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REVIEW

# Pulmonary aspergillosis: a clinical review

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**ABSTRACT:** ***Aspergillus*** **is a mould which may lead to a variety of infectious, allergic diseases depending on the host's immune status or pulmonary structure. Invasive pulmonary aspergillosis occurs primarily in patients with severe immunodeficiency. The significance of this infection has dramatically increased with growing numbers of patients with impaired immune state associated with the management of malignancy, organ transplantation, autoimmune and inflammatory conditions; critically ill patients and those with chronic obstructive pulmonary disease appear to be at an increased risk. The introduction of new noninvasive tests, combined with more effective and better-tolerated antifungal agents, has resulted in lower mortality rates associated with this infection. Chronic necrotising aspergillosis is a locally invasive disease described in patients with chronic lung disease or mild immunodeficiency. Aspergilloma is usually found in patients with previously formed cavities in the lung, whereas allergic bronchopulmonary aspergillosis, a hypersensitivity reaction to** ***Aspergillus*** **antigens, is generally seen in patients with atopy, asthma or cystic fibrosis. This review provides an update on the evolving epidemiology and risk factors of the major manifestations of** ***Aspergillus*** **lung disease and the clinical manifestations that should prompt the clinician to consider these conditions. Current approaches for the diagnosis and management of these syndromes are discussed.**

**KEYWORDS:** **Aspergillosis, diagnosis, management, pulmonary, risk factors**

*Aspergillus* spp. are widespread in the environment and are commonly isolated from both the outdoor environment (*i.e.* soil, plant debris) and indoor environment, including hospitals. Pulmonary disease is caused mainly by *Aspergillus fumigatus* and has a spectrum of clinical syndromes (fig. 1) [1].

Invasive pulmonary aspergillosis (IPA) is a severe disease, and can be found not only in severely immunocompromised patients, but also in critically ill patients and those with chronic obstructive pulmonary disease (COPD). Chronic necrotising aspergillosis (CNA) is locally invasive and is seen mainly in patients with mild immunodeficiency or with a chronic lung disease. Aspergilloma and allergic bronchopulmonary aspergillosis (ABPA) are noninvasive forms of *Aspergillus* lung disease. Aspergilloma is a fungus ball that develops in a pre-existing cavity within the lung parenchyma, while ABPA is a hypersensitivity manifestation in the lungs that almost always affects patients with asthma or cystic fibrosis [2].

This review systematically describes the main clinical syndromes associated with pulmonary aspergillosis, covering their incidence, risk factors, clinical presentations, radiological features, diagnostic criteria, management options and outcome.

## INVASIVE PULMONARY ASPERGILLOSIS

IPA was first described in 1953 [3]. Due to widespread use of chemotherapy and immunosuppressive agents, its incidence has increased over the past two decades [4, 5]. Of all autopsies performed between 1978 and 1992, the rate of invasive mycoses increased from 0.4% to 3.1%, as documented by GROLL *et al.* [6]. IPA increased from 17% to 60% of all mycoses found on autopsy over the course of the study. The mortality rate of IPA exceeds 50% in neutropenic patients and reaches 90% in haematopoietic stem-cell transplantation (HSCT) recipients [7, 8].

### *Risk factors*

Alveolar macrophages are the first line of defence against inhaled *Aspergillus* conidia. In the lungs, pathogen recognition receptors, such as Toll-like receptors, dectin-1 and mannose-binding lectin, identify specific fungal wall components and produce cytokines that stimulate neutrophil recruitment, the main defence mechanism against *Aspergillus* hyphae [9]. The major risk factor for IPA is immunodeficiency (table 1), which

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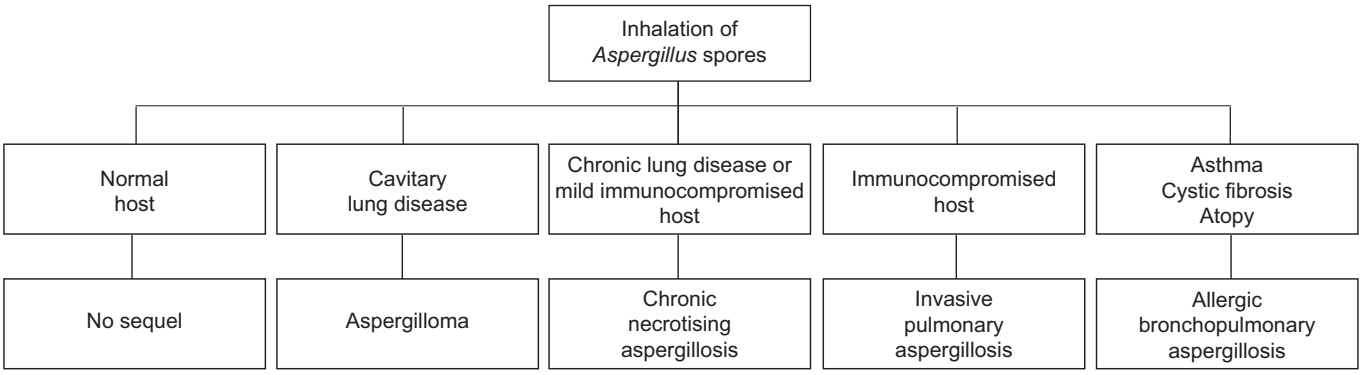


**FIGURE 1.** The spectrum of pulmonary aspergillosis.

includes neutropenia, HSCT and solid-organ transplantation, prolonged therapy with high-dose corticosteroids, haematological malignancy, cytotoxic therapy, advanced AIDS and chronic granulomatous disease (CGD) [1, 10, 15].

The most important risk factor is neutropenia, especially when there is an absolute neutrophil count of $<500$ cells·mm$^{-3}$. The risk of IPA correlates strongly with the duration and degree of neutropenia. The risk in neutropenic patients is estimated to increase by 1% per day for the first 3 weeks and then by 4% per day thereafter [10]. HSCT and solid-organ transplantation (especially lung transplantation) are also significant risk factors [11, 23] Several other factors predispose patients with transplantation to acquire IPA: multiple immune defects including prolonged neutropenia in the pre-engraftment phase of HSCT; the use of multiple anti-rejection or anti-graft *versus* host disease (GVHD) therapy (such as corticosteroids and cyclosporine); parenteral nutrition; use of multiple antibiotics; and prolonged hospitalisation.

There has been a steady increase in the documented cases of IPA following HSCT, where the risk is much higher following allogeneic rather than autologous HSCT (incidences of 2.3–15% and 0.5–4%, respectively) [8, 12–14, 24]. In allogeneic HSCT, the highest risk is in patients with severe GVHD (grade III–IV). The timeline of IPA in these patients follows a bimodal distribution, with a peak in the first month following HSCT, which is associated with neutropenia. The second peak is during the treatment of GVHD (median 78–112 days post-transplantation) [8, 13, 25]. Currently, the first peak is less significant because of the routine use of stem cells instead of bone marrow for transplantation, nonmyeloablative regimens, the use of colony-stimulating factors during neutropenia and the widespread use of antifungal agents [13, 26]. The second peak has become more significant, especially with the higher incidence of GVHD associated with unrelated allogeneic transplantation and treatment with intensive immunosuppressive therapy, including corticosteroids, cyclosporine A, anti-TNF agents, and other T-cell depleting strategies [13, 14, 17, 27–29].

In a study by MARR *et al*. [14], the probability of IPA reached approximately 5% at 2 months, 9% at 6 months, 10% at 1 year and 11.1% by the third year following allogeneic HSCT. In addition, there is evidence that cytomegalovirus (CMV) infection in these patients increases the risk of IPA [14, 30] the hazard ratio for IPA in the setting of CMV disease increases 13.3-fold (95% CI 4.7–37.7) [8].

Neutrophil dysfunction is another risk factor for IPA and is seen primarily in CGD. IPA is an important cause of mortality in these patients [22].

IPA is relatively uncommon in patients with HIV infection, especially with the routine use of highly active anti-retroviral therapy. The incidence of aspergillosis in a large cohort of patients with HIV infection was 3.5 cases per 1,000 person-yrs [18]. A low CD4 count ($<100$ cells·mm$^{-3}$) is present in almost all cases of AIDS-associated aspergillosis, and half of HIV-infected patients with IPA have coexistent neutropenia or are on corticosteroid therapy. The rest of the cases appear to have no particular risk factors other than advanced AIDS [19–21]. There is increased incidence of tracheobronchial involvement in these patients in addition to the usual clinical picture of IPA [21, 31]. Since isolation of *Aspergillus* from respiratory secretions has poor predictive value for invasive IPA in AIDS patients, a histopathological diagnosis is usually required to establish the diagnosis [32]. Response to therapy in this patient group tends to be particularly poor [19–21, 32, 33]. The prognosis of HIV-infected patients with IPA is generally poor, with median survival of 3 months following diagnosis [18].

