Medical Grand Rounds
Parkland Memorial Hospital

P U L M O N A R Y A S P E R G I L L O S I S

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In 1976, aspergillosis was the third most common systemic fungal infection leading to hospitalization in the United States. When this infection was the primary diagnosis, it caused a case-fatality ratio of 10.4% (1). This fractional death rate was the highest among all fungal diseases. Moreover, between 1970 and 1976 the incidence increased 158%, a rate more rapid than any other fungal diseases. Since *Aspergillus* infections usually occur in immunocompromised patients, and since the number of these patients is increasing, it is reasonable to believe that this upward trend in incidence has continued. The lung is by far the most frequent organ infected by *Aspergillus* (2).

In addition to infection, there are several syndromes of an allergic pulmonary response to this fungus, and new information is becoming available about these reactions (3-5). For these several reasons a review of pulmonary aspergillosis seems timely.

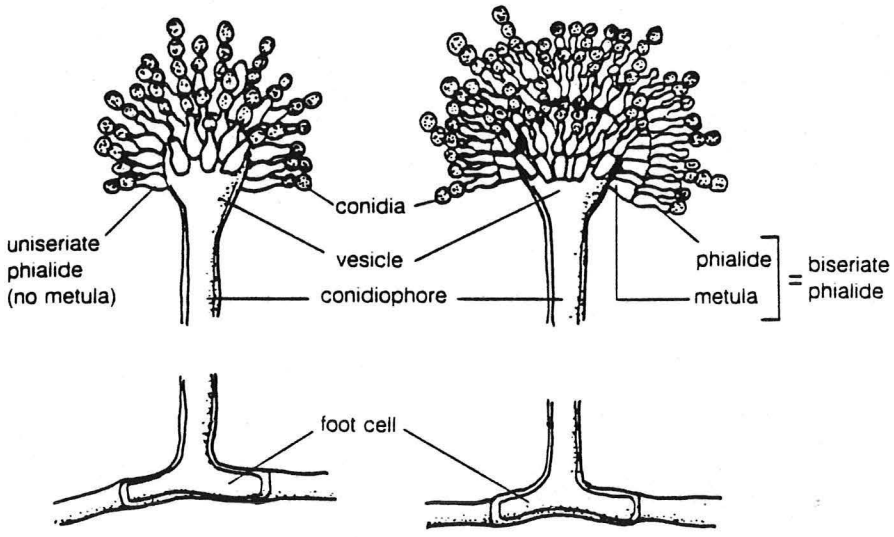
Aspergillus species

MYCOLOGY

The aspergilli are filamentous saprophytic molds made up predominately of masses of septate branching hyphae of uniform size which varies among species from 2.5 to 8 μm in width (6-10). The distinguishing feature is the periodic occurrence of elongated branches termed conidiophores growing up from foot cells in the hyphae (Figure 1).

Figure 1

Conidiophores of *Aspergillus*



Larone, Davise H.: In: Medically Important Fungi. Chapter 6, second edition, Elsevier Sci. Publ., N.Y., 1987, p. 89.

Depending on the species the conidiophore may be from 0.25 to 10 mm in length. This stalk is enlarged at the tip forming a swollen vesicle which is 10 to 180 μm in diameter. The vesicles are partially or completely covered by flask-shaped projections called phialides. These may arise directly from the vesicle or occur as a two-part branch, the first part of which is referred to as a metula. From these branches arise chains of mostly round, sometimes rough spores called conidia which are 2-5 μm in diameter. The conidia are colored causing the fungal colony on culture media to assume the same color.

When the organism is suspected, culture material is usually plated on Sabouraud agar or Czapek solution agar which contain antimicrobial agents to suppress the growth of bacteria. However, *Aspergillus species* are common airborne contaminants of all surfaces, and they grow well on a variety of simple media including blood agar plates. Thus, it is important for the laboratory to protect cultures against accidental inoculation which would cause a false positive report. Identifiable colonies usually are present within three days, although some species are slower growing. The colonies have a velvety or cottony texture. When first visible they are usually white but then change to any shade of yellow, green, brown or black depending on the species. These identifying characteristics are rarely present, however, in tissue specimens from patient material.

Figure 2

Invasive Aspergillosis in Tissue

Rippon, John Willard: The pathogenic fungi and the pathogenic actinomycetes. In: Medical Mycology, second edition, Chapter 23, W. B. Saunders Company, Philadelphia, 1982, p. 584.

If *Aspergillus* is growing within a cavity or airway, conidiophores may sometimes be observed and a definitive diagnosis established. However, these elements do not occur in fungi invading tissues where only hyphal

elements are observed (Figure 2). The hyphae usually stain reasonably well with hematoxylin and eosin, but to ensure observation silver stains should be used when aspergillosis is a possibility. The hyphae are relatively uniform in diameter ranging from 2.5 to 4.5 μm, and they usually have multiple septation. Many strands demonstrate repeated dichotomous branching, with the branches arising at about 45^{0} angles. Several hyphae are typically oriented in the same direction giving a brush like appearance. Conidia are not seen in tissues, but hyphae cut in cross section may be confused with conidia or yeasts. The appearance of *Aspergillus* in tissue sections, however, does not always allow it to be differentiated from other opportunistic fungal infections.

There are between 300 and 600 species in the genus *Aspergillus* (3, 8), but only a limited number have been implicated in human diseases (Table 1) (8, 11).

Table 1

Aspergillus Species Implicated in Human Disease

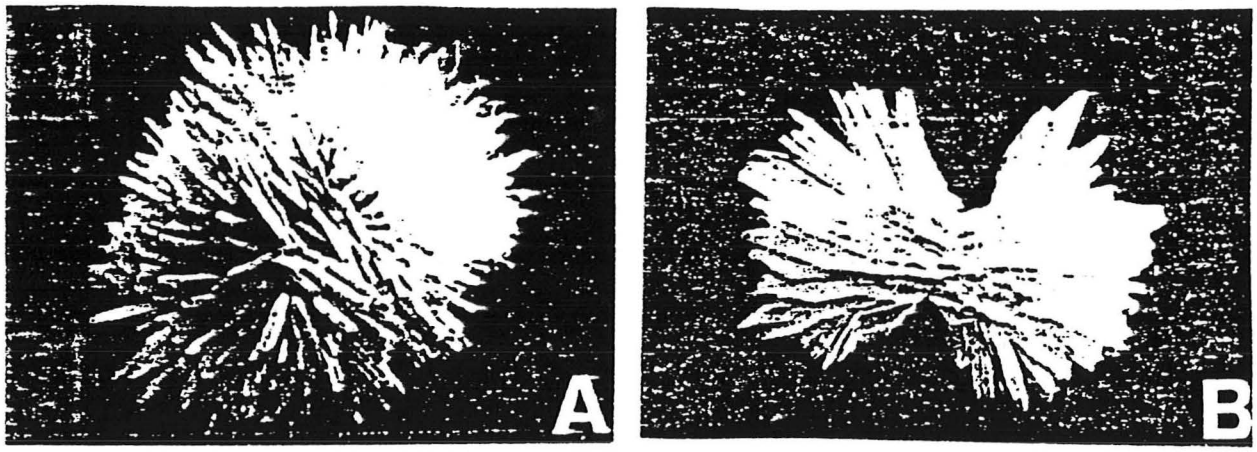
A. fumigatus	*A. carneus*	*A. oryzai*
A. flavus	*A. clavatus*	*A. sycowi*
A. niger	*A. restrictus*	*A. ochraceus*
A. terreus	*A. sulphureus*	*A. niveus*
A. nidulans	*A. glaucus*	*A. amsteloidami*

Among the species of *Aspergillus* reported to cause human disease, *Aspergillus fumigatus* accounts for almost all cases, both allergic and infectious. *Aspergillus flavus* is the second most prevalent species, and in North America *Aspergillus niger* is reported with some frequency. The remainder of the species are sufficiently unusual to allow for case reports. Since such reports continue to implicate species not previously known to cause human disease, there is every reason to believe that even more species will be found to be occasional pathogens in humans.

In some patients with either aspergilloma or invasive *Aspergillus* infection an *in vivo* cultural property of some strains may be helpful in diagnosis. It has long been known that some strains of *A. niger* produce appreciable quantities of oxalic acid. Although the entire mechanism is not known, oxalate is probably produced through the tricarboxylic acid cycle with the degradation of oxaloacetate (12). In an alkaline or neutral environment, the fungus excretes oxalic acid during growth. This acid combines with the patient's serum calcium or the calcium ions in tissue fluid to form calcium oxalate crystals (13). These crystals were first observed in 1958 (14), but it was not until 1973 that their diagnostic importance was realized (13). In 1978 it was suggested that cytopathology specimens of sputum be used to detect calcium oxalate crystals (15).

Figure 3

Scanning EM of Calcium Oxalate Crystals in Sputum



Farley, Mabry, Munoz and Diserens: Acta Cytol 29:737, 1985.

The importance of this observation has been confirmed in subsequent studies (16, 17). The crystals in respiratory secretions occur as a rosette arrangement of needlelike crystals or as more platelike crystals in a wheat-sheaf-like arrangement (Figure 3).

Table 2

Calcium Oxalate Crystals in Sputum Cytology
of Patients with *Aspergillus* in Sputum Cultures

Aspergillus sp.	No. Pts.	Crystals Present No.	%
A. niger	11	5	46
A. flavis	25	4	16
A. fumigatus	15	1	7
A. species	12	1	8
Total	63	11	17

Farley, Mabry, Munoz and Diserens: Acta Cytol 29:737, 1985.

In the only quantitative study available, in which most patients had an aspergilloma, crystals were found in cytology specimens of 46% of patients with *A. niger*, 16% of patients with *A. flavus*, 7% with *A. fumigatus* and 8% with nonspeciated *Aspergillus* (Table 2) (16). It has also been stressed that sputum may be positive for crystals more than a year before sputum cultures become positive and more than five years before a fungus ball is identified radiographically. Crystals also occur in pathological specimens of the lung and are thought by some to be implicated in tissue damage (18, 19). It has also been suggested that analysis for the oxalic

acid content of bronchoalveolar lavage fluid from immunocompromised patients believed to have invasive pulmonary aspergillosis may be of diagnostic value (20). However, the overlap of values of patients who did or did not have aspergillosis suggests poor sensitivity of that measurement.

It should also be mentioned that many species of *Aspergillus* produce toxic metabolites. The exact role of these mycotoxins in producing disease has yet to be elucidated. It has been suggested that some human disease may be due to one of these factors, aflatoxin, following the ingestion of contaminated food, but a discussion of this possibility does not directly pertain to the subject at hand.

