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Incidence and Management of Fungal Infections in Oral and Maxillofacial Surgery

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Abstract
Mucormycosis are life-threatening fungal infections especially affecting immunocompromised or diabetic patients. This review provides an update on mucormycosis management. The latest recommendations strongly recommend as first-line therapy the use of liposomal amphotericin B (≥ 5mg/kg) combined with surgery whenever possible. Isavuconazole and intravenous or delayed-release tablet forms of posaconazole have remained second-line. Many molecules are currently in development to fight against invasive fungal diseases but few have demonstrated efficacy against Mucorales. Despite in vitro efficacy, combinations of treatment have failed to demonstrate superiority versus monotherapy. New approaches assessing relationships between host, fungi, and antifungal drugs, and new routes of administration such as aerosols could improve mucormycosis treatment.

Keywords: Mucorales; antifungal drugs; nebulization; polyenes; azoles; prophylaxis

Fungal infections:

Background

The change in the technology and practices in medicine of the recent years has given a way to the dramatically increase in the frequency of opportunistic infections. Patients may present with infections that can be superficial or indicative of a more serious systemic illness.[1] Fungal infections being the commonest of opportunistic infections have increased in frequency as a result of the widespread use of immunosuppressive drug therapies, long term use of antibiotics and downfall of overall systemic health. Fungi are eukaryotic organisms comprising molds, yeasts, mushrooms, and similar organisms. More than 100,000 species of fungi have been described. Only about 0.1% are recognized as human pathogens, although the number capable of producing disease in the immunocompromised host continues to increase.[2]Most organisms are soil saprophytes; only the dermatophytes are capable of host-to-host transmission.[3] Mycosis is defined as an infection caused by fungi and is categorized into four major groups based on portal of entry and the major site of infection (Table 1)[3]. Human defence against fungal infections is mediated on several levels, any of which may break down and allow a route for infection. Fungal infections of the oral cavity, pharynx, and esophagus Almost all fungal infections of the mouth are caused by candidal species with most of these secondary to C. albicans. Indeed up to 60% of the healthy population can have C. albicans cultured from the oral mucosa without having evidence of disease.[4] Other rare fungal infections occurring in the mouth include blastomycosis, histoplasmosis, coccidioidmycosis, cryptococcosis, geotrichosis, and phycomycosis. Generally speaking, candidal infections require the presence of a pre-existing immunosuppressed condition to become pathogenic. This immunosuppression

can range from seemingly benign conditions such as decreased salivation to the more commonly known diabetes, pernicious anaemia , chemotherapy, human immunodeficiency virus (HIV), and radiation therapy to the oral cavity. Oropharyngeal candidiasis is frequently associated with HIV, diabetes, the use of dentures, orally inhaled steroids, and chemotherapy.[5] The clinical presentation can vary widely. Patients may be relatively asymptomatic or experience dysphagia, odynophagia, burning or pain in the mouth, tongue, or pharynx, and white patches on the oropharyngeal mucosa.[5] Additional findings may include subtle erythematous patches or even simple irritation presenting like a mild mucositis. Diagnosis can be elusive and may require mucosal scraping with potassium hydroxide (KOH) preparation or even biopsy, in addition to a high degree of suspicion.

A number of available medications have reasonable efficacy against Candida, but it is inappropriate to disregard the inciting factor. Therefore, before administration of antifungal agents, the clinician should ensure that the underlying cause is treated first. This treatment may include relatively simple measures such as appropriate cleaning of dentures or more complex management issues such as optimizing glucose control in the diabetic patient. The most commonly used antifungal agents for thrush are a nystatin swish-and-spit or a clotrimazole oral troche (1 to 2 tabs providing 200,000 U per tab four to five times per day) continued until symptoms have resolved for 48 hours . Other oral preparations that are effective include amphotericin B, miconazole, itraconazole, and fluconazole. Fluconazole and itraconazole work systemically rather than topically and are held in reserve for cases of topical failure.