There are increasing numbers of reports documenting IPA in immunocompetent patients who do not have the classic risk factors. Two at-risk groups stand out: patients with severe COPD and critically ill patients. IPA is an emerging serious infection in patients with COPD. The majority of these patients have advanced COPD and/or are on corticosteroid therapy. Patients with COPD have increased susceptibility to IPA for several reasons, including structural changes in lung architecture, prolonged use of corticosteroid therapy [16], frequent hospitalisation, broad-spectrum antibiotic treatment, invasive procedures, mucosal lesions and impaired mucociliary clearance, and comorbid illnesses such as diabetes mellitus, alcoholism and malnutrition. It is also possible that abnormalities or deficiencies in surfactant proteins, alveolar macrophages and Toll-like receptors play a role in the pathogenesis of IPA in some patients with COPD [34–38].

It has been documented that chronic lung disease predisposes to colonisation of airways by *Aspergillus* spp., and it is possible, under certain circumstances, that this colonisation transforms

**TABLE 1** Classical risk factors for invasive pulmonary aspergillosis

| |
|---|
| Prolonged neutropenia (<500 cells·mm$^{-3}$ for >10 days) [10] |
| Transplantation (highest risk is with lung transplantation and HSCT) [11–14] |
| Prolonged (>3 weeks) and high-dose corticosteroid therapy [10, 15, 16] |
| Haematological malignancy (risk is higher with leukaemia) [5, 7] |
| Chemotherapy [5, 7, 17] |
| Advanced AIDS [18–21] |
| Chronic granulomatous disease [22] |

HSCT: haematopoietic stem-cell transplantation.

to an invasive disease [39]. In a review of 65 cases of IPA in patients with COPD who did not have the traditional risk factors for IPA [40], 75% were on corticosteroid therapy for a median 2.6 yrs prior to the diagnosis of IPA. The dose was increased in 34% of cases following hospitalisation (usually for the treatment of acute exacerbation of COPD) and prior to the diagnosis of IPA. Several patients in the study had low forced expiratory volume in 1 s or were described to have severe or very severe COPD. Only 43% of the cases had documented comorbidities including atypical mycobacteria, remote history of *Mycobacterium tuberculosis*, polymyalgia rheumatica, asthma, cirrhosis, diabetes mellitus, pneumoconiosis, Dressler's syndrome and lung cancer. 59 (91%) patients died; the main cause of death was progressive respiratory failure. 31 (48%) patients were reported to have received mechanical ventilation, and 13 (20%) patients had evidence of disseminated IPA [40]. Potential explanations of the high mortality of IPA in these patients, also reported in other studies [41–43], are the delayed diagnosis secondary to low index of suspicion of this infection in this patient population, older age, poor pulmonary reserve and multiple comorbid illnesses. Since the clinical and radiological presentation of IPA in patients with COPD is nonspecific, to avoid delay in the diagnosis and management, a high index of suspicion is warranted. The isolation of *Aspergillus* spp. from a lower respiratory tract specimen should not be routinely dismissed as colonisation [40, 41].

IPA is also becoming an important infectious disease in intensive care unit (ICU) patients without the classical risk factors (neutropenia, leukaemia, HSCT), and the mortality is also devastating in these apparently less immunocompromised patients. *Aspergillus* spp. are isolated from lower respiratory patients, and in about half of these patients, this finding represents IPA [44–48]. In one retrospective study in a medical ICU, an incidence of invasive aspergillosis of 5.8% was found with pulmonary involvement in most cases. 70% of the cases were found in patients without leukaemia or cancer and the disease had a mortality rate exceeding 90% [47]. In another study of 172 critically ill patients who had positive sputum samples for *Aspergillus*, 83 had invasive disease, and 60% of these patients had no classic risk factors for IPA [44]. Critically ill patients are prone to developing disturbances in immunoregulation during their stay in the ICU, which renders them more vulnerable to fungal infections. Risk factors such as COPD, systemic corticosteroid therapy, non-haematological malignancy, chronic renal disease, liver failure, diabetes mellitus, near-drowning, HIV infection, autoimmune diseases, malnutrition and extensive burns have been described [44–47, 49].

The clinical signs and symptoms of IPA and its radiographic features are often nonspecific in ICU patients. The finding of *Aspergillus* spp. in respiratory tract samples in these patients should not be routinely discarded as colonisation, even if these patients are immunocompetent [44]. Therefore, in order not to miss a critical window of therapeutic opportunity, adapted clinical diagnostic criteria should be used for this category and further diagnostic evaluation with early antifungal therapy should be considered once IPA is suspected in critically ill patients [50, 51]. IPA in this patient population carries an attributable mortality of 18.9% after adjusting for confounding factors [47]. A report suggests that the isolation of *Aspergillus* from lower respiratory tract samples was associated with a worse ICU outcome, regardless of whether the finding represented IPA or colonisation [52].

### *Clinical presentation*

In most cases, *Aspergillus* is introduced to the lower respiratory tract by inhalation of the infectious spores. Less commonly, IPA may start in locations other than the lungs, such as sinuses, the gastrointestinal tract or the skin (*via* intravenous catheters, prolonged skin contact with adhesive tapes or burns) [53–56].

Symptoms are nonspecific and usually mimic bronchopneumonia: fever unresponsive to antibiotics, cough, sputum production and dyspnoea. Patients may also present with pleuritic chest pain (due to vascular invasion leading to thromboses that cause small pulmonary infarcts) and haemoptysis, which is usually mild, but can be severe. IPA is one of the most common causes of haemoptysis in neutropenic patients, and may be associated with cavitation that occurs with neutrophil recovery [57].

*Aspergillus* infection may also disseminate haematogenously to other organs, including the brain (fig. 2). This can lead to seizures, ring-enhancing lesions, cerebral infarctions, intracranial haemorrhage, meningitis and epidural abscesses. Other organs such as the skin, kidneys, pleura, heart, oesophagus and liver may be less frequently involved [58].

*Aspergillus t*racheobronchitis (ATB) is a unique feature of IPA. It represents isolated invasion of the tracheobronchial tree by *Aspergillus* spp. Predisposing factors for ATB are similar to those for IPA; however, certain patient groups are more likely to develop this entity. These include lung transplantation recipients, patients with AIDS and cancer patients with mediastinal involvement and/or treatment [59–61]. DENNING [62] proposed classifying ATB into three forms. Obstructive ATB is characterised by thick mucus plugs full of *Aspergillus* spp. without macroscopic bronchial inflammation. Pseudomembraneous ATB is characterised by extensive inflammation of the tracheobronchial tree and a membrane overlaying the mucosa containing *Aspergillus* spp. Ulcerative ATB is reserved to patients with limited involvement of the tracheobronchial tree, and is usually found at the suture line in lung transplantation recipients. Pseudomembraneous ATB is the most severe form and usually presents with cough and dyspnoea. Haemoptysis is not frequent. Radiological findings are not specific; however, evidence of segmental or lobar collapse may be present [61]. The diagnosis of ATB is usually made by the characteristic findings on bronchoscopy combined with microscopic analysis of respiratory specimens obtained during the procedure. The outcome

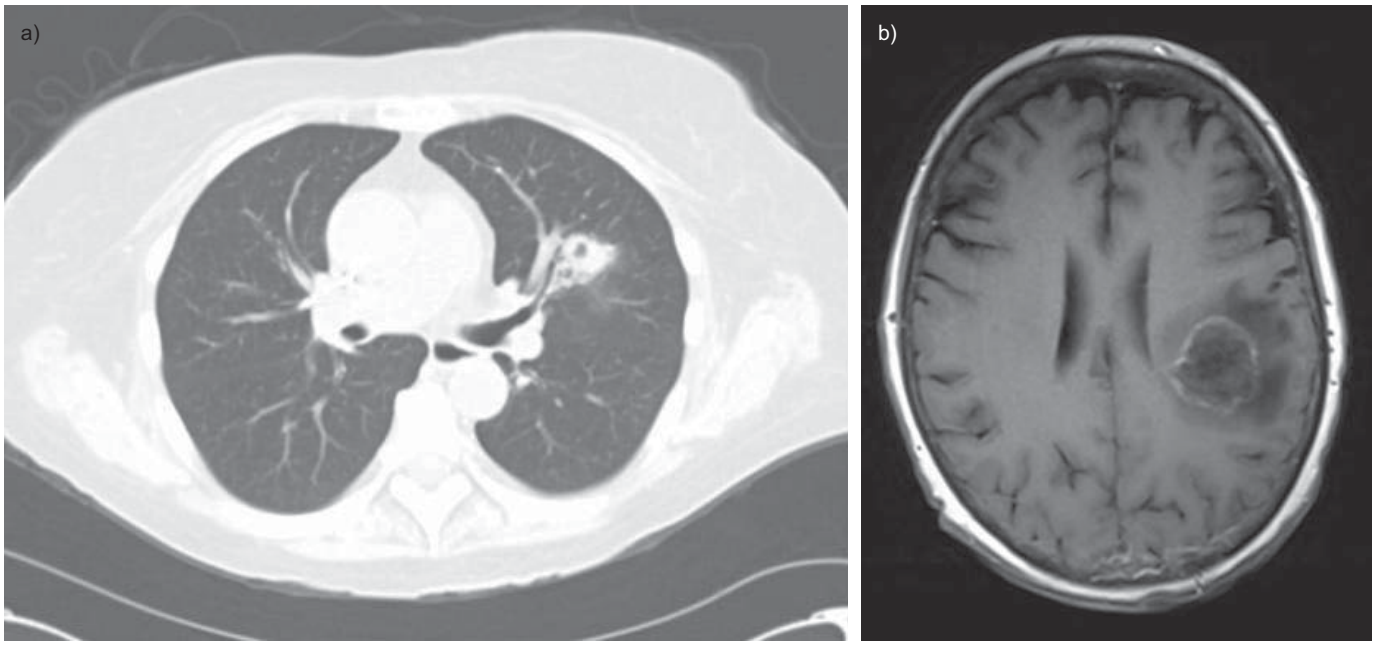


**FIGURE 2.** a) Chest computed tomography image showing left upper lobe cavitary lesion consistent with invasive pulmonary aspergillosis (IPA) in an allogeneic haematopoietic stem-cell transplantation recipient. b) Brain magnetic resonance image from the same patient showing left parietal ring enhancing lesion due to disseminated IPA.

of ulcerative ATB is generally favourable with antifungal therapy. On the other hand, the prognosis is poor in patients with pseudomembranous and obstructive ATB, with mortality reaching 78% [63]. The need for mechanical ventilation is a predictor of high mortality in these patients [63]. High index of suspicion of ATB, early diagnosis and prompt antifungal therapy may be associated with improved outcome [61].

