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ZYGOMYCOSIS: AN UPDATE ON TREATMENT OPTIONS

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Zygomycosis, also referred to as Mucormycosis, is a rare angioinvasive fungal infection caused by a class of fungi called Zygomycetes. The class is comprised of orders Mucorales, Mortierellales, and Entomophthorales. Infection with zygomycetes progresses rapidly, frequently resulting in fatality in patients with underlying illnesses. Zygomycetes are commonly found in the environment, mostly on soil and decaying vegetation; these fungi reproduce rapidly and release airborne spores which are frequently inhaled. Zygomycete spores are inhaled frequently, yet rarely cause infection, supporting the knowledge that some predisposing factor usually exists in patients who develop zygomycosis. It is estimated that there are approximately 1.7 cases per million people per year, or 500 cases per year in the United States.[5] Almost all human infections caused by zygomycetes have some underlying compromising condition.[1]

The most common organisms within the zygomycetes class causing infection are *Rhizopus*, *Mucor*, and *Cunnighamella*, while the genera *Rhizomucor*, *Saksenaea*, and *Apophysomyces* are implicated in fewer infections. There are several sites within the body where infection may arise: rhino-orbital-cerebral sites, pulmonary, renal, gastrointestinal, and cutaneous. Rhino-orbital-cerebral and pulmonary infections are the most common. Rhino-orbital-cerebral and pulmonary infections are caused by inhalation of zygomycete spores. In normal individuals, these spores will be transported via cilia to the pharynx and eliminated from the body through the gastrointestinal tract. In susceptible individuals, the fungus begins growing in the nasal turbinates or alveoli of the lungs.[1] The present article will discuss the pathophysiology of zygomycosis, with a focus on reviewing current treatment options and medical literature.

RISK FACTORS

Individuals who are immunocompromised, either from hematologic disease, diabetes, or solid organ or hematopoetic cell transplant, are the most likely to develop zygomycosis. A review of 929 cases of zygomycosis found diabetes to be the most common risk factor (36%), followed by hematologic malignancies (17%), and solid organ or hematopoietic stem cell transplantation (12%).[1,2] Predisposing factors to infection are also related to the site of infection. The majority of infections in diabetics occur in the rhino-orbital-cerebral area whereas many infections in patients with hematologic malignancies occur in the lungs.[2] Other underlying factors that may impart risk for infection are metabolic acidosis, deferoxamine therapy, iron overload, glucocorticoids, HIV/AIDS, intravenous drug use, and malnutrition.

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Table 1. Comparison of Antifungal Drug Therapy Options

	Amphotericin B (Fungizone®)	**Posaconazole** (Noxafil®)	**Caspofungin** (Cancidas®)
MECHANISM OF ACTION	• Binds ergosterol in fungal cell membrane, altering cellular permeability, causing leakage of cellular components	• Inhibits fungal cell membrane synthesis via fungal CYP inhibition	• Inhibits synthesis of beta (1,3)-D-glucan, a major fungal cell wall component
DOSE	• Deoxycholate: 1-1.5 mg/kg/d IV infusion • Lipid Formulations: Initially 5 mg/kg/d IV infusion • Max: 15 mg/kg/d IV	• Available as suspension only • Dose: 800 mg/d in 2-4 divided doses • Must be administered with a full meal	• Not established for zygomycosis • 70 mg IV infusion on day (loading dose), followed by 50 mg IV
KINETICS	• Metabolism unknown • Slowly excreted by the kidneys Dosage Adjustments: • Use cautiously in renal impairment; may extend dosing interval to 24-36 h	• Substrate of p-gp • Metabolized by glucuronidation • $t_{1/2}$ = 35h • >98% bound to albumin	• Metabolized by hydrolysis and N-acetylation • Small amount (1%) excreted unchanged in urine • Active metabolites cleared through biliary system

ADVERSE EFFECTS	• Infusion-related reactions
	• Nephrotoxicity
	• Normochromic, normocytic anemia
	• Electrolyte abnormalities
	• GI toxicity
	• Increased LFTs
	• Neurologic effects
		• >10%: Fever, headache, N/V/D	• Well-tolerated
			• Occasional: Histamine-related reactions
			• Rare:
			  • Fever
			  • Phlebitis
			  • N/V
			  • Headache

COST	AmB deoxycholate: • $17/day @ 1mg/kg/d ABLC: • $805/day @ 5mg/kg/d AmBi: • $1,316/day @ 5mg/kg/d ABCD: • $448/day @ 4mg/kg/d[14]	~$190/day	$411.80/day[13]