Classification of fungal sinusitis

There are five recognized forms of fungal sinusitis, each with its own pathophysiology and clinical presentation. They include acute fulminant invasive fungal sinusitis, chronic invasive fungal sinusitis, granulomatous invasive fungal sinusitis, fungus ball, and allergic fungal rhinosinusitis (AFS).

Acute fulminant invasive fungal sinusitis is less than 4 weeks in duration and nearly universally involves patients who have some form of immunosuppression.[7] This incompetence may result from diabetes mellitus, immunosuppressive drugs, primary or secondary immunodeficient conditions, or cancer. The fungus, most commonly of the Mucoraceae family (usually Rhizopus) or Aspergillus fumigatus, is angioinvasive and destroys both bone and tissue. It has a relatively high mortality rate and requires extensive surgical de´bridement of all nonviable tissue as well as systemic intravenous antifungal medication, typically amphotericin B. If possible, the underlying causative immunocompromised state should be reversed. Because recovery of normal neutrophil count is mandatory for survival, new adjunctive therapies such as granulocyte infusion or administration of granulocyte colony-stimulating factor are being investigated.

Chronic invasive fungal sinusitis (also known as nongranulomatous chronic invasive fungal sinusitis) is most commonly found in patients with diabetes mellitus; Aspergillus fumigatus is the most common pathogen. De Shazo [6] has reported that all patients in his series with this form of fungal sinusitis had diabetes mellitus. Granuloma formation requires an appropriate cell-mediated immune response that may be limited in diabetes. Patients often have little or no immunosuppression. The disease is characterized by a low-grade inflammatory reaction with tissue necrosis but minimal or no evidence of vascular invasion. Its duration is longer than 4 weeks. Extension into the orbit often produces proptosis. Like acute fungal

sinusitis, chronic invasive fungal sinusitis demands wide surgical de´bridement with systemic intravenous antifungal medication, often of prolonged duration (6 weeks or more).[7]

Granulomatous invasive fungal sinusitis has also been called indolent fungal sinusitis. It is considered the counterpart to chronic invasive fungal sinusitis, but with an intact cell-mediated immune response. It is clinically indistinguishable from the nongranulomatous form; histologic examination is required to distinguish the two. It also predominates in immunocompetent individuals. The immune response limits the invasion to the superficial mucosa. Granulomas surround the invasive fungal elements and limit deeper penetration. Multinucleated giant cells, pallisading nuclei, and eosinophils can be seen surrounding the granulomas. Treatment is somewhat controversial: some authors suggest surgical de´bridement alone as effective, whereas others cite the need for antifungal medications in addition to surgery[7].Antifungal treatment consists of intravenous amphotericin B followed by itraconazole. If P. boydii is the pathogen, imidazole may be the preferable intravenous agent.[8] Although prognosis is hard to ascertain in many patients, in general it is considered to be better than for the nongranulomatous form because of the intact cell-mediated immunity.

Fungus balls, or mycetomas, usually present as a unilateral opacification of either the maxillary or sphenoid sinus.[9] Only rarely are they found in the ethmoid or frontal sinuses. There are no reported pediatric patients, and women are more predominately affected, accounting for about two thirds of patients. Patients are classically immunocompetent without evidence of atopy. The fungus ball is composed of tightly packed hyphae most often from Aspergillus, Alternaria, or P. boydii .[9] Treatment is surgical and must include removal of debris and wide ventilation of the involved cavity. Medical therapy is of little utility, and recurrence is unusual after appropriate surgical management.

Allergic fungal sinusitis

Allergic fungal sinusitis (AFS), more appropriately called allergic fungal rhinosinusitis, is the fifth classification of fungal sinusitis. Indeed, a large amount of controversy exists regarding the etiology and pathogenesis of this entity. In fact, recent research challenges the current definition and pathophysiology of allergic fungal sinusitis.