### *Diagnosis*

The diagnosis of IPA remains challenging. Early diagnosis of IPA in severely immunocompromised patients is difficult, and a high index of suspicion is necessary in patients with risk factors for invasive disease. The gold standard in the diagnosis of IPA is histopathological examination of lung tissue obtained by thoracoscopic or open-lung biopsy [64]. The presence of septate, acute, branching hyphae invading lung tissue along with a culture positive for *Aspergillus* from the same site is diagnostic of IPA (fig. 3). Histopathological examination also allows for the exclusion of other diagnoses, such as malignancy or nonfungal infectious diseases. The histopathological findings associated with IPA have been shown to differ according to the underlying host. In patients with allogeneic HSCT and GVHD, there is intense inflammation with neutrophilic infiltration, minimal coagulation necrosis and low fungal burden. In neutropenic patients, IPA is characterised by scant inflammation, extensive coagulation necrosis associated with hyphal angio-invasion, and high fungal burden. Dissemination to other organs is equally high in both groups [5].

The significance of isolating *Aspergillus* spp. in sputum samples depends on the immune status of the host. In immunocompetent patients, it almost always represents colonisation with no clinical consequences. In a study of 66 elderly hospitalised patients with *Aspergillus* isolated from the sputum, 92% were consistent with colonisation and only 4.5% had IPA [39]. Similar observations have been reported by others [65–67]. Therefore, in immunocompetent patients with *Aspergillus* isolated from the sputum, antifungal therapy is generally not indicated, but appropriate diagnostic studies should be considered to exclude IPA. However, isolation of an *Aspergillus* species from sputum is highly predictive of invasive disease in immunocompromised patients. Studies have shown that sputum samples that are positive for *Aspergillus* in patients with leukaemia, or in those who have undergone HSCT, have a positive predictive value of 80–90% [66, 68, 69]. Conversly, negative sputum samples do not rule out IPA; negative sputum studies have been noted in 70% of patients with confirmed IPA [69, 70]. Blood cultures are rarely positive in patients with confirmed IPA [71].

Chest radiography is of little use in the early stages of disease because the incidence of nonspecific changes is high. Usual findings include rounded densities, pleural-based infiltrates suggestive of pulmonary infarctions, and cavitations. Pleural effusions are uncommon [72, 73]. Chest computed tomography (CT), especially when combined with high-resolution images (HRCT), is much more useful (fig. 2). The routine use of HRCT of the chest early in the course of IPA leads to earlier diagnosis and improved outcomes [74, 75]. It also aids further diagnostic studies such as bronchoscopy and open-lung biopsy [76]. Typical chest CT scan findings in patients suspected to have IPA include multiple nodules and the halo sign, which is mainly seen in neutropenic patients early in the course of infection (usually in the first week) and appears as a zone of low attenuation due to haemorrhage surrounding the pulmonary nodule. Another late radiological sign is the air crescent sign, which appears as a crescent-shaped lucency in the region of the original nodule secondary to necrosis [73, 77]. Neither sign is sensitive or pathognomic of IPA. The halo sign may be found in many other situations: as a result of

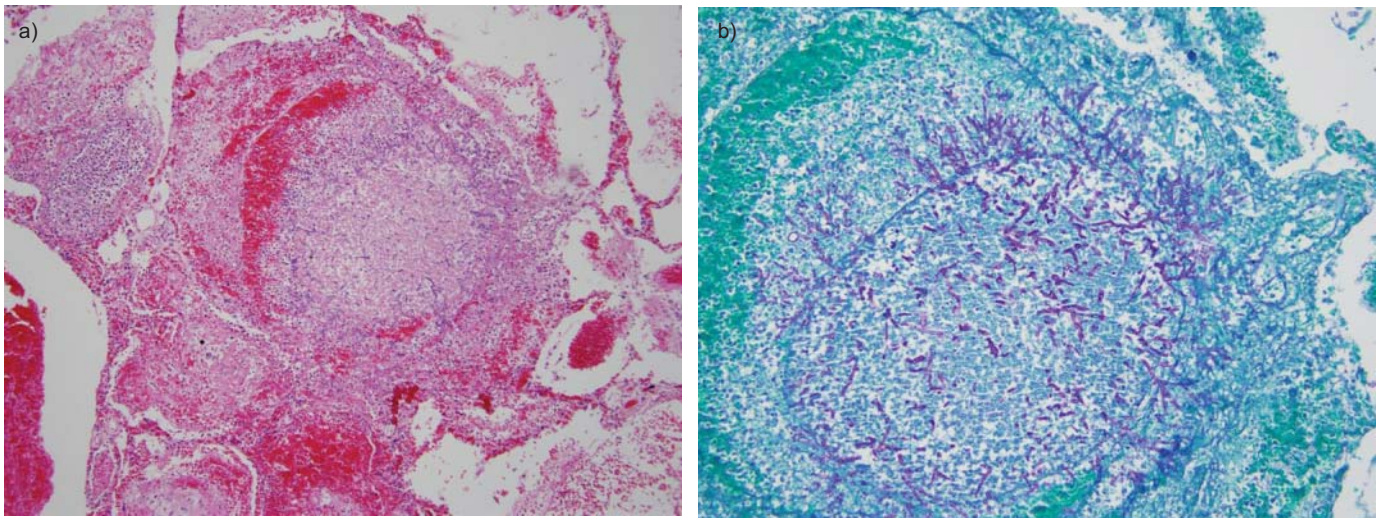


**FIGURE 3.** Invasive pulmonary aspergillosis. a) Pulmonary parenchyma with necrosis and pulmonary haemorrhage and *Aspergillus* hyphae (haematoxylin and eosin 100×). b) Branching *Aspergillus* hyphae involving lung parenchyma (Grocott Methenamine silver fungus stain 200×). Images courtesy of Dr. Mousa Al-Abbadi (East Tennessee State University, Johnson City, TN, USA).

metastasis, bronchoalveolar carcinoma, bronchiolitis obliterans organising pneumonia, eosinophilic pneumonia or other fungal infection [78]. GREENE [79] found that 94% of 235 patients with a confirmed diagnosis of IPA had at least one nodular region. In another report on HRCT chest findings in febrile neutropenic patients with pneumonia, the findings associated with IPA were ill-defined nodules (67%), ground-glass appearance (56%), and consolidation (44%) [80]. In a retrospective study of 45 patients, none of the early HRCT signs (nodule, consolidation, peribronchial infiltrates) predicted patient outcome or the development of pulmonary haemorrhage [81]. However, pulmonary haemorrhage is expected to occur in the presence of large cavitating lesions or consolidations located close to larger pulmonary vessels.

Bronchoscopy with bronchoalveolar lavage (BAL) is generally helpful in the diagnosis of IPA, especially in patients with diffuse lung involvement. The sensitivity and specificity of a positive result of BAL fluid are about 50% and 97%, respectively, but this diagnostic yield of BAL in the diagnosis of IPA is not consistent, and much lower yields have been reported [66, 68, 82–86]. However, BAL is still a safe and useful tool in high-risk patients suspected to have IPA. In addition to obtaining samples for fungal stain and culture, it may also be useful in detecting *Aspergillus* antigens in the BAL fluid as well as excluding other infections. Transbronchial biopsies may be considered in selected patients.

It is always important to send the samples of the workup (sputum, BAL fluid or lung tissue) for culture as well as for histological examination. This is because a similar histological appearance to *Aspergillus* may be present with other fungal species, such as *Scedosporium, Pseudallescheria* and *Fusarium* [87]. In addition, there are many species of *Aspergillus* that may lead to IPA. While *A. fumigatus* is the most common, there are increasing reports of IPA in cancer patients due to other species such as *Aspergillus niger, Aspergillus terreus and Aspergillus flavus* [88–92]. Some of these species (such as *A. terreus* and *Aspergillus nidulans*) are resistant to amphotericin B [89, 92]. In a review of 300 cases with proven IPA, *A. terreus* was the second commonest species, with a frequency of 23% of the cases. The risk factors and outcome for *A. terreus* infection were similar to those for *A. fumigatus* infection, but *A. terreus* was significantly more likely to be nosocomial in origin and more likely to be resistant to amphotericin B [91]. The new triazole antifungal agents such as voriconazole and posaconazole have significantly better efficacy against *A. terreus* [89, 90, 93].

