

## Chapter 8 – Fungal infections in immunocompromised patients\*

Capítulo 8 – Infecções fúngicas em imunocomprometidos

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### Abstract

Pulmonary complications are the most common cause of morbidity and mortality in immunocompromised patients, who lack of the basic mechanisms of cellular defense. Regardless of the cause of the immunodeficiency, the most common complications are infections (bacterial, viral or fungal). Among the fungal infections, aspergillosis is the most common (incidence, 1-9%; mortality, 55-92%) following organ transplant. Although pulmonary involvement is the most common form of aspergillosis, central nervous system involvement and sinusitis are not uncommon. On CT scans, the halo sign represents an area of low attenuation around the nodule, revealing edema or hemorrhage. The gold standard for the diagnosis is the culture identification of the fungus in sputum, BAL fluid or biopsy samples. Failing this identification, the detection of galactomannan, which is one of the fungal wall components, has shown sensitivity and specificity of 89% and 98%, respectively. Amphotericin B, liposomal amphotericin B, caspofungin and, especially, voriconazole are effective against the fungus. Although *Pneumocystis jirovecii* pneumonia can be fatal, the incidence of this disease has decreased due to the prophylactic use of trimethoprim-sulfamethoxazole. In immunocompromised patients presenting with dyspnea and hypoxemia, screening for fungi is indicated. A 14- to 21-day course of trimethoprim-sulfamethoxazole in combination with corticosteroids is usually efficacious. Another rare fungal infection is disseminated candidiasis, which is caused by *Candida* spp.

**Keywords:** Pneumonia; Immunosuppression; Lung diseases, fungal.

### Resumo

As complicações pulmonares se constituem na maior causa de morbidade e mortalidade no hospedeiro imunocomprometido, devido à deficiência nos mecanismos básicos de defesa. Independente da causa da imunodepressão, infecções bacterianas, virais e fúngicas são as mais frequentes. Entre as infecções fúngicas, a aspergilose é a mais comum (incidência de 1-9% e mortalidade de 55-92%) nos diferentes tipos de transplantados. Embora a forma pneumônica seja a mais frequente, lesões do sistema nervoso central e sinusite não são raras. O sinal do halo em TC de tórax representa uma área de baixa atenuação em volta do nódulo, revelando edema ou hemorragia. O padrão ouro para o diagnóstico é a identificação do fungo por cultura de escarro, amostras de LBA ou biópsia. Na falta dessa identificação, a detecção de galactomanana, um dos componentes da parede celular de *Aspergillus* sp., tem mostrado sensibilidade e especificidade de 89% e 98%, respectivamente. Anfotericina B, anfotericina B lipossomal, caspofungina e voriconazol têm efeito sobre o fungo, com destaque para esse último. A pneumonia por *Pneumocystis jirovecii*, que pode ser fatal, teve sua incidência reduzida pelo uso preventivo de sulfametoxazol/trimetoprima. Dispneia e hipoxemia em pacientes imunodeprimidos indicam a necessidade da pesquisa de fungos. O uso de sulfametoxazol/trimetoprima por 14-21 dias associado com corticosteroides costuma ser eficaz. A candidíase disseminada é outra rara enfermidade fúngica causada por *Candida* spp.

**Descritores:** Pneumonia; Imunossupressão; Pneumopatias fúngicas.

### Introduction

Pulmonary complications are the most common cause of morbidity and mortality in immunocompromised patients. The multiple treatment options for patients with malignant diseases—especially the various chemotherapy regimens and the increasing use of organ transplantation or hematopoietic cell trans-

plantation—as well as the increased survival of patients with autoimmune diseases, have greatly increased the number of immunocompromised patients. These patients are characterized by susceptibility to infections caused by organisms whose virulence is low in normal patients.

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Immunocompromised patients are at a higher risk of developing infection because they lack the basic mechanisms of cellular defense. Granulocytopenia, cell dysfunction (principally T lymphocyte dysfunction), congenital humoral immunodeficiency, acquired humoral immunodeficiency, splenectomy and mechanical complications (especially due to the presence of catheters) are the principal factors that interfere with the defense of organs in immunocompromised patients. These various types of defects are more commonly associated with certain microorganisms in the development of infections. The lack of humoral defense is most commonly associated with infection caused by *Streptococcus pneumoniae*; impaired cellular defense is most commonly associated with infection caused by mycobacteria; and granulocytopenia is most commonly associated with gram-negative bacteria and *Staphylococcus aureus*.<sup>(1)</sup>

In children, immunological defects represent a major risk factor for pulmonary involvement. Syndromes such as severe combined immunodeficiency and the Wiskott-Aldrich syndrome cause high mortality in children who develop pulmonary infection.

