# Medical management of invasive fungal sinusitis

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**Citation**

P Parida. *Medical management of invasive fungal sinusitis*. The Internet Journal of Otorhinolaryngology. 2006 Volume 7 Number 1.

**Abstract**

The incidence of fungal infection continues to rise as the population of immunocompromised individuals increases. Despite the enlarging numbers of infections, there are only a few antifungal agents for treatment of deep seated invasive infections. This article focuses on general concepts of antifungal therapies and provides a detailed review of each antifungal agent available for treatment of deep seated mycoses of nose and paranasal sinuses.

## INTRODUCTION

Treatment of fungal sinusitis depends on accurate diagnosis of the type of fungal sinusitis. There are two basic types of fungal sinusitis: invasive and noninvasive. Invasive fungal sinusitis are of two types; acute invasive and .chronic invasive (both granulomatous and non-granulomatous).The non-invasive fungal sinusitis are of 3 types (1).fungal balls (mycetoma), (2).saprophytic colonization, and (3).allergic fungal sinusitis (AFRS).This classification is founded on the immunologic relation of the fungus to the host [1] .

Fulminant (acute) invasive fungal sinusitis: Regulation of diabetes mellitus and a decrease in the dose of immunosuppressive drugs facilitate the treatment. Reversibility of the immunocompromised state is mandatory to control the spread of infection. The mainstays of treatment are extensive debridement of craniofacial lesion till the tissue bleeds and antifungal drugs, of which amphotericin B is most commonly used. Granulocyte colony stimulating factor and hyperbaric oxygen are occasionally used.

Chronic indolent fungal sinusitis: Surgical debridement and a prolonged course of antifungal agent are required to treat this condition.

## PRINCIPLES OF ANTIFUNGAL TREATMENT

1. Correct identification of the fungus
2. Use of standard published antifungal regimens
3. Clinician should consider initial therapy as an induction phase with optimization in both dose and antifungal drug, which gives maximum fungicidal activity at site of infection; consider combination therapy in certain cases.
4. Control of underlying medical or immunosuppressive conditions is mandatory.
5. Clinician must pay particular attention to the drug interaction, pharmacokinetics, and resulting toxicities; this may require measurement of drug levels in certain circumstances.
6. After apparent stabilization of clinical symptoms and signs of infection with treatment, consideration of a consolidation drug regimen in dose or drug to complete a defined course of therapy is required.
7. Follow-up for relapse/reinfection after treatment should be at least 6 months to a year depending on fungus and type of infection.

## ANTIFUNGAL AGENTS

### AMPHOTERICIN-B

Amphotericin B is a polyene antifungal agent, with antifungal activity first isolated by Gold et al from Streptomyces nodosus in 1955 remains the standard drug for most life threatening systemic fungal infections [3] . Amphotericin B is now available in four formulations. The classic amphotericin B deoxycholate (Fungizone™) formulation has been available since 1960 and is a colloidal suspension of amphotericin B. A bile salt, deoxycholate, is used as the solubilizing agent. This preparation has a number of toxicities that are partially ameliorated when a lipid carrier is used. Three lipid preparations of amphotericin B are: Amphotericin B Colloidal Dispersion (ABCD;

Amphocil™ or Amphotec™), Amphotericin B Lipid Complex (ABLC; Abelcet™), and Liposomal Amphotericin B (LAMB; Ambisome™).

## MECHANISM(S) OF ACTION

Amphotericin B binds to sterols, preferentially to the primary fungal cell membrane sterol, ergosterol. This binding disrupts osmotic integrity of the fungal membrane, resulting in leakage of intracellular potassium, magnesium, sugars, and metabolites and then cellular death [3,4].

## IMMEDIATE ADVERSE EFFECTS AND PREMEDICATION

Acute reactions to amphotericin B are seen within 90 minutes of the infusion and usually remit by 3-4 hours. Most common is fever with or without chill and rigors, headache, nausea, vomiting, malaise and generalized aches. Hypotension and anaphylaxis are rare. Up to 50% of patients will have immediate infusion-related adverse reactions [11]. Tolerance to the immediate reactions usually develops over time. Therefore if premedications are used in the treatment course, their need should be reevaluated weekly.

## SUGGESTED PREMEDICATIONS

Acetaminophen 650-1000 mg per oral /per rectal. 30 minutes prior to amphotericin B. Other non-steroidal anti-inflammatory drugs (NSAIDS) like aspirin, ibuprofen and diphenylhydramine can be used if not contraindicated [4,5,6]. Hydrocortisone: if patients experience severe rigors with previous infusion, start at 25 mg IV 30 minutes prior to amphotericin B (may increase to 50 mg and can be added directly to the transfusion bottle [5]).Nausea and vomiting generally are managed by administration of phenothiazines such as prochlorperazine or promethazine. Meperidone is used most commonly for the treatment of amphotericin-B related rigors [7].

