Fungal disease of the nose and paranasal sinuses

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Fungal infections of the nose and paranasal sinuses represent a spectrum of diseases ranging from colonization to invasive rhinosinusitis. Clinical manifestations are largely dependent on the immune status of the host, and given the ubiquitous nature of these organisms, exposure is unavoidable. Noninvasive disease includes asymptomatic fungal colonization, fungus balls, and allergic fungal rhinosinusitis. Invasive disease includes indolent chronic rhinosinusitis, granulomatous fungal sinusitis, and acute fulminant fungal rhinosinusitis. A differentiation of these somewhat overlapping syndromes and the disparate treatment regimens required for effective management are the focus of this review. (J Allergy Clin Immunol 2012;129:321-6.)

Key words: *Fungal colonization, fungus balls, allergic fungal rhinosinusitis, chronic rhinosinusitis, granulomatous fungal sinusitis, acute fulminant fungal rhinosinusitis*

Rhinosinusitis refers to inflammation of the nasal and paranasal sinus mucosa and is exceedingly common, affecting up to 13% of the population.[1] Occurring in both acute and chronic forms, rhinosinusitis represents a heterogeneity of patients' risk factors, pathophysiologic processes, and prognoses.

Fungi are ubiquitous in nature, and exposure to the sinonasal and respiratory epithelium is thus unavoidable. Inhalation of these organisms can cause both acute and chronic rhinosinusitis, and the spectrum of disease ranges from noninvasive disease to acute and fulminant infection (Table I), each with distinct clinical and histopathologic features. Topical or systemic antifungal therapy plays a limited role in the treatment of noninvasive infection; however, these agents can play a critical role and should be partnered with surgical intervention in the management of patients with invasive fungal rhinosinusitis.

Considerable debate exists on the terminology, pathogenesis, and treatment options available for fungal rhinosinusitis. This review will use consensus definitions from the recently convened International Society for Human and Animal Mycology Fungal Rhinosinusitis working group.[2]

Abbreviations used
AFRS: Allergic fungal rhinosinusitis
CT: Computed tomographic

NONINVASIVE FUNGAL SINUSITIS

Saprophytic fungal infestation/fungal colonization

Anatomic abnormalities of the paranasal sinuses impair drainage and predispose the patient to fungal colonization of these areas. Mucosal injury from comorbidities also can cause pooling of mucus and colonization by fungi; however, colonization is seldom of clinical consequence, patients are typically asymptomatic, and fungi identified during procedures performed for other reasons should not be treated because numerous species, including *Aspergillus* species, are commonly found in the sinonasal passages.[3]

Allergic fungal rhinosinusitis

Eosinophilic fungal rhinosinusitis, eosinophilic mucin rhinosinusitis, and allergic fungal rhinosinusitis (AFRS) are poorly differentiated syndromes, and all refer to chronic rhinosinusitis (>12 weeks' duration) that is accompanied by sinus opacification with allergic mucin or thick inspissated mucus that ranges in color from tan to brown or black. It remains unclear whether patients with chronic rhinosinusitis with eosinophilic mucin but without fungal elements represent a different clinical and pathologic entity from patients with AFRS. Further complicating definitions, others have recently proposed the concurrent presence of AFRS and allergic bronchopulmonary aspergillosis and termed the collective process sinobronchial allergic mycosis syndrome.[4] This review will focus primarily on AFRS.

Despite more than 100,000 molds recognized in the environment, few genera are associated with allergic disease. *Aspergillus* species and the dematiaceous molds *Alternaria* species and *Cladosporium* species are those most frequently implicated, although *Bipolaris* and *Curvularia* species have also been reported. Considerable regional variation regarding the causal pathogen has been described.[5] The incidence of AFRS also appears to have a geographic predisposition, with an increased incidence of allergic fungal sinusitis seen within the southern United States.[6]

It is believed that fungal allergens elicit IgE-mediated allergic and possibly type III (immune complex)–mediated mucosal inflammation in the absence of invasive infection. This hypothesis has gained support after the demonstration of heightened humoral immune responses to fungal pathogens in patients with chronic rhinosinusitis,[7] evidence of fungal desensitization improving

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Disclosure of potential conflict of interest: G. R. Thompson has received research support from Pfizer. T. F. Patterson has consultant arrangements with Pfizer, Viamet Pharmaceuticals, Toyama, Merck, and Astellas Pharma US and has received research support from Astellas Pharma US, Merck, and Pfizer.

