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An algorithmic approach to aspergillus sinusitis

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Abstract
The effective management of paranasal sinus aspergillosis requires early diagnosis, histological classification, surgery and where appropriate, chemotherapy. Fungal sinusitis may be easily missed unless a high index of suspicion is maintained and specific culture and histology requested. The disease is classified into invasive and noninvasive types, each being divided into two subgroups: invasive aspergillosis may be either fulminant or indolent and noninvasive disease localized or allergic. The literature is reviewed and an algorithmic approach to aspergillus sinusitis proposed. The importance of histologically differentiating invasive from noninvasive aspergillosis prior to selecting the appropriate treatment options is stressed. CT scan should precede definitive surgery, and be used in follow-up. Close and prolonged follow-up is essential.

Key words: Aspergillus; Sinusitis; Algorithms

Introduction

The increasing volume of literature on aspergillus sinus infection is confusing, because different authors stress different aspects of the disease. There is a range of aspergillus disease, from allergic aspergillus sinusitis to an often fatal fulminant invasive form. In order to be clinically useful, a disease classification should exist which enables clinicians to make correct management decisions for their patients. Although usually benign, aspergillosis may be aggressive depending on the duration of the disease, its location and the patient's immunological status (Sarti *et al.*, 1988). To manage fungal sinusitis correctly, the principal differentiation is between histologically invasive and noninvasive disease (Washburn *et al.*, 1988). Each type can be divided into two subgroups: invasive disease may be fulminant (acute) or indolent (chronic); and noninvasive disease may be localized (aspergilloma), or allergic aspergillus sinusitis.

Noninvasive aspergillosis of the nose and paranasal sinuses was first described by Schubert in 1855 (Stammberger *et al.*, 1984) and invasive fungal sinusitis first reported by Oppe in 1897 (Washburn *et al.*, 1988), while Hora (1965) and McGill *et al.* (1980) described the chronic and fulminant forms of invasive fungal sinusitis in the modern literature. Fungal sinusitis in otherwise healthy individuals is increasingly recognized (Washburn *et al.*, 1988). *Aspergillus spp.* are the most common organisms in fungal sinusitis (Bardana, 1980; Stevens, 1981). A. flavus sinusitis appears to be particularly common in the Sudan (Veress *et al.*, 1973). Dematiaceous fungi (black moulds) are morphologically similar, as shown by histology, to *Aspergillus spp.* and are capable of causing invasive fungal sinusitis in healthy individuals (Manning *et al.*, 1991; Zieske *et al.*, 1991). They were previously considered to be nonpathogenic in man, but should always be reported by the laboratory.

Invasive aspergillus sinusitis is characterized by spread of fungal mycelium from sinus air spaces into adjacent structures with tissue necrosis, chronic inflammation and fibrosis (Hora, 1965; Jackson *et al.*, 1987; Milroy *et al.*, 1989). Blood vessels may be invaded producing thrombosis and infarction (Bodey and Vartivarian, 1989), In these cases fungal hyphal elements are always identified on deep biopsy, within the submucosa or bone (Washburn *et al.*, 1988).

Fulminant invasive aspergillosis occurs principally in neutropenic and bone marrow transplant patients where rapidly progressive, gangrenous mucoperiosteitis is frequently fatal (McGill *et al.*, 1980). Indolent invasive sinusitis is a more slowly destructive disease process, usually in immunologically normal, diabetic or AIDS patients, where a granulomatous response to the disease is characteristic (Denning, 1992). Langhan's giant cells containing hyphae and histiocytes, plasmocytes and often eosinophils are present (Veress *et al.*, 1973; Washburn *et al.*, 1988).

In localized noninvasive aspergillosis there is an extra mucosal ball of tangled fungal mycelium (aspergilloma) usually affecting a single sinus only (Jonathan *et al.*, 1989; Milroy, *et al.*, 1989; Manning *et al.*, 1991). This mass may enlarge over a long period of time with episodic spurts of growth (Stammberger *et al.*, 1984). This tends to be associated with chronic sinusitis.