The most recent advances in the diagnosis of IPA are related to detecting *Aspergillus* antigens in body fluids, mainly galactomannan and (13)-β-D-glucan (both are cellular wall constituents). Galactomannan is a polysaccharide released by *Aspergillus* during growth. A double-sandwich ELISA for the detection of galactomannan in serum is the best characterised test and was approved by the US Food and Drug Administration (FDA) for the diagnosis of IPA with a threshold of 0.5 $ng \cdot mL^{-1}$. It is reported that serum galactomannan can be detected several days before the presence of clinical signs, chest radiographic abnormalities or a positive culture. Thus, galactomannan detection may allow earlier confirmation of the diagnosis; it may also assist in the assessment of the evolution of infection during treatment if serial serum galactomannan values are obtained [94, 95].

To assess the accuracy of a galactomannan assay for diagnosing IPA, a meta-analysis was undertaken by PFEIFFER *et al*. [96] of 27 studies from 1996–2005. The cases were diagnosed with IPA according to the European Organization for Research on Treatment of Cancer/Mycoses Study Group (EORTC/MSG) criteria [97]. Overall, the assay had a sensitivity of 71% and specificity of 89% for proven cases of IPA. The negative predictive value was 92–98% and the positive predictive value was 25–62% [96]. PFEIFFER *et al.* [96] also concluded that the galactomannan assay is more useful in patients who have a haematological malignancy or who have undergone allogeneic HSCT than in solid-organ transplant recipients or non-neutropenic patients.

Galactomannan is found in food and may be absorbed by the digestive tract, especially in patients with post-chemotherapy

mucositis, resulting in a false-positive reaction. Also, medications such as β-lactam antibiotics (*e.g.* piperacillin/tazobactam) may be associated with a false-positive assay, while antifungal agents with activity against *Aspergillus* may lead to a false-negative result [98–101].

One of the major limitations of the galactomannan test is the species-specificity of the assay: it is not possible to exclude involvement by other moulds such as *Fusarium, Zygomycetes*, and dematiaceous fungi [102]. Therefore, galactomannan detection does not remove the need for careful microbiological and clinical evaluations.

Galactomannan is detected in other body fluids such as BAL, urine, and cerebrospinal fluid (CSF), and there is evidence that these tests may become positive prior to clinical and radiological findings suggestive of IPA [102–105]. In one study, incorporating galactomannan and quantitative PCR assays into standard BAL fluid analysis appeared to enhance bronchoscopic identification of *Aspergillus* species as the cause of pulmonary disease in HSCT recipients [103]. Some prospective and retrospective studies have tried to assess the importance of galactomannan detection in BAL samples in different patient categories and situations; they found a higher sensitivity and similar specificity compared to serum samples. It also appeared that galactomannan detection in BAL fluid performed significantly better in diagnosing IPA than its detection in serum or BAL fungal stain and culture. Besides, it facilitated more rapid antifungal therapy among these patients [106–109].

Detection of galactomannan in the CSF for diagnosis of cerebral aspergillosis appears promising. A study [110] with a small number of patients suggested it might be diagnostic for high-risk patients with compatible neurological symptoms. Further studies on larger patient populations are necessary fully to evaluate the role of this test in the diagnosis of neurological aspergillosis.

PCR is another way to diagnose IPA by the detection of *Aspergillus* DNA in BAL fluid and serum. The sensitivity and specificity of PCR of BAL fluid samples are estimated to be 67–100% and 55–95%, respectively [111], while for serum samples the sensitivity and specificity have been reported as 100% and 65–92%, respectively [111–114]. However, PCR is often associated with false-positive results, because it does not discriminate between colonisation and infection. PCR for *Aspergillus* DNA detection remains restricted to highly specialised laboratories and cannot be considered as a routine clinical test.

Detection of serum (13)-β-D-glucan, a fungal cell wall constituent, has also received FDA approval and is a highly sensitive and specific test for invasive deep mycosis. This could be useful in immunocompromised patients, including those with candidiasis, fusariosis, and aspergillosis [115]. In one retrospective study [116], the sensitivity, specificity, and positive and negative predictive values for this test in diagnosing IPA were similar to those of galactomannan. The combination of the two tests showed improved specificity and positive predictive value compared with each test individually.

The role of serological studies in the diagnosis of IPA is evolving. Both galactomannan and (13)-β-D-glucan assays (but not PCR) were incorporated in the revised EORTC/MSG criteria for diagnosing IPA. However, their roles in different hosts, as surveillance tools, and their impact on the outcome for patients remain unclear. Ongoing prospective studies are attempting to address these issues, but until solid data are available, these tests should be considered as adjunct diagnostic studies. They should not replace appropriate clinical and radiological evaluation (and in selected cases, invasive procedures) to confirm the diagnosis of IPA.

The revised EORTC/MSG criteria (table 2) for the diagnosis of invasive fungal infections retained the original classifications of ''proven,'' ''probable,'' and ''possible'' invasive disease. However, the definition of ''probable'' has been expanded, whereas the scope of the category ''possible'' has been diminished. The category of proven invasive fungal disease can apply to any patient, regardless of whether or not the patient is immunocompromised, whereas the probable and possible categories are proposed for immunocompromised patients only. The revised definitions apply to immunocompromised patients but not necessarily to critically ill patients in the intensive care unit who, nonetheless, may develop possible or probable IPA [49]. The EORTC/MSG criteria are meant to serve as a guide for clinical and epidemiological research and thus do not need to be present in every patient in order to treat for IPA [97, 117, 118].

### *Treatment*

Despite the introduction of several new antifungal agents, treatment of IPA remains difficult and mortality rates are still

**TABLE 2** Diagnostic criteria for invasive pulmonary aspergillosis

| Diagnosis | Criteria |
|---|---|
| **Proven** | Histopathological or cytopathological examination of lung tissue showing hyphae from needle aspiration or biopsy specimen with evidence of associated tissue damage<br>OR<br>positive culture result for *Aspergillus* from a sample obtained by sterile procedure from the lung<br>AND<br>clinically or radiologically abnormal site consistent with infection |
| **Probable** | Host factor (table 1)<br>AND<br>mycological evidence (positive *Aspergillus* microscopy or culture from the sputum or BAL or positive antigen assay[#])<br>AND<br>clinical criteria consistent with infection[¶] |
| **Possible** | Host factor (table 1)<br>AND<br>clinical criteria consistent with the infection[¶] |

BAL: bronchoalveolarlavage. [#]: Positive antigen assay: galactomannan antigen detected in plasma, serum, BAL fluid or cerebrospinal fluid, or β-D-glucan detected in serum. [¶]: Clinical criteria: new characteristic infiltrates on computed tomography imaging (dense, well-circumscribed lesion(s) with or without a halo sign, air-crescent sign, or cavity), tracheobronchitis seen by bronchoscopy, or noncharacteristic new infiltrates with a specific pulmonary symptom or sign (such as pleural rub, pleural pain, haemoptysis). Adapted from [117].

high (table 3). Therapy should be considered as soon as there is a clinical suspicion of IPA, and while a workup is under way. Amphotericin B has been the first line of therapy for IPA for many years, with a recommended dose 1–1.5 $mg \cdot kg^{-1} \cdot day^{-1}$. However, it can cause serious side-effects, including nephrotoxicity, electrolyte disturbances and hypersensitivity. To reduce these side-effects, newer lipid-based preparations of amphotericin B (like liposomal amphotericin B and lipid complex amphotericin B) have been introduced, but higher doses of the lipid formulations are needed for equivalent antifungal efficacy. A recent large randomised trial demonstrated no additional benefits of high-dose liposomal amphotericin B (10 $mg \cdot kg^{-1} \cdot day^{-1}$) compared with lower-dose liposomal amphotericin B regimens (3 $mg \cdot kg^{-1} \cdot day^{-1}$), and outcomes were generally good with the lower dose, suggesting utility of liposomal amphotericin B in the low doses, and therapeutic risk associated with excessive toxicities at the higher doses [124].

