

COMBINATION AND SEQUENTIAL ANTIFUNGAL THERAPY FOR INVASIVE ASPERGILLOSIS: REVIEW OF ALL IN VITRO, IN VIVO, AND CLINICAL ANTIFUNGAL TREATMENT

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The incidence of invasive aspergillosis (IA) has increased significantly in the last several decades and the overall survival rate among patients treated with amphotericin B remains dismal. A recent practice survey found that combination antifungal regimens were seldom used for invasive aspergillosis. There has been a recent surge in the development of newer antifungals and drawing from other infectious disease examples combination antifungal therapy is logical. Presently, no controlled clinical trial supports combination therapy for IA and its efficacy has not been conclusively established. The sparse data on combination or sequential antifungal therapy for IA depict interactions ranging from synergy to antagonism. This is the first study to synthesize the available data on combination and sequential antifungal therapy for IA, reviewing all in vitro, in vivo, and clinical published reports and recent abstracts.

Methods and Results. A MEDLINE search was performed from 1966 - 2001. Combination reports from 1966 until 1990 are utilized from a previous review of 2,121 published cases by Denning and Stevens and supplemented with an additional 4,160 cases of IA treatment in the last 12 years. Clinical reports were excluded if antifungals were not used at accepted treatment doses or treatment was < 14 days. The previous 1990 review revealed 89 clinical cases of combination therapy and the subsequent 12 years added 386 clinical cases, totaling 475 combination reports in 290 articles. Exclusion eliminated 215 cases and the 249 cases analyzed yielded 23 different antifungal combinations, including 16 different double antifungal and 7 triple antifungal regimens.

Amphotericin B + 5-FC was the most common combination regimen (49.4%), followed by amphotericin B + itraconazole (16.5%), and amphotericin B + rifampin (10.8%). Clinical improvement was seen in 63.5% of patients treated with combination antifungal therapy. The 27 reports of in vitro combination antifungal therapy yielded synergy (37.6%), additivity (24.7%), indifference (27.3%), and antagonism (10.4%). The 18 reports of in vivo combination antifungal therapy demonstrated synergy (14.3%), additive (20%), indifference (51.4%), and antagonism (14.3%). Excluding the common approach of amphotericin B followed by itraconazole yielded 34 clinical cases of sequential antifungal therapy in 27 reports from 1990 - 2001. Itraconazole followed by amphotericin B was almost 30% (10/34) of cases and 67.6% of patients with sequential antifungal therapy showed improvement.

Conclusion. A review of 6,281 cases of IA therapy from 1966-2001 shows combination and sequential antifungal therapy for invasive aspergillosis hold promise. However, data are inconclusive and drawn from small samples with variable and confounding conditions in the laboratory and patients. With the recent increase in the number of antifungals available, combination antifungal therapy for IA needs to be further studied.