EPIDEMIOLOGY

Since aspergilloma and the hypersensitivity syndromes are usually community acquired, while *Aspergillus* infections are frequently hospital acquired, the epidemiology of each will be reviewed separately.

Table 3

Environmental Distribution of *Aspergillus*

1. Most frequent environmental fungus
2. Worldwide distribution
3. Highest concentration in moldy hay and straw and in leaf and grass compost
4. Differences in prevalence exist among temperate regions
5. Seasonality of prevalence varies among regions

Aspergillus is the most frequent fungus encountered by man (Table 3). In an analysis of 94 separate world-wide surveys it was found that *Aspergillus* ranked between first and fifteenth in order of incidence of airborne molds and represented up to 22% of the total air spora sampled (21). *Aspergillus species* are found in soil, water and air throughout the world (22). *Aspergillus* spores are found not only in temperate regions but in the snow of the Antarctic (23) and the sands of and winds over the Sahara Desert. *Aspergillus* spores have even been recovered from the upper atmosphere. Mycological cultures were taken from surfaces of the Skylab Space Craft before launch and during flight, and widespread contamination of the craft with *Aspergillus species* was detected on the third mission (24). The highest concentration of the fungus is in moldy hay and straw, and in leaf and grass compost (25, 26). Indeed, it has been shown that up to 112 million *Aspergillus*-like spores may be released per gram of agitated hay (27). These materials are thought to provide the most important source of *Aspergillus* for domesticated animals and fowls, many of which have a high incidence of diseases due to this fungus (3). In addition, these barnyard materials provide an inoculum for agricultural workers who sometimes develop a hypersensitivity pneumonitis as a result.

Differences in prevalence of recovery of *Aspergillus* spores exist among temperate regions. The concentration of spores is probably higher in Great Britain, and perhaps other areas of Europe, than in the United States (28-31). A seasonality of recovery of *Aspergillus* from air samples also varies among temperate regions. Although the magnitude of exposure may vary from one region of the world to another and from one time of year to another, people everywhere have the opportunity to breathe the conidia of *Aspergillus* into their lungs.

Table 4

Principal Molds in Outside Air in Great Britain

Spores	$\bar{M}$ Conc/m^3	$\bar{M}$ Size (μm)
Cladosporum sp	986	12 x 5
Basidospores	792	5-20
Ascospores	694	2-40
Sporobotomyces roseus	221	4 x 3
Penicillium sp	102	2-12
Tilletiopsis sp	54	6 x 1
Ustilago sp	39	7-12
Aspergillus fumigatus	25	2.5-3
All others	<25	-

Mullins and Seaton: Clin Allergy 8:525, 1978.

The most complete study of the inhalation of *Aspergillus* in humans was carried out by Mullins and Seaton in Great Britain (32). Ambiant air samples were obtained once weekly for two years at one site (Table 4). *A. fumigatus* was the only *Aspergillus* species to be recovered consistently, and its average concentration in outside air was considerably less than that of many other fungi. However, the mean size of its spores was smaller than that of other fungi which were present in more profusion. Since the likelihood of pulmonary deposition of respirable particles is inversely related to their diameter, it would be predicted that *A. fumigatus* would be more likely inhaled into the lung than the other fungi.

Table 5

Prevalence of Molds in Sputum and Lung Specimens

Molds	2446 Sputa (%)	Molds	295 Lung Specimens (%)
Candida albicans	67.2	*Candida albicans*	62.0
Aspergillus fumigatus	19.2	*Aspergillus fumigatus*	44.3
Penicillium sp	18.6	*Phoma sp*	21.4
Cladosporium sp	17.0	*Aspergillus niger*	12.4
Aspergillus niger	2.1	*Penicillium sp*	7.4
Aspergillus sp	1.9	*Cephalosporium sp*	7.1
Others (each)	<1.5	Others (each)	<7.0

Mullins and Seaton: Clin Allergy 8:525, 1978.

The investigators also determined the fungi present in 2,446 sputa samples and peripheral lung specimens from 295 necropsied patients, 211 of which had died outside the hospital, during the same two year interval (Table 5). *Candida albicans* was the most frequent fungus recovered from sputa and lungs. This organism does not have airborne spores but lives saprophytically as a yeast within the respiratory tract. Most of the fungi recovered frequently from air were not recovered in sputum samples. This is thought to be due to the large size of their spores preventing deep penetration of the respiratory tract. None of the fungi with large spores was found in the lung specimens, tending to substantiate this concept. *Aspergillus fumigatus* was the most frequent airborne fungus recovered in sputum, and all *Aspergillus species* were found more frequently than would be predicted from the airborne concentration. This same relationship is even more apparent in the specimens of alveolated areas of lung. Spores which reach the periphery of the lung are thought to be killed by phagocytes. In experiments with guinea pigs the removal of *A. fumigatus* from the lungs requires 12 days suggesting substantial resistance of this organism to killing or physical removal (33).

Thus, environmental studies have demonstrated that humans are exposed to the spores of *Aspergillus* on an almost continual basis and that this fungus is able to inoculate the lung more frequently than other fungi present in higher concentrations in the atmosphere. Animal studies suggest a relatively weak phagocytic system for the elimination of *Aspergillus* from the lung. These features assume even greater importance among immunocompromised patients in hospitals.

In recent years there have been many reports of nosocomial *Aspergillus* infections in immunocompromised patients (34-45). That this form of aspergillosis is a hospital acquired infection was first suggested by the data of Rose (46).

Table 6

Patients with Aspergillosis in a Hospital with Natural Ventilation (Old) and in One with Mechanical Ventilation (New)

Diagnosis	Old Hospital May 1961-1966	New Hospital May 1966-1971
Aspergilloma	3	8
Terminal *Aspergillus* pneumonia	12	0

Rose, H.D.: Am Rev Resp Dis 105:306, 1972.

In May, 1966, a new hospital was completed at the Veterans Administration Center, Wood, Wisconsin, and patients were moved from an adjacent 43 year old hospital that had been naturally ventilated. In the naturally ventilated hospital the fungal flora of the air would be expected to be the same as that in the general atmosphere surrounding the hospital (47). In the old hospital there were three admissions for community acquired aspergillomas, and 12 patients developed a terminal *Aspergillus* pneumonia after admission during the five years prior to the opening of the new hospital (Table 6). During the five years after opening of the new hospital, which had a filtered air conditioning system which reduced substantially the number of airborne spores (46), there were eight cases of community acquired aspergilloma but no cases of terminal *Aspergillus* pneumonia. Similar data were reported when Memorial Hospital in New York moved from a naturally ventilated hospital building to a new facility with a central filtered ventilation system in 1973 (48). These data suggest that among hospitalized immunocompromised persons who develop *Aspergillus* pneumonia, the lung inoculation occurs while in the hospital and is not a result of previously inhaled organisms.

Table 7

External Sources of Nosocomial *Aspergillus* Pneumonia Contaminating A/C Filters and Ducts

Gage, et al: Arch Surg 101:384, 1970	Pigeon excreta
Kyriakides: Am J Surg 131:246, 1976	Bird droppings
Mahoney, et al: J Pediat 95:70, 1979	Malfunctioning exhaust
Stone, et al: J Trauma 19:765, 1979	Unknown
Lentino, et al: Am J Epidemiol 116:430, 1982	Outside construction

Since the advent of filtered air handling systems in virtually all hospitals, epidemics of nosocomial *Aspergillus* pneumonia among immunocompromised patients have been due to one of two types of problems.

The first of these is an overloading of the filtering mechanism by an excess load of *Aspergillus* conidia from an external source (Table 7). In two epidemics (34, 36) it was found that pigeons and other birds were not screened from access to air inlet ducts and heavily contaminated these areas with droppings rich in *Aspergillus*. In another epidemic (40) a malfunctioning exhaust system allowed the filtering mechanism to be bypassed. In yet another epidemic (42), construction of a road contiguous to the hospital apparently caused a large environmental contamination by *Aspergillus* which lead to contamination of the air intake filters.

Table 8

Internal Sources of Nosocomial *Aspergillus* Pneumonia

Arnow, et al: Am Rev Respir Dis 118:49, 1978	Renovation
Krasinski, et al: Infect Control 6:278, 1985	Renovation
Opal, et al: J Infect Dis 153:634, 1986	Renovation
Aisner, et al: JAMA 235:411, 1976	Fireproofing material

Additional nosocomial *Aspergillus* pneumonia epidemics have been due to sources within the hospital (Table 8). Even very good filtering systems do not remove all spores from the air (49). *Aspergillus* spores that enter the hospital gradually settle out leading to dust with high concentrations of fungus in air ducts and other sites that are not cleaned frequently. *A. fumigatus* does not grow in these areas, so the dust collections do not add fungus to the air until disturbed at which time they may produce a burst of airborne conidia. This event most commonly occurs during hospital renovation (38, 43, 44). Especially dangerous locals have been found to be the tops of the tiles used in false ceilings, and in one instance contaminated fireproofing material (37). If the potential for dissemination of fungi is recognized, isolation and cleaning procedures can be employed which obviate the risk of renovation.

Although all immunocompromised patients are at risk for *Aspergillus* pneumonia, it has been estimated that bone marrow transplant recipients have a 10-fold greater incidence than other immunocompromised patient populations (45). Even the very low exposure received in a well filtered hospital may not prevent disease in this type of patient. It has been demonstrated that reducing the spore count to near 0 with high-efficiency particulate air (HEPA) filtration is necessary to protect these patients (39, 45, 49).

CLINICAL ASPERGILLOSIS

Table 9

Clinical Aspergillosis

Aspergilloma
Hypersensitivity-induced Aspergillosis
1. Asthma
2. Allergic bronchopulmonary aspergillosis
3. Mucoid impaction of bronchi
4. Bronchocentric granulomatosis
5. Eosinophilic pneumonia
6. Hypersensitivity pneumonitis
Invasive Pulmonary Aspergillosis

In 1952 it was recognized that there are three types of diseases caused by *Aspergillus* (49). There is a saprophytic form manifested by a fungus ball, termed aspergilloma, growing within a body cavity. Second, there are several types of hypersensitivity reactions by the host to *Aspergillus* in the lungs. This form is also saprophytic in the sense that the fungus does not invade tissue. The third type of disease is an infection by the fungus which invades and destroys pulmonary tissue. These three types of disease will be described sequentially.