Received for publication October 18, 2011; revised November 22, 2011; accepted for publication November 23, 2011.

Available online December 28, 2011.

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0091-6749/$36.00

doi:10.1016/j.jaci.2011.11.039

TABLE I. Clinical forms of fungal rhinosinusitis

Noninvasive	Invasive
Saprophytic/fungal colonization	Chronic invasive fungal sinusitis
Fungus ball (mycetoma)	Granulomatous invasive (indolent) fungal sinusitis
AFRS	Acute fulminate invasive fungal sinusitis

patient symptoms,[8] and an observed recurrence of upper and lower airway symptoms when exposed to an area with a high fungal content.[9] Additionally, changes in total serum IgE and antigen-specific IgG levels have been reported to coincide with symptoms.[10] It is of interest that species-specific serum IgE levels do not always correlate with the species found on surgical intervention.

However, controversy has surrounded the pathophysiology of AFRS after reports of certain fungi eliciting an eosinophilic inflammation in the absence of confirmed type I hypersensitivity. Further confounding the above hypothesis, IgE specific for *Staphylococcus aureus* superantigens also correlate with total serum IgE levels, have been strongly implicated in chronic rhinosinusitis and nasal polyp formation, and have been found to be contributory to atopic dermatitis in most patients, findings that have lead others to speculate superantigens might be a cofactor required for the development of AFRS.[11,12]

In this condition generalized sinonasal inflammation combined with production of viscous mucin effectively blocks normal drainage of the sinus pathway. After ubiquitous exposure, fungi can then persist within this environment and begin a cycle of destructive immune responses, with further inflammation and poor drainage leading to remodeling of the sinonasal passages. Mounting evidence has also implicated bacterial biofilms in the propagation and recalcitrant nature of chronic rhinosinusitis, although how they contribute to the pathogenic process and persistent inflammation remains unclear.[13]

Unmitigated inflammation can expand and involve the adjacent sinuses and produce sinus expansion, mucocele formation, and potentially contiguous bone erosion, despite a lack of tissue invasion. In fact, proptosis, diplopia, and vision loss have all been described secondary to AFRS alone, even in the absence of fungal invasion.[14]

Undoubtedly, host immunogenetics also contribute to the development of AFRS. An association between the class II MHC and AFRS has recently been recognized. HLA-DQB1*0301 and HLA-DQB1*0302 have been shown to be significant risk factors for the development of AFRS, findings implicating innate immunity in the pathogenesis of this disease.[15]

Diagnostic criteria have been proposed and include the following: (1) type I hypersensitivity demonstrated by skin tests or RASTs; (2) nasal polyposis; (3) characteristic computed tomographic (CT) scan findings, including sinus expansion or heterogeneous opacification; (4) the presence of fungi on direct microscopy or culture of sinus contents; and (5) allergic mucin often mixed with Charcot-Leyden crystals and fungal elements without evidence of tissue invasion.[16] These criteria have been questioned because of the frequent lack of nasal polyps in patients with a history of sinus surgery for other reasons and the difficulty in detecting hyphae (branching filamentous structures) or spores (small round fungal elements) within sinus content. Additionally, skin testing has a low sensitivity and specificity for this disease. For these reasons, all 5 criteria are not necessary for diagnosis, and fungus-specific staining is recommended for histologic examination.

Diagnostic confusion can be reduced by avoiding the temptation to culture nasal secretions in the office setting. Cultures in this setting often reveal only normal nasal flora and are expected to return with numerous different saprophytic organisms, making clinical determination of the involved pathogen difficult. For this reason, intraoperatively obtained specimens are more reliable for fungal culture.[17]

No prospective studies have been performed to guide treatment decisions, and current recommendations are based largely on retrospective case series and expert opinion. AFRS therapy begins with paranasal sinus surgery to remove all obstructing allergic mucin and diseased/hypertrophic sinus mucosa.[17] Failure to remove all areas of disease leads to higher relapse rates and the need for additional surgical intervention at a later time.[18]

