Meeting the Challenges of an Emerging Pathogen: The Henry Schueler 41&9 Foundation International Forum on Mucormycosis

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Invasive mucormycosis comprises a group of uncommon but emerging life-threatening pulmonary, sinal, rhinocerebral, and disseminated infections, which cause debilitating morbidity and severe mortality in our most vulnerable pediatric and adult immunocompromised patients. While important advances are being achieved in understanding the epidemiology, molecular taxonomy, pathogenesis, pharmacology, host defenses, and microbiology of these infections, there are critical needs for improving these approaches for diagnosis, treatment, and prevention. This supplement is dedicated to the memory and courage of Hank Schueler, who fought valiantly against this infection. It provides a comprehensive resource for current approaches to management of this infection and also reviews the key advances against invasive mucormycosis.

BACKGROUND

Invasive mucormycosis causes devastating pulmonary, sinal, rhinocerebral, and disseminated infections in immunocompromised patients. Affecting our most vulnerable pediatric and adult immunocompromised patients, the morbidity and mortality caused by this infection are severe.

Dr Thomas Walsh, director of the Transplantation-Oncology Infectious Diseases Program at Weill Cornell University Medical Center, had the honor of helping Dr David Margolis, director of Blood and Marrow Transplantation of Children’s Hospital of Wisconsin (Milwaukee), care for Hank Schueler in the management of his invasive mucormycosis. Hank underwent allogeneic hematopoietic stem cell transplantation for curative treatment of his hypodiploid acute lymphoblastic leukemia in Chicago, Illinois, in March 2007. He returned to his school, where he graduated with his eighth-grade class in June 2007. He also returned to playing baseball on 7 June 2007.

Following the unfortunate relapse of his leukemia in early September 2007, he received reinduction chemotherapy at Children’s Hospital of Wisconsin. Hank subsequently developed invasive mucormycosis of the frontal sinuses. This infection became refractory to all available modalities of antifungal therapy and progressed to fatal cerebral hemorrhagic infarction on 14 December 2007.

The devastating effects of invasive mucormycosis (zygomycosis) on a patient and a family are compellingly expressed by Matthew Schueler, Hank’s father, in the first full article of this supplement [1]. The suffering caused by this terrible infection is recapitulated many times throughout the world. As a rare disease, mucormycosis is not well understood by the general medical community.

HENRY SCHUELER 41&9 FOUNDATION INTERNATIONAL FORUM ON MUCORMYCOSIS

Following the establishment of the Henry Schueler 41&9 Foundation (www.HenrySchueler.org), Hank’s father Matt conferred with Dr Bruce Bloom of Partnership...
for Cures and with Dr Walsh, and all agreed that the foundation’s mission should include an effort to advance our understanding of mucormycosis. Development of an international forum dedicated to reviewing the current science of invasive mucormycosis was determined to be a most fitting way to honor Hank’s courage and memory. The forum brought together, in Chicago, the world’s internationally recognized experts in the field of mucormycosis to discuss the current state of the science and to identify the directions for future investigations of this infection, including taxonomy, nomenclature, epidemiology, pathogenesis, host defenses, clinical manifestations, laboratory diagnosis, and antifungal pharmacotherapeutics. Each of these topics was discussed vigorously by the speakers in a roundtable format, while questions and comments were offered by invited guests from the greater Chicago medical community. The video and audiotapes of these lectures will be included on the Henry Schueler 41&9 Foundation Web site.

**SUPPLEMENT ON MUCORMYCOSIS**

This supplement of *Clinical Infectious Diseases* has 3 purposes: it memorializes the brief, inspiring, and heroic life of Hank Schueler [1]; it reviews the subjects discussed at the forum; and it provides the medical community with a comprehensive resource for understanding the multiple biological, pathological, epidemiological, clinical, immunologic, diagnostic, and therapeutic facets of invasive mucormycosis [2].

Mr Schueler opened the forum with a poignant description of the impact on the family of their courageous son’s lost battle with mucormycosis. The insights shared by Mr Schueler in his article have universal implications for parents striving to help their child through a catastrophic illness.

The next article is written by Dr June Kwon-Chung [3], who discusses recent developments in molecular taxonomy showing that the class Zygomyces is not monophyletic; that is, the molecular characteristics of this class indicate that the orders Mucorales and Entomophthorales are sufficiently distinct as to warrant their separation into 2 subphyla: Mucormycotina and Entomophthoromycotina. The results of redefining these relationships also are logically consistent with the distinct epidemiology, clinical manifestations, and treatment of mucormycosis versus those for entomophthoromycosis [1]. Moreover, as the class of Zygomyces did not fulfill the requisite criteria of nomenclature for a Latin description when it was introduced, the term for this class has not been accepted in retrospect.