Allergic aspergillus sinusitis as first described by Katzenstein *et al.* (1983) occurs in immuno-competent patients and generally involves more than one sinus.

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These patients commonly have asthma, nasal polyps and a history of atopy. There is an accumulation of abundant, thick, inspissated 'allergic mucin', containing eosinophils, inflammatory cells, Charcot-Leyden crystals and fragmented septate fungal hyphae, on an oedematous, chronically inflamed sinus mucosa. The disease is thought to be analagous to allergic bronchopulmonary aspergillosis.

The relative rarity of fungal sinusitis may lead to treatment along empirical lines. We have conducted an extensive literature review in an attempt to formulate a more logical therapeutic approach, which is contained in the accompanying algorithmic approach to aspergillus sinusitis (Figure 1).

Index of suspicion

This is vital to the diagnostic process because in non-immunocompromised patients the clinical presentation of fungal sinusitis is often nonspecific. Symptoms such as headache, rhinorrhoea, nasal discharge and postnasal drip may be present (Bodey and Vartivarian, 1989). Patients most commonly present with a history of prolonged relapsing sinusitis, often refractory to standard medical treatment (Zieske *et al.*, 1991). Examination of the nose often show nonspecific changes with normal or oedematous mucosa, nasal polyps, or a mass on the lateral wall (Jahrsdoerfer *et al.*, 1979).

This is explained by the pathogenesis of aspergillosis. Messerklinger (1978) has stressed the importance of antomical variations in the osteomeatal complex which produces abnormalities within the anterior ethmoidal air cells through which the frontal and maxillary sinuses drain. These predispose to recurrent sinusitis, and fungal sinusitis may be considered as a complication of recurrent sinusitis (Stammberger *et al.*, 1984). Recurrent sinusitis has been implicated in providing a relatively anaerobic environment, with a low pH, impaired mucociliary clearance, and 'nourishing' purulent secretions which promote the growth of fungi. Studies in rats suggest that a viral infection of the nasal airways enhances susceptibility to aspergillus rhinosinusitis (Rhem *et al.*, 1988). Fungal mycelium within a sinus can produce sinusitis either by acting as a foreign body or by producing a hypersensitivity reaction.

It has been suggested that the high incidence of fungal sinusitis in Northern Sudan and the Southern States of the USA may be due to dusty, arid conditions predisposing to rhinitis and recurrent sinusitis facilitating the growth of saphrophytic fungal spores (Rifkind *et al.*, 1966; Milosev *et al.*, 1969; Veress *et al.*, 1973; McGuirt and Harrill, 1979). Beck-Managetta and Nececk (1983; 1986) noted an association between aspergillus sinusitis and endodontic work to the upper molar and premolar teeth during which zinc oxide, which accelerates aspergillus growth *in vivo* and *in vitro*, may be introduced into the antrum.

Invasive fungal sinusitis is more common in patients whose resistance is lowered by immuno-suppression, diabetes, malignant disease, burns, trauma and, rarely, by steroids or in solid organ transplant patients (Veress *et al.*, 1973; Rinaldi, 1983; Stammberger *et al.*, 1984; Denning and Stevens, 1990; Zieske *et al.*, 1991). Patients who have previously had aspergillus sinusitis are especially prone to relapse or re-infection during any further episodes of immuno-compromise due to leukaemic relapse or chemotherapy (Viollier *et al.*, 1986; Talbot *et al.*, 1991).

In the fulminant invasive disease, a range of signs and symptoms may be present though diagnosis is often delayed. In a 10-year review of leukaemic patients, Talbot *et al.* (1991) found that a persistent pyrexia was the most common presenting feature (100 per cent), with cough (64 per cent), crusting of the nasal mucosa (57 per cent), epistaxis and headaches (50 per cent each), followed by nasal discharge, sinus pain, tenderness and a sore throat.

