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Aerosolized amphotericin B as prophylaxis for invasive pulmonary aspergillosis: a meta-analysis

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SUMMARY

Objectives: Invasive pulmonary aspergillosis (IPA) is associated with high mortality in high-risk (immunosuppressed) patients. Many studies have investigated whether prophylactic inhalation of amphotericin B (AMB) reduces the incidence of IPA, but no definitive conclusions have been reached. The present meta-analysis was performed to evaluate the efficacy of prophylactic inhalation of AMB for the prevention of IPA.

Methods: MEDLINE and other databases were searched for relevant articles published until December 2013. Randomized controlled trials that compared aerosolized AMB with placebo were included. Two reviewers independently assessed and extracted the data of all trials.

Results: Six animal studies and two clinical trials involving 768 high-risk patients were eligible. The animal studies showed lower overall mortality rate among animals that underwent aerosolized AMB prophylaxis (odds ratio (OR) 0.13, 95% confidence interval (CI) 0.08–0.21). Similarly, the clinical trials showed a lower incidence of IPA among patients who underwent aerosolized AMB prophylaxis (OR 0.42, 95% CI 0.22–0.79).

Conclusions: This analysis provides evidence supporting the notion that the prophylactic use of aerosolized AMB effectively reduces the incidence of IPA among high-risk patients.

1. Introduction

Invasive aspergillosis (IA) is an increasingly frequent cause of morbidity and mortality in immunosuppressed patients, especially those undergoing solid organ or hematopoietic stem cell transplantation and those with prolonged neutropenia.[1] Invasive pulmonary aspergillosis (IPA) is the most common form of IA. Despite the fact that new non-invasive laboratory methods have been developed to improve the diagnostic yield, including the Aspergillus galactomannan assay, the (1,3)-β-D-glucan assay, and PCR techniques, IPA remains associated with a high fatality rate. In one systematic review, 70% of 1941 patients with aspergillosis exhibited pulmonary involvement, and the case-fatality rate was >60% despite the administration of intensive antifungal therapy.[2] Therefore, prophylactic therapy is important in high-risk patients. However, there is no consensus on the optimal agent or administration route.

Amphotericin B (AMB) was the first commercially significant antifungal drug. It has a broad spectrum of activity against many different fungal species and has been the standard IA treatment for decades.[3] Although new agents such as voriconazole and itraconazole have been recommended for patients with IPA, AMB is still considered to be the primary therapeutic agent for some patients and is included in many prophylactic regimens for fungal infection.[4] One study showed that the prophylactic administration of intravenous AMB to patients undergoing bone marrow transplantation was associated with fewer fungal microorganisms and higher survival rates compared to the placebo group; however, significantly greater numbers of infusion-related side effects occurred.[5] Therefore, aerosolized AMB represents an attractive alternative for the prevention of IPA because the administration of drugs by inhalation ensures a high drug concentration in the respiratory tract and a lower incidence of side effects.

Since the 1990s, many studies have been conducted to elucidate the feasibility, tolerability, and effectiveness of aerosolized AMB for the prevention of Aspergillus infection.[6–11] A retrospective study of 99 patients who underwent heart transplantation with

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no prophylaxis and 120 patients who underwent prophylactic inhalation of AMB demonstrated a significant difference between the two groups; prophylaxis with AMB effectively prevented IPA.[12] Another retrospective study evaluated the impact of prophylactic AMB inhalation on IA in 611 recipients of allogeneic stem cell transplantation and examined the recipients' tolerance of the inhalation therapy. The incidence of IA was lower in the prophylactic AMB inhalation group than in the placebo group, and the inhalation therapy was well tolerated.[13] However, other studies have reached different conclusions. In another study that investigated the effectiveness of aerosolized AMB as prophylaxis against IPA, 28% of the patients developed proven or possible infections. Inhalation of AMB does not appear to be useful in preventing IPA in patients with granulocytopenia.[14]

The present meta-analysis was performed to assess the prophylactic effect of aerosolized AMB against IPA by examining the IPA-associated mortality among immunocompromised animals and the incidence of IPA among high-risk patients.

2. Materials and methods

2.1. Search strategy

Two separate electronic searches were conducted to identify eligible studies. MEDLINE, Embase, the Chinese Biomedical Literature Database, and the Cochrane Library were searched for relevant articles published until December 25, 2013. The following search terms were used: "inhaled" or "inhalational" or "aerosol" or "aerosolized" or "nebulized" or "nebulization" and "amphotericin". No limitations were placed on language or year. The reference lists of related reviews and original papers were also checked for relevant trials.