P-gp = p-glycoprotein; $T_{1/2}$ = elimination half-life; LFT = liver function test; IV = intravenous; GI = gastrointestinal; N/V/D = nausea/vomiting/diarrhea; CYP = cytochrome P450 enzyme system

Patients in diabetic ketoacidosis (DKA) are at highest risk for infection due to elevated blood glucose and metabolic acidosis. *Rhizopus* organisms contain an enzyme, ketone reductase, that allows survival in an acidic environment with high glucose content. Ketone reductase places both uncontrolled type I and type II diabetics at a high risk for zygomycosis infections, especially if in diabetic ketoacidosis.

Deferoxamine is an iron and aluminum chelator used to treat iron and/or aluminum toxicity or chronic overload conditions. Individuals with renal insufficiency or individuals requiring frequent blood transfusions are generally the population of patients prescribed this medication. Deferoxamine can increase not only growth of the fungus, but also pathogenicity; many patients infected with zygomycosis with concomitant use of deferoxamine will develop generalized disseminated infection associated with an extremely high mortality rate.

Posaconazole (Noxafil®) is a new triazole antifungal with a broad spectrum of activity. The following organisms are generally considered susceptible to posaconazole: *Aspergillus sp, Candida sp, Coccidioides immitis, Cryptococcus neoformans, Fusarium sp, Mucor sp, Rhizopus sp, and Scedosporium sp*. Posaconazole is available only as an oral suspension, and must be administered with full meals in 2 to 4 divided doses daily. The C_{max} and AUC are approximately 3 times higher when posaconazole is given with a full meal; C_{max} and AUC are approximately 4 times higher when administered with a high -fat meal, relative to the fasting state.[12] Posaconazole possesses a 35 hour half-life, thus it takes approximately 5-7 days to reach steady state levels. This is not an ideal kinetic profile for use as monotherapy in initial treatment of zygomycosis. Zygomycosis is not currently an FDA-approved indication for posaconazole but has been shown in two compassionate trials to be effective as salvage therapy for refractory infection.[6,7]

Van Burik and colleagues conducted a retrospective study in 91 patients with either refractory zygomycosis or intolerance to amphotericin B treatment. Most subjects were initially treated with lipid formulations of AmB with 26% of subjects receiving conventional AmB. Subjects were given posaconazole 800 mg/d in divided doses with meals or enteral feedings to optimize drug exposure. Overall success, defined as complete or partial response 12 weeks after initiation of posaconazole, was achieved in 60% of the study subjects. Complete response was defined as resolution of infection, while partial response was defined as a clinically meaningful improvement. Fourteen percent of patients had a complete response, 46% had a partial response, 21% had stable disease, 17% experienced treatment failure, and 2% had an undetermined outcome. Most participants (80%) were given posaconazole for at least 30 days, with the longest course of therapy lasting 1,005 days. Thirty-five patients (38%) died while receiving posaconazole or within one month of follow-up. Fifteen of 35 patients died due to zygomycosis; most of them received less than 30 days of treatment, reflecting the aggressive nature of the infection. Importantly noted, approximately one half of the participants received antifungal prophylaxis with azoles (voriconazole, fluconazole, or itraconazole) prior to the development of zygomycosis. This supports findings of increased numbers of zygomycosis cases in patients receiving immunosuppressive therapy coupled with the use of antifungal therapies that do not have activity against zygomycetes.[7]

In a study by Greenberg et al., data of 24 participants from two open-label, nonrandomized, multicenter compassionate trials were analyzed. Posaconazole was administered at 800 mg/day in divided doses to 19 patients refractory to standard zygomycosis treatment and 5 patients intolerant to standard therapy. The mean and median duration of treatment with posaconazole was 292 and 182 days respectively with a 79% treatment success rate (complete and partial responses). Seventy-nine percent (19 of 24 enrollees) survived the infection; none of the treatment failures received greater than 31 days of treatment, with most investigators reporting evidence of improvement within 2 weeks of initiating posaconazole.[6]

