

# Hearing Loss with Amphotericin B Therapy in Patients with Rhinocerebral Aspergillosis: Is it a Reality?

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## ABSTRACT

**Context:** Study carried out to investigate the relationship of amphotericin B (AmB) therapy with hearing loss developing in patients with rhinocerebral aspergillosis during prolonged AmB therapy.

**Aim:** To study the effect of prolonged AmB therapy on the hearing acuity of patients suffering from invasive fungal sinusitis.

**Setting and design:** Nonrandomized prospective study carried in Department of Otolaryngology and Head and Neck Surgery from January, 2010 to June, 2013.

**Materials and methods:** High frequency pure tone audiometry (PTA) and cold caloric test (CCT) were done for all patients before starting of therapy with AmB. Both tests were repeated at 500 mg, 1 and 2 gm of AmB administration. Follow-up was done for all patients at 3 and 6 months after completion of therapy.

**Results:** Twenty-four patients of invasive fungal sinusitis included. On prolonged AmB therapy some patients had deterioration in hearing. But these changes were not statistically significant. The changes were mild and shift was one grade above or below. It was also seen that the hearing complaints were reported in the middle of the therapy although all these patients had baseline hearing loss.

**Conclusion:** Amphotericin B does cause some change in hearing pattern; although not statistically significant. A further study is required with more number of patients so as to say definitively that AmB causes a change in hearing. Though these patients have numerous factors which can affect hearing in many ways, a systematic study is required to go a long way in clearing the doubts attached to AmB therapy.

**Keywords:** Rhinocerebral aspergillosis, Hearing loss, Amphotericin B.

**Key message:** Amphotericin related hearing loss has not been reported in English literature till date. Our study focuses on the effect of AmB on hearing. Amphotericin B does cause some change in hearing pattern, although not statistically significant. All the patients complained of hearing deterioration while some

showed improvement on audiogram (though not significant) showing a paradoxical feature.

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## INTRODUCTION

Invasive fungal sinusitis cases have been increasing in number for last few years, especially in immunocompromised patients. The course of this infection is rapidly progressive and potentially fatal if not treated early. Treatment includes a combination of surgical debridement, antifungal therapy and control of underlying risk factors. The agent of choice among antifungals remains Amphotericin B (AmB). However, therapy with this drug is associated with many adverse effects.

Amphotericin B is a polyene antifungal drug, often used intravenously for systemic fungal infections. Amphotericin B binds with ergosterol present in fungal cell membranes, forming a transmembrane channel that leads to monovalent ion ( $K^+$ ,  $Na^+$ ,  $H^+$  and  $Cl^-$ ) leakage, which is the primary effect leading to fungal cell death. Amphotericin B molecules can form pores in the host membrane as well as the fungal membrane as both contains ergosterol in its membrane. This impairment in membrane barrier function can have lethal effect.<sup>1,2</sup>

Intravenously administered AmB has also been associated with multiple organ damage in therapeutic doses. Nephrotoxicity (kidney damage) is a frequently reported side-effect, and can be severe and/or irreversible. In addition, electrolyte imbalances (e.g. hypokalemia and hypomagnesemia) may also result. In the liver, increased liver enzymes and hepatotoxicity (up to and including fulminant liver failure) are common. In the circulatory system, several forms of anemia and other blood dyscrasias (leukopenia, thrombocytopenia), serious cardiac arrhythmias (including ventricular fibrillation), and even frank cardiac failure have been reported.<sup>3-6</sup> Skin reactions, including serious forms, are also possible. In ototoxic side-effects, although tinnitus<sup>7</sup> is a known side effect but hearing loss has not been reported due to AmB.

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During the in-hospital management of invasive fungal sinusitis, numerous patients complained of hearing loss. Our main objective in carrying out this study was to have a clear idea whether AmB is causing ototoxicity in these patients. Amphotericin B, related ototoxicity in the form of decreased hearing acuity has not yet been reported in the English literature to best of our knowledge.

The main aim of this study was to study the effect of prolonged AmB therapy on the hearing acuity of patients suffering from invasive fungal sinusitis.

**MATERIALS AND METHODS**

A prospective nonrandomized unblinded study conducted in the Department of Otolaryngology and Head and Neck surgery at our institute from January 2010 to June 2013. Twenty four consecutive patients of rhino-orbitocerebral fungal sinusitis (invasive) who received AmB were included in the study. The study group at baseline acted as control group for later comparison. Patients of invasive fungal sinusitis proved histopathologically and having no evidence of compromised immunity only were included. Patients were considered immunocompetent if they did not have history of any malignancy, end-stage renal disease, human immunodeficiency virus (HIV) infection, congenital immunodeficiency, chemotherapy, steroids or other immunosuppressive drugs. Patients with known allergy to AmB and immunocompromized patients were excluded.

