

## Invasive pulmonary aspergillosis in children with hepatic transplant: a survivor

### Aspergilosis pulmonar invasora en pacientes pediátricos con trasplante hepático, a propósito de una sobreviviente

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#### Abstract

**Introduction:** Mycotic infections due to *Aspergillus spp.* are the main mycotic associated infections in liver transplant patients, with mortality rates up to 90% of the cases. Almost 50% of patients will develop an infection during the first months after transplantation, of which 10% are associated with opportunistic agents. **Objective:** To describe the diagnosis and management of an Invasive Pulmonary Aspergillosis (IPA) episode in a liver transplant patient. **Case report:** 11-months-old patient with liver transplant due to a biliary atresia who developed severe pneumonia associated with mechanical ventilation. The bronchoalveolar lavage showed high levels of galactomannan and positive culture for *Aspergillus fumigatus* leading to an IPA diagnosis. This episode was treated with antifungal with a favorable outcome. **Conclusion:** The IPA is an opportunistic infection in liver transplant patients, with high mortality rates, that must be suspected in this group of patients since an early diagnosis and treatment reduce mortality.

#### Keywords:

*Aspergillus*;  
Invasive Pulmonary  
Aspergillosis;  
Live Transplant

## Introduction

Infections are the main complication in liver transplant patients, and it is estimated that about 50% of patients will undergo an infectious process in the first months after transplantation, due to liver alteration and immunosuppressive treatment<sup>1</sup>. Invasive fungal infection (IFI) is considered an opportunistic infection in the solid organ transplant (SOT) recipient<sup>2,3</sup>. It occurs in up to 5-20% of transplants and has a mortality rate of 25-80%; in patients with liver transplantation, the incidence of invasive aspergillosis is 2%. The risk factors for IFI in patients with SOT have been divided into four categories, (i) those related to patient factors (previous colonization history, cytomegalovirus disease, renal dysfunction and chronic rejection), (ii) surgery related (surgical time, technique, transfusions and complications), (iii) microbiological selection due to prior use of antimicrobial agents, and (iv) derive from immunosuppression<sup>4-6</sup>. In these cases, the group of opportunistic microorganisms, including fungi, is especially interesting. The main fungus that is responsible for infectious events is *Aspergillus spp*, which is capable of generating invasive lung processes, with mortality rates of up to 90%.

## Clinical case

Female patient, with biliary atresia diagnosis since the first month of life and failed portoenteroanastomosis. At 11 months of age, a cadaveric donor liver transplantation is performed with immunosuppression post-transplantation with tacrolimus (1 mg every 12 hours), methylprednisolone (10 mg/kg/day), mycophenolate mofetil (125 mg every 12 hours). 24 hours after surgery, the patient is extubated without alterations, however, at 48 hours she presents fever spikes, acute respiratory compromise, and on the fourth postoperative day she developed multiorgan failure due to respiratory distress syndrome with need for ventilatory support, renal failure due to anuria, volume overload, metabolic acidosis and hyperkalemia, for which a Mahurkar catheter was placed. Laboratory tests were performed, finding neutropenia and blood cultures positive for *Enterobacter cloacae* (central venous catheter and arterial line), which was carbapenemase-resistant, therefore, it was handled with polymyxin B (40.000 u/kg/day) for 26 days, meropenem (100 mg/kg/day every eight hours) for 52 days, and ertapenem (15 mg/kg every 12 hours) for 24 days, having negative follow-up blood cultures (10.11.16).

However, despite treatment, the patient persists with lung deterioration with respiratory acidosis, episodes of bronchospasm and neutrophilia with elevated

C-reactive protein. The chest x-ray revealed the presence of bilateral alveolar infiltrates predominantly in the left lung, and right parahilar and apical infiltrates (figure 1).

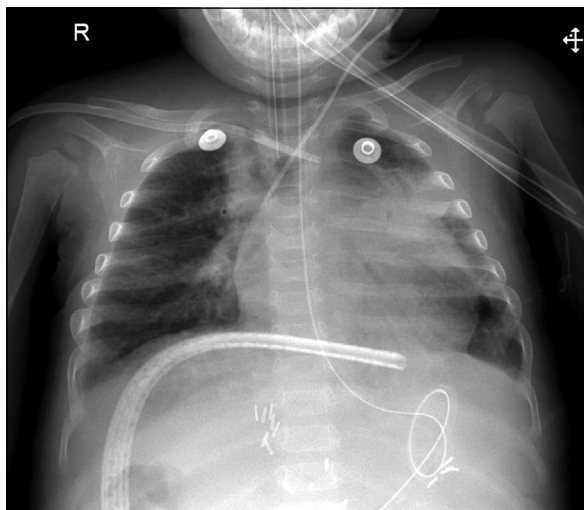
On suspicion of an opportunistic infection 13 days after transplant, a bronchoalveolar lavage (BAL) was performed with a study of galactomannan antigen with a value of 7,873 (positive) and a direct stain that shows hyaline septate hyphae. With this information, antifungal treatment with amphotericin B was initiated for 14 days. At the seventh day, in the BAL culture grew *Aspergillus fumigatus* in Sabouraud Agar medium and negative in Mycosel Agar, therefore, the therapy was adjusted to voriconazole (7 mg/kg every 12 hours), during 42 days. A second BAL was performed 30 days after transplantation with negative Galactomannan and negative culture results. The patient presented a clinical improvement without requiring surgery (figure 2). The patient is currently in post-transplantation follow-up.