Alexander and colleagues reported the findings of a post-hoc analysis from an open-label, multicenter study in which posaconazole was administered as salvage therapy to 23 solid organ transplant patients with proven or probable invasive fungal infections (IFIs).[16] Primary causative pathogens were: *Aspergillus* (n = 12), *Candida* (n = 3), *Fusarium* (n = 2), *Cryptococcus* (n = 1), *Zygomycetes* (n = 2), and others (n = 4). Participants with zygomycosis were considered refractory to standard therapy if they showed disease progression or no clinical improvement after 7 days of treatment. Intolerance to standard therapy was classified as renal impairment, severe infusion-related toxicity, or high-risk for toxicity based on underlying conditions or medications. The primary endpoint was response at the end of treatment with complete and partial responses defined as success, and stable disease or failure defined as non-success. Posaconazole was administered as 800mg per day in divided doses with food; most patient received posaconazole for at least 30 days. Overall, 13 of 23 (57%) patients had a complete or partial response. Of the 2 patients with zygomycosis, 1 had a successful response but the other failed treatment. Treatment-related adverse events were reported in 12 of 23 participants and included: nausea (4), vomiting (2), elevated LFTs (2), and increased levels of cyclosporine and/or tacrolimus (3).

NEW TREATMENT OPTIONS

With increasing incidence of mucormycosis and its high mortality rate, the development of new anti-

Table 2. Summary of Clinical Trials for Treatment of Zygomycosis

AUTHORS	STUDY DESIGN	DRUG	ENDPOINTS	RESULTS
Greenberg R, et al (2006)[6]	Retrospective data collected from two open-label, nonrandomized, multicentered, compassionate trials	Posaconazole 800mg/day in divided doses	Primary: Response (complete, partial, failure)	79% survived the infection (complete or partial response) Mean and median treatment duration was 292 and 182 days, respectively
Van Burik J, et al (2006)[7]	Retrospective case series data	Posaconazole 800mg/day in divided doses	Primary: Overall success (complete, partial, stable disease, treatment failure)	Overall success (complete and partial) was 60% after 12 weeks of posaconazole therapy
Alexander B, et al (2008)[16]	Retrospective data from an open-label, multicenter trial	Posaconazole 800mg/day in divided doses	Primary: Global response at the end of treatment (complete, partial responses, stable disease, failure)	Overall success (complete and partial responses) documented in 13 of 23 patients. One of two participants with zygomycosis experienced treatment success.
Reed C, et al (2008)[11]	Retrospective review of rhino-orbital-cerebral zygomycosis cases	Polyene monotherapy vs. combination polyene & caspofungin AmB 0.3-1.5mg/kg ABLC 5-10mg/kg; LAmB 5-10mg/kg	Primary: Success (alive and not needing hospice care) at 30 days after discharge Secondary: Kaplan-Meier survival time	Participants treated with polyene-caspofungin had superior success (100% vs 45%, p = 0.02) and improved Kaplan-Meier survival time

AmB = Conventional amphotericin B; ABLC = amphotericin B lipid complex; LAmB = Liposomal amphotericin B

fungal drug therapies for treatment of zygomycosis is important.[11] The echinocandins are a class of antifungal medications with activity against synthesis of beta (1,3)-D-glucan, a major fungal cell wall component. Traditionally echinocandins were thought to have no in vitro activity against zygomycetes, but recent data has shown that *Rhizopus oryzae*, the most common zygomycete to cause zygomycosis, expresses the target enzyme of the echinocandins. Caspofungin (Cancidas®) is effective in combination with AmB for the treatment of zygomycosis in murine models.[10] Caspofungin has a favorable side effect profile because the target enzyme of the drug is not present in mammalian cells. Common adverse reactions consist of: histamine-related reactions (1-4%), fever (3-26%), nausea/ vomiting (3.8-7.2%), headache (6-11%), reduction in serum potassium levels (10.8%), reversible elevation of hepatic enzymes, and injection-site reactions (1.5-12%).[3] Caspofungin also has few significant drug interactions because it is neither a substrate nor inhibitor of cytochrome P450.[15]

A retrospective review of 41 patients with rhino-orbital-cerebral zygomycosis treated with either AmB or AmB plus caspofungin from 1994 through 2006 was conducted by Reed et al.[11] Patients were predominantly Hispanic males with diabetes (83%), and all participants had predisposing factors for rhino-orbital-cerebral zygomycosis: cancer (34%), active corticosteroid therapy (46%), neutropenia (12%), or transplantation (10%). Patients were treated with ABLC (n = 20), AmB (n = 15), or liposomal AmB (n = 4) at average doses of 5 mg/kg/day, 1 mg/kg/day, and 5 mg/kg/day, respectively. Six evaluable pa-

tients were treated up-front with a combination of polyene (mostly ABLC) and caspofungin therapy. Patients treated with polyene-caspofungin combination therapy initially had superior success (100% vs. 45%; p = 0.02) and Kaplan-Meier survival time (*p* = .02) compared to patients treated with any AmB formulation as monotherapy. Combination therapy of AmB-caspofungin appears to be a promising therapeutic option for zygomycosis based on these results. The limitation of this study however, was that the majority of participants were non-neutropenic and diabetic. Therefore, these findings may not be generalizable to immunocompromised patients with neutropenia.

