

Chapter 5 – Aspergillosis: from diagnosis to treatment*

Capítulo 5 – Aspergilose: do diagnóstico ao tratamento

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Abstract

Aspergillosis is a multifaceted disease whose clinical manifestations (allergic, saprophytic and invasive forms) are determined by the host immune response. Allergic bronchopulmonary aspergillosis is characterized by corticosteroid-dependent asthma, fever, hemoptysis and destruction of the airways, which can evolve to fibrosis with honeycombing. The treatment consists of the combined use of a corticosteroid and itraconazole. Invasive pulmonary aspergillosis, which has a worse prognosis, is diagnosed based on histopathological documentation and positive culture of a sterile specimen. The treatment response obtained with voriconazole is better, in terms of survival and safety, than that obtained with amphotericin B. In patients with chronic pulmonary disease who are mildly immunocompromised, chronic necrotizing pulmonary aspergillosis causes progressive destruction of the lung. Such patients are treated with oral itraconazole. Chronic cavitary pulmonary aspergillosis causes multiple cavities, with or without aspergilloma, accompanied by pulmonary and systemic symptoms. In patients with chronic pulmonary disease, the aspergilloma is characterized by chronic productive cough and hemoptysis, together with a cavity containing a rounded, sometimes mobile, mass separated from the cavity wall by airspace. Surgical resection is the definitive treatment for both types of aspergillosis. Triazole fungicides provide long-term treatment benefits with minimal risk.

Keywords: Aspergillosis; Pulmonary aspergillosis; Lung diseases, fungal.

Resumo

A aspergilose é uma doença multifacetada cujas manifestações clínicas são determinadas pela resposta imune do hospedeiro; podem se apresentar de forma alérgica, saprofítica ou invasiva. A aspergilose broncopulmonar alérgica caracteriza-se por asma corticoide dependente, febre, hemoptise e destruição da via aérea, que pode progredir para fibrose com faveolamento. O tratamento consiste da associação de corticosteroide e itraconazol. A aspergilose pulmonar invasiva requer documentação histopatológica e cultura positiva de material estéril para o diagnóstico. Possui pior prognóstico. O voriconazol apresenta melhor resposta terapêutica, proporcionando maior sobrevida e segurança do que a anfotericina B. A aspergilose pulmonar necrotizante crônica causa destruição progressiva do pulmão em pacientes com doença pulmonar crônica e leve grau de imunossupressão. O tratamento é realizado com itraconazol oral. A aspergilose pulmonar cavitária crônica causa múltiplas cavidades, contendo ou não aspergilloma, associadas a sintomas pulmonares e sistêmicos. O aspergilloma é caracterizado por tosse produtiva crônica e hemoptise em portadores de doença pulmonar crônica, associados a uma cavidade contendo massa arredondada, às vezes móvel, e separada da parede por espaço aéreo. A ressecção cirúrgica é o tratamento definitivo para ambas. Antifúngicos triazólicos promovem benefício terapêutico a longo prazo com risco mínimo.

Descritores: Aspergilose; Aspergilose pulmonar; Pneumopatias fúngicas.

Introduction

Aspergillus spp. are fungi of universal distribution in nature, and the most common site of infection is the airway; the fungi have emerged as the cause of severe and life-threatening infection in immunocompromised patients.⁽¹⁻³⁾ This

increasing population is represented by patients with advanced HIV infection, prolonged neutropenia and primary immunodeficiency, as well as by lung transplant recipients and bone marrow transplant recipients.⁽¹⁾

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Microorganism: Impact of the species

Historically, *A. fumigatus* is the most common causative agent of the various forms of presentation of aspergillosis.⁽¹⁾ However, there has been a progressive increase in aspergillosis that is caused by other species, such as *A. flavus*, *A. niger* and *A. terreus*, the last being resistant to amphotericin B.⁽²⁾

Clinical manifestations

Clinical manifestations are determined by the host immune response and are classically defined as the invasive form, the saprophytic form and the allergic form.^(1,2)

Clinical syndromes, diagnosis and treatment

Allergy

There is cumulative evidence for asthma caused by *Aspergillus* spp., as well as for the association between *Aspergillus* spp. and severe and lethal asthma.⁽²⁾