Nasal mucosal changes may be observed, reflecting ischaemia induced by fungal vasculitis. Early erythematous or oedematous mucosa becomes dusky or necrotic, before progressing to ulceration beneath an eschar. The

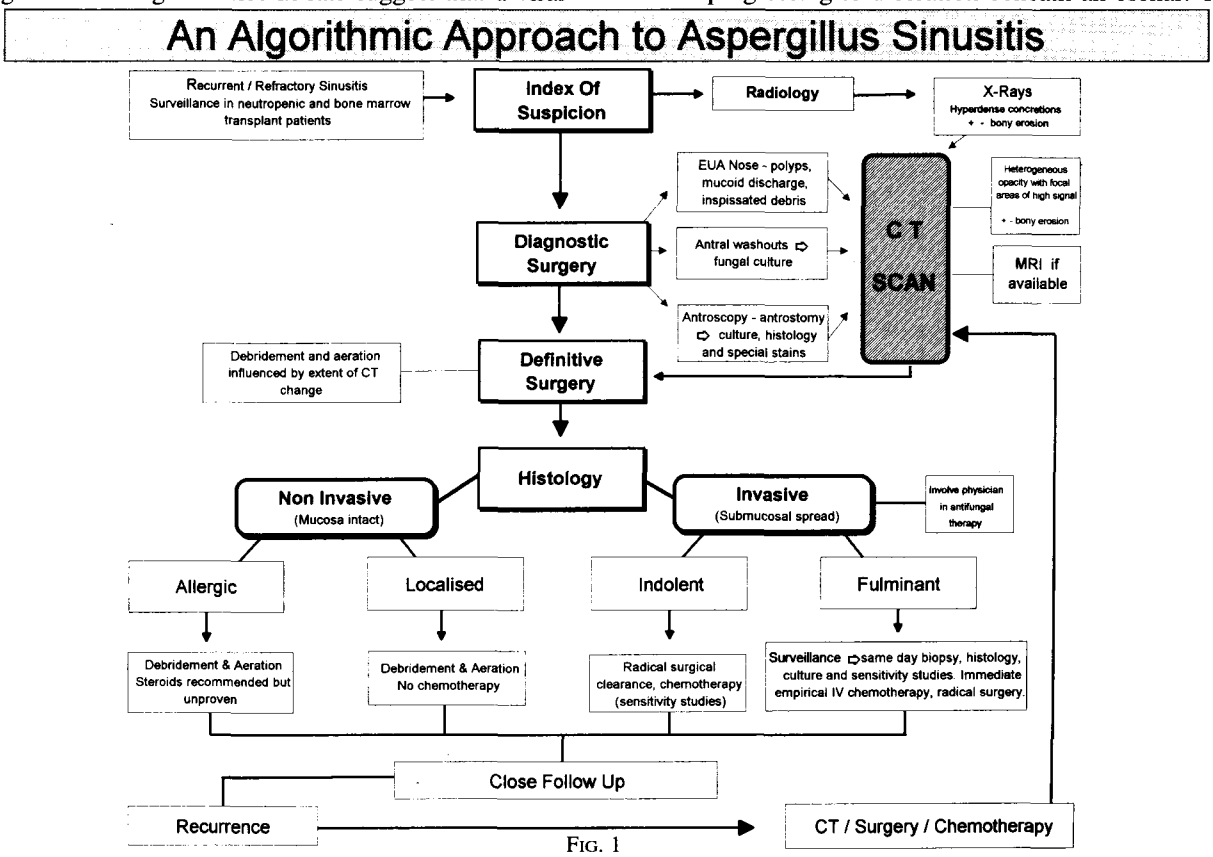

FIG. 1

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crusting may overly a gangrenous, insensitive inferior turbinate. These signs may precede the rapid onset of facial swelling, orbital symptoms and systemic dissemination to involve the lungs, liver and spleen (McGill *et al.*, 1980; Goering *et al.*, 1988; Bodey and Vartivarian, 1989). Intensive surveillance is particularly vital in neutropenic and bone marrow transplant patients.

Nasal ulceration in immunocompromised patients mimicking aspergillosis may also occur in mucor mycosis, HSV infections and *Pseudomonas aeruginosa* infection (Berlinger, 1985).