SUMMARY

Zygomycosis is a rare, angioinvasive fungal infection most commonly found in immunocompromised patients or individuals with predisposing factors such as: diabetes mellitus, immunosuppressive drug therapy, deferoxamine drug therapy and IVDU. Zygomycosis is associated with a poor prognosis evidenced by an overall survival rate (with treatment) of only 40-50%. Successful treatment relies on early diagnosis, removal of predisposing factors, surgical debridement of infected tissue, and aggressive antifungal drug therapy. A lipid formulation of amphotericin B remains the drug of choice for treatment of zygomycosis and many other fungal infections because of its broad spectrum of activity and few instances of antifungal resistance. Posaconazole has been shown in 2 retrospective studies to be effective as salvage therapy for patients refractory or intolerant to AmB. Echinocandins initially were thought to be ineffective against zygomycetes *in vitro* and *in vivo*. However, recent evidence suggests that *Rhizopus sp* express the target enzyme of the echinocandins. Combination polyene-caspofungin therapy has been shown to be a promising option for treatment of rhino-orbital-cerebral zygomycosis in diabetics in both murine models and humans.

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DRUG UPDATE

Fenofibric Acid (TriLipix®) - *Abbott Pharmaceuticals*

In December 2008, the FDA approved the use of fenofibric acid, the active metabolite of fenofibrate. Like the other 'fibrates,' fenofibric acid is most effective at treating lipid disorders associated with high levels of serum triglycerides. It is the only fibrate currently approved for combination use with statins in the management of mixed dyslipidemia. In clinical trials, patients taking fenofibric acid monotherapy experienced myalgias at a rate similar to those taking combination therapy with statins (3.3% vs. 3.1-3.5%). However, caution should still be exercised before initiating dual therapy, particularly in patients with renal failure. TriLipix® is available as 45 mg or 135 mg delayed-release capsules. Starting dose for adults is 45 to 135 mg once daily with dose titration after 4 to 8 weeks as needed. Maximum daily dose is 135 mg daily. Fenofibric acid may be administered without regard to meals. The most common adverse effects include headache and gastrointestinal effects.

Zoledronic Acid (Reclast®) - *Novartis Pharmaceuticals*

The FDA recently approved injectable zoledronic acid for the treatment of osteoporosis in men. It is the first of the bisphosphonates to receive an indication for the treatment of both sexes. Zoledronic acid is one of only a handful of bisphosphonates with data supporting a reduced incidence of vertebral, nonvertebral and hip fractures. However, FDA approval for the treatment in men was based on a two year randomized, active control, non-inferiority trial comparing changes in bone mineral density among participants taking zoledronic acid once yearly and alendronate 70mg once weekly for 2 years. Approved dose in men is a 5 mg infusion over 15 minutes once yearly. Administration of zoledronic acid is considered a medical procedure covered by Medicare Part B. Most Medicare Part B carriers should now cover Reclast® infusions for men.

MEDICAL NEWS

Influenza Update

Preliminary surveillance data from the Centers for Disease Control (CDC) suggests high levels of circulating influenza A virus, predominantly the H1N1 subtype. Of the 88 preliminary samples tested nationally, 86 (98%) are resistant to oseltamivir (Tamiflu®), the most widely prescribed antiviral worldwide. These samples have shown no resistance to zanamivir (Relenza®) or the older adamantane antivirals, amantadine or rimantidine. However, some strains of influenza A (H3N2) and all strains of influenza B virus remain resistant to the adamantanes.

The CDC recommends the use of zanamivir alone or oseltamivir and rimantidine combination therapy over oseltamivir therapy alone for the treatment of influenza infection during the current season. Influenza testing can help determine which strain is present and may help streamline antiviral choice. Influenza infection rates are expected to rise throughout the remainder of the flu season, so influenza vaccination should continue to be recommended.

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