A new broad-spectrum triazole, voriconazole, has been approved as the initial treatment of invasive aspergillosis and is currently considered the treatment of choice in many patients with IPA [119–121]. In a large prospective, randomised, multicentre trial, voriconazole was compared to amphotericin B as the primary therapy for IPA [122]. Patients receiving voriconazole had a higher favourable response rate at week 12 (53% *versus* 32% in patients receiving amphotericin B) and a higher 12-week survival (71% *versus* 58%). Voriconazole is available in both intravenous and oral formulations. The recommended dose is 6 $mg \cdot kg^{-1}$ twice daily intravenously on day 1, followed by 4 $mg \cdot kg^{-1} \cdot day^{-1}$. After 7 days, switching to 200 mg *p.o.* twice daily may be considered. Voriconazole has a milder side-effect profile and is much better tolerated than amphotericin B. The most frequent adverse effect is visual disturbances, described as blurred vision, photophobia and altered colour perception. Liver function test abnormalities and skin reactions are less common side-effects. However, voriconazole is associated with a significant number of drug–drug interactions, such as with cyclosporine, warfarin, terfenadine, carbamazepine, quinidine, rifampin, statins and sulfonylureas [119]. Since there is inter-individual and intra-individual variability in voriconazole plasma levels, therapeutic drug monitoring for voriconazole should be considered in cases of refractory fungal infection or concerns about drug toxicity [147]. Another broad-spectrum triazole, posaconazole, is effective and safe as salvage therapy in patients with IPA refractory to standard antifungal therapy [22, 93, 125].

Echinocandin derivatives such as caspofungin, micafungin and anidulafungin are also effective agents in the treatment of IPA refractory to standard treatment, or if the patient cannot tolerate first-line agents [126, 127]. While polyenes and azoles target the fungal cell membrane, echinocandins inhibit the (13)-β-D-glucan constituent of the fungal cell wall. Therefore, a combination antifungal therapy could be a strategy to treat refractory IPA [148, 149]. There are *in vitro* and limited clinical studies (case reports and retrospective case series) that suggest a benefit from combining antifungal agents as salvage therapy in refractory IPA [149–152]. The combination of caspofungin and liposomal amphotericin B as a salvage therapy showed an overall response rate of 42%, although in patients with documented progressive IPA, the response rate was only 18% [149]. A survival advantage of voriconazole plus caspofungin compared with voriconazole alone was reported in one retrospective analysis of salvage therapy for IPA [151]. This combination was also compared with liposomal amphotericin B as primary therapy for IPA in solid-organ transplant recipients in a prospective, multicentre, observational study [153]. The combination was associated with improved survival in subsets of recipients with renal failure or *A. fumigatus*. Conversely, another report showed no difference in the response rate between patients who received micafungin alone or those who received it in combination with other antifungal agents as primary or salvage therapy for acute IPA [154]. Combination therapy of an echinocandin with either a lipid formulation of amphotericin B or triazole agent appears promising and should be considered in critically ill patients [155], but cannot be recommended for the routine treatment of primary IPA. Controlled randomised prospective studies are needed to document the value of this approach. Because galactomannan is covalently bound to (13)-β-D-glucan in the fungal cell wall, an initial increase in circulating galactomannan might be expected in patients treated with echinocandins, which inhibit the (13)-β-D-glucan constituent [156].

According to the recent statement of the American Thoracic Society for treating fungal infections in adults [123], the duration of IPA therapy should be individualised to the

**TABLE 3** Treatment recommendations for pulmonary aspergillosis

| Disease | Primary treatment | Other treatments |
|---|---|---|
| **Invasive pulmonary aspergillosis** | Voriconazole [119–123] | Alternative therapy: liposomal amphotericin B [124]<br>Continuation therapy: voriconazole or itraconazole [122, 123]<br>Salvage therapy: echinocandin or posaconazole [125–127] |
| **Chronic necrotising aspergillosis** | Voriconazole [120, 123] | Alternative therapy: itraconazole [128, 129]<br>Severe cases: intravenous voriconazole or liposomal amphotericin B [123, 128, 130]<br>Consider surgical resection [130] |
| **Aspergilloma** | Observation [123] | Bronchial artery embolisation [131]<br>Surgical resection [132–135]<br>Consider itraconazole [136–138] |
| **Allergic bronchopulmonary aspergillosis** | Corticosteroids [139–142] | Itraconazole or voriconazole as steroid-sparing agents [143–146] |

patient's clinical and radiological response. The treatment is often prolonged, lasting several months to >1 yr. Prerequisites for discontinuing treatment include clinical and radiographic resolution, microbiological clearance and reversal of immunosuppression. Reinstating therapy in patients who have responded should be considered if immunosuppression is resumed, or if the patient requires additional cytotoxic therapy or another HSCT.

Surgical resection has generally a limited role in the management of patients with IPA, but it becomes important in cases with invasion of bone, burn wounds, epidural abscesses and vitreal disease [123]. It should also be considered in cases of massive haemoptysis, pulmonary lesions close to the great blood vessels or pericardium, or residual localised pulmonary lesions in patients with continuing immunosuppression or those who are expected to have immunosuppressive therapy in the future. Several reports have shown the relative efficacy and safety of surgical intervention, in addition to antifungal therapy, in these situations [75, 157–162].

Immunomodulatory therapy could be used to decrease the degree of immunosuppression and as an adjunct to antifungal therapy for the treatment of IPA. This includes colony-stimulating factors, like granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF), and interferon-γ. Colony-stimulating factors stimulate the bone marrow to produce more neutrophils, and have been shown to augment the phagocytic activity of neutrophils against fungi, including *Aspergillus* spp. [163–165]. There is a theoretical advantage to adding these agents to the treatment of neutropenic patients suspected to have IPA. In one randomised study in patients receiving chemotherapy for acute myelogenous leukaemia, prophylaxis with GM-CSF led to a lower frequency of fatal fungal infections compared with placebo (1.9% *versus* 19%, respectively) and reduced overall mortality [166]. It is recommended to consider colony-stimulating factors in neutropenic patients with serious infections, but there are no definitive studies that show benefit in patients with IPA [167]. Interferon-γ is another cytokine that has been shown *in vitro* and in animal models to augment immunity by increasing neutrophil and monocyte activity against *Aspergillus* [164, 168, 169]. It has been used to decrease the risk of *Aspergillus* infection in patients with CGD [170]. Evidence on the value of adding interferon-γ as an adjunct treatment of IPA is limited to case reports and small reports, and there are no guidelines on its role in the treatment of IPA [171]. There was a concern about the use of interferon-γ in allogeneic HSCT recipients, since it may worsen GVHD; however, in a recent trial, GVHD actually improved during this therapy [172].

Granulocyte transfusion is another potential supportive therapy, especially for patients with prolonged neutropenia and life-threatening infections refractory to conventional therapy. It has been shown that it is safe for potential donors to donate neutrophils by granulocytophoresis, but there are no randomised studies that prove the benefit of adjuvant granulocyte transfusion in the treatment of IPA [173]. It is also important in patients with IPA, whenever possible, to decrease the dose of systemic corticosteroids and immunosuppressive agents.

The management of IPA is difficult, and an important approach to this problem is prophylaxis in patients at increased risk for IPA. Avoiding the hospitalisation of patients in areas where there is construction and the use of high-efficiency particulate air (HEPA) filtration, with or without laminar air flow ventilation, have both proven useful [174]. A meta-analysis suggested that itraconazole was effective in preventing fungal infections in neutropenic patients [175]. Recent studies confirmed the efficacy of posaconazole as IPA prophylaxis in patients with acute myelogenous leukaemia, myelodysplastic syndrome or HSCT [176–178]. Currently, chemoprophylaxis trials using other antifungal agents (such as voriconazole, caspofungin, micafungin, and inhaled amphotericin B formulation) are under way in high-risk patients [123].

## CHRONIC NECROTISING ASPERGILLOSIS

CNA, also called semi-invasive or subacute invasive aspergillosis, was first described by GEFTER *et al*. [179] and BINDER *et al*. [130] in 1981. It is an indolent, cavitary and infectious process of the lung parenchyma secondary to local invasion by *Aspergillus* species, usually *A. fumigatus* [128]. In contrast to IPA, CNA runs a slowly progressive course over weeks to months, and vascular invasion or dissemination to other organs is unusual. This syndrome is rare, and the available literature is based on case reports and small case series [128, 130, 179].

### *Risk factors*

CNA usually affects middle-aged and elderly patients with altered local defences, associated with underlying chronic lung diseases such as COPD, previous pulmonary tuberculosis, thoracic surgery, radiation therapy, pneumoconiosis, cystic fibrosis, lung infarction or sarcoidosis [180]. It may also occur in patients who are mildly immunocompromised due to diabetes mellitus, alcoholism, chronic liver disease, low-dose corticosteroid therapy, malnutrition, or connective tissue diseases such as rheumatoid arthritis and ankylosing spondylitis [130]. Mannose-binding lectin polymorphism may play a role in the pathogenesis of CNA [181]. It may be difficult to distinguish CNA from aspergilloma, especially if a previous chest radiograph is not available [182]. However, in CNA there is local invasion of the lung tissue and a pre-existing cavity is not needed, although a cavity with a fungal ball may develop in the lung as a secondary phenomenon due to destruction by the fungus. In a report of aspergillomas in AIDS patients, progression over time was seen, with considerable morbidity and some mortality [182]. This probably reflects the possibility that an aspergilloma may invade the cavity wall, causing local parenchyma destruction, as seen in patients with CNA [128]. Due to this overlap between the CNA and aspergilloma, some authors put them in one group called chronic cavitary pulmonary aspergillosis which is primarily a non- or semi-invasive disease that is seen mainly in nonimmunocompromised patients with chronic lung diseases [183].