After surgery, most would recommend postoperative oral corticosteroids in attempts to reduce disease activity and the need for further surgical intervention.[18,19] It is of interest, however, that the use of systemic antifungal medications has not been effective in the treatment of chronic rhinosinusitis, although specific subgroups have not been adequately evaluated.[18,20] A double-blind placebo-controlled trial showed no benefit to topical amphotericin B use[21]; however, concerns regarding topical therapy have been raised after a subsequent study demonstrating no significant effect on activation markers of nasal inflammatory cells in chronic rhinosinusitis after topical amphotericin B therapy.[22] Additionally, oral terbinafine administered at 625 mg daily versus placebo also did not show efficacy in terms of symptomatic or radiographic improvement.[23] In contrast to the treatment of allergic bronchopulmonary aspergillosis, attempts to reduce corticosteroid dependence with antifungal medications are not usually recommended after the results of a previous randomized study showing no clear benefit to this approach when used with concurrent surgical intervention.[24]

Immunotherapy has not been prospectively evaluated, yet retrospective studies have suggested a benefit to this modality.[20,25] When used as an adjunct to endoscopic sinus surgery, endoscopic office debridement, saline irrigation, systemic steroids, and nasal steroids, the effects of immunotherapy might be less apparent,[20] yet attempts to reduce sinonasal allergic reactivity to the lowest possible levels reduces relapse rates, corticosteroid dependence, and the need for future surgical procedures, and for these reasons, consideration of immunotherapy should be given to all patients with AFRS.[17,26]

Rarely, patients with allergic sinusitis present with symptoms of mass effect caused by inflammation extending into the contiguous spaces, including the orbits. In this patient group surgical treatment and corticosteroid treatment are recommended.

Saprophytic fungus ball

Infrequently, a fungus ball can form within 1 or more of the sinus cavities; these are predominantly caused by *Aspergillus* species. Previously termed mycetoma or aspergillomas, consensus recommendations have suggested these designations be removed in favor of more descriptive terms: localization plus fungus ball with or without causative fungus (eg, maxillary sinus fungus ball caused by *Aspergillus fumigatus*).

Interestingly, sinus fungus balls are more common in female subjects compared with other forms of aspergillosis, which are

TABLE II. Antifungal spectrum of activity against common agents of fungal rhinosinusitis

Organism	AMB	FLU	ITR	POS	VOR	ANI	MFG	CAS
Aspergillus fumigatus	+	−	+	+	+	+	+	+
Aspergillus flavus	+/−	−	+	+	+	+	+	+
Aspergillus terreus	−	−	+	+	+	+	+	+
Aspergillus niger	+	−	+/−	+	+	+	+	+
Fusarium species	+/−	−	−	+	+	−	−	−
Phaeohyphomycosis	+	−	+	+	+	+	+	+
Scedosporium apiospermum	+/−	−	+/−	+	+	−	−	−
Scedosporium prolificans	−	−	−	+/−	+/−	−	−	−
Mucormycoses	+/−	−	−	+	−	−	−	−

AMB, Amphotericin; *ANI*, anidulafungin; *CAS*, caspofungin; *FLU*, fluconazole; *ITR*, itraconazole; *MFG*, micafungin; *POS*, posaconazole; *VOR*, voriconazole.
(+), Implies antifungal activity against isolates; *(−)*, implies no or limited activity against isolate; *(+/−)*, implies variable activity against isolates.[31]

more common in male subjects, although the reasons for this remain unclear.[27] Risk factors for fungus ball development have not been adequately defined, and despite previous reports suggesting overfilling of dental cavities was a risk factor, more recent evidence has questioned this assertion. In fact, Dufour et al[27] found overfilling of a dental cavity in only 18 (10.4%) of 173 patients with maxillary sinus fungus balls.

The clinical presentation of fungus balls is nonspecific, and chronic nasal discharge, nasal obstruction, headache, and facial pain have all been reported, although asymptomatic cases are not uncommon. Patients might complain of cacosmia (the perception of foul odor when none exists). CT images often confirm the presence of heterogeneous opacities with discrete calcification or densities within the involved sinus cavity, with the maxillary sinus most frequently affected, followed by the sphenoid sinus.[28] These densities have been attributed to zinc oxide from overfilled cavities and calcium and magnesium salts deposited within necrotic areas of the mycelium but, of note, can also be found in nonfungal maxillary sinusitis.[27] This predilection for the maxillary sinus is not fully understood.