Allergic bronchopulmonary aspergillosis

Allergic bronchopulmonary aspergillosis constitutes a form of pulmonary hypersensitivity associated with destruction of the airways in response to *Aspergillus* spp. It is characterized by episodes of acute corticosteroid-responsive asthma or of corticosteroid-dependent asthma with unusual symptoms of fever and hemoptysis accompanied by destruction of the airways. If treated inappropriately, permanent lung injury progresses to fibrosis.^(1,2)

Diagnosis

The diagnostic criteria are as follows: episodic bronchial obstruction; peripheral eosinophilia; presence of specific antibodies against *Aspergillus* spp. antigen; immediate skin reaction to *Aspergillus* spp. antigen; elevated serum levels of IgE; pulmonary infiltrates that resolve with corticosteroids; and central bronchiectasis. The secondary diagnostic criteria are as follows: detection of *Aspergillus* spp. in respiratory specimens; expectoration of bronchial casts; elevated levels of specific IgE against *Aspergillus* spp.; and late skin reaction.

Key recommendations

The treatment consists of the combined use of a corticosteroid and itraconazole.⁽¹⁾

The corticosteroid improves pulmonary function and reduces the number of episodes of recurrent consolidation.

The use of itraconazole (200 mg p.o. every 12 h for 16 weeks) reduces the required dose of corticosteroid, eosinophilia and IgE concentration, improving pulmonary function and the quality of life.

Invasive pulmonary aspergillosis

Invasive pulmonary aspergillosis (IPA) has emerged as an infectious disease of high morbidity and mortality in immunocompromised patients.^(1,2)

Diagnosis

Confirmation through culture is important in order to distinguish IPA from infections caused by the following: other filamentous fungi; *Scedosporium* spp.; and *Fusarium* spp. The positive predictive value of culture of a nonsterile respiratory specimen increases with increased immunosuppression.^(1,2)

Blood culture is of limited use due to negative results even in disseminated infection.

The use of BAL fluid, percutaneous transthoracic needle biopsy sample and video-assisted thoracoscopy biopsy sample is a standard procedure to diagnose IPA. False-negative results can occur in situations of previous use of antifungal agents or when the procedure cannot reach the affected area.^(1,2)

Since the histological finding of septate hyaline hyphae with 90°C ramifications is not specific for *Aspergillus* spp., other methods, such as PCR, might be necessary to identify the fungus.^(1,2)

The identification of the halo sign and of the air crescent sign on a CT scan of the chest facilitates the diagnosis of IPA in neutropenic patients with hematologic diseases. Other infectious diseases present these signs and should be included in the differential diagnosis (zygomycetes, *Fusarium* spp., *Scedosporium* spp., *Pseudomonas aeruginosa* and *Nocardia* spp.).^(1,2)

The detection of galactomannan, a cell wall polysaccharide of *Aspergillus* spp., contributes as a diagnostic marker for IPA in the absence

of culture. This test is quite sensitive for IPA in patients with hematologic malignant disease. In 2003, two groups of authors reported a sensitivity of 73% and 66.7% and a specificity of 96% and 98%, respectively. The positive predictive values and negative predictive values were, respectively, 73% and 98% and 66.7% and 98%.^(4,5) In addition to facilitating an early diagnosis, serial antigenemia with galactomannan can aid in the evaluation of the therapeutic response. Therefore, the duration of the treatment can be determined by the normalization of antigenemia, as well as by the resolution of clinical and radiological symptoms.^(1,2)

The combination between antigenemia and a CT scan of the chest should allow early diagnosis and treatment.^(1,2)

Another potential marker is β -d-glucan. The presence of β -d-glucan translates to invasive fungal infection; the test, however, is not specific.^(1,2)

The use of PCR is promising; however, it has yet to be standardized.^(1,2)

Key recommendations

The diagnosis is confirmed by histopathological documentation of the infection and by positive culture of a sterile specimen.⁽⁶⁾

A presumed diagnosis is established based on three criteria: host risk factors; clinical and radiological manifestations; and microbiological evidence (culture/antigenemia).

Treatment

Due to the potential for disease progression, it is recommended that treatment be initiated early (while the diagnostic evaluation is still underway) in cases of high suspicion.