### *Clinical presentation and diagnosis*

Patients frequently complain of constitutional symptoms such as fever, malaise, fatigue, and weight loss of 1–6 months' duration, in addition to chronic productive cough and haemoptysis, which varies from mild to severe [182]. Occasionally, CNA may be asymptomatic.

Imaging studies, such as chest radiograph and chest CT scan, usually show consolidation, pleural thickening and cavitary lesions in the upper lung lobes. Aspergilloma may be seen in nearly 50% of patients [130]. The adjacent pleural thickening may progress to form a broncho–pleural fistula, so it is considered an early indication of a locally invasive process [179, 184]. Characteristically, these radiological findings tend to progress over weeks to months [184].

The vast majority of patients with CNA have positive serum immunoglobuling (Ig)G antibodies to *A. fumigatus*, but this varies over time and may be negative at some points in the course of CNA [182]. Immediate skin reactivity for *Aspergillus* antigens is another helpful, but not diagnostic, test. Culture of sputum and bronchoscopy samples is usually positive for *Aspergillus* spp. [182].

Confirmation of the diagnosis requires a histological demonstration of tissue invasion by the fungus and the growth of *Aspergillus* species on culture. Pathologically, CNA is characterised by necrosis of lung tissue, acute or chronic inflammation of the cavity wall and presence of hyphae consistent with *Aspergillus* species [185]. The yield of transbronchial biopsy specimens or percutaneous aspirates is relatively poor, and a thoracoscopic or open-lung biopsy is rarely performed in these patients. As a result, confirmation of the diagnosis is commonly delayed, which may contribute to the morbidity and mortality associated with CNA. The combination of characteristic clinical and radiological findings and either serological results positive for *Aspergillus* or the isolation of *Aspergillus* from respiratory samples is highly indicative of CNA [186]. DENNING *et al*. [186] have proposed criteria for diagnosis of chronic pulmonary aspergillosis, including CNA (table 4).

### *Treatment*

The mainstay of treatment for CNA is the antifungal therapy (table 3). Amphotericin B was initially used in doses of 0.5–1 $mg^{-1}\cdot kg^{-1}\cdot day^{-1}$ (4–5 $mg\cdot kg^{-1}\cdot day^{-1}$ for the lipid formulation) with favourable results [128, 130]. Itraconazole later became an effective alternative to the relatively toxic amphotericin B [128, 129]. More recently, voriconazole has emerged as a primary therapy for CNA. In a recent prospective study, where voriconazole 200 mg was given twice daily for a period of 4–24 weeks as primary or salvage therapy for 39 patients with CNA [120], a complete or partial response was seen in 43% of patients, and improvement or stability was seen in 80%. The recent statement of the American Thoracic Society favours giving either voriconazole or itraconazole for mild to moderate disease until resolution or stabilisation of the clinical and radiographic manifestations, while in patients with severe disease, initial therapy with intravenous amphotericin B or intravenous voriconazole should be considered [123].

Evaluation of the response to treatment is best done by following clinical, radiological, serological and microbiological parameters [182]. Useful parameters of response include weight gain and enhanced energy level, improved pulmonary symptoms, falling inflammatory markers and total serum IgE level, improvement in paracavitary infiltrates, and eventually a reduction in cavity size [182].

Surgical resection has a minor role in the treatment of CNA, being reserved for healthy young patients with focal disease and good pulmonary reserves, patients not tolerating antifungal therapy and patients with residual localised but active disease despite adequate antifungal therapy. BINDER *et al*. [130] reported that 90% of patients who underwent surgical resection had good responses, but surgery was associated with significant post-operative complications.

The reported mortality of CNA varies widely and may be limited by incomplete follow-up [128]. Mortality was 39% in American reports, but less than 10% in European reports using itraconazole [128].

## ASPERGILLOMA

Aspergilloma is the most common and best-recognised form of pulmonary involvement by *Aspergillus* species, and it usually develops in a pre-existing cavity in the lung. The aspergilloma (fungus ball) is composed of fungal hyphae, inflammatory cells, fibrin, mucus, and tissue debris. The most common species of *Aspergillus* recovered from such lesions is *A. fumigatus*; however, other fungi, such as *Zygomycetes* and *Fusarium*, may cause the formation of a fungal ball. Many cavitary lung diseases are complicated by aspergilloma, including tuberculosis, sarcoidosis, bronchiectasis, bronchial cysts and bullae, ankylosing spondylitis, neoplasm, and pulmonary infection [187, 188]. Of these, tuberculosis is the most common [189]. In a study of 544 patients with pulmonary cavities secondary to tuberculosis, 11% had radiological evidence of aspergilloma [190]. Less frequently, aspergilloma has been described in cavities caused by other fungal infections [191, 192]. It is thought that inadequate

**TABLE 4** Diagnostic criteria for chronic necrotising aspergillosis

| Diagnostic criteria | Characteristics |
|---|---|
| **Clinical** | Chronic (>1 month) pulmonary or systemic symptoms, including at least one of: weight loss, productive cough or haemoptysis |
| | No overt immunocompromising conditions (*e.g.* haematological malignancy, neutropenia, organ transplantation) |
| **Radiological** | Cavitary pulmonary lesion with evidence of paracavitary infiltrate |
| | New cavity formation, or expansion of cavity size over time |
| **Laboratory** | Elevated levels of inflammatory markers (C-reactive protein, plasma viscosity or erythrocyte sedimentation rate). Isolation of *Aspergillus* spp. from pulmonary or pleural cavity, or positive serum *Aspergillus* precipitin test. Exclusion of other pulmonary pathogens, by results of appropriate cultures and serological tests, that are associated with similar disease presentation, including mycobacteria and endemic fungi |

Adapted from [186].

drainage can facilitate the growth of *Aspergillus* on the walls of these cavities.

The fungus ball may move within the cavity, but it does not usually invade the surrounding lung parenchyma or blood vessels, although exceptions have been noted [193, 194]. The lesion remains stable in the majority of cases, but it may decrease in size or resolve spontaneously without treatment in 10% of cases [195]. Rarely, the aspergilloma may increase in size.

### *Clinical presentation*

Most patients with aspergilloma are asymptomatic. When symptoms are present, most patients experience mild haemoptysis, but severe and life-threatening haemoptysis may occur, particularly in patients with underlying tuberculosis [196]. The mortality rate from haemoptysis related to aspergilloma ranges between 2–14% [197–201]. The source of bleeding is usually the bronchial blood vessels, and it may be caused by local invasion of blood vessels lining the cavity, endotoxins released from the fungus, or mechanical irritation of the exposed vasculature inside the cavity by the moving fungus ball [193, 202, 203]. Less commonly, patients may develop cough, dyspnoea that is probably more related to the underlying lung disease and fever that could be secondary to the underlying disease or bacterial superinfection.

Risk factors for poor prognosis of aspergilloma include the severity of the underlying lung disease, increase in size or number of lesions as seen on chest radiographs, immunosuppression (including corticosteroid therapy and HIV infection), increasing *Aspergillus*-specific IgG titres, recurrent large volume haemoptysis and underlying sarcoidosis [204].

### *Diagnosis*

The diagnosis of pulmonary aspergilloma is usually based on clinical and radiographic features along with serological or microbiological evidence of *Aspergillus* spp. Chest radiography is useful in demonstrating the presence of a mass in a pre-existing cavity. Aspergilloma appears as an upper-lobe, mobile, intra-cavitary mass with an air crescent in the periphery [205]. A change in the position of the fungus ball after moving the patient from supine to prone position is an interesting but variable sign [206]. Chest CT scan may be necessary to visualise aspergilloma that is not apparent on chest radiograph [206] (fig. 4). These radiological appearances may be seen in other conditions such as neoplasm, abscess, hydatid cyst and granulomatosis with polyangiitis (Wegener's granulomatosis). Aspergilloma may also coexist with any of the above-mentioned conditions [207, 208]. Sputum cultures for *Aspergillus* spp are positive only in 50% of cases [209]. Serum IgG antibodies to *Aspergillus* are positive in most cases but may be negative in patients on corticosteroid therapy [194]. *Aspergillus* antigen has been recovered from the BAL fluid of patients with aspergilloma, but the diagnostic value of this test is variable [210, 211].

### *Treatment*

Treatment is considered only when patients become symptomatic, usually with haemoptysis (table 3). There is no consensus on the best treatment approach. Inhaled, intracavitary and endobronchial instillations of antifungal agents have been tried and reported in small numbers of patients, but without consistent success [200, 212, 213]. CT-guided percutaneous administration of amphotericin B can be effective for aspergilloma, especially in patients with massive haemoptysis, and can lead to resolution within few days [214, 215]. The role of intravenous amphotericin B is uncertain; small studies failed to show a benefit [216].