Among adults, immunodeficiency is most commonly seen in patients with leukemia, lymphoma or AIDS, as well as in those submitted to immunosuppressive therapy, related or not to organ transplantation or bone marrow transplantation.

In organ transplant recipients (principally liver transplant recipients and kidney transplant recipients), pneumonia occurs during one of two phases. The first is the immediate phase, defined as the first month after transplantation, during which nosocomial bacterial pneumonia predominates. The second is the post-immediate phase, from the second to sixth months after transplantation, which is characterized by pulmonary infections caused by other agents, such as viruses, fungi, *Pneumocystis jirovecii* and mycobacteria.<sup>(1)</sup>

The most common causal agents of fungal pneumonia are *Aspergillus* spp., which are present in the localized and disseminated forms of the disease.

The incidence of pneumocystosis among organ transplant recipients ranges from 2% to 4%, decreasing after the prophylactic use of the trimethoprim-sulfamethoxazole combination.

In bone marrow transplant (BMT) recipients, for instance, pulmonary infection caused by the various agents constitutes the most common isolated complication.<sup>(2)</sup> Pulmonary infection is related to the immune status of the recipient. Therefore, most types of bacterial and fungal pneumonia are diagnosed in the neutropenic period, before bone marrow engraftment. In addition to this major defect, problems such as the destruction of anatomical barriers (upper respiratory mucosa) and impairment of the cough reflex can occur. Another serious problem is graft-versus-host disease (GVHD), which increases the risk of opportunistic infection through mechanisms that have yet to be thoroughly defined.<sup>(1)</sup>

Among the GVHD-related causes of pneumonia, cytomegalovirus pneumonia and fungal infections (especially those caused by *Aspergillus* sp.) are the most noteworthy. This can be attributed to impaired cellular defense (mediated by T lymphocytes), as well as to deficiencies in the number and function of macrophages.

Although diagnostic resources are in constant development and the availability of new drugs (especially azole antifungal agents) is increasing, pulmonary infection remains as the most common documented form of invasive infection in immunocompromised patients.

Aspergillosis is one of many opportunistic fungal infections that principally affect the lungs. The incidence of aspergillosis in kidney transplant recipients, liver transplant recipients, BMT recipients and lung transplant recipients is, respectively, 1%, 2%, 7% and 9%. The mean mortality rate for this population is 55-92%, which represents 10-15% of the deaths among all transplant recipients.<sup>(3)</sup>

Regarding immune defense mechanisms, evidence shows that there is innate immunity and immunity that develops through an evolutionary process during infection or disease. This last type of immunity is known as adaptive immunity. For many years, cell-mediated immunity was considered to be the most effective, and humoral immunity was thought to be of secondary importance. However, it is currently accepted that cell-mediated immunity is the principal form of defense. Nevertheless, certain types of humoral immune responses are protective.

In general, Th1-mediated immunity is used for clearance of the fungal infection, whereas Th2-mediated immunity habitually acts on the susceptibility to infection.<sup>(4)</sup>

A competent cell-mediated defense requires an effective contingent of lymphocytes: T-helper cells; T-suppressor cells; and effector lymphocytes.

Many neoplastic diseases, especially Hodgkin's lymphomas, hairy cell leukemia and chronic lymphocytic leukemia, are associated with the malfunctioning of the cell-mediated defense. Corticosteroid use, which is quite common in these diseases, typically results in further impairment of cellular immunity.

In diagnostic terms, various aspects related to immunocompromised patients in general, should be taken into consideration: first, an aggressive protocol of etiologic investigation is needed, since a delay in the diagnosis increases the risk of death; second, if pulmonary infiltrate is identified early, fiberoptic bronchoscopy should be performed (fiberoptic bronchoscopy allows the identification or exclusion of an infectious etiology); and third, early CT scans of the chest typically reveal lesions that are not seen on routine chest X-rays.<sup>(5)</sup>

## Fungal pneumonia

Due to its incidence and morbidity, fungal pneumonia is one of the most severe infections in immunocompromised patients, accounting for 30% of all deaths among BMT recipients.<sup>(1)</sup>

Pulmonary involvement habitually results from systemic dissemination of the fungus. Large-scale use of antibiotics and prolonged periods of granulocytopenia, as well as corticosteroid therapy, are extremely important factors for the occurrence of fungal infection. Fungi of the genus *Aspergillus* are the most common causal agents. Other fungi, such as those of the genera *Mucor*, *Fusarium*, *Rhizopus*, *Petriellidium*, *Cryptococcus*, *Histoplasma*, *Coccidioides* and *Candida*, have also been identified as causal agents.

