



## Medical Management of Fungal Sinusitis

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### Abstract:

Medical therapy constitutes an useful adjunct to surgery in the management of fungal sinusitis. Drugs used include both antifungal and steroids in the form of systemic / topical sprays. In certain cases medical treatment administered prior to surgery reduces the size of polypi making it easily operable. Commonly medical management is used during the follow up period after surgery in order to reduce the rate of recurrence. The aim of this article is to review the currently published literature in this topic.

### Introduction:

Fungal sinusitis is rather common these days. Surgical debridement happens to be the most commonly used treatment modality. Fungal sinusitis occur in different forms each requiring specific treatment modality / schedules. It should also be borne in mind that these antifungal agents currently used have toxicity. Before deciding on any adjunct medical management it is better to weigh benefit verses toxicity ratio. Only if the therapeutic benefit out weighs the toxic effects of the drug should it be administered. The newer less toxic antifungal agents are very expensive. Studies reveal that allergic fungal sinusitis had a recurrence rate of close to 100% even after diligent surgical debridement under vision, if not followed up with medical management.<sup>1</sup>

### Indications of medical management of fungal sinusitis:

1. As a adjunct to surgical debridement to reduce recurrence rate.
2. Preoperatively in order to reduce the vascularity and size of the polypoidal lesion
3. In managing patients who are poor surgical risk
4. For managing relapse of the lesion

### Treatment regimen depends on:

1. Accurate identification of the offending organism
2. The phase of therapy
3. Underlying diabetes / immunocompromised state

Drugs used in the management of fungal sinusitis:

Amphotericin B:

This is a polyene antifungal agent isolated by Gold et al from streptomyces nodosus in 1955. This still remains the standard drug of choice in managing life threatening fungal infections. This drug is available in four formulations:

1. Amphotericin B deoxycholate (Fungizone) is actually a colloidal suspension of amphotericin B. Deoxycholate is actually a bile salt and is used as a solubilizing agent in this formulation. This formulation is known to cause lots of toxic reactions.
2. Amphotericin B colloidal dispersion
3. Amphotericin B lipid complex
4. Liposomal amphotericin

Mode of action of amphotericin B:

This drug binds to sterols, more preferentially to primary fungal cell membrane sterol (ergosterol). This combination disrupts the osmotic integrity of the fungal cell membrane causing potassium ion leakage from inside the cell. This leads ultimately to cell death.<sup>3</sup>

Immediate adverse reactions of amphotericin B:

This is most common when Amphotericin B deoxycholate infusion is used. The reactions usually begin within 1-1.5 hours after starting the infusion. Common reactions include:

1. Fever with / without chills
2. Headache
3. Nausea
4. Vomiting
5. Acute anaphylaxis (rare)

Adverse reactions are known to affect nearly 50%<sup>4</sup> of patients treated with amphotericin B infusion. Patients become tolerant to immediate effects of the drug on repeated administration. It is the first few episodes of adverse reactions that prove to be troublesome and need to be managed.

Administration of acetaminophen in doses of 650-1000 mg either orally / per rectum<sup>5</sup> an hour before actual infusion of amphotericin B will prevent fever.

Role of steroids in avoiding adverse reactions due to amphotericin B infusion:

If the patient experiences rigors during prior infusion of the drug then hydrocortisone is indicated. Usually it is administered as a starting dose of 25mg intravenously 30 mins prior to amphotericin B infusion. If need arises this dose can be increased up to 50 mg. Hydrocortisone can also be added to the infusion itself.<sup>5</sup> Meperidine<sup>6</sup> is the commonly used drug to treat rigors due to amphotericin B infusion. For managing rigors it is administered in doses of 12.5-50 mg as a slow intravenous push.

Intermediate adverse reactions of amphotericin B include:

Nephrotoxicity – This is common in nearly 70% of patients. Symptoms are caused due to electrolyte wasting (potassium, magnesium) due to impaired urinary concentrating ability. These patients also have distal renal tubular acidosis. This condition is reversible and can be minimized by 500 ml of normal saline before and after infusion of amphotericin B<sup>7</sup>. This drug is contraindicated in patients with chronic renal failure.

Thrombophlebitis – This is another common intermediate complication<sup>8</sup> of amphotericin B infusion. This can be reduced by ensuring that the concentration of amphotericin B does not exceed 0.1 µg/ml. Incidence of thrombophlebitis can further be reduced by slowing down the rate of infusion or by diluting the concentration of the infused drug still further. Heparin can be added to the infusion in a dosage of 1000 units / litre of fluid infused. If feasible peripheral veins should be avoided and the drug should be administered using central venous catheter.

Normocytic normochromic anaemia due to depression of erythropoietin. Neutropenia and thrombocytopenia have also been documented in these patients.