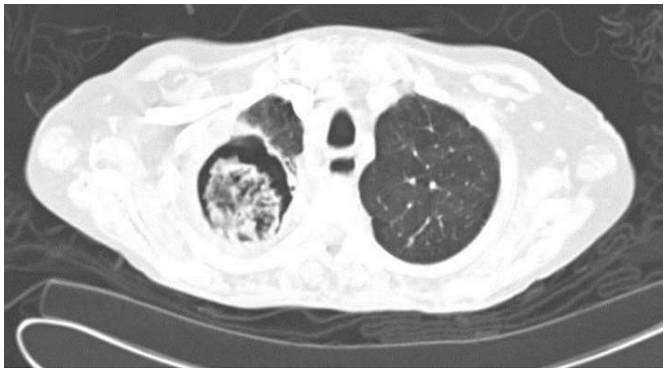

**FIGURE 4.** Chest computed tomography image showing a right upper lobe aspergilloma in a patient with sarcoidosis.

Itraconazole may be useful in the management of selected patients with aspergilloma because it has a high tissue penetration. Oral itraconazole has been used with radiographic and symptomatic improvement in one-half to two-thirds of patients. Occasionally patients have a complete response [136–138]. In one study, significant itraconazole levels within the aspergilloma cavities were demonstrated after using the standard dose of itraconazole (100–200 $mg \cdot day^{-1}$) [217]. The major limitation of itraconazole is that it works slowly and would not be useful in cases of life-threatening haemoptysis [210].

Surgical resection of the cavity and removal of the fungus ball is usually indicated in patients with recurrent haemoptysis, if their pulmonary function is sufficient to allow surgery. It is associated with relatively high mortality rates, ranging from 7–23% [132–135, 197, 198, 203]. The most common causes of death post-operatively are severe underlying lung disease, pneumonia, acute myocardial infarction, and IPA [135, 200]. Other post-operative complications include haemorrhage, residual pleural space, bronchoalveolar fistula, empyema and respiratory failure.

Bronchial artery embolisation should be considered as a temporary measure in patients with life-threatening haemoptysis, since haemoptysis usually recurs as a result of massive collateral blood vessels [131]. The role of newer antifungal azoles such as voriconazole in the treatment of aspergilloma has yet to be determined.

## ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS

Allergic bronchopulmonary aspergillosis (ABPA) is a pulmonary disease that results from hypersensitivity to *Aspergillus* antigens, mostly due to *A. fumigatus*. The majority of cases occur among people with asthma or cystic fibrosis. It is estimated that 2% of asthmatics, and 7–14% of corticosteroid-dependent asthmatics have ABPA. Also the incidence of ABPA is higher in patients with atopy [218]. In the case of cystic fibrosis, 1–15% of patients may develop ABPA [219–222].

Sensitisation to *Aspergillus* antigens is an important phenomenon in asthmatics, especially those with atopy. In a meta-analysis of 21 studies, the prevalence of sensitisation to *Aspergillus* antigens in selected patients with asthma was 28% [223]. The prevalences of ABPA in patients with asthma and those with *Aspergillus* hypersensitivity were 12.9% and 40%, respectively. In addition to increasing the risk of ABPA, sensitisation to *Aspergillus* antigens appears to increase the severity of asthma. In a study of 105 patients with asthma, 28.5% of patients were sensitised to *Aspergillus* antigens [224]. About one-third of this group had ABPA. Patients with sensitisation to *Aspergillus* antigens had significantly more severe airflow obstruction and more prescriptions for oral corticosteroids. Similar findings were reported in another study from Cleveland (OH, USA) and London (UK) [225]. These observations suggest that it is crucial to screen asthmatic patients for sensitisation to *Aspergillus* antigens and to monitor these patients more closely and exclude the presence of ABPA. Among patients with cystic fibrosis, ABPA is more commonly seen in those who are males, have a history of asthma or atopy, have lower lung function or have *Pseudomonas* in sputum cultures [220].

The pathogenesis of ABPA is not completely understood. There does not appear to be a correlation between *Aspergillus* load in the environment and the development of ABPA [226]. Many immune responses appear to be involved, including *Aspergillus*-specific IgE-mediated type I hypersensitivity reactions, specific IgG-mediated type III hypersensitivity reactions, and abnormal T-lymphocyte responses [227–230].

### *Clinical presentation and diagnosis*

ABPA is usually suspected on clinical grounds. The diagnosis is confirmed by radiological and serological testing. Almost all patients have clinical asthma, and patients usually present with episodic wheezing, expectoration of sputum containing brown plugs, pleuritic chest pain, and fever [231]. Chest radiograph may be normal in the early stages of the disease. During acute exacerbations, fleeting pulmonary infiltrates are a characteristic feature of the disease that tend to appear in the upper lobe and are central in location. Due to mucoid impaction of the airways, there may be transient areas of opacification, which may present as band-like opacities emanating from the hilum with rounded distal margin (gloved finger appearance) [232]. The ''ring sign'' and ''tram lines'' are radiological signs that represent the thickened and inflamed bronchi and may be seen in chest radiography. At later stages, central bronchiectasis and pulmonary fibrosis may develop. Chest HRCT is helpful for better defining bronchiectasis and is also more sensitive in demonstrating the above changes (fig. 5). Typically, total serum IgE is elevated (usually >1000 IU·mL$^{-1}$), and sputum cultures reveal *Aspergillus* spp. Serum IgE could be used as a marker for flare-ups and response to therapy [233]. However a positive sputum culture is not necessary to diagnose ABPA. Immediate skin test reactivity to *A. fumigatus* antigens and elevated levels of serum IgG and IgE antibodies to *Aspergillus* are usually documented [227]. Although pulmonary function tests are not characteristic of ABPA, they usually show reversible obstructive lung disease that may become irreversible in later stages. Restrictive lung disease with reduction in diffusion capacity may be observed during acute exacerbations or late stages. Pulmonary function tests may be useful in following up the progress of disease over time. Bronchoscopy is not necessary for the diagnosis of ABPA; however, if performed, BAL may show increased levels of eosinophils and IgE concentration. *Aspergillus* may rarely be detected on fungal stain or culture [234].

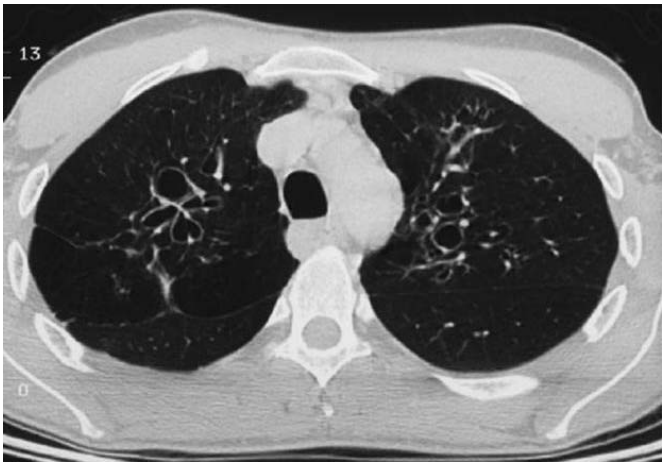


**FIGURE 5.** Chest computed tomography image showing central bronchiectasis in a patient with allergic bronchopulmonary aspergillosis.

Lung biopsies are rarely performed since ABPA is usually suspected on clinical rounds [230]. In one pathological study, 18 specimens were taken from patients diagnosed with ABPA and the most significant findings were involvement of the bronchi and bronchioles, with bronchocentric granulomas in 15 specimens and mucoid impaction in 11 [235]. Other findings included granulomatous inflammation consisting of palisading histiocytes surrounded by lymphocytes, plasma cells, and eosinophils. Fungal hyphae were seen, but without evidence of tissue invasion [235]. ROSENBERG *et al.* [231] and GREENBERGER *et al.* [233] have standardised the criteria for the diagnosis of ABPA (table 5), not all of which need to be present for the diagnosis to be made.

As delayed treatment may result in irreversible pulmonary damage, early detection and treatment of ABPA before the development of all clinical symptoms and bronchiectasis is paramount. Patients with ABPA can be subdivided into two groups: patients with or without central bronchiectasis (CB)

**TABLE 5** Diagnostic criteria for allergic bronchopulmonary aspergillosis

| |
|---|
| Asthma |
| Immediate skin reactivity to *Aspergillus* |
| Serum precipitins to *Aspergillus fumigatus* |
| Increased serum IgE and IgG to *Aspergillus fumigatus* |
| Total serum IgE >1000 IU·mL$^{-1}$ |
| Current or previous pulmonary infiltrates |
| Central bronchiectasis |
| Peripheral eosinophilia (1000 cells·μL$^{-1}$) |

Ig: immunoglobulin. Adapted from [231, 233].

(ABPA-CB and ABPA-seropositive, respectively) [1]. The minimum essential criteria to diagnose patients with ABPA-CB include asthma, immediate skin reactivity to *Aspergillus* antigens, serum IgE level >1,000 ng·mL$^{-1}$ and central bronchiectasis. The minimum criteria to diagnose ABPA-seropositive patients include asthma, immediate skin reactivity to *Aspergillus* antigens, serum IgE >1,000 ng·mL$^{-1}$, history of pulmonary infiltrates and elevated levels of serum IgE or IgG antibodies to *A. fumigatus* [236].