Management

The effective management of paranasal sinus aspergillosis requires early diagnosis, histological classification, surgery and where appropriate, chemotherapy. The initial treatment of fungal sinusitis should always be surgical. The objectives of surgery are debridement and wide aeration of the infected sinus as well as providing specimens for histological study (Waxman *et al.*, 1987; Jonathan *et al.*, 1989; Zieske *et al.*, 1991). As outlined in the algorithm, diagnostic surgery in combination with radiology allows the confirmation of the diagnosis and the planning of further, definitive surgery if required.

Non-immunocompromised patients often present with sinusitis which is refractory to medical therapy, and simple surgery including examination under anaesthesia, antral lavage, antroscopy and antrostomy may precede the suspicion of aspergillosis. The intra-operative findings may arouse clinical suspicions of fungal involvement and the surgery is essentially diagnostic, although this may be all that is required in noninvasive aspergillosis. It is vital that adequate specimens are obtained to confirm the diagnosis by histology and culture. Histology should distinguish between invasive and noninvasive disease, determining the course of further treatment. Radiological investigations, including CT, should be requested to assess the extent, if any, of spread and bony involvement. These can be used to plan further, more radical, definitive surgery if required.

Immunocompromised patients are particularly at risk from fulminant invasive aspergillosis and their management should include surveillance for signs of the disease, immediate biopsy, empirical chemotherapy and radical surgery if the aspergillosis progresses.

Radiology

The radiological diagnosis of fungal sinusitis on plain X-rays may be difficult. Aspergillosis may involve one or more sinuses. A nodular mucosal thickening, and the absence of air/fluid levels in homogeneously cloudy maxillary and ethmoidal sinuses, with or without bony destruction, have been described. These appearances have led to diagnoses ranging from chronic sinusitis to malignancy (Jahrsdoerfer *et al.*, 1979; Sarti *et al.*, 1988; Zinreich *et al.*, 1988). Although unusual, air/fluid levels on pain X-ray of immunocompromised patients with aspergillus sinusitis have been described (Talbot *et al.*, 1990; Berlinger, 1985). The presence of hyperdense fungal concretions on plain X-rays is almost pathognomonic of fungal sinusitis. These concretions may be calcium deposits within a central necrotic region of the fungal mycelium, or represent zinc oxide following endodontic treatment to molar and premolar teeth (Beck-Managetta and Nececk, 1983, 1986; Stammberger *et al.*, 1984).

A more relaible radiological diagnosis can be made on CT, and this is the best way to identify bony destruction. Any intracranial spread or orbital involvement can be assessed. Typically, a heterogeneous opacity of the antrum is seen with focal areas of high signal on noncontrast view (Zinreich *et al.*, 1988). Sinus wall expansion and/or destruction may be demonstrated in the invasive form of aspergillosis although sinus wall erosion due to pressure and atrophy in allergic aspergillosis has been reported (Katzenstein *et al.*, 1983; Manning and Weinberg, 1989; Manning *et al.*, 1991). A CT scan showing bony erosion should alert the clinician to the possibility of invasive fungal disease but the definitive diagnosis can only be made on histological confirmation of mucosal or bony invasion. The CT, most importantly, plays a vital role in determining the extent of the disease prior to further definitive surgery, if required.

Magnetic resonance imaging (MRI) was found to be even more sensitive than CT in diagnosing fungal sinusitis by Zinreich *et al.* (1988) although only a small number of cases was considered. A decreased signal intensity on T_1 and a very decreased signal intensity on T_2-weighted magnetic resonance images appears to be characteristic of fungal sinusitis. This may be due to the presence of ferromagnetic elements within the fungal concretions. MRI is also desirable to provide information about areas of critical importance, such as the cavenous sinuses and the brain (Zinreich *et al.*, 1988; Talbot *et al.*, 1991).