ASPERGILLOMA

A mycetoma is a ball of matted fungal mycelia lying free in a preformed, poorly drained lung space which communicates with the atmosphere. Mycetomas have occasionally been described with fungi other than *Aspergillus* (50-56), but these cases remain controversial (4). Thus the terms mycetoma and fungus ball are virtually synonymous with aspergilloma. The pre-existing cavity is apparently inoculated with inhaled conidia which grow from the bottom of the cavity along and up its sides (57). Pieces of the mycelia drop off and accumulate in the cavity along with serum and debris and gradually produce a ball which may be several centimeters in diameter. Within the ball there are both live and dead mycelia, and some of the latter may become calcified (58, 59). The walls of most cavities are lined by cylindrical or metaplastic squamous epithelium which may be thin or absent where it comes in contact with the fungal mass. Granulation tissue develops in areas lacking epithelium. The granulation may involve the more peripheral portions of the mycelia and thus incorporate parts of the fungus. This tissue also may contain numerous, markedly congested capillaries, the presence of which correlates with the finding of hemoptysis (60).

Table 10

Demographics of 218 Patients with Aspergillomas

Authors	No. Pts.	Dates of Series	Age (yrs) Avg.	Age (yrs) Range	Men	Women
Varkey and Rose	15	1964-74	54	40-76	15*	-
Faulkner, et al	42	1955-77	56	26-80	38	4
Rafferty, et al	23	1953-82	59	40-81	11	12
Jewkes, et al	85	1956-80	45	16-73	53	32
Daly, et al	53	1953-84	58	4-86	40	13
Total/Average	218	23 yrs	52	4-86	142*	61

*Not Included in Total (VA Hospital)

The demographics of patients who develop aspergillomas are reflected by 218 patients in five representive series (Table 10) (61-65). It is important to appreciate that virtually all series of this entity are retrospective reviews of cases occurring over many years. These series began in the 1950's or early 60's and spanned an average of 23 years. Patients are usually middle aged, but even children and octagenarians have been reported to have aspergillomas. About 70% of the patients are men; whether this represents a predilection of *Aspergillus* for men or a greater prevalence of cavitary lung disease among men is not clear.

Table 11

Underlying Pulmonary Diseases in 289 Patients with Aspergillomas

Disease	No. Pts.	Percent
Tuberculosis	98	34
Sarcoidosis	33	11
COPD	25	9
Abscess	20	7
Bronchiectasis	16	6
Other*	97	33

*None, Histoplasmosis, Silicosis, ABPA, Ankylosing Spondilitis, Congential Cyst, Cancer, Rheumatoid Arthritis, Pulmonary embolus, Other

The most common underlying pulmonary diseases are indicated for 289 patients reported in eight series (Table 11) (61-68). Healed tuberculosis with a residual cavity is the most frequently reported site of aspergilloma formation. In 1968 the Research Committee of the British Tuberculosis Association found that 11% of patients with healed tuberculosis and a persistent cavity 2.5 cm or more in diameter had an aspergilloma (69).

Follow-up two years later found that a few aspergillomas had disappeared spontaneously but that more new colonizations had occurred leading to 17% of patients having aspergillomas (70). However, the epidemiology of aspergilloma is changing. Tuberculosis is decreasing as an underlying site for mycetoma due to fewer cases and to better chemotherapy allowing less lung cavitation. Sarcoidosis may now be the most common underlying process (71, 72). Indeed, hemorrhage from aspergilloma is the second most common cause of death in patients sarcoidosis (72). Other frequently colonized lung spaces include bullous emphysema, residual cavities from lung abscess and bronchiectasis. However, virtually anything that causes an abnormally large lung space may be the site of a fungus ball.

Table 12

Most Frequent Symptoms Among
172 Patients with Aspergillomas

Symptom	No. Pts.	Percent
Cough with sputum	142	83
Hemoptysis	104	60
Dyspnea	46	27
Fever	30	17
Weight Loss	16	9

Varkey and Rose; Faulkner, et al; Rafferty, et al; Daly, et al; Nolan, et al; McCarthy and Pepys

Most patients with aspergilloma have chronic cough with purulent sputum production at some time during their illness (Table 12) (61-63, 65-68). Since most of these patients have some type of lung destruction, it is not clear whether the aspergilloma or the underlying disease leads to this symptom in most patients. Hemoptysis is the most frequent symptom clearly arising from the fungus ball. The incidence of this symptom in the various series ranges from 50 to 85% with an average of 60%. The hemoptysis ranges from blood streaking of sputum to brisk life threatening bleeding, usually defined as 600 mls in 48 hours. The occurrence of minor hemoptysis does not necessarily lead to more marked bleeding, nor does gross or life threatening hemoptysis invariably recur after the initial episode has abated. It is not clear if the hemoptysis is due to mechanical effects of the fungus ball on granulation tissue or if mycotoxins are involved. However, the bleeding site is clearly the granulation tissue which is supplied by bronchial and systemic arteries. The rate of growth or size of the fungus ball does not predict minor or overt hemoptysis. Thus a patient may have the onset of life threatening hemoptysis without sentinel blood streaking of the sputa.

A substantial fraction of patients also have dyspnea, which is related to the severity of the underlying disease. Episodes of fever occur in a small fraction and is thought to be due to superimposed bacterial infection.

Others have weight loss which is probably not directly related to the fungus ball.

Figure 4

The Radiographic Appearance of a Mycetoma

A mycetoma is usually suspected because of the radiographic appearance of a solid, rounded mass of water density within a spherical or ovoid cavity (Figure 4) (73). The mass is separated from the wall of the cavity by a crescent-shaped air space. This lesion appears much more commonly in upper than lower lobes and is bilateral in a substantial fraction of patients. The cavity may be thin-walled with little surrounding parenchymal lung disease, termed a simple aspergilloma, or thick-walled with substantial surrounding parenchymal disease, termed complex aspergilloma (65). Calcification of the mass may occur as scattered nodules, as a fine rim around the periphery or involving virtually the entire ball. Although the mass and air crescent appearance is frequently considered diagnostic, it is sometimes caused by a blood clot, necrotic lung abscess, bronchogenic carcinoma or tuberculoma. In endemic areas, hydatid disease is the most common cause of the air crescent sign (74). Since aspergillomas usually lie free within the cavity, decubitus radiographs frequently reveal a shift of the mass to the dependent side, a finding which may help separate a fungus ball from other etiologies.

Table 13

Use of Sputum Culture and Serum Precipitins in the Diagnosis of Aspergilloma

Sputum Cultures			Serum Precipitins		
No. Cult.	No. Pos.	Percent	No. Done	No. Pos.	Percent
237	172	73	76	63	83

Varkey and Rose; Faulkner, et al; Rafferty, et al; Daly, et al; McCarthy and Pepys; Kilman, et al; Reddy, et al; Garvey, et al; Soltansadeh, et al; Hargis, et al

Sputum cultures and serum precipitins may be useful in the diagnosis of aspergilloma (Table 13) (61-63, 65, 67, 75-79). Among 237 patients with aspergilloma who had sputum cultures, *Aspergillus* was recovered in 73%. When one sputum is positive the organism can usually be recovered from multiple sputa. Thus, sputum cultures are moderately sensitive. Since the organism can be recovered from the sputa of patients who apparently do not have aspergillosis 4 to 7% of the time (32, 80), its finding is not absolutely specific.

Serum precipitins against *Aspergillus* antigen are present in almost 85% of cases. Indeed, some investigators (67) believe that precipitins are necessary to make the diagnosis. Other syndromes of aspergillosis may also have precipitins in serum but in a much smaller fraction of patients.

Table 14

Therapy for Patients with Aspergillomas

Medical Therapy
- Supportive care
- Amphotericin B

Bronchial Artery Embolization

Surgical Resection

Aspergillomas may increase in size, regress, or remain stable for many years. Spontaneous lysis occurs in up to 10% of cases (70, 81). Although invasive aspergillosis has been reported to result from a mycetoma (63, 82), this event is sufficiently rare that therapy of most patients is not dictated by this potential. The primary indication for therapy is the extent of hemoptysis (83).

Medical therapy between episodes of hemoptysis is directed at the underlying disease process and may involve antimicrobials for apparent superinfection with bacteria, corticosteroids for patients with sarcoidosis or allergic bronchopulmonary aspergillosis and bronchodilator drugs for patients with airway disease. During episodes of hemoptysis medical therapy may include cough suppression, blood transfusions when indicated and general supportive care. Even in patients with brisk hemoptysis, the bleeding usually subsides in a few days. Amphotericin B has also been used by many clinicians. There are virtually no well documented cases of lysis of a mycetoma or cure of hemoptysis with systemic administration of this antifungal agent. Direct intracavitary installation of Amphotericin B has also been attempted. Some patients tolerate this procedure poorly with fever and other systemic symptoms, and the procedure rarely leads to disappearance of the mycetoma. However, a recent study reports improvement in four of five patients when a total dose of 500 mg of Amphotericin was instilled percutaneously (76). It would be reasonable to attempt this form of therapy in patients with recurrent hemoptysis who are unable to tolerate resectional surgery.

In patients with life threatening hemoptysis whose pulmonary function precludes resectional surgery embolization of bronchial arteries may alleviate the bleeding (84). Among all patients with gross hemoptysis this procedure is successful about 85% of the time. However, in patients with aspergilloma the success rate is only about 65%. Further, among all patients who are successfully treated recurrent hemoptysis occurs in about 15%; recurrence of bleeding in patients with aspergilloma is about 75%. This less satisfactory result for mycetoma is due to the fact that the granulation tissue in the wall of the cavity is frequently supplied not only by bronchial arteries but also by the axillary and subclavian arteries by way of pleural adhesions. Thus, bronchial artery embolization is reasonable in patients who are not surgical candidates and whose hemoptysis continues on medical therapy, but the procedure is not successful in a substantial fraction of patients.

Surgical resection of the segment or lobe which contains the aspergilloma is considered the procedure of choice for massive hemoptysis in patients who can withstand the surgery. This recommendation is not controversial. However, there is considerable disagreement about which other patients should be operated. Some physicians advocate resectional surgery for patients with any degree of hemoptysis, and others believe all patients with aspergilloma should be operated to prevent potential episodes of fatal hemoptysis. This issue can best be addressed by comparing medical and surgical therapy in patients followed for a protracted interval.

