

# INVASIVE PULMONARY ASPERGILLOSIS ASSOCIATED WITH INFLUENZA

**L. Boyanova**

National Centre of Infectious and Parasitic Diseases

## ABSTRACT

The aim of this review is to present the increased frequency of influenza-associated invasive pulmonary aspergillosis (IPA) cases reported from several countries. Classic risk factors or additional immunosuppression may not be observed in affected patients. Therefore, influenza-associated IPA might be diagnosed with a delay and consequently result in worse patient outcomes.

## KEYWORDS:

invasive pulmonary aspergillosis (IPA), *Aspergillus*, influenza virus

Invasive pulmonary aspergillosis (IPA) can complicate viral infections though influenza predisposes to increased risk of bacterial superinfections (9, 10).

The development of IPA is associated with immunocompromised status but there are reports on aspergillosis in patients without major risk factors (10).

Cases of IPA in influenza patients have been described since 1952. After the influenza pandemic in 2009 there was an increase in the number of reports.

Influenza A virus is associated with IPA in most of the cases but there are also cases involving influenza B virus (10).

Despite inhaling large numbers of conidia (*Aspergillus* spores) every day, most people do not develop disease. Manifestations of

the disease may range from allergic disorders to invasive aspergillosis depending on the immunocompetence of the human host, and mortality rates may reach up to 90% if there is no effective antifungal treatment (10).

Risk factors are summarised as follows:

- Immunocompromised status with underlying disease – viral hepatic cirrhosis, diabetes mellitus, acute myeloid leukaemia, prolonged neutropenia, chronic obstructive pulmonary diseases (COPD), lymphopenia (8, 9);
- Corticosteroid therapy – long-term administration of high-dose corticosteroids (methylprednisolone up to 3 weeks) for acute respiratory distress syndrome causes induced immunosuppression with leucopenia, tissue destruction, ischemic necrosis and angioinvasion (8, 9, 11);
- Transplant-related factors – immunosuppressive therapy and chemotherapy (cyclosporine, tacrolimus, cytarabine, etoposide and others) (8);
- Respiratory viruses – respiratory syncytial virus, influenza A/B and parainfluenza viruses, adenoviruses, cytomegalovirus (8);
- Blood transfusion, haemodialysis (8);
- Worsening of respiratory symptoms after initial improvement in the patient's condition (8);
- Age of more than 40 years (8);
- Antibiotic treatment of influenza patients;
- Others – mechanical ventilation, advanced liver disease, congestive heart failure and major infections (10, 11).

Role of viral infections in facilitating fungal pathogens:

- Impaired phagocytosis in macrophages;
- Impaired formation of nitric oxide (NO);
- Inhibition of apoptosis;
- Lymphopenia (decreased proliferation and migration of lymphocytes, T-cell defects);
- Decreased production of pro-inflammatory cytokines (8);
- Decreased counts of alveolar dendritic cells – the professional antigen-presenting cells (APC) (8, 11).

Upon inhalation of spores (conidia), factors contributing to angioinvasion followed by ischemic necrosis, dissemination and development of invasive

## ADDRESS FOR CORRESPONDENCE:

National Centre of Infectious  
and Parasitic Diseases  
26 Yanko Sakazov Blvd.  
1504 Sofia, Bulgaria  
e-mail: miraanbo@abv.bg

# Acute Invasive Aspergillosis

**Sequential high-resolution CT scans in 25 patients with neutropenia and invasive pulmonary aspergillosis at diagnosis: median number of lesions=2, bilateral in 48%**



**Baseline: halo**



**Day 4: ↑size, ↓halo**



**Day 7: air crescent**

**Halo transitory: <5 days; increased volume for 1 week → stabilization → air crescent**

Caillot D, et al. *J Clin Oncol.* 2001;19:253-259.

**Figure 1.** Radiographic presentation of *Aspergillus* pneumonia and evolution over time.

*J Clin Oncol.* 2001;19:253-259

aspergillosis, are impaired natural immunity, APC dysfunction (including macrophages, dendritic cells and T-lymphocytes), lack of pulmonary protection, damaged ciliary epithelium and corticosteroid-induced immunosuppression (8, 11).

The clinical forms of aspergillosis are:

- Chronic necrotizing aspergillosis with local invasion and cavitation forms (8);
- Invasive aspergillosis with angioinvasion and "halo sign" (or "air crescent sign") (8) – Fig.1.