Demographic data including age, sex, and place of origin were noted. Detailed ENT and ophthalmological history was taken. Detailed general, systemic, otolaryngological and ophthalmological examination was performed. Contrast-enhanced computed tomography (CECT) paranasal sinuses and orbit was done in all patients and magnetic resonance imaging (MRI) was done in case of intracranial extension of the disease. Routine blood investigations including RFT and LFT were done in every patient. A high frequency pure tone audiometry (PTA) (upto 18000 Hz) and cold caloric test (CCT) were done for all patients before starting of therapy with AmB. Both tests were repeated at 500, 1 and 2 gm of AmB administration. Follow-up was done for all patients at 3 and 6 months after completion of therapy and both tests were performed.

Hearing was graded according to the World Health Organization (WHO) grading system:

Grade	Hearing loss	Interpretation
1	0-25 dB	No impairment
2	26-40 dB	Slight impairment
3	41-60 dB	Moderate impairment
4	61-80 dB	Severe impairment
5	> 80 dB	Profound impairment

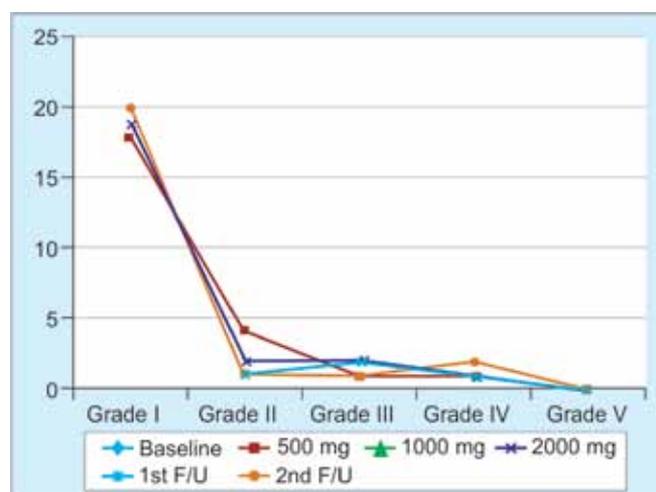
**RESULTS**

Twenty four consecutive patients of rhino-orbital-cerebral invasive fungal sinusitis were included in this study. Among them eight were females and 16 were males. Mean age of patients was 33.95 years (11-54 years). One patient had chronic obstructive pulmonary disease (COPD) and one patient had allergic bronchopulmonary aspergillosis (ABPA). All the patients were subjected to surgery to obtain tissue for histopathology and debridement of disease. Postoperatively patients were given intravenous AmB. High-frequency pure tone audiometry was performed before starting the treatment and then at 500, 1000 and 2000 mg of AmB. All the patients in the study group who complained of hearing loss were found to have either a sensorineural or mixed hearing loss (Table 1).

In baseline PTA on right side (Graph 1); 19 (79%) patients had grade I hearing; 2 (8%) had grade II; 2 (8%) had grade III; 1(4%) had grade IV and none of the patients had grade V hearing impairment. After completion of 500 mg of AmB; one patient had deterioration of hearing from grade I to II but 2 patients had improvement from grade III to grade II. The changes were not significant (p-value 1.00). At completion of 1 gm; one had improvement from grade II to I and one from grade III to II and 2 had deterioration from grade II to III. While comparing this to baseline PTA; it was not found to be significant (p-value 1.00). At 2 gm no changes in hearing were noticed as compared to that at 1 gm and on comparing

**Table 1:** p-value between hearing levels in right and left ears during and after treatment with AmB

	Right ear	Left ear
PTA baseline vs 500 mg	1.000	0.705
PTA baseline vs 1000 mg	1.000	0.317
PTA baseline vs 2000 mg	1.000	0.564
PTA baseline vs 1st F/U	0.317	0.564
PTA baseline vs 2nd F/U	1.000	0.564



**Graph 1:** Pattern of hearing in right ear as obtained by high-frequency PTA

to baseline it was not significant (p-value 1.00). At first follow-up one patient had improvement from grade II to I and at second follow-up one had deterioration from grade III to IV. Both were not significant as compared to baseline (p-value >0.05).

On left side (Graph 2) 16 (66%) patients had grade I hearing; 2 (8%) had grade II; 1 (4%) had grade III; 3 (12%) had grade IV and 2 (8%) had grade V hearing impairment. After completion of 500 mg of AmB; two patients had deterioration of hearing; one from grade I to III and other from grade IV to V and two had improvement; one from grade V to IV and other from grade IV to III. These changes were not significant (p-value 0.70). Three patients had hearing improvement after 1 gm of AmB; one from grade V to IV; one from grade III to II and one from grade II to I. The changes were not significant (p-value 0.31). After 2 gm only one patient had deterioration from grade III to grade IV. When compared to baseline the changes were not significant (p-value 0.56). During follow-up after 3 and 6 months there were no changes in audiograms as compared to at 2 gm and were not significant (Table 1). There was no vestibular dysfunction observed during the study.