Table 15

Medical Versus Surgical Therapy
for 189 Patients with Aspergillomas

Author	Medical Therapy		Surgical Resection		
	No. Pts.	Dead from Hemoptysis	No. Pts.	Op. Death	Complications
Varkey and Rose	10	0	5	1	2
Faulkner, et al	31	1	11	1	1
Rafferty, et al	21	3	2	1	1
Jewkes, et al	36	3	41	3	6
Solit, et al	19	4	13	0	5
Total	117	11 (9%)	72	6 (8%)	15 (21%)

When comparing patients who received nonspecific medical therapy with those who received surgical resection (Table 15), it is once again important to realize the limitations of these largely retrospective series collected over long intervals. Perhaps the most serious deficiency is the variable length of follow-up which may bias the results in favor of medical therapy. That is, patients may have died from massive hemoptysis months or years after last being seen by the authors, whereas all surgery operative deaths are reported. Conversely, patients treated medically usually had more severe underlying disease which prevented them from being surgical candidates and adversely affected their survival. Nevertheless, these data are the best available.

The number of medically treated patients dying of massive hemoptysis is approximately the same as the number of patients receiving surgical resection who died postoperatively. Moreover, surgery is associated with a high incidence of postoperative complications (65, 85, 86). These complications are frequently severe and disabling such as empyemas, continued air leaks and residual air spaces which may require additional surgery including thoracoplasty. Considering these data, it seems reasonable to operate patients with simple aspergilloma with good lung function for any episode of gross hemoptysis, but patients with complex aspergillomas and borderline lung function should be operated only for episodes of life threatening hemoptysis. Prophylactic surgery is not indicated.

HYPERSENSITIVITY-INDUCED ASPERGILLOSIS

Table 16

Hypersensitivity-Induced Aspergillosis

Asthma
Allergic Bronchopulmonary Aspergillosis
Mucoid Impaction of Bronchi
Bronchocentric Granulomatosis
Eosinophilic Pneumonia
Hypersensitivity Pneumonitis

Aspergillus may cause or contribute to six types of hypersensitivity-induced syndromes (Table 16). Only one of these, allergic bronchopulmonary aspergillosis (ABPA), will be discussed in detail. Two other syndromes, mucoid impaction of bronchi and bronchocentric granulomatosis, will be discussed only as they overlap with ABPA. Two syndromes, eosinophilic pneumonia and hypersensitivity pneumonitis, will not be dealt with further.

Asthma

Table 17

Prevalence of Sensitization to *Aspergillus* Antigens
Among Asthmatic Patients

Site	Prick Test Reactivity			Serum Precipitins		
	No. Pts.	No. Pos.	% Pos.	No. Pts.	No. Pos.	% Pos.
Cleveland	93	26	28	93	7	8
London	100	23	23	76	8	11
Montreal	200	43	22	-	-	-
Cape Town	299	97	32	58	13	22
Singapore	76	9	12	-	-	-

Schwartz, et al; Malo and Paquin; Benatar, et al; Lim, et al.

As previously indicated, *Aspergillus* has a world wide distribution, and the conidia of this fungus are inhaled by persons everywhere. Several studies have indicated that some asthmatic patients develop immediate hypersensitivity to *Aspergillus* antigens (Table 17) (87-90). A skin prick test which introduces an antigen into the epidermis leads to a wheal and

flare reaction within 20 minutes in persons who have immediate hypersensitivity to the antigen. Asthmatic patients who had demonstrated hypersensitivity to at least one antigen were studied for additional reactivity to *Aspergillus* in Cleveland, London, Montreal and Cape Town. In North American and England similar rates of 21 to 28% of hypersensitivity to *Aspergillus* were found, and in Cape Town a slightly higher reactivity rate was noted. These latter patients were a more selected population by virtue of being referred to specialists for severe asthma. In the Singapore study it is not clear whether the patients tested for *Aspergillus* included all patients with asthma or, as in the other studies, only patients who had hypersensitivity reactions to other antigens. Thus, the lower reactivity rate to *Aspergillus* may be due to testing a different patient population. Serum precipitins were infrequent except in the Cape Town study.

In the first four studies patients who reacted to *Aspergillus* tended to have the onset of their asthma during childhood, to be more broadly allergic to other antigens, to have additional manifestations of allergy other than asthma, and to have more severe airways obstruction. Thus, *Aspergillus* may be one of several antigens to which an allergic asthmatic is sensitive and may precipitate both immediate and delayed asthmatic attacks (91, 92). Moreover, these patients are at risk for developing the syndrome of allergic bronchopulmonary aspergillosis.

Allergic Bronchopulmonary Aspergillosis

Perhaps the best, and certainly the most current, definition of allergic bronchopulmonary aspergillosis is that of Greenberger (93). "Allergic bronchopulmonary aspergillosis is a complication of asthma which results in transient roentgenographic infiltrates often in the upper lobes, proximal bronchiectasis, and a clinical course that can vary from remission to end-stage fibrotic lung disease". Greenberger also notes "ABPA is indolent and has clinical and laboratory features that are not specific in that many features of this condition that are used in diagnosis also occur in patients with asthma without ABPA". Thus, his definition recognizes the controversy concerning diagnostic criteria that has existed since the entity was described in 1952 (49). Indeed, many of the major series of ABPA devote considerable discussion to the diagnostic criteria (94-104).

Table 18

Symptoms Among 256 Patients with ABPA

Asthma
Cough with mucopurulent sputum
Sputum plugs
Hemoptysis
Febrile episodes
Chest pain

Henderson; McCarthy and Pepys; Safirstein, et al; Khan et al; Radha and Viswanathan

The symptoms experienced by patients with ABPA have varied considerably in different series (Table 18) (94-96, 99, 100, 104). All patients have asthma, most commonly with an early age of onset. The asthma may have existed for years before the onset of other symptoms. Although ABPA may occur at any age, more recent series report a substantial fraction of patients with onset as young adults. Most patients have cough with mucopurulent sputum production; in some it is continuous while in others intermittent. Many patients expectorate sputum plugs. These are casts of bronchi which sometimes have a brownish discoloration on one end. On microscopic examination, the discoloration is due to *Aspergillus* hyphae. About half of patients with ABPA have episodes of hemoptysis which is usually only blood streaking of sputum. About half of patients also have febrile episodes associated with radiographic infiltrates which are not due to bacterial infection. A small fraction of patients have chest pain in association with these episodes. In some it is described as pleuritic, whereas in others the character suggests chest wall pain.

The diagnosis of ABPA is suggested by the finding of a radiographic abnormality typical of this syndrome in an asthmatic patient who may or may not have any of the symptoms indicated.

Table 19

Radiographic Manifestations of ABPA

Infiltrates
Consolidation
Parallel line shadow
Tram-line shadow
Ring shadow
Band (toothpaste) shadow
Perihilar infiltrates
Glove-finger shadow
Volume loss
Air fluid levels

McCarthy, et al; Malo, et al; Mintzer, et al; Phelan and Kerr; Mendelson, et al.

The radiographic manifestations of ABPA have been well described (105-109) and have been correlated with the pathological changes in the lung (Table 19) (49, 110, 111). These abnormalities are listed in the approximate order of their frequency with the most common first. Infiltrates are alveolar in type and are generally subsegmental in size. They may appear nodular up to about 1 cm in diameter with either well or ill-defined margins. Consolidation refers to water densities frequently involving an entire segment or lobe which characteristically do not contain air bronchograms. These two types of densities are due to an eosinophilic pneumonia of lung parenchyma. Changes of lipid pneumonia, lymphocytic interstitial pneumonia, desquamative interstitial pneumonia and vasculitis have also been reported. These types of infiltrates are acute reactions which resolve rapidly after the initiation of corticosteroid therapy.

Tram-lines are two parallel hairline shadows extending from the hili in the direction of bronchi. The width of the air density between the lines is that of a normal bronchus. Parallel line shadows are similar to tram-line shadows excepting that they are farther apart indicating a dilated, bronchiectatic airway. Histologically the bronchial walls are inflammed with a mixed cellular infiltration of lymphocytes, plasma cells, eosinophils, and occasional neutrophils. Granulomas are sometimes seen. Although *Aspergillus* hyphae may sometimes be seen in the bronchial lumens, the fungus does not invade the bronchial wall. Ring shadows are round water densities of the same width of tram-lines with the diameter of the central air lucency similar to the distance between either tram-lines or parallel lines. These represent thickened bronchial walls of either normal sized or dilated bronchi. Lines and rings of normal bronchial diameter may disappear completely with therapy, while lines and rings of abnormally large diameter indicate permanent, central bronchiectasis.

Band, or toothpaste, shadows represent dilated bronchi filled with inspissated mucus containing Curschmann's spirals, Charcot-Leyden crystals, mononuclear cells, eosinophils, and fibrin. Glove-finger shadows are similarly dilated bronchi which are filled with secretions with additional dilatation of their distal branches. These types of shadows are often transient and clear if the patient coughs vigorously. After clearing, parallel line shadows may sometimes remain in the evacuated area.

Perihilar shadows are secondary to peribronchial infiltrates surrounding dilated central bronchi which are filled with secretions. Their appearance may occasionally simulate hilar adenopathy. Volume loss is frequent in areas of consolidation and in areas of permanent interstitial infiltrates which are due to pulmonary fibrosis. Air fluid levels sometimes occur in dilated bronchi.

The changes indicated may be unilateral or bilateral, and several may exist concurrently in the same radiograph. There is a tendency for most changes to occur more frequently in upper lung zones, but they may be seen in any part of the lung.

The bronchiectasis indicated by parallel line and large ring shadows and by large band and glove-finger shadows is distinctive for ABPA. The dilated bronchi are central in location and taper distally to a normal bronchial diameter. Small airways are normal. This is in contradistinction to the usual form of bronchiectasis in which the distal airways are totally destroyed and proximal airways end abruptly. The characteristic findings may not be present on standard radiographs even when bronchiectasis is present. Bronchograms were formerly used to demonstrate these lesions, but bronchography in patients with asthma may lead to serious bronchospasm. Tomography is now used to demonstrate the characteristic bronchiectasis; it is considered more sensitive for this purpose than CT scanning (112). Although some investigators still demand the presence of central bronchiectasis to make the diagnosis of ABPA, Patterson and his group have argued that this requirement necessitates permanent lung damage and that earlier disease may be diagnosed by a combination of clinical and laboratory findings (113).

Table 20

Diagnostic Criteria of ABPA

Criteria	Comments
1. Asthma	Severity variable
2. Radiographic infiltrates	May be absent at time of diagnosis
3. Peripheral eosinophilia	May be absent in patient on corticosteroids
4. Immediate cutaneous reaction to *Aspergillus*	Prick or intracutaneous test
5. Elevated total serum IgE	>1000 ng/ml unless in remission
6. Precipitating antibodies to Af	Unless suppressed by steroids, sera may require 5-fold concentration
7. Elevated IgE-Af and IgG Af	IgE Af $\geq$ 2 X sera of asthmatics
8. Central bronchiectasis	Yes, sine *qua non* of classic ABPA

Greenberger and Petterson: Ann Allergy 56:444, 1986.

