Sino-orbital Aspergillosis Treated With Combination Antifungal Therapy
Successful Therapy After Failure With Amphotericin B and Surgery

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ASPERGILLOSIS of the paranasal sinus and orbit is well recognized. Local invasion of the sinus or orbit by Aspergillus has been managed successfully with surgery, whereas amphotericin B as sole therapy is considered inadequate. However, when sinus invasion is complicated by decreasing visual acuity and neurological signs, the course has invariably been fatal, even when aggressive surgery was combined with amphotericin B therapy. (A reference list will be provided with reprint requests.) We present a case of sinus aspergillosis that showed malignant progression despite surgery, treatment with amphotericin B, and the results of in vitro susceptibility testing for the fungus involved.

When combination antifungal therapy (viz, addition of flucytosine and rifampin to the amphotericin B regimen) was instituted, a dramatic clinical response was noted, with gradual resolution of symptoms and neurological abnormalities.

Materials and Methods
Suscceptibility testing was performed by the broth dilution method, using yeast nitrogen base (YNB) supplemented with 1.0% glucose and 0.15% asparagine. The broth was buffered with MOPS/tris buffer, pH 7.2. Flucytosine and rifampin were dissolved in distilled water and serially diluted in YNB to yield concentrations ranging from 0.05 to 100 μg/mL. Amphotericin B was dissolved in dimethyl sulfoxide at concentrations of 0.01, 0.05, 0.1, 0.5, and 1.0 μg/mL in YNB. Synergy testing was performed, using a checkerboard titration. Twofold serial dilutions of flucytosine and rifampin, ranging from 0.05 to 100 μg/mL, were prepared in YNB for each concentration of amphotericin B. An inoculum was prepared by washing a Sabouraud slant culture with saline solution and adjusting the spore suspension to 10^5 colony-forming units per milliliter. Each dilution and control received 0.05 mL of the inoculum. All tests were incubated at 30 °C and visually inspected for growth after 48 hours. The minimal inhibitory concentration (MIC) was defined as the lowest concentration of drug that prevented visible growth of the organism. Synergy was defined as fourfold reduction in the MIC of flucytosine or rifampin in the presence of an otherwise subinhibitory concentration of amphotericin B.

Results
The MIC of the A fumigatus isolated was as follows: flucytosine, 12.5 μg/mL (susceptible); amphotericin B, greater than 1 μg/mL (resistant); rifampin, greater than 100 μg/mL (resistant). Synergy was not demonstrated in vitro for combinations of amphotericin B and rifampin or of amphotericin B and flucytosine.

Report of a Case
A 37-year-old maintenance worker had lived his entire life in West Virginia and

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had been in good health. His chief complaint of headache with right periauricular and facial pain began in March 1978. Treatment with oral antibiotics and analgesics by his private physician failed to alleviate his symptoms. In June 1978, diplopia, tinnitus, and weight loss were noted. The patient was admitted to the Pittsburgh Veterans Administration Medical Center in August 1978. Results of physical examination were normal except for a right-sided paresis of cranial nerve VI. Sinus x-ray films, skull tomograms, and computerised tomography all revealed small masses within the sphenoid sinuses and nasopharynx and erosion of the right aspect of the floor of the sella turcica.

A malignant neoplasm was suspected, and the patient underwent a transoral transsphenoidal sphenoidotomy in September 1978. Three cyst-like masses within the sphenoid sinus were removed. Biopsy specimens from the walls of the sphenoid sinus and the floor of the sella disclosed filamentous, septate, dichotomously branching fungi. *Aspergillus fumigatus* was cultured from this material. Postoperatively, the patient was given intravenous amphotericin B. He noted gradual resolution of the right-sided facial pain and was transferred to a convalescent hospital for maintenance amphotericin B therapy.