**DISCUSSION**

Invasive fungal sinusitis should be treated with thorough surgical debridement and anti-fungal chemotherapy, and even this combined approach is disappointing in some patients.<sup>3</sup>

Amphotericin B still is the first-line treatment for invasive fungal sinusitis especially mucormycosis. Amphotericin B binds to ergosterol, which disrupts osmotic integrity of fungal membrane, resulting in leakage of intracellular potassium, magnesium, sugars, and metabolites and then cellular death. The mechanism of action is same for all the preparations and is due to intrinsic

antifungal activity of AmB.<sup>4</sup> Therapy is often prolonged and can be complicated by adverse effects, the most serious of which is renal dysfunction.<sup>5</sup> The narrow therapeutic window and toxicities of AmB are well-recognized. Infusion toxicity occurs in 60% of patients and impairment in renal function in 80% of patients receiving a 2 weeks course of AmB.<sup>6</sup>

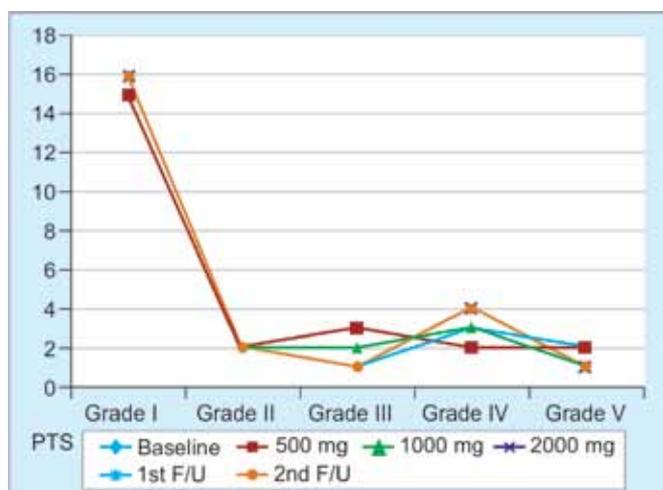
Though AmB has been reported to cause tinnitus<sup>7</sup> but frank ototoxicity has not been reported in literature. There have been incidences of ototoxicity with use of combination aminoglycoside-steroid-antifungal creams or ointments.<sup>8</sup> Fungal infection *per-se* can cause damage to ears. There are reports in literature of cryptococcal meningitis presenting as sudden deafness.<sup>9</sup> A case reporting disseminated histoplasmosis presenting as unilateral cranial nerve VII mass has also been reported in the literature.<sup>10</sup> A case report of mucormycosis of the tympanic membrane in a diabetic patient with facial palsy has also been reported which recovered completely after institution of AmB therapy.<sup>11</sup>

In the present study, it was observed that some patients of fungal sinusitis complained of hearing loss during AmB treatment. All the patients receiving AmB were subjected to audiometric tests. During the study, it was found that there were changes in the hearing pattern at various dosages of AmB. Some patients had improvement in hearing and others had deterioration. But these changes were not statistically significant (Table 1). The changes were mild and shift was one grade above or below. It was also seen that the hearing complaints were reported in the middle of the therapy although all these patients had baseline hearing loss. The explanation to this can be as follows; due to fungal sinusitis the symptom of hearing loss was masked and as the therapy was started; the symptoms related to fungal sinusitis decreased and hearing loss became a prominent feature. Most of the patients did not have any change in hearing during the treatment course. Some patients had improvement in hearing by one or two grades during the treatment. This might be possible in patients with occult temporal bone involvement by fungal sinusitis who later on improved with AmB therapy. Some patients had deterioration of hearing during the therapy but that was not statistically significant so as to call it due to AmB therapy.

The vestibular functions were also recorded by doing CCT. There were no changes observed in CCT.

**CONCLUSION**

Amphotericin related hearing loss has not been reported in English literature till date. Our study focuses on the effect of AmB on hearing. Although the number of patients in the present study are very less to comment



**Graph 2:** Pattern of hearing in left ear as obtained by high-frequency PTA



upon the hearing changes; AmB does cause some change in hearing pattern; though not statistically significant. All the patients complained of hearing deterioration while some showed improvement on audiogram (though not significant) showing a paradoxical feature. A further study is required with more number of patients so as to say definitively that AmB causes a change in hearing. Though these patients have numerous factors which can affect hearing in many ways, a systematic study is required to go a long way in clearing the doubts attached to AmB therapy.

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