Dose:

0.25 – 1 mg / kg / day for a period of 10 days in patients suffering from invasive type of fungal sinusitis. Prior to actually administering the drug a test dose should be administered. 1 mg of amphotericin B mixed in 50 ml of 5% dextrose is infused as a test dose to the patient for a period of 20 mins. Evidence for immediate reactions should be sought. If no reactions were noticed then the complete dose of the drug can be administered. This drug is administered only during the acute phase of the disease.

Amphotericin B can be replaced after acute phase of the disease remits by ketokonazole / Itraconazole. The major advantage of these drugs is that they are less toxic and can be administered orally.

Renal parameters of these patients should be monitored on a regular basis.

Liposomal amphotericin B:

This is actually a lipid formulation of amphotericin B<sup>9</sup>. This drug is supposed to be of lower toxicity with almost similar efficacy as amphotericin B. Studies reveal that liposomal amphotericin B is concentrated in the reticuloendothelial system and is then redistributed. This is a true single bilayer liposomal drug delivery system. These liposomes are less than 100 nm in diameter. This is actually non pyrogenic and less nephrotoxic.

Advantages of Liposomal amphotericin B:

1. It is non pyrogenic
2. It is not nephrotoxic
3. It is well tolerated by the patient
4. Has high therapeutic index with very rare drug resistance

Only disadvantage of this drug being the cost factor. It is expensive.

Azoles:

These drugs are imidazoles and triazoles.

Examples of imidazoles include:

Clotrimazole  
Miconazole  
Ketoconazole

Examples of Triazoles include:

Itraconazole  
Fluconazole

These drugs inhibit cytochrome P450 activity which is essential for sterol biosynthesis. Inhibition of sterol biosynthesis increases the permeability of fungal cell wall causing the cell to die.

Ketoconazole has been used successfully for treating invasive mycosis<sup>10</sup>. Major advantage of this drug is that it can be administered orally. Currently this drug is being replaced by triazoles especially itraconazole.

Itraconazole:

This is the currently used Triazole. Major problem with this drug is that its oral absorption and availability is highly variable and unpredictable. Gastric absorption of this drug is affected by presence of food, gastric pH etc<sup>10</sup>. Oral Itraconazole is better absorbed when administered along with food / co-administration of acid beverages. Patients with achlorhydria / or on H<sub>2</sub> receptor antagonists will have rather unpredictable absorption if administered orally.

Side effects of azoles:

1. Gastritis
2. Elevation of liver enzymes (mild to moderate)
3. Alopecia following long term administration
4. Aldosterone like effect causing elevation of blood pressure
5. Not safe to administer in pregnant mothers

Preparations of Itraconazole:

Capsules  
Oral solution  
Intravenous infusion

Dose:

Initial dose – 600-800 mg /day in two divided doses for 3 days (loading dose).

Maintenance dose – 200 – 400 mg / day in two divided doses for 6-8 months.

Intravenous preparation is used as loading dose. 200 mg IV – BD - 2 days  
Followed by 200 mg IV OD for 2 weeks, or supplemented with oral preparation.

Voriconazole:

This drug is a second generation triazole, a synthetic derivative of fluconazole. This drug is suitable in managing invasive aspergillosis.

Dose: 6mg / kg IV every 12 hours for the first day.

Followed by 4mg / kg IV 12 hours for 30 days.

On signs of improvement it can be changed to 200mg bd orally for 3 months.

Toxicity of this drug include visual disturbances, and hepatotoxicity.

Echinocandins:

Drugs belonging to this category have fewer side effects. These drugs inhibit enzyme 3-B-D glucan synthase present in the fungal cell wall thereby hastening its destruction. This drug has been approved by FDA for the treatment of invasive aspergillosis which is resistant to conventional antifungal agents. Drugs belonging to this group include: Caspofungin, Micafungin and Anidulafungin.

Recommended dose and route of administration <sup>11</sup>:

Intravenous administration of 70 mg loading dose.

This is followed by 50 mg iv for 15 days.

Despite all these newer introductions amphotericin B happens to be widely used. This is because of its effectiveness and cost effectiveness too.

Duration of medical therapy for fungal sinusitis:

1. Till there is complete resolution of all symptoms pertaining to fungal infections of nose and sinuses for atleast a minimum period of 2 weeks.
2. Till there is resolution of radiological findings
3. Till fungal cultures become negative
4. Till the reversibility of underlying risk factors like neutropenia

Conclusion:

Even though surgical debridement is needed for managing patients with fungal sinusitis, it should be followed by antifungal medications, especially in patients with invasive fungal sinusitis. Patients with non invasive fungal sinusitis like fungal ball need not receive antifungal medications. Commonly used antifungal drug to prevent recurrence of symptoms happens to be amphotericin B, with Itraconazole used for long term maintenance.

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