INTRODUCTION

SUPPLEMENT ARTICLE

Advances against Aspergillosis

William J. Steinbach,1 David A. Stevens,2 David W. Denning,4 and Richard B. Moss3

1Division of Pediatric Infectious Diseases, Department of Pediatrics, and Duke University Mycology Research Unit, Duke University, Durham, North Carolina; 2Division of Infectious Diseases, Department of Medicine, Santa Clara Valley Medical Center, and California Institute for Medical Research, San Jose, and Division of Infectious Diseases and Geographic Medicine, Department of Medicine, and 3Division of Pediatric Pulmonology, Stanford University Medical School, Stanford, California; 4School of Medicine, University of Manchester, Hope Hospital, Salford, and Wythenshawe Hospital, Manchester, United Kingdom

As contemporary medicine advances treatment of life-threatening diseases with the addition of newer, aggressive chemotherapeutic regimens and the frequent use of bone marrow and organ transplantation, the rising incidence of invasive aspergillosis has paralleled the marked increase in immunocompromised patients. The incidence of invasive mold infections following hematopoietic stem cell transplantation has tripled in some series [1], with Aspergillus species the most common pathogen. Unfortunately, the overall survival rate among patients treated with the historical standard of amphotericin B is dismal, and until recently there were only 2 antifungals with inherent activity against Aspergillus, amphotericin B deoxycholate and itraconazole.

Treatment of invasive aspergillosis is now at a critical junction. More than a decade ago, Clinical Infectious Diseases published an exhaustive review of old and new treatments for aspergillosis, compiling the results of reports on 2121 patients [2]. This landmark analysis had an unprecedented scope and has served as a reference point for many subsequent analyses. In the interval, there have been several comprehensive reviews of the area, including reviews of treatment results [3], analysis of the significance and consequences of a positive culture result [4], synthesis of current approaches to therapy by an Infectious Diseases Society of America committee [5], update of the biology of the organism [6], study of the epidemiology and costs of the diseases [7], new consensus definitions of disease for future clinical trials [8], and some updating of the earlier analysis [9, 10]. This journal, designed for the busy infectious diseases clinician, has provided a forum for many of these articles and opinions, as well as reviews of individual antifungals.

Although the developmental pipeline of therapeutic options for invasive aspergillosis has been quiescent for many years, there has been a recent expansion in the armamentarium of newer antifungals. In a field in which options for decades included a known toxic agent with only moderate efficacy, even under ideal circumstances (a patient with immunoreconstitution and a timely diagnosis), or an oral azole with erratic absorption and a myriad of interactions, there is now new hope. There has never been a time with so many new antifungals under development or in clinical trials, including new formulations of older drugs (i.e., cyclodextrin-itraconazole and polyethylene glycol-amphotericin B) and entirely new classes of drugs with novel targets.

Newer strategies with unique combination antifungal therapies as well as cytokine therapy with or without antifungals to ameliorate the host response system are also beginning to be explored. For the first time, there is evidence favoring consideration of alternatives to amphotericin B, particularly voriconazole. The total number of therapeutic options for invasive aspergillosis has so markedly increased in the last few years that the clinician needs to be aware of both the proven therapies of today and the anticipated treatments of tomorrow. This supplement is designed to update the clinician on several exciting fronts in the therapy of invasive aspergillosis.

We first review the available reports on the experimental and clinical investigations of newer antifungals against invasive aspergillosis, presenting in vitro studies, animal models, and clinical reports on the agents already approved for clinical use, those undergoing clinical trials, and several new compounds on the horizon. We focus on reviewing the treatment of suspected or proven invasive aspergillosis and, instead of reiterating the existing guidelines [5], adding consideration of the many recent advances and future directions in the treatment of invasive aspergillosis.