Surgery in non-immunocompromised patients

As mentioned before, the first diagnostic step is usually antral lavage or intranasal biopsy. Wash-outs may be falsely negative, either due to the inspissated nature of the fungal debris within a sinus or due to failure to request specific fungal culture. The initial surgical approach to the maxillary antrum is generally via an intranasal antrostomy because malignancy may still be suspected at the time of surgery. This allows the collection of material for histopathology and culture as well as facilitating aeration of the sinus.

At surgery, if dark (particularly black or green) coloured sinus debris, inflamed and necrotic sinus mucosa or thick mucous is found, then fungal culture and histology should be undertaken (Robb, 1986; Jonathan *et al.*, 1989; Zieske *et al.*, 1991). Fungal culture may be negative in more than 60 per cent of cases of proved fungal sinusitis (Jarsdoerfer *et al.*, 1979). Prolonged incubation, up to six weeks in our experience, may be necessary to demonstrate fungal involvement. Special histological stains such as Grocott silver stain or periodic acid shift (PAS) should be used as the fungal hyphae may be missed on routine haematoxylin and eosin staining (Jonathan *et al.*, 1989; Zieske *et al.*, 1991).

The histology should be specific as to whether there is submucosal involvement (invasive) or the mucosa is intact (noninvasive disease), as this is the key factor in deciding whether adjuvant medical therapy is required.

All sinus exudates and pus should be submitted for fungal culture in cases of recurrent or refractory sinusitis. A case can be made for submitting every surgically obtained

specimen of sinus contents for fungal culture and a full microbiological assessment including anaerobic culture. Most laboratories do not perform fungal culture unless specifically asked. Once the diagnosis is confirmed, removal of all fungal elements from all the involved sinuses can be achieved by more extensive, definitive surgery. This should be preceded by CT assessment of the extent of fungal disease.

Depending upon the extent of the disease, surgical clearance can be performed via a Caldwell-Luc approach, a transantral ethmoidosphenoidectomy, external ethmoidectomy, functional endoscopic sinus surgery, lateral rhinotomy or an osteoplastic frontal sinus approach, as appropriate (Robb, 1986; Jonathan *et al.*, 1989; Zieske *et al.*, 1991). Definitive surgical treatment alone is satisfactory for the vast majority of non-immunocompromised patients. In invasive disease, chemotherapy is also required.

Immunocompromised patients

Immunocompromised patients present a much more significant problem. In neutropenic patients, the role of surgery is less certain and may be associated with increased mortality (Denning and Stevens, 1990). Surgery in severely ill, neutropenic and thrombocytopenic patients may be difficult and complicated by severe, even fatal haemorrhage as well as post-operative pneumonia (Goering *et al.*, 1988; Talbot *et al.*, 1991).

The combination of early diagnosis by biopsy, empirical amphotericin B, and if there is disease progression during medical therapy, aggressive surgery, has yielded improved mortality in neutropenic patients. Infection control and survival are absolutely dependent on recovery of bone marrow function and the production of circulating neutrophils (Burch *et al.*, 1987; Goering *et al.*, 1988). These cases should be treated with extreme urgency in view of the high mortality of fulminant invasive aspergillosis. Daily surveillance of the nasal mucosa in neutropenic and bone marrow transplant patients for mucosal pallor or crusting should be performed. Growth of *Aspergillus spp.* in routine nasal surveillance swabs is likely to reflect early invasion, even if not clinically detectable, and merits prompt treatment (Talbot *et al.*, 1991). Any mucosal changes or unexplained pyrexia (especially whilst taking broad spectrum antibiotics) should be followed by 'same day' biopsy, urgent histology, culture, surgery and immediate empirical medical therapy. A physician experienced in the administration and complications of intravenous antifungal agents should be involved from the outset.