A randomized controlled clinical trial showed that the treatment response obtained with voriconazole is better, in terms of survival and safety, than that obtained with amphotericin B.^(1,6,7)

Voriconazole is indicated as the treatment of choice. The intravenous formulation is recommended for patients with severe disease.⁽⁸⁾

Voriconazole is also indicated as the treatment of choice in cases of uncommon manifestations of invasive aspergillosis, such as osteomyelitis and endocarditis.⁽⁸⁾

Liposomal amphotericin B can be an alternative to the treatment of choice in some cases.⁽¹⁾

In cases of liver disease or other contraindication to the use of voriconazole, the lipid formulations of amphotericin B are effective and less toxic than are conventional formulations.⁽¹⁾

In refractory cases, disease management includes changing the route of administration to i.v. administration, monitoring the levels of the medication and changing the class of medication or the combination of drugs (or a combination of the two).⁽¹⁾

In cases of intolerance or refractoriness, the diagnosis should always be confirmed, and the lipid formulations of amphotericin B, posaconazole or itraconazole are indicated, except in cases of previous use of voriconazole, caspofungin or micafungin.⁽¹⁾

Combination therapy is not routinely recommended as the treatment of choice. However, the recommendation is valid in cases of intolerance or refractoriness.⁽¹⁾

The primary treatment of infection caused by *A. terreus* consists of administering triazole derivatives, which is due to the resistance of this fungus to amphotericin B.⁽¹⁾

The duration of the treatment has yet to be defined. However, it generally ranges from 6 to 12 weeks. In immunocompromised patients, the medication should be maintained until immunosuppression has improved and the lesions are reabsorbed.⁽¹⁾

The therapeutic response is monitored through the evaluation of the signs, symptoms and radiological findings at regular intervals. A progressive increase in antigenemia translates to a poor prognosis; however, the normalization of antigenemia cannot be adopted as the single criterion for treatment cessation.⁽¹⁾

For patients who received previous treatment for IPA and who will be submitted to immunosuppression, the use of an antifungal agent prevents recurrent infection.⁽¹⁾

In cases of chronic immunosuppression, antifungal therapy during immunosuppression seems to be associated with a more favorable progression. Antigenemia with galactomannan constitutes a promising resource.⁽¹⁾

Surgical resection should be considered in cases of lesions that are contiguous with the great vessels or with the pericardium (or with a combination of the two), in cases of solitary lesion that causes hemoptysis or in cases of chest wall invasion.⁽¹⁾

Factors that increase the risk of death

The following are factors that increase the risk of death: infection after transplantation; transplant rejection; neutropenia; infection caused by cytomegalovirus; prolonged use of corticosteroids and immunosuppressants; disseminated IPA; monocytopenia; fungal load; accompanying pleural effusion; renal failure; recurrent bacterial infection; and advanced age.⁽¹⁾

IPA and COPD

The occurrence of IPA in patients without known risk factors, such as in patients with COPD, is currently increasing. The chronic use of oral corticosteroids at a mean dose higher than 20 mg/day, exacerbation of the disease, antibiotic therapy and comorbidities are some of the risk factors.^(3,9)

Diagnosis

The diagnosis is established through the isolation of hyphae of *Aspergillus* spp. from tissue or from a sterile specimen, in association with a consistent clinical profile.

A presumed diagnosis is established through the isolation of *Aspergillus* spp. from culture or from cytologic material from respiratory secretions (sputum, BAL fluid and tracheal aspirate), in association with a consistent clinical and radiological profile.

The radiological profile presents alterations in 78% of the cases. An X-ray/CT scan of the chest reveals infiltration/consolidation in 43% of the cases, cavitary lesions in 20% of the cases and multiple nodules or a solitary nodule in 4% of the cases. The halo sign is more common in neutropenic patients, in the acute phase (first week) of IPA.

Microbiology/serology/PCR

The positive predictive value of a positive culture for *Aspergillus* spp. in a nonsterile respiratory specimen is proportional to the immune status of the patient. The test is highly predictive in immunocompromised patients and can indicate the need for antifungal therapy.

The presence of *Aspergillus* spp. in secretions from the lower respiratory tract should be carefully evaluated in order to rule out IPA. A

negative culture in these specimens does not rule out the diagnosis. In such cases, a consistent clinical profile, chest CT scan findings, serology results and bronchoscopy results should be taken into consideration. Critically ill patients should receive antifungal therapy.