Microbiological diagnosis can be performed with the following methods:

- Fungal culture of bronchoalveolar lavage fluid and sputum. This method has low sensitivity for the diagnosis of invasive aspergillosis, as positive results are obtained only in about 25-65% of patients. However, higher sensitivity of 63-88% was reported in patients with influenza-

associated IPA (10);

- Biopsy sample collected with bronchoscopy and stained with GMS (Gomori's methenamine silver) (12);
- Serological methods for detection of galactomannan antigen, indirect immunofluorescence (IIF) for detection of antibodies in serum (1, 3);
- PCR molecular techniques for diagnosis of invasive fungal infection (4, 5, 6, 7).

The diagnosis of invasive pulmonary aspergillosis is based on a combination of clinical, microbiological and radiological criteria.

The most frequently isolated species are *Aspergillus fumigatus*, followed by *Aspergillus versicolor* and *Aspergillus niger* (14).

Specific antiviral therapy such as early treatment with oseltamivir was shown to decrease the

incidence of influenza-associated complications (11). The development of resistance to azole antifungals in *Aspergillus* strains limits treatment options in some patients and has been related to increased mortality (10). However, initiation of appropriate antifungal therapy might prove to be important in decreasing the mortality of influenza-associated aspergillosis (13).

## CONCLUSION

*Aspergillus* species are widespread in the environment. IPA is a severe disease and immunodeficiency is the major risk factor. However, there is an increasing number of reports describing patients without the classic risk factors. Influenza patients may develop pulmonary aspergillosis as a co-infection and there are numerous reports on influenza pneumonia complicated by *Aspergillus* infection. Isavuconazole or voriconazole are used as first-line therapy (15). Patient management includes bronchoalveolar lavage, computed tomography imaging, antifungal and antiviral therapy in order to curb the co-infections.

## REFERENCES

1. Kantardjiev T. *Etiologic diagnosis and etiotropic therapy of mycoses*. 2012, Sofia, National Centre of Infectious and Parasitic Diseases.
2. Kantardjiev T, Levterova V, Brankova N, Ivanov I, Angelov P, Panaiotov S. *Role of fluorescent amplified fragment length polymorphism analysis*

- in taxonomy, identification and epidemiological examinations of yeast pathogens*. Biotechnol Biotechnol Equip. 2006; 20(1):103-106.
3. Kantardjiev T, Levterova V, Panaiotov S, Ivanov I. *Use of Amplified Fragment Length Polymorphism analysis as a tool for identification and typing of yeast isolates*. Mykologia Lekarska (Medical Mycology). 2004; 11(2):113-117.
4. Buess M, Cathomas G, Halter J. *Aspergillus-PCR in bronchoalveolar lavage for detection of invasive pulmonary aspergillosis in immunocompromised patients*. BMC Infect Dis. 2012; 12(1):237.
5. Johnson GL, Bibby DF, Wong S, Agrawal SG. *A MIQE-compliant real-time PCR assay for Aspergillus detection*. PLoS One. 2012; 7(7):e40022.
6. Valero C, Cruz-Villar L. *New Panfungal Real Time PCR Assay for diagnosis of Invasive Fungal Infection*. J Clin Microbiol. 2016; 54:2910-2918.
7. Somogyvari F, Horvath A, Serly J, Majoros H, Vagvolgyi C, Peto Z. *Detection of Invasive Fungal Pathogens by Real Time PCR and High-resolution Melting Analysis*. 2012; 26(6):979-983.
8. Garcia-Vidal C. *The interaction between Influenza and Aspergillus*. ECCMID April 2018, Infectious Diseases Department.
9. Fischer J, Walker D. *Invasive pulmonary Aspergillosis associated with influenza*. JAMA. 1979; 241(14):1493-1494.
10. ECDC. *Influenza-associated invasive pulmonary aspergillosis*, Europe. Report from 30 November 2018, Stockholm.
11. Lat A, Bhadelia N, Miko B. *Invasive Aspergillosis after pandemic (H1N1) 2009*. Emerg Infect Dis. 2010; 16(6):971-973.
12. Shah MM, Hsiao EI, Kirsch CM, Gohil A, Narasimhan S, Stevens DA. *Invasive pulmonary aspergillosis and influenza co-infection in immunocompetent hosts: case reports and review of the literature*. Diagn Microbiol Infect Dis. 2018; 91(2):147-152.
13. van de Veerdonk FL, Kolwijck E, Lestrade PP, Hodiament CJ, Rijnders BJ, van Paassen J, et al. *Influenza-associated Aspergillosis in critically ill patients*. Am J Respir Crit Care Med. 2017; 196(4):524-527.
14. Nancy F. Crum-Cianflone. *Invasive Aspergillosis Associated With Severe Influenza Infections*. Open Forum Infect Dis. 2016; 3(3):ofw171.
15. Koehler P, Bassetti M, et al. *Intensive care management of influenza-associated pulmonary aspergillosis*. Clin Microbiol Infect. 2019 [Epub ahead of print].