The reduction of exposure of immunocompromised patients to aspergillus spores by removal of environmental sources and the use of particulate air filters and laminar flow systems is desirable. Prophylactic antifungal chemotherapy for at risk patients is limited by the morbidity of intravenous amphotericin B usage, though oral agents may hold promise (Talbot *et al.*, 1991). Prophylactic amphotericin B may be appropriate in patients with previous aspergillus disease in whom further neutropenia is anticipated (Burch *et al.*, 1987). Amphotericin B nasal spray may pay a role in preventing pulmonary aspergillosis in neutropenic patients, but no effective trial of this treatment has been performed (Meunier-Carpentier *et al.*, 1984).

Medical treatment

The issue of adjuvant antifungal therapy is at present unresolved. Systemic amphotericin B is the antifungal of choice in aspergillosis, particularly in invasive or recurrent disease, and has been recommended in conjunction with surgery (Titche, 1978; Jarsdoerfer *et al.*, 1979; Yu *et al.*, 1980; Zieske *et al.*, 1991). Its use is associated with considerable morbidity and although it has been used for over 30 years in humans, the optimum dose and duration of treatment are still unclear. Clinically, the dose of amphotericin B is often titrated against the patient's toxic (especially nephrotoxic) side effects. In fulminant aspergillosis a dose of 1.0 to 1.5 mg/kg/day initially is considered appropriate.

The amphotericin B/lipid complex of liposomal amphotericin B can be given at much higher concentrations than free amphotericin B as it is less toxic to mammalian cells while retaining its antifungal activity (Denning and Stevens, 1990; Zieske *et al.*, 1991). Its very high cost is likely to restrict its use to patients unresponsive to, or unable to tolerate the nephrotoxity of conventional amphotericin B (Baxter, 1992).

Topical amphotericin B by intra-operative sinus irrigation or repeated packing of the antral cavity with amphotericin soaked ribbon gauze has been reported (Robb, 1986; Zieske *et al.*, 1991). Although we have used this technique, it is difficult to assess objectively the efficacy of this line of treatment as surgery alone may be curative.

Other systemic antifungal agents such as Itraconazole, a relatively nontoxic, oral antifungal agent with proven efficacy in aspergillosis, have been successfully used, either singly or in combinaiton with amphotericin B (Jonathan *et al.*, 1989; Denning and Stevens, 1990; Zieske *et al.*, 1991).

When using antifungal agents, susceptibility studies may assist management decisions in the event of non-response or when combination therapy is contemplated, because synergy and antagonism with amphotericin B are seen with equal frequency (Dennings and Stevens, 1990). We advocate seeking expert advice on medical treatment in view of the choice of antifungal agents and the high morbidity associated with their use.

Systemic corticosteroids have been proposed in the management of allergic aspergillus sinusitis, extrapolating from the experience gained with allergic bronchopulmonary aspergillosis (Saferstein *et al.*, 1973; Waxman *et al.*, 1987; Manning *et al.*, 1991). However, surgery alone may be curative in allergic aspergillus sinusitis, and in none of the 38 cases of allergic fungal sinusitis reported by Jonathan *et al.* (1989), Manning and Weinberg (1989), Manning *et al.* (1991) and Zieske *et al.* (1991) was prolonged, systemic corticosteroid therapy used. This may be because allergic aspergillus sinusitis is less analagous to bronchopulmonary fungal disease than assumed, principally because of the accessibility of sinus fungal disease to surgical debridement and aeration, which may fundamentally alter the prognosis of the disease.

All patients with aspergillus sinusitis should be closely followed-up for evidence of recurrence. Clinicians should have a low threshold for repeated CT scans, particularly following invasive disease. Aggresive multimodal treatment may be required to eliminate recurrent disease.

Conclusions

(1) Without developing a high index of suspicion, the

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diagnosis of fungal sinusitis may be delayed or missed until extensive disease is present.

(2) Specific fungal culture should be requested on sinus exudates and pus.

(3) The histological classification into invasive or non-invasive sinus disease is a vital prerequisite to choosing the correct treatment.

(4) CT scanning should be used to assess the extent of disease pre-operatively and in the post-operative follow-up of these patients.

(5) Close follow-up and rapid multimodal intervention to treat recurrence is advocated.