The diagnostic criteria of ABPA continue to be debated in numerous review articles (4, 5, 114-124). The criteria presented here are those of the Northwestern Medical School group (93, 125) which has performed the greatest number of investigations and followed the largest number of patients in North America (Table 20).

All patients with ABPA have asthma, although in many it is not very severe. Many patients are very atopic with seasonal allergic rhinitis and conjunctivitis, food allergies and drug hypersensitivity (125). However, a few patients have few manifestations of allergy. Radiographic infiltrates occur at some time in the course of ABPA, but they may be absent at the time of the initial diagnosis. Peripheral eosinophilia in the range of 8 to 40% is the usual finding but may be absent in patients on corticosteroids. Since eosinophilia is common in patients with allergic asthma without ABPA, it is not very specific for this syndrome. All patients exhibit an immediate cutaneous reaction to *A. fumigatus* or mixed *Aspergillus* antigen (96, 101). Prick tests are as satisfactory as intradermal injections for demonstrating immediate reactions (126). Arthus-type (3 to 5 h) reactions occur in about 25% of patients with ABPA (97). This phenomenon is not as likely following prick as intradermal testing. Since this finding is an insensitive index of ABPA, and since some patients may experience anaphylaxis from intracutaneous injections (120), a prick test is considered preferable.

A markedly elevated total serum IgE is usually present at the time of diagnosis, sometimes reaching levels of 40,000 ng/ml (normal approximately 300 ng/ml) (127-129). Following six to eight weeks of Prednisone there is at least a 35% decline in total serum IgE (129). Thus, IgE concentrations may not exceed 1000 ng/ml in patients in remission or in patients who have been treated with Prednisone for asthma. Further, increases of 100% or more

in total IgE often precede the development of new radiographic infiltrates (130). Since about one-third of patients with radiographic infiltrates from ABPA are asymptomatic (99), the periodic measurement of total serum IgE may be used to diagnose exacerbations of disease.

A classic laboratory feature of ABPA is precipitating antibodies to *Aspergillus* in the serum, which may be IgG, IgM or IgA (96, 131, 132). It may be necessary to concentrate the serum 5-fold to detect these antibodies, and they may be absent following Prednisone administration (133). It should also be recalled that at least 85% of patients with aspergilloma and approximately 10% of patients with asthma who are hypersensitive to *Aspergillus* may also have precipitating antibodies; thus, this finding is not specific for ABPA. Class-specific antibodies against *Aspergillus* have been identified for IgE, IgG, IgA, IgM and IgD (128, 134-138). The sera from patients with ABPA have at least two and often as high as ten to twenty times the IgE and IgG antibody activity to *A. fumigatus* as do sera from asthmatics who are prick positive to *A. fumigatus* but who do not have ABPA. The peak in serum IgE-Af may occur several months after the radiographic infiltrate (133). Conversely, serum IgG-Af peaks at the time of the radiographic infiltrate.

Central bronchiectasis is the sine *qua non* of classic ABPA. The Northwestern group, however, suggests that the diagnosis of ABPA-S (sera) be utilized if the first seven criteria are compatible with ABPA. If all eight criteria are compatible, the suggested term is ABPA-CB (central bronchiectasis).

Criteria which have been considered necessary for the diagnosis by some include a dual bronchial response following inhalation of *Aspergillus*, and production of sputum plugs harboring *Aspergillus*. The former may lead to very severe asthma in some patients, and the latter is not present until permanent lung damage has occurred. Thus, they are not considered essential for the diagnosis.

Table 21

Laboratory Findings in Different Stages of ABPA

Stage	Total Serum IgE	Precipitating Antibody to AF	Peripheral Eosinophilia	Serum IgE-Af	Serum IgG-Af
I (Acute)	+++	+	+	+	+
II (Remission)	+	+/-	-	+/-	+/-
III (Exacerbation)	+++	+	+	+	+
IV (Corticosteroid Dependent Asthma)	++	+/-	+/-	+/-	+/-
V (Fibrotic)	+	+/-	-	+/-	+/-

Greenberger: Pulm Crit Care Update 3:1, 1987.

The Northwestern group has described five stages of allergic bronchopulmonary aspergillosis (Table 21) (113, 130). These stages are not considered as phases of the disease, since patients do not necessarily progress from Stage I to V. Stage I, acute disease, refers to patient with all of the classic features of ABPA. Total serum IgE is markedly elevated, and precipitating antibodies to *Aspergillus*, peripheral eosinophilia and isotypic IgE and IgG antibody to *Aspergillus* are present. Most of the total serum IgE is not explained by antibodies to *Aspergillus*. However, compared to sera of patients with asthma, ABPA is associated with marked elevations in serum IgE-Af. Patients with acute disease treated with corticosteroids have a decline in total serum IgE of at least 35% by six weeks, and other symptoms resolve. Stage II, remission, indicates no return of radiographic infiltrates for at least six months after Prednisone has been discontinued. The total serum IgE stabilizes, usually at an elevated level. Similarly, the other laboratory features decrease in intensity or return to normal. Some patients enter a permanent remission while others ultimately exacerbate. One patient was followed in remission for seven years before an exacerbation occurred (139).

Stage III, exacerbation, occurs when a new radiographic infiltrate is associated with at least a 100% rise in total serum IgE. Since many patients are asymptomatic despite radiographic changes, and since some exacerbations are indicated only by an increase in serum IgE, patients in Stage II are followed by repeated measurement of total serum IgE. During exacerbation the other laboratory features previously present also recur.

Some patients develop corticosteroids-dependent asthma after the diagnosis of ABPA is made, Stage IV (140, 141). Total serum IgE is usually elevated, although usually less than in acute or exacerbation phases. Other laboratory tests may or may not be positive, but isotypic IgE and IgG antibodies are commonly elevated compared to that seen in patients with asthma but without ABPA. The dose of oral steroids used for prevention of asthma may or may not prevent additional episodes of ABPA.

Stage V, fibrotic ABPA, is characterized by irreversible obstructive and restrictive pulmonary abnormalities and extensive fibrosis on chest x-ray (142, 143). The total serum IgE may be elevated in some patients, and some may continue to have precipitating or isotypic antibodies in their serum. Clinical features may include those of other end stage lung disease such as chronic sputum production, weight loss, clubbing, arterial hypoxemia and hypercapnia.

Although partially conflicting, recent studies of immunoglobulins obtained from the lung of patients with ABPA by bronchoalveolar lavage (BAL) (124, 144, 145), suggest that there is pulmonary production of IgE-Af and IgG-Af but not IgA-Af. The ratio of total IgE in BAL is not increased over peripheral blood, an observation consistent with the hypothesis that the lung produces antigen-specific antibodies to *Aspergillus* (IgE and IgA) but different mechanisms control the production of total serum IgE. In addition to the various isotypic antibodies produced and the high concentration of total serum IgE, basophils from patients with ABPA have marked hyperreactivity to *A. fumigatus* compared to basophils from asthmatics (126). Basophils from patients in Stages IV and V also have greater *in vitro* histamine release to *A. fumigatus* than basophils from patients in Stages I-

III. If bronchial mast cells function analogously, pulmonary destruction might occur due to greater mast cell degranulation and release of inflammatory mediators.

Table 22

Recommended Therapy for ABPA

1. During acute episodes Prednisone 0.5 mg/kg daily X 14 days, then on alternate days X 3 mos., then d/c unless needed for asthma
2. Total serum IgE every 1-2 mos.
3. Continuing outpatient management
   a. For control of asthma
   b. For detection of exacerbation by doubling of IgE and radiographic infiltrate

Patterson, et al: Arch Intern Med 146:916, 1986.

The Northwestern group has proposed a protocol for the therapy of ABPA (Table 22) (113, 125, 146). For treatment of patients in Stages I (acute) or III (exacerbation) Prednisone 0.5 mg/kg is given as a single daily dose for 14 days and then converted to alternate day therapy for an additional three months. It is then tapered and discontinued unless it is needed for therapy of the patient's asthma. Total serum IgE is then measured every one to two months for a year, since exacerbations of ABPA may not produce clinical symptoms and this measurement may be the only indication of abnormality. The IgE may remain elevated during this interval, and higher doses of steroids will not cause a return to normal. Patients are treated with usual asthma therapy and may sometimes require steroids in the absence of an exacerbation of ABPA. It is also suggested that chest roentgenograms be contained every three to six months during the first year of follow-up and on a yearly basis thereafter. Patterson and his colleagues indicate that utilizing this approach they have had no patients progress to Stage V disease under their observation.

There are no data which indicate that the patient should be advised to move to some other area of the country where molds may be less prevalent. It is reasonable, however, to advise the patient to avoid occupations or hobbies which lead to very intense exposure to *Aspergillus*.

Mucoid Impaction of Bronchi

It has long been known that patients dying of asthma virtually always have obstruction of major bronchi by viscid mucocellular casts (146a). In 1951, however, Dr. Robert Shaw of this institution described a new syndrome of inspissated mucus secretions in living patients which he termed mucoid impaction of the bronchi (147). He noted that "Mucoid impaction of the bronchi results from a localized accumulation of inspissated mucus in the bronchi. Typically, this impaction occurs in the second order branch

bronchi distal to a bifurcation. The impaction grows in size, layer by layer, in a laminated manner to finally dilate the bronchus in which it lies to many times its normal diameter". Dr. Shaw and his co-workers have subsequently twice added patients to the original series (148, 149) and have described the pathologic findings in detail (150). By 1968 128 cases had been described from various parts of the world (151). An additional 300 patients with a condition termed plastic bronchitis, which may or may not be an identical syndrome (152, 153), have been reported primarily from Great Britain.

Table 23

Clinical Features of Mucoid Impaction of Bronchi in 119 Patients

	No. Pts.	%
Asthma, bronchitis	96	81
Productive cough	79	66
Hard plugs or casts	40	34
Fever	43	36
Chest pain	36	30
Hemoptysis	31	26
Asymptomatic	7	6

Urschel, Paulson and Shaw: Ann Thorac Surg 2:1, 1966.
Morgan and Bogomoletz: Thorax 23:156, 1968.

The clinical features of mucoid impaction of the bronchi are similar in the two largest series (Table 23) (149, 151). About 80% of patients have either asthma or bronchitis. The underlying disease may start at any age, and there is no predilection for men or women. Most patients have a cough productive of mucoid or mucopurulent secretions. About a third of patients report coughing up hard plugs or casts of bronchi. About a third also have episodes of fever and chest pain in association with the radiographic abnormalities that lead to diagnosis. About one-quarter have episodes of hemoptysis consisting of blood streaking of sputum; massive hemoptysis has not been reported. An occasional patient may be entirely asymptomatic at the time a radiographic abnormality is noted.