While “zygomycosis” has been used widely with good rationale in the biomedical literature during the past quarter-century, this supplement reintroduces the term “mucormycosis” to reflect the evolving changes in nomenclature and molecular taxonomy. The term “mucormycosis” by definition excludes members of the order entomophthoromycosis (ie, infections caused by Entomophthorales). The articles written for this supplement are focused on Mucorales species.

Dr Ashraf Ibrahim and colleagues provide a thoughtful and authoritative review of the pathogenesis of mucormycosis [4]. Among the many potential virulence factors of *Rhizopus oryzae*, the role of iron in the pathogenesis of mucormycosis is especially important. Altered iron metabolism is a critical factor in the pathogenesis of patients with diabetes mellitus. The excessive glycosylation of proteins such as transferrin and ferritin also result in decreased affinity for iron and its availability as a free ion to *R. oryzae* and other Mucorales species. The crucial role of iron in the pathogenesis of mucormycosis is further underscored by an increased susceptibility to infection during long-term receipt of deferoxamine therapy and in iron overload states, such as those found in patients with hematological malignancies who have had multiple transfusions. Deferoxamine increases the risk for development of disseminated and localized mucormycosis by serving as a false siderophore. By comparison, hydroxypyridinone iron chelators, such as deferasirox, do not act as siderophores for Mucorales organisms and subsequently are not associated with increased susceptibility to mucormycosis. Instead, deferasirox protects mice from mucormycosis through deprivation of iron from *R. oryzae*. Well-designed and carefully conducted clinical trials are warranted to assess the safety, tolerability, and efficacy of this intervention.

Dr George Petrikkos and colleagues review the current understanding of the epidemiology and clinical manifestations of mucormycosis [5]. Following candidiasis and aspergillosis, mucormycosis is the third most common cause of invasive fungal infection in patients with hematological malignancies and patients who have received a transplant. Mucormycosis also is an uncommon but serious infection in patients with diabetes mellitus and those with traumatic injury. Invasive mucormycosis can be classified on the basis of the anatomic site of involvement as sinal, rhinocerebral, pulmonary, cutaneous, gastrointestinal, disseminated, and extrapulmonary solitary deep visceral lesions.

Underlying comorbidities are important determinants of clinical presentation and prognosis of invasive mucormycosis. For example, Roden et al reported in a comprehensive literature review of 929 cases fulfilling prespecified criteria that the overall mortality of invasive mucormycosis in patients with diabetes mellitus was 44%; in those with no underlying condition, 35%; and in those with neoplastic disease, 66% [6]. Mortality varied with site of infection: Death occurred in 96% with disseminated disease, 85% with gastrointestinal infection, and 76% with pulmonary infection. Most patients with malignancy and a hematopoietic stem cell transplant (60%) had pulmonary disease, while most patients with diabetes (66%) had sinus disease. Consistent with this observation, rhinocerebral infection occurred more frequently in
patients with diabetes mellitus (33%), while developing in only 4% of patients with malignancies.

Dr Olivier Lortholary presented the results of studies conducted in France that further define the epidemiology of mucormycosis. Lanternier et al describe in this supplement a retrospective analysis of cases of mucormycosis reported during 2005–2007 in medical centers throughout France [7]. This study of 101 cases of proven or probable mucormycosis occurred predominantly in males. The most common underlying conditions were hematological malignancies, diabetes mellitus, and trauma. The relationships between sites of invasive mucormycosis and types of underlying condition were similar to those reported by Roden et al, with pulmonary disease occurring predominantly in patients with hematological malignancies and rhinocerebral infection predominating in patients with diabetes mellitus. While identification of R. oryzae as the most common species causing invasive mucormycosis (in 32% of patients) was expected, the identification of Lichtheimia (formerly Absidia) species as the second most common species (in 29% of patients) suggests a geographic specificity for this organism that has not been previously appreciated. Treatment consisted of surgery in 59% and antifungal agents in 87% (liposomal amphotericin B was given in 61%). Among patterns of site of infection and type of underlying condition, disseminated infections and hematological malignancies, respectively, carried the most ominous prognoses. The study underscores the relatively high frequency of cutaneous mucormycosis and the favorable prognosis of localized infection.

In a review of published literature, Rammer and colleagues analyze 169 published cases of proven or probable zygomycosis attributed to healthcare procedures that occurred between 1970 and 2008 [8]. Among the potential environmental sources of nosocomial organisms causing outbreaks and clusters were adhesive bandages, wooden tongue depressors, ostomy bags, a damaged water delivery system, and construction in an adjacent building.

Dr Walsh and colleagues review the standard methods and recent advances in early laboratory diagnosis of mucormycosis [9]. Strategies for direct examination of respiratory secretions, wound drainage, tissue imprints, and histopathology are reviewed. The authors also discuss a novel strategy, introduced by their research team, of using real-time calcofluor-based intraoperative staging of resection of cutaneous, deep soft tissue and bone in a manner similar to but distinct from that of Moh’s surgery. The approach is more rapid than obtaining a hematoxylin and eosin–stained frozen section. The authors then address the new advances in molecular detection of culture specimens and molecular diagnosis of mucormycosis from respiratory secretions, as well as from serum. Their article looks to the future for wider application of advanced molecular diagnostic techniques that will further aid in the early detection and diagnosis of this lethal infection.

