REVIEW 10.1111/1469-0691.12566

Mucormycosis – from the pathogens to the disease

U. Binder, E. Maurer and C. Lass-Flörl

Division of Hygiene and Medical Microbiology, Medical University Innsbruck, Innsbruck, Austria

Abstract

Mucormycosis is an emerging fungal infection worldwide, with devastating disease symptoms and diverse clinical manifestations. The most important underlying risk factors are immunosuppression, poorly controlled diabetes, iron overload and major trauma. The aetiological agents involved in the disease have been re-classified due to changes in taxonomy and nomenclature, which also led to appropriately naming the disease 'mucormycosis'. This article shortly explains the new nomenclature, clinical manifestations and risk factors and focuses on putative virulence traits associated with mucormycosis, mainly in the group of diabetic ketoacidotic patients.

Keywords: Angioinvasion, iron overload, ketoacidosis, mucorales, mucormycosis, risk factors, zygomycetes
Article published online: 29 January 2014
Clin Microbiol Infect 2014; **20** (Suppl. 6): 60–66

Corresponding author: U. Binder, Department of Hygiene, Microbiology and Social Medicine, Division of Hygiene and Medical Microbiology, Medical University Innsbruck, Fritz Pregl Str. 3/3, A-6020 Innsbruck, Tirol, Austria
E-mail: ulrike.binder@i-med.ac.at

Introduction

Invasive fungal infections caused by the members of *Mucorales* (mucormycosis) are relatively rare but have increased in the last years [1]. These aggressive and highly destructive infections occur predominantly in immunocompromised hosts, especially in patients with haematological malignancies or those receiving hematopoietic stem cell transplantation. Diabetic patients with ketoacidosis and patients with transfusional/dyserythropoetic iron overload are unique risk groups. The difficulties in diagnosis and subsequent antifungal treatment, partly due to a highly intrinsic resistance to many of the commonly used antifungal drugs [2,3], still leads to high mortality rates in certain patient groups [4].

Compared to other fungal pathogens, such as *Aspergillus fumigatus* or *Candida albicans*, only little is known so far on fungal properties leading to successful infection and host immune response to the various representatives of the Mucorales.

The Pathogens-Taxonomic Changes and Biological Characteristics

These pathogens display a highly diverse group, whose classification is in a constant state of flux. Until more than a decade ago, the phylum Zygomycota comprised the Mucorales, Entomophtorales and eight other orders which included fungi that were not considered to be human pathogens [5]. A comprehensive phylogenetic re-analysis of the kingdom Fungi, based on molecular methods [6], resulted in elimination of the polyphyletic phylum Zygomycota and placing the various taxa into the phylum Glomeromycota divided into four subphyla: Mucoromycotina, Entomophthoromycotina, Kickxellales and Zoopagomycotina (elevating the orders Mucorales and Entomophthorales to a subphylum status). Various gene regions have been used to separate lineages of the Glomeromycota, including ribosomal RNA subunits, elongations factors, α- and β-tubulins and mitochondrial small subunit ribosomal DNA [7–10]. This classification scheme might undergo further revision, but the

Mucoromycotina and Entomophthoromycotina are clearly separated into two different clades and are not related.

The changes in taxonomy were accompanied by a renaming of the disease caused by these aetiologic agents. The term 'zygomycosis', defined in 1976 by Ajello *et al.* [11], and describing any invasive fungal infection caused by species of the former phylum Zygomycota was replaced by either 'mucormycosis' or 'entomophthoromycosis' [9]. Due to the differences in morphology, ecology, epidemiology and the clinical pictures, the various causative agents are able to induce, 'mucormycosis' or 'entomophthoromycosis' is clinically a more specific name than 'zygomycosis'.

The Entomophthoromycotina, natural insect pathogens represented by the two genera Conidiobolus and Basidiobolus, are found in tropical and subtropical regions of the world, where they can cause chronic subcutaneous infections mostly in otherwise healthy patients [12].