Table 24

Radiographic Manifestations of MIB

Most frequently upper lobes
Lesions may be elliptical, rounded or oval with smooth marginations
Frequently V or Y shaped with the apex toward the hilus
A combination of the above with atelectasis, alveolar infiltrate or cystic bronchiectasis

Carlson, et al: Am J Radiol 96:947, 1966.

In a patient with asthma the diagnosis of MIB may be strongly suspected because of the characteristic radiographic manifestations (Table 24) (154). Although the lesions may appear in any part of the lung, they are most frequently located in upper lobes. The lesions may be elliptical, rounded or oval, and usually have smooth margins. The inspissated mucus almost always occurs in segmental and contiguous subsegmental bronchi. Thus, the lesions are central and frequently are V or Y shaped with the apex toward the hilus. The bronchial obstruction frequently leads to atelectasis, an alveolar infiltrate or the air fluid levels of distal cystic bronchiectasis. When an alveolar infiltrate occurs, histology frequently reveals an eosinophilic pneumonia.

Table 25

Features Suggesting MIB is not Always ABPA

Twenty percent of MIB patients do not have asthma
Lack of peripheral eosinophilia in some patients
Serum precipitins to *Aspergillus* negative
MIB does not respond to corticosteroids

It is apparent that the clinical syndrome of mucoid impaction of bronchi is similar to that of allergic bronchopulmonary aspergillosis. To ensure that the two processes are different would require testing each patient with presumed mucoid impaction for peripheral eosinophilia, immediate cutaneous reaction to *Aspergillus*, elevated total serum IgE, precipitating antibodies to *Aspergillus*, and isotypic IgE and IgG antibodies to *Aspergillus*. No patient reported with MIB has been so tested.

Nevertheless, certain features suggest that mucoid impaction of bronchi is not always caused by allergic bronchopulmonary aspergillosis (Table 25).

Approximately one-fifth of patients with MIB do not have asthma. Although nonasthmatic patients have been diagnosed as having ABPA in the past, asthma is now considered an absolute criteria for this latter syndrome. Peripheral eosinophilia is also considered necessary for the diagnosis of ABPA in symptomatic patients who are not receiving steroids. Although most patients with presumed MIB in whom blood eosinophils are reported have eosinophilia, there are several reported patients who do not (155, 156). Several authors have performed *Aspergillus* prick tests on a fraction of their patients and found immediate hypersensitivity to be present. Others have grown *Aspergillus* from the sputum or resected surgical specimens from some patients. However, when serum precipitins to *Aspergillus* were sought in these patients, they were found to be absent (157-161). The Northwestern Medical School group notes that the serum may need to be concentrated by 5-fold in order to demonstrate *Aspergillus* precipitins in patients with ABPA, and there is no indication that such concentrations has been performed in patients with presumed MIB. Nevertheless, the absence of precipitins in unconcentrated serum is evidence against ABPA in these patients. A final feature suggesting that MIB may be separate from ABPA in some patients is the fact that MIB is said by virtually all authors to not respond to corticosteroid administration. There is no confirmation of this statement in most reports, but if it is correct, MIB may be clearly differentiated from ABPA. The most successful therapy for MIB is the injection every one to two hours of 3 ml of 5% Acetylcysteine into the affected bronchus by means of a tracheal catheter inserted through the skin into the second tracheal space below the cricoid cartilage (149, 158). This mucolytic agent rapidly softens the mucoid impaction so that it may be expectorated by the patient.

Bronchocentric Granulomatosis

In 1973 Liebow described another related syndrome which is distinguished by histological features (162). He and his colleagues subsequently reported additional cases and offered the following definition (163). Bronchocentric granulomatosis is a syndrome of bronchial destruction often associated with asthma, the presence of noninvasive fungi and mucoid impaction of bronchi. "The lesion consists of granulomatous replacement of bronchial mucus membrane, often with heavy eosinophilic reaction within and about the involved bronchi, and chondritis". The lesion has subsequently been reported by others predominately in association with ABPA (164-166).

Table 26

Clinical Features of Bronchocentric Granulomatosis

	Asthmatics (n=10)	Nonasthmatics (n=13)
Age, yrs (M, R)	22 (9-48)	50 (32-76)
Wheezing, cough	10	4
Systemic symptoms	3	9
Chest pain	5	1
Fever	4	3
Eosinophilia	9	2
Increased ESR	4/4	4/4
Aspergillus precipitins	3/7	0/4
Hyphae in tissue	9	0

Liebow: ARRD 108:1, 1973.
Katzenstein, Liebow, Friedman: ARRD 111:497, 1975.

Only 40% of Liebow's patients were asthmatics (Table 26) (163). These patients were typically adolescents or young adults who had a lifelong history of asthma. The nonasthmatic patients, however, tended to be middle aged or older. As would be expected, all of the asthmatic patients had the symptoms of wheezing and cough, but only 4 nonasthmatic patients had similar symptoms which began with the onset of bronchocentric granulomatosis. Other findings such as systemic symptoms, chest pain and fever were similar to those found in the other syndromes already presented. Ninety percent of the patients with asthma had eosinophilia, while the minority of nonasthmatic patients had this finding. In contradistinction to ABPA and MIB the erythrocyte sedimentation rate was elevated in all patients in whom it was measured. *Aspergillus* precipitins were found in a few of the asthmatic but none of the nonasthmatic patients. Fungal hyphae were seen in resected specimens in all except one patient with asthma but no nonasthmatics. Total serum IgE and isotypic IgE and IgG antibodies were not measured in any patient.

Table 27

Radiographic Manifestations of Bronchocentric Granulomatosis

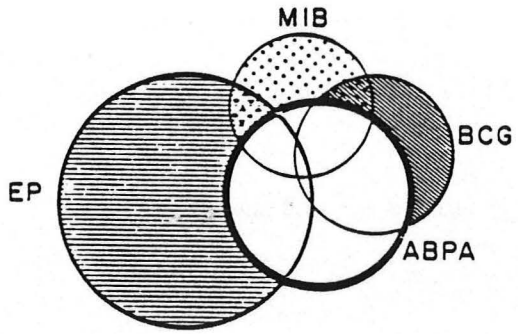
Consolidation, atelectasis or infiltrate of a whole lobe (22%) or less (70%)
One or more nodules >2 cm (22%)
Small nodules (<2 cm) with linear streaking (22%)
Cavities or dilated bronchi (26%)

The radiographic manifestations of bronchocentric granulomatosis are similar to those of ABPA and MIB, although pathological findings are less likely to reveal bronchiectasis or gross mucoid impaction (Table 27). About 20% of patients have consolidation, atelectasis or infiltrate of a whole lobe, while 70% have these findings on a segmental basis. About 20% of patients have one or more nodules larger than 2 cm in diameter. Smaller nodulation with linear streaking is seen in another 20%. Parenchymal cavities or dilated bronchi are noted in about a quarter of patients. These findings are unilateral in 75% of patients, and the upper lobes are involved twice as frequently as other lobes.

The patients with bronchocentric granulomatosis received no uniform therapy except for lung resection which allowed the histological diagnosis to be made. Three patients with asthma and one without asthma received corticosteroids with apparent benefit. No concerted follow-up studies were performed. A few patients had recurrent lesions, but the majority apparently had no further findings of this lesion.

Figure 5

Interrelationships of Hypersensitivity-Induced Pulmonary Aspergillosis



Katzenstein, Liebow, Friedman: ARRD 111:497, 1975.

Liebow and his associates have proposed the interrelationships between the hypersensitivity-induced pulmonary aspergillosis syndromes in a Venn diagram (Figure 5) (163). Allergic aspergillosis may be expressed as the lesions of allergic bronchopulmonary aspergillosis, mucoid impaction of bronchi, bronchocentric granulomatosis, or by the syndrome of the eosinophilic pneumonia which has not been discussed. Additionally, each of the syndromes except ABPA represent distinguishable types of tissue response to a number of agents of which hypersensitivity to *Aspergillus* is only one. Indeed, Liebow generated data to suggest that some cases of bronchocentric granulomatosis are due to *Candida albicans*, and lung biopsies of patients with rheumatoid arthritis may show a very similar lesion. Eosinophilic pneumonia is known to be caused by a wide variety of non-fungal agents (4). Further elucidation of the etiologies of these allergic responses awaits further investigation.

INVASIVE PULMONARY ASPERGILLOSIS

As indicated at the outset, aspergillosis has become a common cause of fungal infection with the highest death rate among all fungal diseases (1). The lung is involved in about 90% of *Aspergillus* infections, and it is the only site in about 70% (167).

Table 28

Predisposing Factors of Invasive Aspergillosis

Diseases or Conditions	Therapies
Hematopoetic malignancy	Cytotoxic agents
Lymphoreticular malignancy	Antilymphocyte sera
Other malignancies	Corticosteroids
Organ transplantation	Antimicrobials
Other immunodeficiencies	
Recent bacterial infection	
Granulocytopenia	

Invasive pulmonary aspergillosis has been especially associated with factors which suppress the immune response (Table 28). Among diseases predisposing to invasive aspergillosis, it has long been recognized that patients with hematopoetic or lymphoreticular malignancy are especially at risk. In two series from cancer services totaling 191 patients, acute lymphocytic and myelogenous leukemias accounted for 54% of patients, chronic lymphocytic and myelogenous leukemias 10%, and lymphoreticular malignancies 18% (168, 169). Thus, these malignancies were associated with over 80% of all invasive aspergillosis. Patients receiving organ transplantation, especially bone marrow transplants, are also at significant risk for

invasive aspergillosis, especially during episodes of organ rejection when immunosuppressive therapy is intensified (45, 170, 171). Indeed, any immunodeficiency syndrome is thought to predispose to this infection. It has also been reported that tissue damage caused by recent or concomitant infections, frequently due to *Pseudomonas aeruginosa* or *Candida albicans*, may predispose to *Aspergillus* infection by allowing easier fungal invasion of tissues (172, 173).

Both clinical and experimental evidence indicates that cytotoxic agents predispose to aspergillosis by inducing leukopenia, immunosuppression, and perhaps by augmenting gastrointestional entry of the fungus due to tissue toxicity (46, 168, 170, 174, 175). It has been suggested that anti-lymphocyte sera makes renal transplant patients especially prone to aspergillosis (176).