PATTERSON *et al*. [237] have also subdivided ABPA into five stages on the basis of clinical course, which helps to guide the management of the disease [237]. These stages do not need to occur in order. The first four are potentially reversible with no long-term sequel. Stage I, the acute stage, is the initial acute presentation with asthma, elevated IgE level, peripheral eosinophilia, pulmonary infiltrates, and IgE and IgG antibodies to *A. fumigatus*. In practice, patients are seldom identified in this stage. In stage II, the remission stage, the IgE falls but usually remains elevated, eosinophilia is absent, and the chest radiograph is clear. Serum IgG antibodies to *Aspergillus* antigen may be slightly elevated. Stage III, the exacerbation stage, is the recurrence of the same findings as in stage I in patients known to have ABPA. IgE rises to at least double the baseline level. Stage IV, the corticosteroid-dependent stage, occurs in patients who have asthma dependent on chronic use of high-dose corticosteroid therapy. Exacerbations are marked by worsening asthma, radiographic changes and a potential increase in IgE levels. Frequently, the chest CT scan will show central bronchiectasis. Unfortunately, most patients are diagnosed at this stage [238]. In stage V, the fibrotic stage, bronchiectasis and fibrosis develop usually leading to irreversible lung disease. Patients in this stage may present with dyspnoea, cyanosis, rales, and cor pulmonale. Clubbing may be present. The serum IgE level and eosinophil count might be low or high. Fortunately, few patients progress to this stage.

### *Treatment*

Treatment of ABPA aims to treat acute exacerbations of the disease and limit progressive lung disease and bronchiectasis. Oral corticosteroids are the main treatment for ABPA (table 3). They suppress the hypersensitivity and inflammatory response provoked by *A. fumigatus* rather than eradicating the organism. Treatment with corticosteroids leads to the relief of bronchospasm, the resolution of radiographic infiltrates and a reduction in serum total IgE and peripheral eosinophilia [139, 140]. 2 weeks of daily therapy of oral prednisone (0.5 mg·kg$^{-1}$·day$^{-1}$), followed by gradual tapering, has been recommended for new ABPA-related infiltrates [141, 142]. The duration of therapy should be individualised according to the patient's clinical condition. However, most patients require prolonged low-dose corticosteroid therapy to control their symptoms and decrease the rate of relapse [141, 142]. Total serum IgE serves as a marker of ABPA disease activity. It should be checked 6–8 weeks after the initiation of therapy and then every 8 weeks for 1 year after that to determine a baseline range for each individual patient [239]. Inhaled corticosteroids may help to control symptoms of asthma, but small studies have failed to demonstrate the efficacy of inhaled corticosteroids in preventing the progression of lung damage in patients with ABPA [240, 241].

Several studies have been done on the utility of the antifungal agent itraconazole in the management of patients with ABPA. It has been effective in improving symptoms, facilitating weaning from corticosteroids, decreasing *Aspergillus* titres and improving radiographic abnormalities and pulmonary function [210]. A randomised, double-blind, placebo-controlled trial of itraconazole 200 mg twice daily for 16 weeks for patients with ABPA already receiving corticosteroids was recently conducted by STEVENS *et al*. [143]. 46% of patients treated with itraconazole achieved significant response, defined as a reduction of at least 50% in the corticosteroid dose, decrease of at least 25% in the serum IgE concentration, and one of the following: a 25% improvement in exercise tolerance or pulmonary function test results or partial or complete resolution of pulmonary infiltrates. Of note, however, itraconazole may augment the activity of corticosteroids *via* inhibition of their metabolism, which may lead to abnormal adrenocorticotropic hormone stimulation and adrenal insufficiency [242]. Recently, voriconazole has also been tried in the treatment of ABPA and showed a favourable therapeutic response in the few case reports available [144–146]. In one study of small number of children with cystic fibrosis and ABPA, voriconazole treatment demonstrated significant clinical and serological improvements [243]. Randomised trials are needed to assess the efficacy of voriconazole in the management of ABPA. Few case reports have described the beneficial use of the anti-IgE monoclonal antibody (omalizumab) in patients with ABPA. They have shown rapid improvement of the respiratory symptoms and lung function [244, 245].

## PULMONARY *ASPERGILLUS* OVERLAP SYNDROMES

The above-mentioned *Aspergillus* syndromes may co-exist (*e.g.* fungal balls in patients with ABPA) or may progress from one entity to another (*e.g.* IPA in a patient with ABPA) (fig. 6). These *Aspergillus* overlap syndromes have been reported in case reports or small case series. The proposed mechanisms for the development of *Aspergillus* overlap syndromes include coincidence, the presence of severe underlying lung disease (*e.g.* a patient with aspergilloma who develops CNA), corticosteroid therapy (IPA in a patient with aspergilloma or ABPA), or *Aspergillus* fungal load. It is also possible that genetic factors may predispose patients to progress from one form of aspergillosis to another. For example, CFTR gene mutation may lead to ABPA, and mannose-binding lectin gene mutations may result in CNA or IPA. Viral illnesses (in a patient with ABPA or aspergilloma) have been rarely reported as a risk factor for IPA [183].

The emergence of fungal balls in patients with ABPA has been reported infrequently in the literature. It may occur as an early event as well as a late phenomenon. In early cases, the bronchiectatic areas affected by ABPA may enlarge to form cavities that colonise with *Aspergillus* spp., creating fungal balls that may present as haemoptysis and/or a cavitary mass [142, 246]. The knowledge that aspergillomas may develop in patients with ABPA helps avoid unnecessary invasive procedures to rule out alternative aetiologies, such malignancy or tuberculosis. Fungal balls may also be a late finding in patients with fibrosis and cavitation associated with long-standing or poorly treated ABPA. In some of these patients, this aspergilloma could be due to concomitant fibrocavitary disease [247] (such as tuberculosis)

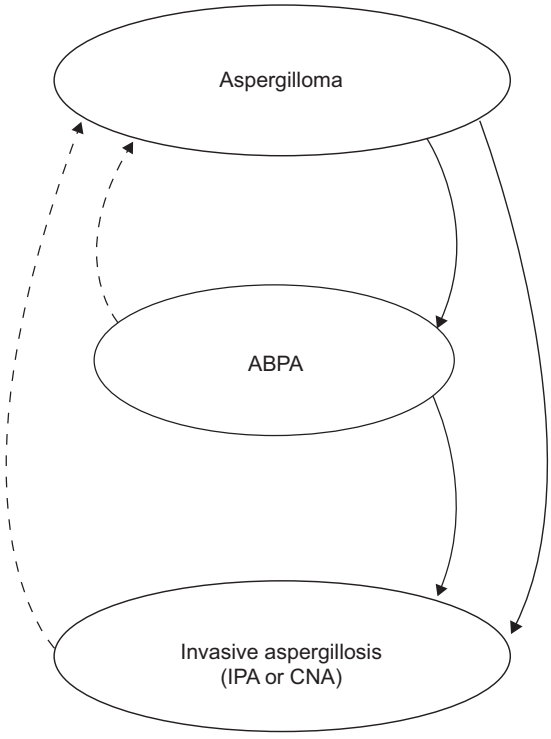


**FIGURE 6.** Clinical scenarios of *Aspergillus* overlap syndromes in the lungs. ABPA: allergic bronchopulmonary aspergillosis; IPA: invasive pulmonary aspergillosis; CNA: chronic necrotising aspergillosis.

that was activated by steroid therapy for ABPA which would accelerate the fibrocavitary changes and the development of fungal balls [142, 248]. In some cases, fungal balls may precede ABPA, and may also have a role in the pathogenesis of ABPA in susceptible hosts. There are reports of patients who developed aspergilloma or CNA associated with pre-existing fibrocavitary disease (such as tuberculosis or sarcoidosis) and later developed ABPA [249]. It is possible that the overgrowth of *Aspergillus* species in these cavities triggers a hypersensitivity reaction in susceptible patients, leading to ABPA. Concurrent ABPA and aspergilloma is likely to increase the severity of the disease with more frequent exacerbations of asthma and possibly increased risk of haemoptysis [250]. Such patients should be monitored carefully and antifungal therapy or resection of the aspergilloma may be necessary in symptomatic patients [250, 251].

IPA in patients with ABPA has been reported sporadically in the literature. In some reports, the invasion by *Aspergillus* species is restricted to the tissues surrounding the bronchiectatic segments with granulomatous reaction [252–254]. Some of these cases are more likely to represent the semi-invasive form of CNA rather than IPA due to their chronic courses. This local invasion by *Aspergillus* probably develops as a result of chronic immunosuppression because of corticosteroids and/or the presence of underlying chronic lung disease. Disseminated IPA has rarely been described in patients with ABPA [255, 256]. Few case reports describe patients with cystic fibrosis on high-dose corticosteroids who acquire a viral infection, like influenza, predisposing them to IPA [257, 258]. However, given the paucity of literature about these cases there are no validated predictors for the development of IPA in patients with ABPA.

*Aspergillus* species may also play a role in the pathogenesis of other pulmonary conditions that are not part of the characteristic diseases caused by this fungus. Although these conditions are thought to develop independently from the *Aspergillus* species, there is evidence that the fungus may be implicated in some cases. These diseases include IgE-mediated asthma, hypersensitivity pneumonitis, mucoid impaction in bronchus and bronchocentric granulomatosis.

## STATEMENT OF INTEREST

None declared.

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