The Mucoromycotina are found worldwide as common saprobes on decaying organic material or agricultural and forest soils. They are fast-growing organisms, characterized by large, ribbon-like hyphae with no or only few septae. Disease caused by representatives of the Mucoromycotina comprises severe and potentially life-threatening infections, particularly in the immunocompromised patient. The genera mainly involved in human disease (summarized in Table 1) are *Cunninghamella, Lichtheimia* (formerly *Absidia*), *Mucor, Rhizomucor, Rhizopus* and, depending on geographical distinction, *Apophysomyces* and *Saksenaea* [9,12,13]. The clinical characteristics will be further explained in the following chapters where we will focus on the Mucoromycotina as they play an increasing role in the clinical setting in the Western world.

The Infection-Clinical Manifestations

Tissue necrosis due to invasion of blood vessels and subsequent thrombosis are the hallmarks of invasive mucormycosis. Furthermore, infections with Mucorales are, in most cases, characterized by rapid progression. Mortality rates vary, depending on the site of infection and the condition of the host. Nevertheless, rates of death are estimated to range between 40 and 70%, even with antifungal therapy [14–19]. The challenge associated with diagnosis of Mucormycosis is not only a reason for high mortality rates, but also makes it difficult to determine the exact incidence of the disease. Furthermore, studies show differences in capture periods, populations, and definition of proven/probable cases. A recent study carried out in France over a 10 year period, showed, that the annual population-based incidence rate increased by 7.4% per year (from 0.7 to 1.2 cases/million persons in 2006) [20]. The specific annual incidence rate rose by 24% per year in patients with haematological malignancies, which increased from 0.02 to 0.2 cases/million over time. Similar, Roden *et al.* [19] reported an increase of mucormycosis in immunocompromised patients in the 1980s and 1990s.

TABLE 1. Classification of clinically relevant fungi formerly regarded as 'zygomycetes' [9,13]

Subphylum	Genus	Species most frequently isolated from patients
Mucormycotina	*Apophysomyces*	*A. variabilis*
	Cunninghamella	*C. bertholletiae*
	Lichtheimia (Absidia)	*L. corymbifera*
		L. ramosa
	Mucor	*M. circinelloides*
	Rhizopus	*R. arrhizus (oryzae)*
		R. microsporus
	Rhizomucor	*R. pusillus*
	Saksenaea	*S. vasiformis*
Entomophthoromycotina	*Basidiobolus*	*B. ranarum*
	Conidiobolus	*C. coronatus*

Classification of mucormycosis is performed according to the anatomic site of infection, reflecting in part the portals of entry in the human body. Spores enter the body either via the respiratory tract, through injured skin or via the percutaneous route (e.g. transmission of spores by contaminated needles or catheters), or via ingestion of contaminated food. Disease may present as rhino-orbital-cerebral, pulmonary, cutaneous/subcutanous, gastrointestinal or disseminated form [21,22].

Rhino-orbital-cerebral disease defines an infection that originates in the paranasal sinuses, following inspiration of spores, and possible extension to the brain. Sequentially, nose, sinuses, eyes and brain are affected. Symptoms at early stage of disease might be sinus pain, nasal congestion, fever, soft tissue swelling and headache. Nasal ulceration might occur as well. Progression of disease, which usually is rapid if not treated, results in extension to neighbouring tissues, thrombosis and further necrosis, causing painful black eschar on the palate or nasal mucosa. Extension to the eyes is possibly, leading to blurred vision or even complete loss of vision. From the eyes the disease can progress towards the central nervous system resulting in altered consciousness, cranial neuropathies or cerebral abscesses [22,23].

Clinical manifestations of pulmonary mucormycosis are very similar to those of pulmonary aspergillosis [15,24]. Chest radiographs from patients with pulmonary aspergillosis are indistinguishable from those with pulmonary mucormycosis. Interestingly, Camilos *et al.* [15,24] found independent predictors for pulmonary mucormycosis in a retrospective study reviewing clinical characteristics and CT features in 45 patients with cancer and either pulmonary aspergillosis or pulmonary mucormycosis. Appearance of more than ten nodules as well as the formation of micronodules were shown to be more