## NEPHROTOXICITY

It occurs up to 80% of patients, manifested by azotemia, eletrolyte wasting (potassium and magnesium), a decrease in urinary concentrating ability, distal renal tubular acidosis [4,5,8]. It is usually reversible after cessation of the drug. Sodium loading may minimize azotemia (administer 500 ml of normal saline both before and after amphotericin B infusion [8,9]).Other nephrotoxic drugs should be avoided if possible. If azotemia occurs with a serum creatinine> 3 mg/dl, the dose of amphotericin B may be reduced or held after a careful assessment of the risks versus benefits to the patient.

## THROMBOPHLEBITIS

Phlebitis can occur with infusion via peripheral veins [4,10]. If peripherally administered, concentration should not exceed 0.1 µg/ml of D5W. Phlebitis can be prevented by decreasing the rate of infusion or further diluting infusion, adding heparin 1000 units/L to the solution, using central vein and rotating the infusion site [4].

## OTHER LESS COMMON ADVERSE EFFECTS

Normochromic, normocytic anemia with decrease in hemoglobin of up to 35% from baseline has been reported routinely following extended therapy with amphotericin B [4,5,10]. The proposed mechanism is a direct suppression of erythropoietin production and a decrease in the production of erythrocytes that may occur in patients with deteriorating renal function [11,12]. Neutropenia and thrombocytopenia is associated infrequently with amphotericin B therapy [4,10,13].

## RECOMMENDED DOSING

Usual dose is 0.25-1.0mg/kg/day (most commonly 0.4 to 0.7 mg/kg/d [4,10]). Maximum daily dose-1.2mg/kg/day in adults and 1.5mg/kg/day in children. Alternate day therapy - double the daily dose to a maximum of 1.5 mg/kg/d. Liposomal amphotericin-B-1-5 mg/kg, ABLC-5mg/kg/day, ABCD-3-5mg/kg/day.Total cumulative dose is of 2-4gms (4-6 gms in case of intracranial extension).

## ADMINISTRATION

Prior to starting treatment, a test dose of 1 mg of amphotericin B in 50 ml of 5% is usually infused over 20 minutes in order to assess the patient for immediate adverse events [4,10]. The patient's vital signs are monitored every 15 minutes for an hour. If no serious adverse reactions occur, the remainder of the desired daily dose is administered over 2-6 hours as follows: Doses < 0.5 mg/kg/day -- infuse over 2 hours, Doses > 0.5 mg/kg/day -- give first full dose over 4 hours and if tolerated, may decrease infusion time to 2 hours

## MONITORING IN PATIENTS RECEIVING AMPHOTERICIN B:

The following should be monitored more aggressively during the therapy:

1. Blood urea nitrogen, Serum-creatinine-twice a week, 2. Potassium, magnesium, sodium, and other electrolytes-twice a week, and 3. Complete blood count-once a week.

## CURRENT STATUS

Amphotericin B still remains as the mainstay of antifungal

therapy. Its lipid formulations, on the other hand, are promising due to their ability to reduce the toxicity of amphotericin B. They are currently licensed for use when amphotericin B therapy fails or is unacceptably toxic. The use of lipid formulations in specific clinical settings is under continuing investigation.

## LIPOSOMAL AMPHOTERICIN B (L-AMB)

Liposomal amphotericin B (L-AMB) is a lipid formulation of amphotericin B [10,14,15,16] . the major goal of developing L-AMB has been to attain a compound with lower toxicity and with at least similar efficacy compared to the parent compound, amphotericin B deoxycholate. L-AMB is composed of amphotericin B complexed with hydrogenated phosphatidylcholine, distearoyl-phosphatidylglycerol, and cholesterol. Unlike the other lipid formulations of amphotericin B, it is a true liposome composed of unilamellar lipid vesicles. Compared to the other lipid formulations of amphotericin B, L-AMB reaches higher concentrations in plasma and remains in the circulation longer. Similar to the other lipid formulations, L-AMB concentrates in reticuloendothelial system [10,14,15,16] . This finally provides a persistent pool of L-AMB in plasma and a sustained delivery to the site of infection. L-AMB attains high concentrations in brain tissue. Elimination of L-AMB from serum is biphasic. This pattern suggests that L-AMB is first concentrated in reticuloendothelial system cells and then is redistributed.