The accumulation of fungal hyphae within 1 or more sinuses without evidence of tissue invasion, predominance of eosinophils, granuloma, or allergic mucin, establishes the diagnosis. Cultures are positive in less than one third of patients despite obvious fungal elements on histopathologic examination in more than 90% of those affected.[27,29,30]

Treatment consists of endoscopic endonasal surgery, and the technique used is dictated by the location of the fungus ball (middle antrostomy, sphenoidotomy, and ethmoidectomy). Treatment in asymptomatic patients is generally recommended as well; however, there is little evidence to support this approach. The complication rates of these procedures are low, with exceptionally high cure rates, and postoperative or perioperative antifungal treatment is not warranted for noninvasive fungal sinusitis.[27]

INVASIVE FUNGAL SINUSITIS

Chronic invasive fungal sinusitis

In patients with chronic invasive fungal rhinosinusitis, the process of invasion of the sinus tissues occurs over a period of weeks or months rather than hours. Many patients with this relatively rare condition have subtle abnormalities in their immune system caused by diabetes mellitus, chronic low-dose corticosteroid use, or other ongoing immunosuppression. This indolent infection is most commonly caused by dematiaceous molds, such as *Bipolaris*, *Curvularia*, and *Alternaria* species, followed by *Aspergillus* species and other hyaline molds, such as *Pseudallescheria boydii* or the mucormycoses (*Rhizopus*, *Rhizomucor*, *Lichtheimia* [formerly *Absidia*], *Mucor*, and *Cunninghamella* species, for example).

TABLE III. Patients' risk factors for invasive fungal rhinosinusitis

Neutropenia
Hematologic malignancy
Hematopoietic stem cell transplantation
Solid organ transplantation
Diabetes mellitus
Glucocorticoids or other immunosuppressive medications
Advanced HIV infection (AIDS)

Patients typically present with eye swelling and blindness. CT imaging reveals a soft tissue mass within 1 or more of the paranasal sinuses, and bony involvement might be apparent. With intracranial extension, it is not uncommon for this condition to mimic malignancy given the mass-like appearance on radiographic imaging.

Urgent surgery is necessary to confirm the diagnosis and to remove all involved tissue. Systemic antifungal treatment is also warranted and is dictated by the causative agent responsible for the disease. It is noteworthy that of the triazole antifungal agents, fluconazole has little to no activity against the most common fungi responsible for fungal sinusitis (Table II).[31]

Granulomatous invasive fungal sinusitis

Granulomatous invasive fungal sinusitis is typically of gradual onset and has been primarily described in the Sudan, India, and Pakistan, although it is unknown whether this disease is a geographic or ethnicity-related entity. Patients are typically immunocompetent and present to clinical attention with proptosis or an enlarging mass within the orbit, nose, paranasal sinuses, or maxillae. CT findings are not significantly different from those found with chronic invasive fungal sinusitis, although they more commonly show multiple sinus involvement.[32]

This condition is histologically characterized by noncaseating granuloma with foreign body or Langerhans-type giant cells, occasional vasculitis, and sparse hyphae. *Aspergillus flavus* is isolated in almost all cases, and the presence of precipitating antibodies against antigens of the causative agent correlate well with disease progression.