The history of AFS itself is somewhat convoluted. Safirstein[10] first noted the combination of nasal polyposis, crust formation, and positive sinus cultures for Aspergillus in 1976. In 1981, Millar et al [11] noted the histologic similarities between AFS and allergic bronchopulmonary aspergillosis (ABPA). Even this first description noted that some patients had all the histologic features of AFS without identifiable fungal hyphae. Robson et al[12] introduced the term allergic fungal sinusitis in 1989 to describe the findings now associated with the disease. The noted lack of fungal hyphae in some patients foreshadows a recent debate in AFS pathophysiology. First, however, researchers set out to determine that AFS represented an immunologically mediated disorder rather than a precursor to invasive fungal disease. Extensive work by Manning[13] Schubert and Goetz[14,15], Mabry[16,,17], and Bent and Kuhn[18] suggests that AFS is an IgE-mediated disease. Allergic fungal sinusitis is typically a disease of younger patients; the average age at diagnosis ranges in the literature from 21.9 to 42.4 years [13,19-21]. It has been estimated that 5% to 10% of patients with chronic rhinosinusitis carry diagnosis of AFS [21-23]. Certainly, however, the incidence depends on location. Diagnostic criteria vary by author, but the most widely accepted are the five described

by Bent and Kuhn [18](1) type I hypersensitivity to fungi, (2) nasal polyposis, (3) characteristic radiographic findings, (4) eosinophilic mucin demonstrating noninvasive fungus, and (5) positive fungal stain or culture.

The clinical presentation of AFS can vary from mild to dramatic. Significant changes may include acute visual loss, gross facial dysmorphia, and complete nasal obstruction. The more typical patient presents with progressive nasal obstruction, rhinorrhea, nasal cast formation, and chronic rhinosinusitis. Classic radiographic findings include unilateral involvement with paranasal sinus cavity expansion. Bone erosion may be present in up to 20% of cases, and a heterogeneous appearance with areas of increased signal intensity highly suggestive of inspissated fungal debris can be seen (Fig. 1) [26]. Laboratory findings are quite variable and are a source of controversy. Several studies have reported elevated levels of both total and fungal-specific IgE levels in addition to evidence of type I allergy in patients with AFS. On the other hand, several investigators have failed to demonstrate these findings, especially elevated fungal specific IgE levels. These later data call into question the IgE-mediated basis for the disease. Work by Bent and Kuhn [18] and Schubert and Goetz [37,38] has demonstrated that changes in total IgE levels in the serum may reflect disease activity and predict recurrence. Based on these data, the underlying mechanism for disease in AFS was believed to be an IgE-mediated hypersensitivity to fungal antigens. This process would lead to eosinophilic infiltration with cellular degranulation and start a cycle that perpetuates the formation of allergic mucin. This cycle was outlined by Marple [27] demonstrating the contributing factors responsible for AFS and the possible cites of treatment

Management Problems

Allergic plant rubor, as outlined by Bent and Richard Kuhn[17] includes a variety of contributive factors related toits progression and so has multiple modalities of treatment. Marple [27] has represented a cycle for AFS pathophysiology following the mechanism represented by Manning and Homan[13] during which atopic allergy, continuous matterexposure, and in- flammation all play roles within the continuance of the unwellness . The mainstay of any combination treatment for AFS remains surgical removal of the allergic glycoprotein and plant parts at the side ofcreation of patent sinus ostia that square measure massive enough to supply surgical access to the sinuses [7,27,34-36]. As one modality, useful examination sinus surgery ends up in a high rate of repeat. This intervention will occur preoperatively within the sort of steroid administration to decrease the intranasal polyposis and in- flammation. additionally, corticosteroids ought to be administered post-operatively each locally and systemically, however the period and best dosing stay unclear [7,36]. Multiple studies [7,14,15,27] have shown improvement in symptoms also as raised time to repeat and improvement in overall repeat rates with steroid administration, and therefore the knowledge appear to support a extended amount than a shorter one.