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References

Bardana, E. (1980) Clinical spectrum of aspergillosis. Classification of saphrophytic, allergic and invasive variants of human disease. *CRC, Critical Review in Clinical Laboratory Sciences,* **13:** 85–159.

Baxter, H. (1992) Fighting mushrooming fungal ills. *Hospital Doctor* **9th April:** 47–48.

Beck-Managetta, J., Nececk, D. (1983) Solitary aspergillosis of maxillary sinus, a complication of dental treatment. *Lancet* **26:** 1260.

Beck-Managetta, J., Nececk, D. (1986) Radiological findings in aspergillosis of the maxillary sinus. *Oral Surgery, Oral Medicine, and Oral Pathology* **62:** 345–349.

Berlinger, N. T. (1985) Sinusitis in immunodeficient and immunosuppressed patients. *Laryngoscope* **95:** 29–33.

Bodey, G. P., Vartivarian, S. (1989) Aspergillosis. *European Journal of Clinical Microbiology and Infectious Disease* **8:** 413–437.

Burch, P. A., Karp, J. E., Merz, W. G., Kuhlman, J. E., Fishman, E. K. (1987) Favourable outcome of invasive aspergillosis in patients with acute leukaemia. *Journal of Clinical Oncology* **5:** 1985–1993.

Denning, D. W., Stevens, D. A. (1990) Anti-fungal and surgical treatment of invasive aspergillosis: review of 2121 published cases. *Review of Infectious Disease* **12:** 1147–1201.

Denning, D. W. (1992) Aspergillose invasive au course du sida. Revue geneuae. *Journal de Mycolode Medicale* **2(supp. I):** 35–41.

Goering, P., Berlinger, N. T., Weisdors, D. J. (1988) Aggressive combined modality treatment of progressive sinonasal fungal infections in immuno-compromised patients. *American Journal of Medicine* **85:** 619–623.

Hora, J. F. (1965) Primary aspergillosis of the paranasal sinuses and associated area. *Laryngoscope* **75:** 768–773.

Jackson, I. T., Schmitt, E., Carpenter, H. A. (1987) Allergic aspergillus sinusitis. *Plastic and Reconstructive Surgery* **79:** 804–808.

Jahrsdoerfer, R. A., Egercito, V., Johns, M. M. E., Cantrell, R. W., Snyder, B. J. (1979) Aspergillosis of the nose and paranasal sinuses. *American Journal of Otolaryngology* **1:** 6–14.

Jonathan D., Lund, V., Milroy, C. (1989) Allergic aspergillus sinusitis – an overlooked diagnosis. *Journal of Laryngology and Otology* **103:** 1081–1183.

Katzenstein, A. A., Sale, S. R., Greenberger, P. A. (1983) Allergic aspergillus sinusitis: a newly recognised form of sinusitis. *Journal of Allergy and Clinical Immunology* **72:** 89–93.

Manning, S. C., Weinberg, A. G. (1989) Allergic aspergillosis: a newly recognised form of sinusitis in the paediatric population. *Laryngoscope* **99:** 681–685.

Manning, S. C., Schaefer, S. D., Close, L. G., Vuitch, F. (1991) Culture positive allergic fungal sinusitis. *Archives of Otolaryngology, Head and Neck Surgery* **117:** 174–178.

McGill, T. J., Simpson, G, Healy, G. B. (1980) Fulminant aspergillosis of the nose and paranasal sinuses: a new clinical entity. *Laryngoscope* **90:** 748–754.

McGuirt, W. F., Harrill, J. A. (1979) Paranasal sinus aspergilloma. *Laryngoscope* **89:** 1563–1568.

Messerklinger, W. (1978) *Endoscopy of the nose.* Urban & Schwarzenberg, Munich, pp 52–54.

Meunier-Carpentier, F., Snoech, R., Gerrain, J. Muller, C., Klastersky, J. (1984) Amphotericin B nasal spray as prophylactic against aspergillus in patients with neutropenia. *New England Journal of Medicine* **311:** 1056 (Letter).