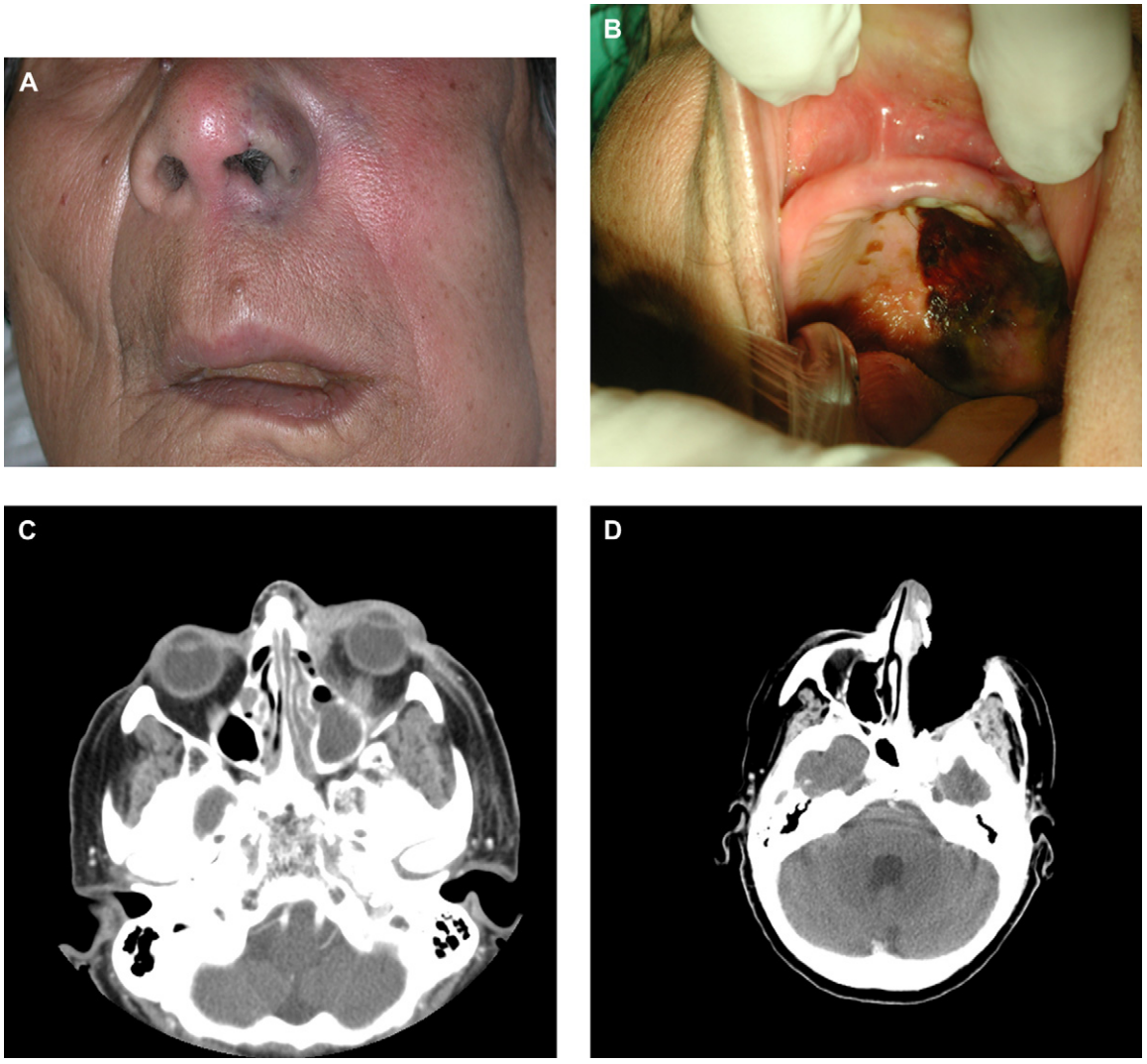

FIG 1. A and **B,** Mucormycosis of the left maxillary sinus extending into surrounding superficial tissue (Fig 1, *A*) and the palate (Fig 1, *B*). **C,** CT imaging revealed inflammatory changes within the left orbit, including the extraocular muscles and choroid: fluid in the bilateral maxillary sinuses, left greater than right, with bony erosion into the posterior orbit. **D,** Treatment required removal of all affected tissue and included a left radical maxillectomy and orbital exenteration.

Treatment consists of surgical debridement of all areas exhibiting signs of invasive infection and the initiation of antifungal treatment. Voriconazole at 6 mg/kg twice daily for 2 doses followed by 4 mg/kg twice daily is the drug of choice for aspergillosis, although itraconazole administered at 200 mg orally 3 times daily for 3 days followed by 200 mg twice daily and posaconazole administered at 400 mg orally twice daily with a fatty meal are viable alternatives. For non-*Aspergillus* molds, empiric amphotericin B is recommended, pending the results of susceptibility testing, and infectious disease consultation is advised. Because of the propensity for recurrent infections, long-term antifungal therapy for more than 1 year might be warranted.[33]

Acute (fulminant) invasive fungal sinusitis

Acute fulminant invasive rhinosinusitis occurs when fungal organisms (most commonly one of the mucormycoses or *Aspergillus* species) invade the sinus tissues in immunosuppressed patients and has increased in frequency over recent years. Classical hosts include those who are neutropenic or have poorly controlled diabetes mellitus (particularly those with diabetic ketoacidosis, Table III).[34] Infection in immunocompromised patients is often attributed to invasion by fungi that had previously colonized the sinuses or to inhalation of fungal spores. Many patients with invasive fungal sinusitis have reported anatomic abnormalities of their sinuses that might predispose to colonization or a history of chronic rhinosinusitis.