## CURRENT STATUS

L-AMB is used as a salvage agent when amphotericin B therapy fails or is unacceptably toxic [14,15] . It is not a first-line drug for any of the fungal infections. It is also licensed as an empirical therapeutic agent in febrile neutropenia not responding to broad spectrum antibiotic treatment more than 96 hours. Its potency in different clinical settings is under continuing investigation. Among the lipid amphotericin B formulations, L-AMB is one of the more commonly used preparations

Advantages over conventional Amphotericin B: 1. Drastically Reduced Toxicity specially Nephrotoxicity. 2. Increased therapeutic effects.3. Reduced morbidity and mortality, well tolerated.4. High therapeutic index, rare drug resistance

Advantages of L- amphotericin B over the other lipid formulations

1. L- amphotericin B has unique lipid composition, a safe formulation with higher therapeutic index than other lipid formulations. 2.In case of other liposomal formulation, before transfusion MLVs (multi-lamellar vesicles) are converted to SUVs (small unilamellar vesicles) but L-amphotericin B does not need reconstitution.3.Infusion time of L- amphotericin B is only one hour.4.L- amphotericin B is most cost effective and affordable.5.Per kg dose of L-amphotericin B is lowest of all the lipid preparations of Amphotericin B.

## AZOLE ANTIFUNGAL DRUGS

They are Imidazoles and triazoles.Imidazoles are clotrimazole, miconazole, and ketoconazole.Two important triazoles are itraconazole and fluconazole.

## MECHANISM OF ACTION

In general, the azole antifungal agents are thought to work principally by inhibiting the cytochrome P450 14a-demethylase (P45014DM) [10,17,18] . This enzyme is involved in the sterol biosynthesis pathway that leads from lanosterol to ergosterol. Inhibition of this enzyme leads to accumulation of lanosterol that in turn leads to perturbation of the fungal cell membrane.

IMIDAZOLE-Ketoconazole has been used successfully for systemic severe invasive mycoses [10,17] . Its use largely has been replaced by triazoles especially itraconazole.

TRIAZOLE- Fluconazole: Both oral, IV preparations are available. It is not used in fungal sinusitis but used in invasive mucocutaneous candidiasis.

Itraconazole: Oral-bioavailability is highly variable and less predictable. Absorption is affected by the presence of food, gastric pH [17,18] . Tab/cap formulation better absorbed with food and co-administration of acidic beverages enhances absortion. Patient with achlorhydria and taking H2 receptor impaired the absorption [19] . Protein binding is greater than 95%. A CSF level is low. Serum half life time is 25-50 hours. Metabolized extensively in liver and excretion occurs primarily in the urine and feces. Dosage adjustment is not required in patient with compromised renal function.

## SIDE EFFECT OF THE AZOLES

Gastrointestinal upset-Most common. Mild elevation in liver enzymes occurs in 1-7% of patients. Rash and headache are less common. Alopecia-following long course of therapy with high dose fluconazole. Aldosterone like effect with hypertension, hypokalemia and peripheral extremity edema when dose of itraconazole exceeds >600mg/day.All azoles

have the potential for embryotoxicity and teratogenicity. Azoles should not be given during pregnancy.

## DOSAGES AND PREPARATIONS-THE TRIAZOLE

Itraconazole. Preparation: capsule, oral solution, and intravenous formulation. Initial dosage of 600 to 8oo mg daily in two divided dose for 3 days and a subsequent dosage of 200 to 400 mg daily in two divided doses continued for 6 to 12 months [17,18] . Itraconazole blood levels are helpful in documenting absorption because of the varying degree of oral absortion 2 hrs after the dose. Measured therapeutic concentration should be at least equal to or greater than 1µg/ml.

INTRAVENOUS ITRACONAZOLE: The excipient for the intravenous formulation of both itraconazole and voriconazole is cyclodextrin [20] . As cyclodextrin is renally excreted, the intravenous formulation of these drugs should be carefully used in patients who have renal impairment particularly when a ceatinine clearance is < 50 ml/min [21] .

Dosing-200 mg ,IV, BD for 4 Doses followed by oral 200mg,IV, OD for 2Wks

Use: Itraconazole has been shown to have a comparable response rate to amphotericin B for invasive aspergillosis in patients who are not strikingly immunosuppresssd, who can tolerate oral medications, and who are adherent to medication intake. An attractive sequence would be the use of intravenous amphotericin B or one of its lipid formulations until the disease progression is halted, followed by oral itraconazole for an extended period of time [22] .

Voriconazole: It is a second-generation triazole anti-fungal agent is a synthetic derivative of fluconazole. INDICATION: Invasive aspergillosis, febrile neutropenic patients who do not respond to at least for 96 hours treatment with antibiotics. DOSING: 6mg/kg IV every 12hrly for two doses followed by maintenance doses of 4mg/kg IV 12hrly for 30 days.In improving patients, the regimen can changed to oral 200 mg bd for 20 weeks completing a total duration of therapy for 24 weeks [23,24] . SIDE EFFECT: Transient visual disturbances (color changes, blurring) in 30% of pts, Hepatotoxicity in 10% and Rash in 5% of patients [24] .