Dr Emmanuel Rolides and coauthors review the current understanding of innate host defense against Mucorales species [10]. While some of the basic elements of innate host defense against Mucorales organisms are similar to those against Aspergillus species, there are distinct features in the response to sporangiospores and invading hyphae of this group of nonascomycetous organisms. Factors such as hyperglycemia, extracellular pH, iron dependency, and disruption of mucocutaneous surfaces may also contribute to a differential host response in the immunopathogenesis of invasive mucormycosis. R. oryzae stimulates healthy human monocytes to release more interleukin 6 and tumor necrosis factor α than all Aspergillus species, including Aspergillus fumigatus [11]. Both Toll-dependent and Toll-independent innate immune responses against Mucorales organisms demonstrate significant differences in comparison to those against Aspergillus species. Functional genomic studies indicate important differences in differential expression of genes encoding key host defense molecules [12]. There are also interspecies differences in host response among organisms in the Mucorales order. R. oryzae and Rhizopus microsporus are similarly susceptible to polymorphonuclear leukocytes. By comparison, Lichtheimia corymbifera, a less virulent species, is damaged much more by polymorphonuclear leukocytes and elicits a greater oxidative response. The increased virulence of Cunninghamamella bertholletiae observed in clinical and experimental studies may also be related to evasion of innate host defenses.

Dr Russell Lewis and coauthors discuss the key molecular pharmacological differences between R. oryzae and A. fumigatus [13]. They observe that whole-genomic sequencing of R. oryzae reveals that a whole-genome duplication event occurred during the evolution of this pathogen, resulting in redundancy of gene families associated with ergosterol production, cell wall biosynthesis, cell growth, iron uptake, and other possible virulence factors. Such gene enrichment through whole-genome duplication is not observed in isolates of A. fumigatus. Dr Lewis and colleagues further hypothesize that whole-genome duplication may confer a genetic plasticity that accounts for this organism’s relative resistance to multiple antifungal classes, as well its rapid growth in adverse environments, including during the innate host inflammatory response.

Dr Brad Spellberg and colleagues review the current status of monotherapy with polyene and antifungal agents in the treatment of mucormycosis [14]. They then provide the rationale and possible mechanisms for novel combinations of antifungal agents. The combination of polyenes and echinocandins, as well as polyenes and deferasirox iron chelation therapy, have demonstrable synergy in murine models of mucormycosis. Retrospective clinical data similarly demonstrate a possible benefit favoring the combination of an echinocandin and a lipid formulation of amphotericin B.
Dr Spellberg and colleagues observe that, since echinocandins and deferasirox are approved for use in humans by regulatory agencies in the United States and Europe, design and implementation of phase III clinical trials that use one of these agents in combination with a lipid formulation of amphotericin B should be feasible. Well-designed, randomized, controlled phase III clinical trials will ultimately determine whether either combination therapy is superior to monotherapy with the lipid formulation of amphotericin B in humans. Barriers to studies of orphan diseases include the difficulty of enrolling a sufficient number of patients, host heterogeneity, comorbidities preventing study participation, and protocol adherence in a multi-institutional setting. Novel approaches for clinical study design are needed to test the hypotheses.

Dr Dimitrios Kontoyiannis and other members of the forum provide a special perspective on the future directions of research in order to advance our understanding of the epidemiology, pathogenesis, host defense, diagnosis, treatment, and prevention of mucormycosis [15]. Epidemiological investigations should address geographic differences, host-dependent risk factors, and the selective effects of antifungal agents. Studies in the pathogenesis of mucormycosis need to integrate discoveries from recent advances in genomics and the cell biology of endothelial receptor biology and from investigations of comparative virulence with Aspergillus species. Research in host defense warrants investigation of the role of the innate host defense molecules mediating protection against mucormycosis, the effects of immunosuppressive agents on these mediators, the transcriptional profiles of host-fungus interaction, and the immunopharmacology of antifungal agents on modulation of immune regulations. Translational research in antifungal pharmacology against mucormycosis will require investigation of new antifungal agents, novel targets, iron metabolism, and combination therapy, especially in comparison to the known paradigms with other invasive mycoses.

Finally, as we discuss the broad visions for advances in knowledge of the epidemiology, taxonomy, pathogenesis, host defense, diagnosis, treatment, and prevention of invasive mucormycosis, we need to reflect on the individual patients afflicted with these terrible infections. The courage of Hank Schueler in battling this infection epitomizes the individual patient for whom we work assiduously in our research and clinical care.

Notes

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