known, but the risk of this side effect can be reduced if the drug is formulated as either an extemporaneous lipid emulsion (AmB-LE) or a liposomal product (AmB-LIPO). Information on the relative nephrotoxicity of these formulations is still scarce, and so assessing whether AmB-LIPO and/or AmB-LE are less nephrotoxic than conventional AmB (ie, AmB deoxycholate, AmB-Dx) is still a matter of interest [1]. This assessment, however, is hampered by the lack of head-to-head trials comparing AmB-LIPO versus AmB-LE; hence, any comprehensive analysis in this area must rely also on indirect comparisons between the 2 lipid-based formulations.

Network meta-analysis is an evidence-based tool that is specifically aimed at these indirect comparisons [2–4]. On the other hand, the similar pattern of nephrotoxicity observed for AmB-LIPO versus AmB-LE [1] raises another methodological question because the indirect comparison between these 2 formulations should be based on a noninferiority design [5].

Figure 1. Network meta-analysis: comparison of 2 lipid-based formulations of amphotericin B (AmB-LIPO and AmB-LE) with conventional amphotericin B deoxycholate (AmB-Dx). The clinical end-point is the rate of nephrotoxicity. A, Graph shows 2 direct comparisons (solid lines) and 1 indirect comparison (dotted line). Both direct comparisons show superiority of the lipid-based formulation whereas the indirect comparison indicates no significant difference between AmB-LIPO and AmB-LE according to a superiority test. In the noninferiority test (B), the values of the 95% confidence interval (CI) for the indirect comparison between AmB-LIPO and AmB-LE (risk difference = −8.61% [95% CI, −27.21% to 9.99%]) provide the statistical proof of the noninferiority of AmB-LE versus AmB-LIPO. Details on the 2 direct comparisons are reported in the Supplementary Data. Symbols in (A): +, more effective at statistical level of P<.05; −, less effective at statistical level of P=.05; no difference; t, indicates which treatment is favored by a trend in cases of no difference. The triangular graph has been plotted as described by Fadda et al [4]. Symbols in (B): the vertical red line indicates the noninferiority margin set at 10%. Abbreviations: AmB-LE, amphotericin B lipid emulsion; AmB-LIPO, amphotericin B liposomal product; CI, confidence interval; RD, risk difference.
The meta-analysis published by Mistro and coworkers [1] has carried out 2 separate superiority comparisons: AmB-LIPO versus AmB-Dx (5 trials) and AmB-LE versus AmB-Dx (9 trials). Both showed a significantly higher nephrotoxicity rate for AmB-Dx; the indirect comparison between AmB-LIPO and AmB-LE was not examined statistically.

In the present analysis, first we reexamined the same trials included in the aforesaid meta-analysis; then we carried an indirect comparison of AmB-LIPO versus AmB-LE using standard network meta-analysis techniques (Bucher’s method [4] combined with noninferiority testing [5]). Point estimates were estimated along with their 95% confidence interval (CI). The end-point of our analysis (incidence of nephrotoxicity) was the same as in Mistro and coworkers’ study. The only difference was that our analysis was based on risk difference (RD) rather than on relative risk. This was because RD is a more intuitive parameter in this context and, more importantly, facilitates the interpretation of noninferiority analyses [6].

Figure 1A shows the results of our network meta-analysis. In the direct comparison between AmB-LIPO and AmB-Dx, the pooled RD was −17.32% in favor of AmB-LIPO (95% CI, −22.90% to −11.73%; 5 trials). Likewise, in the direct comparison between AmB-LE and AmB-Dx, the pooled RD was −25.93% in favor of AmB-LE (95% CI, −43.67% to −8.19%; 9 trials). The indirect comparison of AmB-LIPO versus AmB-LE found an RD of −8.61% in favor of AmB-LE, but the 95% CI (−27.21% to 9.99%) failed to show the superiority of any of these 2 treatments. More important, in the noninferiority test these results demonstrated the noninferiority of AmB-LE in comparison with AmB-LIPO according to a noninferiority margin of 10% (Figure 1B); in fact, the upper extreme of the 95% CI of the point estimate approached the noninferiority margin, but did not cross it.

The value that in general can be recognized to the results of network meta-analyses and to the resulting indirect comparisons is still being debated. In this case, our analysis contributed to generate a more informative conclusion because not only did we demonstrate no proof of difference between the 2 lipid-based products, but we provided also the proof of no difference (according to the noninferiority 10% margin).

**Supplementary Data**

Supplementary materials are available at Clinical Infectious Diseases online (http://cid.oxfordjournals.org). Supplementary materials consist of data provided by the author that are published to enhance the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

**Notes**

Acknowledgments. The authors have carried out this study in the context of their activity at ESTAV Centro, an institution of the Italian national health system.

Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

Andrea Messori,1 Valeria Fadda,1 Dario Maratea,1 Sabrina Trippoli,1 and Claudio Marinai2

1HTA Unit, and 2Therapeutic Drug Committee, ESTAV Toscana Centro, Regional Health Service, Firenze, Italy

**References**


Correspondence: Andrea Messori, PharmD, ESTAV Centro, Area Vasta Centro Toscana, Regional Health System, Via Guimaraes 9-11, 59100 Prato, Italy (andrea.messori.it@gmail.com).

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This material provides further details on our traditional meta-analysis evaluating direct comparisons.

**Forest plot**
The Figure (see below) shows the Forest plot and the study-specific crude rates included in our two meta-analyses evaluating direct comparisons. These crude event rates are the same as those reported by Mistro et al. Symbols in this plot are those traditionally used in standard meta-analysis. The graph shows the comparison of AmB-LIPO vs AmB-Dx (Panel A) and of AmB-LE vs AmB-Dx (Panel B).

**Software used for meta-analysis**
The statistical calculations for indirect comparisons were based on the ITC software (Canadian Agency for Drugs and Technologies in Health, Indirect Treatment Comparison software, Ottawa, Canada), while the OMA software (Open Meta-Analyt, version 4.16.12, Tufts University, url http://tufiscaes.org/open_meta/) was used for estimating the risk difference (RR) for all direct comparisons according to the random-effect model.