Investigational triazoles: POSACONAZOLE AND RAVUCONAZOLE, both are active against Aspergillus species in vitro. Ravuconazole is notable for a half life of approximately 1 week.SCH5962-It is an azole which is being studied for its role in invasive fungal sinusitis and is under phase II trial is considered to be more potent than voriconazole.

## ECHINOCANDINS: (CASPOFUNGIN, MICAFUNGIN, ANIDULAFUNGIN)

Echinocandins belong to a new class of antifungal agents that inhibits enzyme 1, 3-B-D-glucan synthase in the fungal cell wall, and it appears to have fewer side effects in humans [10,23,25,26] . Approved by the FDA for the treatment of invasive aspergillosis that is refractory to conventional therapies. ROUTE OF ADMINISTRATION AND DOSE:- Recommended regimen- administered intravenously, 70 mg loading dose followed by 50 mg daily for 14 days [27] .The most frequently reported adverse effects include: increased liver transaminases, gastrointestinal upset, histamin like acute infusion reactions and headaches [28] .

Other agents: G-CSF- Indicated in neutropenic patients to reverse the netropenic condition. G-CSF increases neutrophil counts, improves chemotaxis, phagocytosis, and the respiratory burst of neutrophils. It is important to keep in mind that even in patients who may not be neutropenic; G-CSF can be valuable.

Fungicidal peptides- These agents are undergoing trial. These are 1.Sordarins, acts by inhibiting protein synthesis, 2. Nikkomycin which is a chitin synthase inhibitor, and 3. Dicationic aromatic compounds.

## COMBINATION AND SEQUENTIAL THERAPY

Having more than one site of antifungal action, combination therapy potentially reduces the likelihood for emergence of resistant strains. Improvement has been noted with amphotericin B or itraconazole followed by voriconazole but not with itraconazole followed by amphotericin B. Because in vitro animal data suggest antagonism, simultaneous therapy with amphotericin B and an azole should be employed with caution. However, it appears that sequential therapy with an azole to complete a course of therapy after treatment with amphotericin B is probably safe. Theoretically, there appears to be a sequence-specific antagonism when amphotericin B is used in patients previously treated with an azole, and these patients could be at risk for treatment failure. This is presumably because the azoles inhibit ergosterol formation that eliminates the site of action of amphotericin B. However, there are no clinical data that have implicated previous azole therapy as a cause of

treatment failure in Aspergillus infection with a polyene such as amphotericin B, but these patients should be carefully monitored

For Aspergillosis Amphotericin-B+Flucytocin shows synergistic action [10] , Amphotericin-B+Imidazole- demonstrated both synergism and antagonism [29] , Amphotericin-B+Triazole- has shown both antagonism and additive effects [30] .

Investigations are ongoing into the use of a combination of an echinocandin, which as a class is not fungicidal against Aspergillus, with either amphotericin or one of the azoles which do show fungicidal activity. In an animal model of invasive aspergillosis, caspofungin with voriconazole showed increased clearance of Aspergillus from tissues. Amphotericin B plus micofungin has also shown a positive interaction, and children with acute myelogenous leukemia with invasive aspergillosis have been successfully treated with this combination.

## LENGTH OF THERAPY

The following factors should be considered in determining the length of treatment of invasive fungal sinusitis: 1.Complete resolution of all symptoms and signs of the underlying infection for at least two weeks while on antifungal therapy; 2.Near-resolution of radiological findings; 3.Negative cultures; and 4.Reversibility of the underlying risks factors, particularly neutropenia.

## SPECIFIC CLINICAL INFECTIONS

1. Invasive aspergillosis [24,31] : Preferred treatment- Voriconazole, Liposomal or conventional amphotericin .Alternatives-Amphotericin B Colloidal Dispersion, Amphotericin B Lipid complex, Itraconazole and Caspofungin.

2. Mucormycosis [32] : The management of mucormycosis consists of regulation of DM, reversal of immunocompromised state, and extensive debridement followed by IV amphotericin-B (convetional/liposomal).Voriconazole and itraconazole are of no value.

Strategies to overcome antifungal drug resistance [33] :

Strategies Tools

Immune modulation----------Cytokines/chemokines
Improvement in drug tolerability-----Lipid formulation
Maximal drug prescriptions/duration---Clinical trial
Combination therapy—----------Amphotericin-B+itraconazole,
Amphotericin-B+voriconazole
Antifungal drug prophylaxis----------Identify high risk patients
Surgery----------Debulks the disease and reduces fungal load
Drug discovery----------New targets and agents

Prophylactic therapy: Indicated in following situations: 1.Febrile neutropenia, 2.Bone marrow/solid organ transplants, and 3.Post surgery in recurrent cases. The drug used most commonly is amphotericin-B at a dose of 0.1 mg /kg/d intravenously [34] .

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