In COPD patients, BAL fluid that is positive for *Aspergillus* spp., with or without transbronchial biopsy, can be useful in the diagnosis and treatment of patients who are clinically and radiologically suspected of having IPA and who do not respond to conventional antibiotic therapy.

The positive predictive values and negative predictive values for antigenemia with galactomannan range from 25 to 62% and from 92 to 98%, respectively.

The positive predictive values and negative predictive values for PCR in blood samples and in BAL fluid range from 67 to 100% and from 55 to 95%, respectively. The PCR cannot distinguish colonization from infection.

A literature review of 65 cases of COPD with IPA showed that 43 patients had a confirmed diagnosis of IPA, and 22 had a presumed diagnosis of IPA; 46 (71%) were treated with antifungal agents, and 19 (30%) were treated with multiple agents. Of the 65 patients, 49 (91%) died (probably as a result of delayed diagnosis, advanced age, comorbidities or impaired pulmonary reserve), and 31 (48%) were submitted to mechanical ventilation. All of those who survived presented confirmed IPA.

IPA and immunosuppression

The reversion of immunosuppression is a key factor to the success of IPA treatment.⁽¹⁾

Patients with prolonged neutropenia (> 10 days) and at risk for IPA can benefit from the use of GM-CSF.

There are reports of individual cases of IFN- δ use in combination with an antifungal agent as an adjuvant therapy for IPA in immunocompromised patients without neutropenia, particularly in those with chronic granulomatous disease.

The discontinuation or reduction in the dose of the corticosteroid is critical to the success of IPA treatment.

Chart 1 – Summary of the recommendations for the treatment of aspergillosis.^(1,8)

Form of presentation	Treatment		Observations
	Treatment of choice	Alternative	
IPA	Voriconazole: 6mg/kg i.v. 12/12 h, followed by 4 mg/kg i.v. 12/12 h and 200 mg p.o. 12/12 h	LAB: 3-5 mg • kg ⁻¹ • day ⁻¹ i.v.; ABLC: 5 mg • kg ⁻¹ • day ⁻¹ i.v.; Caspofungin: attack: 70 mg/day i.v., followed by 50 mg/day i.v.; Itraconazole: dose depends on the formulation Similar to IPA	Since treatment is prolonged, oral administration of a triazole (voriconazole or itraconazole) is preferred
Tracheobronchial aspergillosis	Similar to IPA		
Chronic: CNPA	Similar to IPA	Similar to IPA	
Chronic: Aspergilloma	Surgical resection	Itraconazole or voriconazole, at a dose similar to that for IPA	
Chronic: CCPA	Itraconazole or voriconazole	Similar to IPA	Similar to CNPA.
Complex aspergilloma			Surgical resection might result in high morbidity and mortality
ABPA	Itraconazole	Voriconazole: 200 mg p.o. 12/12 h Similar to IPA	Association with a corticosteroid
Empirical treatment for IA	LAB: 3-5 mg • kg ⁻¹ • day ⁻¹ i.v.; ABLC: 5 mg • kg ⁻¹ • day ⁻¹ i.v.; Caspofungin: attack: 70 mg/day i.v., followed by 50 mg/day i.v.; Itraconazole: 200 mg/day i.v. or 12/12 h; Voriconazole: 6 mg/kg i.v. 12/12 h, followed by 3 mg/kg i.v. 12/12 h and 200 mg p.o. 12/12 h Posaconazole: 200 mg 8/8 h		Use in populations at high risk for IA
IA prophylaxis		Itraconazole: 200 mg i.v. 12/12 h/2 days; then: 200 mg/day i.v. or 200 mg p.o. 12/12h; Micafungin: 50 mg/day i.v.	Effective in patients with neutropenia, AML and myelodysplastic syndrome

IPA: invasive pulmonary aspergillosis; LAB: liposomal amphotericin B; ABLC: amphotericin B lipid complex; CNPA: chronic necrotizing pulmonary aspergillosis; CCPA: chronic cavity pulmonary aspergillosis; ABPA: allergic bronchopulmonary aspergillosis; IA: invasive aspergillosis; and AML: acute myeloid leukemia.

Empirical treatment of neutropenic patients suspected of having IPA

Key recommendations

Empirical treatment with liposomal amphotericin B, voriconazole, itraconazole or caspofungin is recommended for high-risk patients with prolonged neutropenia and persistent fever despite broad-spectrum antibiotic therapy (Chart 1) and should be administered while the diagnostic investigation is conducted.⁽¹⁾

The empirical treatment is not recommended for patients with short-term neutropenia (< 10 days), except when there are findings suggestive of IPA.