We next address the growing trend of clinicians using unique antifungal combinations for therapy of invasive aspergillosis. Although combination therapy is the standard of care for so many other disease processes, the options for invasive aspergillosis were previously so limited that combination therapy was never a viable
option. The development of newer antifungal agents is creating a myriad of new potential combination regimens. However, the efficacy of combination therapy for invasive aspergillosis has not been established; sparse data on combination or sequential antifungal therapy for invasive aspergillosis depict interactions ranging from synergy to antagonism. We present the most comprehensive synthesis of the available data on combination and sequential antifungal therapy for invasive aspergillosis, including a review of reports of 6281 patients treated for invasive aspergillosis. We review published studies, clinical reports, and recent abstracts on combination and sequential antifungal therapy for invasive aspergillosis from 1966 to 2001 to offer a view on the current therapy for invasive aspergillosis. We review published studies, including a review of reports of 6281 patients treated for invasive aspergillosis, a review of reports available data on combination and sequential antifungal therapy for invasive aspergillosis, and recent abstracts on invasive aspergillosis.

To address the growing burden of the allergic response to Aspergillus, an international field of experts was convened by the United States Cystic Fibrosis Foundation in June 2001 to develop a consensus on the diagnosis and treatment of allergic bronchopulmonary aspergillosis, because it is 1 of 2 major diseases besides asthma that complicates cystic fibrosis. Patients with cystic fibrosis do not develop invasive aspergillosis despite large doses of corticosteroids, with few exceptions, unless they undergo lung transplantation. The consensus conference report emphasizes in-depth exploration of Aspergillus fumigatus biology relevant to the pathogenesis of allergic bronchopulmonary aspergillosis, host immune response in animal models and patient settings, as well as clinical recognition, diagnostic, and therapeutic strategies.

Although the term “aspergilloma” has been in common medical parlance for ~50 years, there is also a group of patients with new or enlarging pulmonary cavities and positive Aspergillus serologic test results without a fungal ball. In this supplement, we describe 18 such patients and offer a new approach to these patients with chronic pulmonary aspergillosis, including a new classification system. An understanding of the pathogenesis of this separate clinical entity is required to construct a therapeutic algorithm for these patients.

Finally, we explore invasive aspergillosis in solid-organ transplant recipients, specifically the subpopulation with historically the highest rates of invasive aspergillosis, patients who have undergone heart transplantation. This is the largest series of patients with aspergillosis and heart transplantation reported. The clinical presentation is detailed, and some new predisposing conditions are uncovered.

The editors represent the disciplines of internal medicine and pediatrics, and a unifying bond is that all had part of their training at and/or are presently serving at Stanford University School of Medicine, where the intense activity in the fields of oncology, transplantation, and congenital immunodeficiencies has engendered a common focus on this opportunistic infection in these immunocompromised hosts. We were also able to enlist the collaboration of scientists in other disciplines, especially radiologists, surgeons, microbiologists, immunologists, allergists, epidemiologists, and pharmacologists, particularly for the studies of allergic bronchopulmonary aspergillosis, chronic disease, and disease in patients who have undergone heart transplantation.

We express our deep appreciation to the corporations listed on the title pages involved in diagnostic or therapeutic developments against the diseases, as well as the charitable foundations dedicated to advances in research and treatment. Their support is invaluable as proponents for new therapeutic modalities and education, including generous support of this publication. It is our hope now that the updating of advances against this invasive fungus can proceed via a dedicated recurring open conference, so the information exchange can be a continuing one. We are presently formulating plans for such events, including the first conference which is planned for 9–11 September 2004 in the San Francisco area (see http://www.advancesagainstaspergillosis.org).

Although marred by a past with poor survival rates and few new agents to combat the disease, the art of the treatment of invasive aspergillosis is now embarking on a hopeful future with the addition of so many newer antifungals and newer treatment regimens. Clinicians are now exploring other manifestations of the disease, including allergic and chronic presentations as well as specific transplant subpopulations, to create the best recommendations for these specific patient populations. It is our wish that our present efforts will provide a new landmark for students of the diseases caused by this fungus. The optimal therapy for diseases caused by Aspergillus is likely as heterogeneous as the patient populations afflicted with the disease, but numerous recent advances against aspergillosis offer new hope.

References