Over the next two months, the patient noted new pain around the right eye. Fever appeared and persisted even after amphotericin B was withheld. He was readmitted to the VA Medical Center in December 1978 with a temperature of 37.5°C and a weight loss of 23 kg. Progression of cranial nerve VI paresis was documented. In addition, cranial nerve III paresis manifested by ophthalmoplegia, pupillary dilation, and ptosis was noted for the first time. Proposites had also developed, such that the patient was unable to cover the right eye with his eyelid. Visual acuity in the right eye had deteriorated from 20/70 to complete blindness. A bilateral carotid angiogram showed severe narrowing of the right internal carotid artery above the bifurcation to the cavernous sinus. Ocular plethysmography suggested decreased flow to the right ophthalmic artery.

Because the patient had recurrent severe pain and striking progression of neurological abnormalities despite receiving a total of 1.9 g of amphotericin B therapy, rifampin (600 mg twice daily, orally) and flucytosine (150 mg/kg/day, orally) were added empirically to his regimen in December 1978. He received six weeks of therapy with rifampin and eight weeks with flucytosine. The patient ultimately received a total of 4 g of amphotericin B. Four months after discontinuation of antifungal therapy, the cranial nerve III abnormalities of ophthalmoplegia, pupillary dilation, and ptosis had resolved.

Computerized tomographic scan showed a marked decrease in the size of the sphenoid mass compared with that of previous examinations. The patient's weight had risen, from 50 to 75 kg. Visual acuity had improved to 20/30, and the patient was again able to read. The proposites resolved so that he was able to close his eyelid completely. He remained well and was employed full-time one year after discontinuation of therapy.

**Comment**

Cranial nerve deficits and blindness are dreaded complications of sino-orbital aspergillosis. Ophthalmoplegia, blindness, and proposites can result from fungal invasion of neuromuscular tissue or blood vessels.

Eighteen cases of sino-orbital aspergillosis complicated by onset of neurological and visual defects have been reported; all patients died as a result of their illness. (References are available on request.) Postmortem examination in these cases disclosed direct CNS invasion by the fungus or widespread vascular thromboses. In our patient, symptoms of headache and eye pain recurred, fever developed, and weight loss continued despite aggressive surgery and 1.9 g of amphotericin B. In addition, cranial nerve III deficits, blindness with inability to perceive even light, and propoxtosis developed postoperatively while the patient was receiving amphotericin B.

Because of the progressive clinical deterioration, rifampin and flucytosine were added empirically to the amphotericin B regimen, resulting in a dramatic cure. The patient's pain, fever, anorexia, and cranial nerve abnormalities gradually resolved. Most impressively, his complete blindness also gradually resolved. One year after discontinuation of therapy his vision in the affected eye was 20/30.

Arroyo et al have reported that the addition of rifampin or flucytosine to amphotericin B was more effective than amphotericin B alone for murine aspergillosis. Similar results have also been reported in vitro.3 Ribner et al have described a case of leukemia and pulmonary aspergillosis treated with amphotericin B, rifampin, and flucytosine. Although this patient died, the pulmonary infiltrates became less visible on chest x-ray film after combination therapy. Codish et al have reported a case of *Aspergillus* pneumonia in an alcoholic treated successfully with amphotericin B and flucytosine. However, since amphotericin B is effective as sole therapy in the treatment of pulmonary aspergillosis,4 the actual contribution of the rifampin or flucytosine in these two case reports remains uncertain.

Our case is significant in that we observed definite clinical deterioration in our patient when amphotericin B was used as sole therapy; clinical improvement was not observed until rifampin and flucytosine were added to the amphotericin B regimen.

Subsequent in vitro susceptibility testing showed the *A fumigatus* in our patient to be susceptible to flucytosine and resistant to amphotericin B and rifampin. In vitro susceptibility tests for fungi have not yet been correlated with clinical response in man; however, it is probable that the dramatic response of this patient could be attributed to the addition of flucytosine to his amphotericin regimen.

As the result of our clinical experience, we believe that controlled clinical trials evaluating flucytosine in combination with amphotericin B for life-threatening *Aspergillus* infections are warranted.

**Nonproprietary Names and Trademarks of Drugs**

Amphotericin B—Fungizone.

Dimethyl sulfoxide—Dema sob, Deme so, Dromisol.

Flucytosine—Ancomol.

Rifampin—Rifadin, Rimactane.

**References**


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