Clinically, fungal pneumonia manifests as fever in patients who do not respond to antibiotic therapy. However, the most significant finding is a focal lesion in the lung parenchyma, seen on routine chest X-rays and on CT scans of the chest.

Blood culture, sputum culture and, particularly, BAL fluid culture constitute the methods of identifying the fungi. When these methods fail to detect the etiologic agent, fine-needle aspiration is indicated. Fine-needle aspiration allows the characterization of the fungus in 50-67% of cases. The mean rate of complications is 15%, and complications are more common in patients presenting with a platelet count of approximately 30,000/mm<sup>3</sup>.<sup>(6)</sup>

## Aspergillosis

Invasive aspergillosis is the most common fungal infection among immunocompromised neutropenic patients. In contrast to bacterial infections, caused by cytomegalovirus or by *P. jirovecii*, in which prophylaxis has been shown to reduce the incidence of these diseases, the number of cases of invasive aspergillosis has increased progressively. According to recent studies, invasive aspergillosis affects 10-15% of BMT recipients. In most cases, aspergillosis affects only the lungs. However, a significant portion of patients develop sinusitis and central nervous system infection. The most common symptoms are cough and dyspnea. However, pleuritic pain and hemoptysis can also occur.

The lesions seen on routine chest X-rays include single/multiple nodules, cavities and segmental/subsegmental consolidation. In the initial phase, the most characteristic image seen on CT scans is the halo sign, an area of low attenuation that surrounds the nodule and represents edema or hemorrhage (Figure 1). The halo sign was described in more than 90% of neutropenic patients with invasive aspergillosis when HRCT scans were taken in the initial phase of the disease. At later stages, HRCT scans can show areas of necrosis and sequestration of lung tissue, which detaches itself from the surrounding parenchyma, resulting in the air crescent sign. Unfortunately, the fungus is identified in no more than 30% of the cases. There is a constant search for tests that might indicate the presence of *Aspergillus* sp. in immunocompromised patients. One such example is detection through ELISA or galactomannan, a fungal cell wall component that is released during invasive aspergillosis. Prospective studies have shown a sensitivity of 89.7% and a specificity of 98.0%. Although further studies are needed in order to define its clinical usefulness, there have been

reports stating that a positive serologic test result precedes the definitive diagnosis of aspergillosis by as many as 17 days.<sup>(7)</sup>

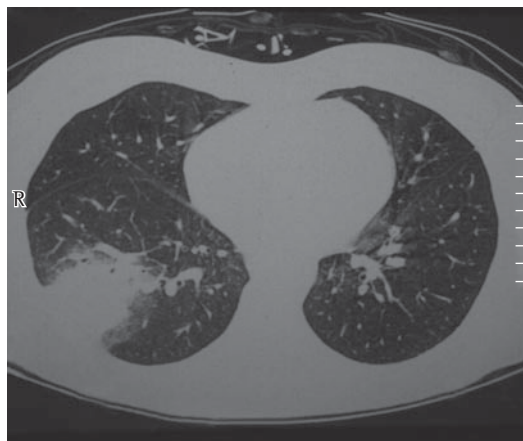
The use of amphotericin B has been the gold standard for the treatment of aspergillosis. However, the rate of therapeutic success remains low. Mortality rates are as high as 70-90%. It has been proposed that, in the presence of nephrotoxicity, liposomal amphotericin B should be used. More recently, the triazole voriconazole has been shown to be more effective and less toxic than amphotericin B.<sup>(8)</sup> The use of caspofungin is yet another option. Caspofungin is an echinocandin and is to be used only in special situations. The rate of success of prophylaxis for invasive aspergillosis is still low. Low doses of i.v. amphotericin B or aerosol amphotericin B, as well as azoles, have been used, although their use has not reduced the incidence or mortality rates.

The most important determinant of survival, however, is the resolution of neutropenia, bone marrow recovery being central to fighting the fungus and preventing the development of fatal complications.

### ***Pneumocystis jirovecii* pneumonia**

*P. jirovecii* pneumonia accounted for as much as 10% of all types of pneumonia that affected HIV-negative immunocompromised patients. This incidence plunged after the trimethoprim-sulfamethoxazole combination began to be used prophylactically. This form of pneumonia has occurred only in patients who are allergic to sulfa drugs, in patients who do not adhere to the preventive treatment and, occasionally, in patients who become infected before prophylaxis.<sup>(9)</sup>

Earlier studies (conducted in the pre-trimethoprim-sulfamethoxazole-prophylaxis era) showed the incidence of *P. jirovecii* pneumonia to be 4% in kidney transplant recipients, 4% in heart transplant recipients, 11% in liver transplant recipients and 33% in heart-lung transplant recipients. In the post-prophylaxis era, a Cleveland Clinic report of 1,299 solid organ transplants showed that only 25 cases occurred.<sup>(10)</sup> In BMT recipients, an incidence of 16% was reported the pre-prophylaxis era. Currently, *P. jirovecii* pneumonia occurs only in patients who discontinue prophylaxis due to intolerance or allergic phenomena.