In experimental animals, corticosteroids enhance tissue invasion by and dissemination of *Aspergillus* (177). Steroids have also been thought to be important clinically (178, 179). However, patients with asthma due to *Aspergillus* hypersensitivity, ABPA and aspergillomas have been treated with steroids with few reports of tissue invasion. Further, patients with diseases which do not lead to immunosuppression but which are treated with prolong courses of steroids, such as asthma or idiopathic pulmonary fibrosis, have not been reported to develop invasive aspergillosis. Thus, it is not likely that steroids alone are a major factor in promoting this infection. Similarly, experimental models suggest that antimicrobials may contribute to the development of invasive aspergillosis (178), and these agents have frequently been implicated in clinical articles. However, it has been noted that antimicrobials are administered no more frequently to at-risk patients who do than to those who do not develop fungal infections (172, 180). Indeed, since almost all of these patients receive antibiotics several times during the course of their primary disease, it would be difficult to prove the association, and such proof would not impact clinical therapy.

The major phagocyte in defending against tissue invasion by *Aspergillus* is the polymorphonuclear leukocyte. Granulocytopenia is a major predisposing factor for infection and may be the common pathway for many of the other predisposing diseases and drugs (168, 169, 180, 181). Indeed, it has been demonstrated that the length of time that a patient with acute leukemia remains granulocytopenic is a major predictor of invasive pulmonary aspergillosis (180). For the first ten days of granulocytopenia, patients developed signs of infection at a rate of approximately 1% per day, but between the 24th and 36th days the rate was 4.3% per day. Phrased differently, of 13 patients who remained granulocytopenic for 28 days, 54% developed invasive pulmonary aspergillosis.

Only about 27 confirmed and 7 probable cases of invasive pulmonary aspergillosis have occurred in nonimmunocompromised, nonneutropenic hosts (182-184). Most of these patients were presumed to be normal by history and physical examination, but some also had extensive immunologic and phagocytic work-ups revealing no abnormalities. The only commonalities among these patients were that 4 were alcoholics and 5 developed pulmonary aspergillosis following influenzae A. Impaired granulocyte function due to alcoholic intoxication has been documented (185, 186), and may be relevant to these

patients. Patients with influenza may also have had phagocytic dysfunction. Although neutrophils are the major defense against hyphae, alveolar macrophages phagocytose conidia (187). It is known that these macrophages are poor phagocytes and killers following influenza (188).

Table 29

Pathology of Invasive Pulmonary Aspergillosis

Aspergillus bronchitis

Nodular lesions
- ≤3 cm in diameter with smooth or shaggy margins
- Small artery invasion by fungi
- Necrotic center with rim of hemorrhage
- May be multiple and confluent

Hemorrhagic infarctions
- Large, wedge shaped, pleural based
- Major artery invasion and thrombosis
- Usually no cavitation

Williams, Krick and Remmington: ARRD 114:359, 1976.
Orr, Myerowitz and Dubois: Cancer 41:2028, 1978.

The pathology of invasive pulmonary aspergillosis is important in considering the clinical and radiological findings in infected patients (Table 29) (168, 189, 190). The mildest form of infection is *Aspergillus* bronchitis. Inhaled conidia may lead to colonization and subsequent endobronchial proliferation of *Aspergillus* organisms. In the immunocompromised host this may result in superficial erosion and alteration of the bronchial mucosa. If the host is not severely immunocompromised, there may be no further tissue invasion. However, patients may not be able to contain the organisms in this locale, and invasion of surrounding lung parenchyma most commonly leads to two basic types of disease. Nodular lesions vary from microscopic up to 3 cm in diameter. The outer margins may be smooth or shaggy and thus may appear as nodules or infiltrates radiographically. An important property of aspergilli is invasion of blood vessels, and in nodules small arteries are invaded and thrombosed by the fungi. This results in a necrotic center surrounded by a rim of hemorrhage with sparse acute inflammation. In most patients with this lesion, there are multiple nodules which may be sufficiently dense to become confluent and appear radiographically as a large infiltrate.

The second basic lesion is a hemorrhagic infarction. These are large, wedge-shaped, pleural-based lesions which often include much of the involved lobe. These are due to invasion and thrombosis of a major pulmonary artery. The infarctions usually do not cavitate.

A few patients have a more typical purulent bronchopneumonia as seen with aerobic bacteria. Microscopically, however, *Aspergillus* hyphae are seen in the inflammatory infiltrate.

Table 30

Signs and Symptoms of Invasive Pulmonary Aspergillosis

Parameter	Criteria	Parameter	Criteria
Fever (^{o}F)		Granulocytopenic days	≥30
Admission	>101	Infiltrate	
Episodes w/o source	≥ 2	Day of onset	≥14
Days ≥ 100^{o}F	≥ 14	Type	Multilobed
During Rx	≥ 19	Cavity/nodule	Present
Pleuritic pain	Present		
Rales	Present		
Nasal/sinus abn	Present		

Gerson, et al: Am J Med. 79:57, 1985.

The signs and symptoms of patients with invasive pulmonary aspergillosis are sometimes helpful in suggesting the diagnosis (Table 30) (191). The table presents the data for a "discriminant scoreboard" for the diagnosis of invasive pulmonary aspergillosis recently published by Gerson, et al (191). The details of the use of this scoreboard will not be reviewed, but the features indicated were found to be suggestive of aspergillosis by these investigators. Initially, the only clinical evidence of infection may be an unremitting fever with or without a pulmonary infiltrate (169, 192). When there is no infiltrate the patient is thought to have *Aspergillus* bronchitis. Patients are likely to have *Aspergillus* who experience two or more episodes with oral temperatures of 100^{o}F or more, occurring over at least a 4-hour period on at least two consecutive days, and separated from a different febrile episode by at least 48 hours, and in whom no source is documented. The greater the number of days with fever during febrile episodes without a source, and the greater the number of febrile days while receiving antibacterial antibiotics, the greater the likelihood that the patient has aspergillosis.

Patients with a hemorrhagic infarction may have signs and symptoms suggesting a pulmonary embolus including the sudden onset of dyspnea, pleuritic chest pain, tachycardia, gallop rhythm, cough, and a pleural friction rub (168, 169, 192). There may be several such episodes. Since radiographic infiltrates develop slowly, these patients are often thought to have bland emboli. The presence of rales in the absence of a radiographic infiltrate is sometimes a helpful sign.

Since *Aspergillus* frequently colonizes nasal and sinus cavities, symptoms of these organs such as a nasal eschar or ulcer, or discharge with epitaxis, or sinus tenderness suggests aspergillosis.

Gerson confirmed the association between prolonged granulocytopenia and *Aspergillus* infection already noted. Although one study noted that infiltrates due to aspergillosis were usually present at time of hospital admission (169), the more usual finding is the development of infiltrates during hospitalization. Indeed, Gerson's group found that infiltrates frequently developed only after several days of hospitalization. The infiltrates tend to be multilobed, and many are cavitary or nodular. Infiltrates are frequently noted only in the last week of life, but in some immunocompromised patients the pneumonia may last for a protracted interval before death. In one series some patients had pneumonia for 19 to 43 days (168), and in another the median time from hospitalization to death was 22 days (193).

Table 31

CT Findings of IPA in 10 Patients with Leukemia

CT halo sign on early scans	8/9
Progression from multiple fluffy nodules or masses to cavitation or air crescents	5/7
Resolution similar to pulmonary infarct on extended follow-up	4/4
Occult IPA in patients with *Aspergillus* infected Hickman catheter sites	2/4

Kuhlman, et al: Chest 92:95, 1987.

Since the original report in 1977 (194), it has been repeatedly demonstrated that computerized tomography of the chest may be helpful in diagnosing invasive pulmonary aspergillosis (Table 31) (195-204). The most helpful finding is the CT halo sign which consists of a pulmonary mass or nodule surrounded by a zone or halo of attentuation less than the center of the mass but greater than air in the surrounding uninvolved lung tissue. In Kuhlman's study it was present in eight out of nine patients in whom early CT scans were obtained. The finding was present during the period of induction therapy when marked granulocytopenia existed. In one patient the CT scan lesion was too small to identify a definite halo. The CT halo sign was positive at a time when standard radiographic findings were nonspecific or questionably present, and it antedated other CT findings of IPA by one to two weeks. This finding is not completely specific, since it may also occur in patients with septic emboli due to aerobic bacteria.

Computerized tomography has revealed that the natural progression of nodules or masses is to cavitation in about half of patients, and of these about 85% demonstrate air crescents (199). The ball in the cavitation which leads to the crescent of air appearance is not a mass of hyphae as exists in aspergillomas. It is a ball of necrotic lung which is caused by the arterial invasion of fungus and subsequent infarction. Since the presence

of granulocytes is crucial for the formation of pulmonary cavitation in IPA, the air crescent sign actually implies improvement in the infection (199). Thus it tends to occur later in the course of the pneumonia than the CT halo sign, and frequently does not occur until after treatment has been started.

IPA heals in a pattern similar to resolving pulmonary infarcts (204). After the appearance of cavitation or air crescent formation, the lesions gradually become smaller by shrinking to ultimately form thin wall cysts with linear scars leading to the pleural surface (204). This finding, of course, is not helpful in early diagnosis.

It has also been noted that hematogenous spread of aspergillosis from remote sites of infection to the lung may be diagnosed earlier with CT than with standard radiographs. Thus, computerized tomography has added very significantly to the early diagnosis and management of invasive pulmonary aspergillosis.

Table 32

Potentially Useful Procedures
to Predict or Diagnose IPA

Sputum cultures
Nasal cultures
Serial serology
Fiberoptic bronchoscopy
Percutaneous needle aspiration
Open lung biopsy

Since *Aspergillus* grows well on laboratory media, it would be reasonable to believe that sputum cultures are a likely means of making a diagnosis of invasive pulmonary aspergillosis. Unfortunately, however, cultures are positive in only 8 to 37% of patient with *Aspergillus* infections (2, 168, 169, 205-207). Further, since *Aspergillus* may colonize the respiratory tract without causing infection, the specificity of a positive sputum culture is controversial (169, 189, 207-209). The best analysis of specificity is probably that recently reported by Yu, et al (210). These investigators indicate poor specificity for non-immunosuppressed patients but very good specificity for patients with neutropenia or leukemia. They believe that empiric Amphotericin B therapy, without the necessity for tissue diagnosis, should be considered for these patient subgroups.