IPA prophylaxis

The selection of high-risk patients is a challenge.

Posaconazole is recommended for bone marrow transplant recipients presenting with transplant rejection and prolonged use of high doses of corticosteroids; and for patients with acute myeloid leukemia or myelodysplastic syndrome who are at high risk for IPA.⁽¹⁾

Itraconazole might be effective; however, tolerability limits its use.

Tracheobronchial aspergillosis

Patients with HIV and those with neutropenia, as well as lung transplant recipients, are at risk for tracheobronchial aspergillosis. There are three forms of presentation: the obstructive form, the pseudomembranous form and the ulcerative form.⁽¹⁾

Diagnosis

Bronchoscopy is the most important initial test, and a CT scan of the chest is useful to evaluate whether the progression of the lesion in the airway has been halted.

Early treatment prevents rupture of the bronchial anastomosis and graft loss, as well as resolving ulcerative lesions in lung transplant recipients.

Key recommendations

Voriconazole is recommended as the treatment of choice.⁽¹⁾

Due to the nephrotoxicity of conventional amphotericin B, liposomal amphotericin B is recommended for lung transplant recipients.

A reduction in the level of immunosuppression is important to improve the therapeutic response.

The use of aerosol amphotericin B might be beneficial because the aerosol releases high concentrations of the medication at the site of infection; however, the procedure has yet to be standardized.

Chronic necrotizing pulmonary aspergillosis

The hallmark of chronic necrotizing pulmonary aspergillosis (CNPA) is the slowly progressive destruction of the lung in patients with chronic pulmonary disease who are mildly immunocompromised, as occurs in cases of prolonged use of systemic corticosteroids or in cases of diabetes.

There is stronger evidence for treatment with oral itraconazole.

Because pharmacological treatment is prolonged, the preferred route of administration is p.o.

Other types of treatment have been described, and these include intracavitary instillation of amphotericin B and, more recently, the use of voriconazole.

Chronic and saprophytic forms: Chronic cavitory pulmonary aspergillosis (complex aspergilloma) and aspergilloma

Patients with chronic cavitory pulmonary aspergillosis or aspergilloma present with underlying pulmonary disease, tuberculous cavitory lesion, histoplasmosis, sarcoidosis, emphysematous bullae or fibrotic lung disease.⁽¹⁾

The complications that pose risk of death include hemoptysis, pulmonary fibrosis and invasive aspergillosis.

Aspergilloma

Aspergilloma is a conglomerate of hyphae of *Aspergillus* spp., mucus, fibrin and cell remnants within pulmonary cavities, cysts and areas of bronchiectasis.

Diagnosis

In patients with chronic pulmonary disease, aspergilloma is characterized by chronic produc-

tive cough and hemoptysis, together with a radiological alteration characterized by a cavity containing a rounded, sometimes mobile, mass of liquid density separated from the cavity wall by airspace (the air crescent sign). Pleural thickening adjacent to the cavity is also observed.

Chronic cavitary pulmonary aspergillosis (complex aspergilloma)

Chronic cavitary pulmonary aspergillosis presents with multiple cavities (with or without aspergilloma) associated with pulmonary and systemic symptoms and with an increase in inflammatory markers. If left untreated, these cavities can increase in size and coalesce. The differential diagnosis should include CNPA.

Treatment for simple aspergilloma and complex aspergilloma

Case reports and uncontrolled clinical trials have been recently published and are currently available.

Surgical resection is the definitive treatment for simple aspergilloma. However, it should be chosen only in special cases of complex aspergilloma due to high morbidity and mortality. The use of itraconazole, of voriconazole and, presumably, of posaconazole provides some therapeutic benefit and minimal risk for those who are not selected for surgery.

Bronchial artery embolization is recommended for those who have life-threatening hemoptysis and who should receive pharmacological or surgical treatment in case hemoptysis stabilizes.

Endobronchial or intracavitary instillation of amphotericin B has been reported to be somewhat successful in isolated cases.

Prolonged, possibly lifelong, antifungal therapy with itraconazole or voriconazole is recommended for patients with chronic cavitary pulmonary aspergillosis.

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