2.2. Study selection

The following inclusion criteria were established before article collection. Animal studies were required to (1) be randomized controlled trials, (2) compare aerosolized AMB with placebo, (3) administer aerosolized AMB before exposure to *Aspergillus fumigatus* conidia, and (4) provide the number of animals sacrificed. Human studies were required to (1) be randomized controlled trials, (2) include adult patients (aged >18 years) scheduled to receive chemotherapy with an anticipated duration of neutropenia $<0.5 \times 10^9$ cells/l of ≥10 days, (3) compare aerosolized AMB with placebo, and (4) administer aerosolized AMB before any signs of proven or probable IPA. When an individual author published several articles involving the same patient population, only the most complete article was included. Studies that did not meet the above-described inclusion criteria were excluded from the meta-analysis.

2.3. Quality assessment

Clinical randomized controlled trials were assessed using the Jadad scale.[15] This scale is used to assess trials according to the following three questions: (1) Was the study described as randomized (i.e., did it use the terms 'randomly', 'random', or 'randomization')? (0–2 points); (2) Was the study described as double-blind? (0–2 points); (3) Was there a description of withdrawals and dropouts? (0–1 point). A study can receive a maximum Jadad score of 5 points.

2.4. Data extraction

Two reviewers (DX and WKS) independently carried out the data extraction and validity assessment, and any discrepancies were resolved by discussion. For the animal studies, a piloted data extraction form was used to collect information on the first author, year of publication, animal species, number of animals in each group, method of inducing immunosuppression, details of experimental drug and placebo treatments, follow-up duration, and final mortality rate. For the clinical trials, a data extraction form was used to collect information on the first author, year of publication, country of origin, Jadad score, number of patients in each group, and incidence of IPA.

2.5. Statistical analysis

The results of prophylaxis for dichotomous outcomes are expressed as odds ratios (ORs) with 95% confidence intervals (CIs) for both the animal studies and clinical trials. The I^2 statistic was used to determine the extent of inconsistency and thus assess the heterogeneity between trials. We considered an I^2-value of >50% and a p-value of <0.1 to indicate heterogeneity. A fixed-effects model was used to estimate the effects of aerosolized AMB. However, if significant heterogeneity was present, a random-effects model was used to generate a more conservative estimate.

Publication bias among the randomized controlled trials involving animals was examined by visual inspection of a funnel plot. Publication bias was suspected when the funnel plot was asymmetrical; in such cases, Egger's test was performed for further analysis of bias.

Sensitivity analyses were conducted by comparing the estimates derived from the random- and fixed-effects models. One study that used AMB inhalation powder (ABIP) as the prophylactic drug was excluded from the sensitivity analyses because this drug is not widely used.

Subgroup analyses of the animal studies were performed to explore important differences that might be expected to alter the magnitude of the prophylactic effect.

3. Results

3.1. Study selection and characteristics

Figure 1 shows the study selection process. In total, 1362 potentially relevant citations were identified from the electronic search, 1348 of which were determined to be non-relevant after reading the titles and abstracts. The remaining 14 studies underwent full review by the two above-mentioned independent reviewers. Eight of these 14 studies met the inclusion criteria and were subjected to the meta-analysis.[16–23] Six studies were initially thought to fulfill the inclusion criteria, but were excluded after detailed examination. One study was not a randomized controlled trial,[24] one evaluated the therapeutic rather than the prophylactic efficacy of aerosolized AMB,[25] one evaluated the beneficial effect of intravenous rather than aerosolized AMB,[26] one evaluated the beneficial effect of aerosolized AMB on the fungal burden rather than on mortality,[27] and two were duplicate publications.[10,28] Of the eight remaining eligible studies, six were animal randomized controlled trials[16–21] and two were human randomized controlled trials.[22,23]

In all six animal studies, a systemic steroid and/or cyclophosphamide was used to induce immunosuppression. The fungal inoculation and drug administration methods were described in detail. The various formulations of aerosolized AMB were AMB desoxycholate (AMB-d), liposomal AMB (L-AMB), AMB lipid complex (ABLC), AMB colloidal dispersion (ABCD), and ABIP. Table 1 lists the details of the six animal studies included in this meta-analysis.

In both of the human studies, randomization was performed using a computer-generated blocked list. Both studies included a description of the patients who withdrew from or dropped out of