Milosev, B., Mahgoub, El-s., Aal, A, Hassan, A. L. (1969). Primary aspergilloma of the paranasal sinuses in the Sudan. *British Journal of Surgery* **56:** 132–137.

Milroy, C. M., Blanshard, J. D., Lucas, S., Michaels, L. (1989) Aspergillosis of the nose and paranasal sinus. *Journal of Clinical Pathology* **42:** 123–127.

Rhem, S., Waalkes, M. P., Ward, J. M. (1988) Aspergillus rhinitis in Wistar rats. *Laboratory and Animal Sciences* **38:** 162–166.

Rifkind, B. M., Gale, M., McNicol, G. P., Douglas, A. S. (1966) Aspergillosis of the paranasal sinuses and orbit in the Northern Sudanese. *Lancet* **2:** 746–747.

Rinaldi, M. G. (1983) Invasive aspergillosis. *Reviews of Infectious Disease* **5:** 1061–1077.

Robb, P. J. (1986) Aspergillosis of the paranasal sinus (a case report and histological perspective). *Journal of Laryngology and Otology* **100:** 1071–1077.

Saferstein, B. A., D'Souza, M. F., Simon, G., Tai, E., Pepys, J. (1973). Five-year follow-up allergic broncho-pulmonary aspergillosis. *American Review of Respiratory Diseases* **108** 450–459.

Sarti, E. J., Blaugrund, S. M., Lin, P. T., Camins, M. B. (1988) Paranasal sinus disease with intracranial extension: aspergillosis *versus* malignancy. *Laryngoscope* **98:** 632–635.

Stammberger, H., Jakse, R., Beaufort, F. (1984) Aspergillosis of the paranasal sinuses: X-ray diagnosis, histopathology and clinical aspects. *Annals of Otology, Rhinology and Laryngology* **93:** 251–256.

Stevens, M. H. (1981) Primary fungal infections of the paranasal sinuses. *American Journal of Otolaryngology* **2:** 348–357.

Talbot, G. H., Huang, A., Provendar, M. (1991) Invasive aspergillus rhinosinusitis in patients with acute leukaemia. *Reviews of Infectious Diseases* **13:** 219–232.

Titche, L. L. (1978) Aspergillosis of the maxillary sinus. *Ear, Nose and Throat Journal* **57:** 62–66.

Veress, B., Malik, O. A., El-Tayeb, A. A., El-Daoud, S., El-Mahgoob, S., El-Hussan, M. M. (1973) Further observation on the primary paranasal aspergillus granuloma in the Sudan. *American Journal of Tropical Medicine and Hygiene* **22:** 765–772.

Viollier, A. F., Peterson, D. E., De Jongh, C. A., Newman, K. A., Gray, W. C., Sutherland, J. C., Moody, M. A. Schimpff, S. C. (1986) Aspergillus sinusitis in cancer patients. *Cancer* **58:** 366–371.

Washburn, R. G., Kennedy, D. W., Begley, M. G., Henderson, D. K., Bennett, J. E. (1988) Chronic fungal sinusitis in apparently normal hosts. *Medicine* **67:** 231–247.

Waxman, J. E., Spector, J. G., Sale, S. R., Katzenstein, A. A. (1987) Allergic aspergillus sinusitis: concepts in diagnosis and treatment of a new clinical entity. *Laryngoscope* **97:** 261–266.

Yu, V. L., Wagner, G. E., Smith, S. (1980) Sino-orbital aspergillosis treatment with combination anti-fungal therapy. *Journal of American Medical Association* **244:** 814–815.

Zieske, L. A., Kopke, R. D., Hammill, R. (1991) Dematiaceous fungal sinusitis. *Otolaryngology – Head and Neck Surgery* **105:** 567–577.

Zinreich, S. J., Kennedy, D. W., Mallet, J., Cutin, H. D., Epstein, J. I., Huff, L. C., Kumar, A. J., Johns, M. E., Rosenbaum, A. E. (1988) Fungal sinusitis: diagnosis with CT and MR imaging. *Radiology* **169:** 439–444.

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