Kuhn and Javer [36] have a surgical protocol victimization oral Deltasone. They suggest zero.4 mg/kg/day for fourdays. This dose is shrunken by zero.1 mg/kg/day in cycles of four days till a dose of twenty mg/day or zero.2 mg/kg/day, whichever is bigger, is reached. This dose is sustained for one month postoperatively and is then adjusted to zero.2 mg/kg/day. This dose is maintained whereas the patient is followed monthly with nasal examination and immune serum globulin levels. The steroid level is adjusted to keep up the patient on a

stage zero secretion membrane look represented by Kupferberg et al[37]. If stage zero is maintained for four consecutive months, the Deltasone dose is reduced to zero.1mg/kg/day, and a nasal steroid spray is begun. If stage zero continues to be maintained for two additional months, the Deltasone is tapered off fully, and therefore the nasal steroid spray is sustained for one year. Patients ought to be followed for a minimum of five years in line with this protocol.

Systemic antifungal preparations are studied with at the best mixed results; actually, prospective, controlled studies don'texist, and therefore the risks of those medications could outweigh the advantages for noninvasive plantunwellness [27.] Ponikau and colleagues [38] square measure testing topical antifungal medications on chronic rhinosinusitis patients to work out if this treatment supports the mechanism they need planned for the unwellness. Prospective, controlled trials also are current to work out whether or not topical medications have an effect on a response in patients with the designation of allergic plant rhinosinusitis. One study printed by Ricchetti et al [39] reports improvement in nasal polyposis with antibiotic drug B nasal irrigation. These patients weren't specifically given a designation of AFS, nor was there an impression group; withal, it's apparent that any investigation is secure supported their findings.

Mabry et al [16,17] have strictly investigated therapy within the treatment of AFS. In their initial report, eleven patients receiving immunother- apy incontestible less crusting and polyposis also as a shrunken would like for steroid medical care [16]. There was no management cluster during this initial study. additional recently, they need accordingsimilar ends up in a study during which an impression cohort was used [17]. each teams received surgical intervention and surgical steroid treatment. The patients receiving immu- notherapy showed a reduced reliance on each general and intranasal corticosteroids. Mabry et al[40] have currently printed knowledge indicating no proof of repeat in eight patients World Health Organization had received and later interrupted therapy for a minimum of three years. In distinction, Ferguson had earlier according a retrospective review of seven patients with AFS World Health Organization received immunotherapy; 5 of those patients either failed to improve or maybe worsened. These patients, however, failed to receive largest surgical or steroid treatment. Clearly, any investigation is needed to delineate totally each the pathophysiology and therefore the treatment of plantrhinosinusitis and its connected disorders. Ever-advancing laboratory technology is probably going to shed lightweighton this advanced set of pathologies. abundant work remains to be completed, however it looks that multiple underlying triggers for chronic rhinosinusitis exist, plant enclosed. As these mechanisms square measure elucidated, patient subgroups are going to be higher outlined.

Summary

Despite the immense literature relating to plant infections of the top and neck, very little has modified in designationor management of those infections except within the nose and sinuses. 3 details relating to plant involvement within the cavum sinuses square measure evident currently. First, fungi is also vital in a very important share of patients with chronic rhinosinusitis. Second, the pathophysiologic mechanism liable for plant rhinosinu- sitis remains unclear. it's going to represent associate degree allergic immune serum globulin response, a cell- mediate reaction, or a mix of the 2. Finally, there's definitely a spectrum of unwellness so

far outlined: allergic plant rubor as defined by Bent and Richard Kuhn [18] leucocyte glycoprotein rhinosinusitis outlined by Ferguson[33], and leucocyte plant rhinosinusitis as planned by Ponikau[28].

Fungal infections of the top and neck square measure bird's-eye in distribution and pathophysiology. They represent a broad vary of unwellness of that life science has solely recently begun to uncover the surface. As analysis begins to unravel the advanced host defense mechanisms against these pathogens from a cellular and even genetic level, the body of information can still increase exponentially and therefore the ability to treat patients stricken by plant infections can improve.

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