**Figure 1** - Fungal pneumonia. The halo sign.

The clinical profile, the diagnostic investigation and the treatment of *P. jirovecii* pneumonia are no different from those described for patients with HIV. The mean time from BMT to the onset of the disease is approximately 6 weeks. Large studies have reported that cough (generally dry cough), dyspnea and fever are the cardinal symptoms, followed by asthenia and weight loss. Interstitial/alveolar lesions and asymmetric infiltrates usually predominate in imaging test results. Cysts, pneumothorax and pleural effusion have also been reported. Hypoxemia is usually present, and the alveolar-arterial oxygen gradient increases significantly. An increase in lactate dehydrogenase is common but nonspecific. The reported sensitivity range of testing induced sputum, BAL fluid and BAL fluid/biopsy samples for the detection of *P. jirovecii* is 35-95%, 79-98% and 94-100%, respectively.<sup>(9)</sup>

The treatment of choice for *P. jirovecii* pneumonia is high doses of trimethoprim-sulfamethoxazole for 14-21 days. The alternative for patients with allergy or intolerance is the use of i.v. pentamidine. The use of corticosteroids in the initial phase of the disease in patients with hypoxemia, as recommended for HIV patients, has been questioned for BMT recipients.

### **Infections caused by *Candida* spp.**

The clinical manifestations of the fungal infections caused by *Candida* spp. range from localized mucosal infection to dissemination with multiple organ involvement. The immune response is central to the type of infection that these fungi will cause. Impaired cellular immu-

nity is usually associated with infections that are more severe, whereas hematogenous dissemination can occur due to anatomical abnormalities (e.g., patients with heart valve prostheses).

Neutropenic patients can suffer hematogenous dissemination of the fungus via the gastrointestinal tract, as occurs in GVHD.

The following are the major risk factors for the invasive form: a) having a hematological malignancy; b) being the recipient of a solid organ transplant or hematopoietic stem cell transplant; and c) having undergone chemotherapy.

Among younger, previously healthy but severely ill patients, such as trauma patients and patients with extensive burns, other risk factors are associated with infection caused by *Candida* spp.: use of central venous catheter; use of total parenteral nutrition; use of broad-spectrum antibiotics; high Acute Physiology and Chronic Health Evaluation II score; hemodialysis; and abdominal surgery with gastrointestinal perforation.<sup>(11,12)</sup>

The clinical presentation of the infections caused by *Candida* spp. can be as follows:

- a) Focal invasive infections, among which are endophthalmitis, osteoarticular infection, meningitis, endocarditis, peritonitis, urinary tract infection, pneumonia, empyema, mediastinitis and pericarditis.
- b) Candidemia and disseminated candidiasis, the latter having been divided into four groups, as follows: catheter-related candidiasis; acute disseminated candidiasis; chronic disseminated candidiasis; and deep-organ candidiasis. The first two are more closely associated with documented candidemia.

The incidence of invasive candidiasis has a bimodal distribution, peaking at both ends of the age spectrum: 75:100,000 in children younger than 1 year of age; and 26:100,000 in adults older than 65 years of age.<sup>(12)</sup>

The principal clinical manifestations include the following: fever that does not respond to broad-spectrum antibiotics, especially in cases of prolonged catheter use or other major risk factor (or a combination of the two); possibility of association with multiple organ infection; macronodular skin lesions or endophthalmitis caused by *Candida* spp.; and, occasionally, septic shock and multiple organ dysfunction.

The current treatment for patients presenting with disseminated candidemia and positive culture for *Candida* spp. aims primarily at removing the catheters and ruling out septic phlebitis, endocarditis and abscess. The prevalent species is *C. albicans*. Stable patients should be treated with fluconazole for another 14 days after the disappearance of all signs and symptoms of the infection. For unstable patients or patients in deteriorating health presenting, in either case, with persistent candidemia for more than 5 days, the combination of caspofungin with fluconazole or amphotericin B should be considered. Likewise, for patients infected with *C. glabrata*, fluconazole (800 mg/day), caspofungin (50 mg/day) or amphotericin B (0.7–1.0 mg • kg<sup>-1</sup> • day<sup>-1</sup>) can be used. For patients infected with *C. krusei*, the initial dose of caspofungin should be increased to 70 mg/day, followed by 50 mg/day or voriconazole (6 mg/kg every 12 h, followed by 3 mg/kg every 12 h).<sup>(12-14)</sup>

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