The use of routine nasal cultures for *Aspergillus* has been reported to be helpful (211). Ten of 11 patients with positive cultures developed definite, and one of 11 probable, pulmonary aspergillosis. Conversely, only 8 of 114 patients without positive nose cultures had invasive disease. This group, therefore, suggests that when patients with positive nasal cultures develop clinical signs and symptoms of infection, they should be treated with Amphotericin B if invasive diagnostic procedures are contraindicated. On the other hand, a negative nose culture does not rule out invasive pulmonary aspergillosis.

Serological studies of a variety of types have given inconsistent results (208, 212-216). As a generality, the results are relatively specific but not very sensitive. The most promising tests appear to be radioimmunoassays for *Aspergillus* antigen rather than antibody detection by enzyme-linked immunosorbent or immunodiffusion assays. Unfortunately, each investigative laboratory produces its own *Aspergillus* antigen, and none is commercially available. The Parkland Serology Laboratory performs an immunodiffusion test against *Aspergillus* antibody.

Fiberoptic bronchoscopy (206, 217-224) utilizing bronchial brushing and washing is a modestly invasive procedure which can be carried out in most critically ill patients even in the presence of serious thrombocytopenia. If bleeding parameters are satifactory, transbronchial biopsy may also be performed with a modest increase in the diagnostic rate. An additional increment may be made by performing bronchoalveolar lavage through the fiberscope, a technique which adds little to morbidity (219, 225). An experimental study validated by two patients with invasive aspergillosis, suggested that radioimmunoassay of lavage fluid for *Aspergillus* antigen may add to the sensitivity of bronchoalveolar lavage (226, 227). Using these various fiberoptic techniques, specific diagnoses have been reported in from about 50 to 75% of patients. When only infectious diagnoses are considered, a sensitivity of 90% has been reported in one study (224).

If the radiographic lesion is localized and peripheral, fluoroscopically or CT guided percutaneous needle aspiration is probably the first procedure of choice. For such lesions fine needle aspiration is probably more sensitived than bronchoscopy, with a diagnosis rate of about 75% (228). Conversely, fine needle aspiration is not nearly so successful in patients with diffuse lung disease. The complications of percutaneous needle aspiration are hemoptysis, which is almost always mild, and pneumothorax. With the use of very small needles, the rate of pneumothorax is under 10% (229).

Thus, fiberoptic bronchoscopy or percutaneous needle aspiration frequently makes the diagnosis of IPA in immunocompromised patients with either localized or diffuse infiltrates. Since these patients are at risk for developing several types of opportunistic infections, and since these procedures may also be successful in diagnosing most of these, it is reasonable to believe that one or both of these should be the first invasive procedures performed in the immunocompromised patient.

The need for open lung biopsy in immunocompromised patients is controversial, and a complete analysis of the available data in this regard is beyond the scope of this presentation. A recent publication summarizes the results of previous series utilizing this and less extensive biopsy procedures and states the argument for early open lung biopsy (230): "A variety of infectious or noninfectious causes may be responsible, and an adequate sample of tissue must be obtained for histopathologic examination, stains, and cultures so that appropriate therapy can be started promptly. In our experience, open lung biopsy (OLB) is the most effective means of obtaining an adequate specimen". Other investigators (224, 231-234) and analysts (235) are less convinced about the utility of open biopsy compared

to less invasive procedures. Their arguments include the fact that sampling error has led to inadequate diagnoses in some open biopsies, and more importantly that the knowledge of the specific diagnosis frequently has not led clinicians to change therapy and has not resulted in improved patient survival. Most recent series of febrile, immunocompromised patients have found the less invasive techniques to be satisfactory in most patients and have reserved open lung biopsy for selected problem cases.

Table 33

Factors Influencing Therapy for Invasive Aspergillosis

Incidence in patients with leukemia	14-23%
Antimortem diagnosis	20-78%
Usually reported survival rate	0-35%
Patients receiving Amphotericin B	~39%
Survival of treated patients	<30%

When considering an approach to patients with potential aspergillosis, there are certain factors which influence one's decision concerning therapy (Table 33). Invasive aspergillosis is a relatively frequent infection in immunocompromised patients. Its incidence in patients with leukemia is from 14 to 23% (211, 236, 237), and it is probably similar in all patients with profound granulocytopenia. Although more recent series indicate a trend for earlier diagnosis, the range for antimortem diagnosis is still only 20 to 78% (208, 211, 236-239). This depressing statistic indicates both a lack of awareness of the frequency of fungal infection in immunocompromised patients and the difficulty in making a definite diagnosis during life. This statistic alsopredicts the usually reported survival rates of 0 to 35% (168, 169, 193, 205, 208, 236, 238, 240). When one reviews these series, it is found that only about 30% of patients receive Amphotericin B therapy. However, the survival of treated patients is also less than 30%. Until December, 1987, the highest reported survival was 66% in 9 patients (239). These data suggest that a very aggressive approach to therapy is necessary if survival rates are to be improved.

Table 34

Infectious Complications in 50 Granulocytopenic Patients with FUO's Treated 7 Days with Antimicrobials Keflin, Gentamicin and Carbenicillin (KGC)

Group	No. Pts.	Infections Bacterial	Infections Fungal	Median Onset	Infect Deaths	Asper. Deaths
1. D/C KGC	16	8	1	d 10	2	0
2. Continue KGC	16	1	5*	d 15	3*	2
3. KGC & Amp B	18	0	1*	d 42	2*	0

**Petriellidium boydii*, Cytomegalovirus

Pizzo, Robichaud, Gill and Witebsky: Am J Med 72:101, 1982.

Many groups inititate empiric broad-spectrum antibiotics immediately following an expeditious evaluation of the febrile patient with granulocytopenia, since bacteria are responsible for the majority of acute infections that can be defined. However, the cause of infection cannot be defined in about half of these patients, and many continue febrile despite a week of antimicrobials. At that juncture the clinician must decide whether to continue the antimicrobials, and a fungal infection must be considered. Because of reports suggesting more satisfactory treatment of fungi when Amphotericin B is started early (240, 241), some clinicians begin this drug for the continued fever. To determine the most rational course of therapy, the infectious complications in 50 granulocytopenic patients with fever of undetermined origin who had been treated for seven days with broad spectrum antimicrobials and who remained febrile at seven days were studied by the Pediatric Oncology Branch of the National Cancer Institute (Table 34) (242). In one group of 16 patients the antimicrobials were discontinued at day 7. Eight of the patients developed bacterial infection, on average within three days. In a second group of 16 patients the antimicrobials were continued, and bacterial infection occurred in only one. However, five of these patients developed a fungal infection, on average by day 15. In a third group of patients who remained febrile at 7 days, the antimicrobials were continued, and Amphotericin B at 0.5 mg/kg daily was administered empirically. In these patients neither bacterial nor fungal infections were common. The one fungal infection that occurred in Group 3 was due to an organism routinely resistant to Amphotericin. The total number of patients dying due to *Aspergillus* infection was two of 50 (4%). These data were supported by additional analysis of the patients whose original infection was of a proven bacterial etiology and by postmortem examinations performed in patients at their institution. An aggressive approach to antifungal therapy has also been taken by other groups with the most impressive results published in December, 1987 (243).

Table 35

Intensive Treatment of Invasive Aspergillosis

Regimen	No. Pts/ No. Survivors (%)	Rx Before of After IA Days $\bar{M}$ (Range)		Dose mg, $\bar{M}$
Empiric Amp-B	10/11 (91%)	18 (3-62)	Before	578
Therapeutic Amp-B				
Low Dose (0.5 mg/kg/d)	0/1 (0%)	62 --	Before	2237
High Dose (1.0-1.5 mg/kg/d)	4/4 (100%)	2 (1-4)	After	2250
High Dose + 5 FC	9/10 (90%)	2 (0-8)	After	2086
Overall survivors	13/15 (87%)			

Burch, et al: J Clin Oncol 5:1985, 1987.

The group at the Johns Hopkins Oncology Center has reported an 87% survival rate in 15 patients with invasive aspergillosis who were treated with an extremely aggressive regimen of antifungal agents (Table 35) (243). Eleven of their patients had received Amphotericin B, 0.5 mg/kg/d, for fever which was unresponsive to antibacterial antimicrobials. In one of these patients the diagnosis of invasive aspergillosis was missed, and the patient died after 62 days and 2,237 mg of Amphotericin. In the remaining 14 patients high dose Amphotericin of 1.0-1.5 mg/kg/d was instituted within two days of the clinical suspicion of aspergillosis. On average, a definite diagnosis of IPA was not made for 10.5 days following initiation of high dose Amphotericin therapy. In ten of these patients 5-fluorocytosine was also administered in a dose that resulted in 30 to 60 μg/ml serum levels. This drug demonstrates antifungal properties *in vitro* and in experimental models. Thus, 13 of 14 patients who received high dose Amphotericin B with or without 5 FC survived invasive aspergillosis. Seven of the 14 patients developed transient renal dysfunction with a creatinine greater than 2.0 mg/dL for a mean of 6.4 days. However, the creatinines regressed to admission levels by time of discharge. This modest renal effect occurred despite the fact that the patients had received Aminoglycoside antibiotics for an average of 22 days before treatment with Amphotericin and continued concurrent admission during treatment.

These data suggest that daily doses of Amphotericin B that exceed the usual recommendations may be more satisfactory. In addition, the available information suggests that granulocytopenic patients should be treated as early in the course of *Aspergillus* infection as possible, at least in hospitals with a high incidence of this pathogen. These practices would likely result in a greater survival rate of infected patients.

SUMMARY

In summary, *Aspergillus* is a ubiquitous fungus the spores of which are inhaled on a regular basis by most humans. If there has been antecedent

lung disease resulting in large air spaces such as cavities, the organism may grow in these spaces into a fungus ball comprised of matted hyphae. Aspergillomas frequently cause hemoptysis which may sometimes be life threatening. In most patients this complication is best managed conservatively.

The fungus is also a good antigen which induces hypersensitivity in some atopic individuals. The hypersensitivity may lead to a variety of syndromes one of which, allergic bronchopulmonary aspergillosis, leads to an unusual proximal bronchiectasis. If ABPA is not treated aggressively with corticosteroids, permanent pulmonary fibrosis may result. Syndromes similar to ABPA, mucoid impaction of bronchi and bronchocentric granulomatous, may sometimes be caused by *Aspergillus* hypersensitivity, but they may apparently arise from other causes as well.

Finally, *Aspergillus* may act as an invasive pathogen in immunocompromised persons, especially those with granulocytopenia. Although the mortality rate for invasive pulmonary aspergillosis is substantial, recent clinical trials of empiric therapy, aggressive diagnostic procedures, and high dose Amphotericin B suggest that it may be possible to improve the survival rate of this patient population.

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