The immunosuppressed nature of these patients and lack of host response to invasive infection can at times make the diagnosis difficult in the early stages. For this reason, inquiry as to fever, nasal symptoms of fullness or drainage, epistaxis, and facial pain, as well as a thorough daily examination of all potentially affected areas is paramount in attempts to improve outcomes in those at high risk. When invasive infection is suspected, consultation with otolaryngologic and endoscopic examination and biopsy of suspicious areas is warranted.[35]

In the early stages necrotic tissue might be present within the sinus passages or on the palate; however, within hours, infection can invade contiguous structures, including the eye, brain, or both. Involvement of the maxillary sinus can be followed by direct invasion into the palate, with subsequent perforation into the oral cavity or perforation of the nasal septum. Involvement of the ethmoid, sphenoid, or frontal sinuses predisposes the host to extension into the cavernous sinuses, causing cranial nerve deficits, carotid artery thrombosis, or both. Invasive infection within the ethmoid sinuses also might extend to the periorbital space, including the extraocular muscles and the globe of the eye.

Brushings and cultures of necrotic or ulcerative lesions should not be homogenized in attempts to recognize the characteristic histopathologic appearance of certain fungi and to facilitate the recovery of mucormycoses. Destruction of tissue with hyphal invasion of blood vessels causing infarction demonstrates the angioinvasive nature of these organisms.

CT imaging is nonspecific but typically shows sinus involvement (the maxillary and ethmoid sinuses are most frequently affected), osseous destruction, and/or extension in the periorbital tissue, cavernous sinus, carotid artery, or brain (Fig 1). Magnetic resonance imaging (MRI) is often used for further evaluation of affected areas when aggressive surgical intervention is planned.[36]

The prognosis is extremely poor without improvement of the host's immune response. Aggressive and urgent surgical debridement of all involved areas and antifungal therapy are urgently indicated. Local irrigation with amphotericin B is often administered by surgical teams as an adjunct to systemic antifungal therapy after debridement; however, the utility of this strategy remains uncertain.

Isolation of the fungal agent responsible is necessary to guide therapy given the differing susceptibility profiles of *Aspergillus* species, the dematiaceous molds, and the mucormycoses. If the infection is known to be secondary to *Aspergillus* species, voriconazole or itraconazole should be initiated at the above listed doses.[37] If voriconazole or itraconazole is to be used as primary therapy, sinonasal mucormycosis must be ruled out given the lack of efficacy of these compounds against this group of organisms. For this reason, empiric therapy pending definitive identification of the causative agent is often with liposomal intravenous amphotericin B (3-5 mg/kg/d). Once the mucormycoses have been ruled out, voriconazole (6 mg/kg administered intravenously for 2 doses and then 4 mg/kg administered intravenously every 12 hours) is an effective option for the treatment of aspergillosis[37] and the dematiaceous molds.[5] Infection caused by *Pseudallescheria boydii (Scedosporium apiospermum)* is generally resistant to amphotericin B, and infections caused by this agent should be treated with voriconazole. For serious infections, serum voriconazole trough levels should be monitored with a goal of between 1 and 5 μg/mL.[38] For patients with mucormycoses, initial treatment should include an amphotericin B formulation followed by a transition to oral therapy with posaconazole at 400 mg twice daily taken with fatty foods. The duration of antifungal therapy remains unclear, and in the presence of ongoing immunosuppression, antifungal therapy should be maintained indefinitely.

Long-term outcomes in patients with invasive fungal rhinosinusitis are poor, with extensive morbidity from extension to the palate, maxilla, orbit, and cranium requiring debridement in up to 43% of patients, although more recent data suggest morbidity with a rapid multidisciplinary approach might have substantially decreased. Mortality is seen in approximately 10% to 40% of patients and is primarily related to an absence of host immune reconstitution and the extent of involvement on recognition of the disease.[35,39]

SUMMARY

Fungal rhinosinusitis encompasses a wide range of fungal infections that range from asymptomatic colonization of the sinus passages to rapidly progressing and ultimately fatal infection. Colonization is exceedingly common, and isolation of potential pathogens from the nasosinal passages requires an understanding of host risk factors and disease syndromes given the vastly different treatment options for these overlapping conditions.

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