## Invasive Pulmonary Aspergillosis

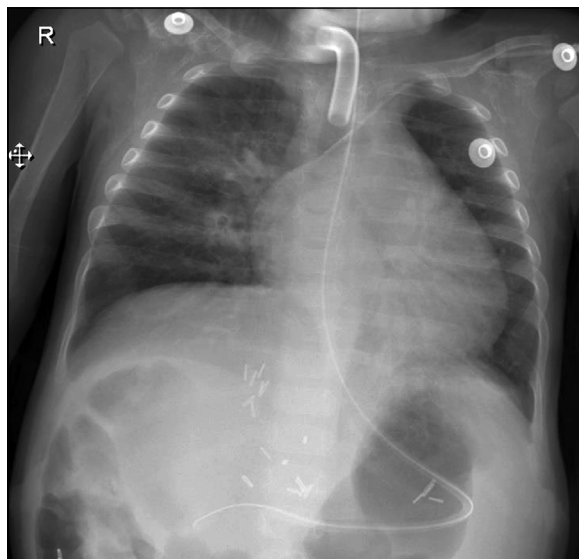
Infections are the most frequent complications in transplant patients and it is estimated that 50% of cases will present an episode in the first months after transplantation<sup>7</sup> donor-derived, or the result of a perioperative complication. The development of opportunistic infections (OIs). The immunological alteration due to pre-transplantation liver damage and the use of immunosuppressive drugs post-transplantation leads to a state of immunosuppression allowing the entry and development of infections by opportunistic agents<sup>8</sup>. The *Aspergillus spp* fungi are the main filamentous fungi associated with infections in transplant patients. However, the incidence of fungal infections is less than 10% among opportunistic microorganisms<sup>9-11</sup>.

The genus *Aspergillus* was first described in 1729 by Micheli. So far, approximately 200 species are recognized, but only a few are pathogenic to humans, the most frequent are *A. fumigatus*, followed by *A. flavus*, *A. terreus* and *A. niger*<sup>12</sup>.

The entry of *Aspergillus spp* into the body occurs by inhaling conidia to the alveolar region. The first barrier line is established through the innate immune response by means of the respiratory epithelium and the mucociliary clearance, which retrogradely transports conidia to be swallowed and eliminated. However, some conidia manage to avoid the clearance procedure and it is when the phagocytic system, mainly macrophages, and neutrophils, regulates the formation and growth of hyphae. The cellular immune response is presented as a secondary response and mediates its action through the Th1 CD4+ T lymphocytes profile limiting the growth and development of the fungus<sup>13</sup>.



**Figure 1.** Chest X-ray presence of bilateral alveolar infiltrates with predominance of the left lung field, and parahiliary and right apical infiltrates, with air trapping (11.10.16).



**Figure 2.** Chest x-ray shows significant improvement of the alveolar infiltrates previously observed (07.11.16).

Studies that have evaluated risk factors for the development of invasive pulmonary aspergillosis (IPA) in transplant patients are few and published data indicate as main factors: neutropenia, primary graft dysfunction, renal dysfunction with hemodialysis, and the increase of immunosuppression in cytomegalovirus co-infection<sup>14</sup>.

Clinical manifestations of IPA include cough, hemoptysis, chest pain, pleuritic pain, and dyspnea. However, in patients with neutropenia, the inflammatory response is altered and symptoms do not clearly develop<sup>15-17</sup>.

Radiologically, the classic finding of the halo sign is rare in patients with IPA; it is more likely to see pulmonary infiltrates, basal pleural densities or cavities. A study in solid organ transplant patients with IPA reports that none of the patients had the halo sign and nonspecific signs were more frequent<sup>30</sup>. The scan is an aid that provides more information on lung involvement, where the presence of nodules smaller than 1 cm and masses with centers of low densities or near to the air density is frequent<sup>10,11</sup>.

The diagnosis of IPA is made using criteria developed by the European Organization for Research and Treatment of Cancer (EORTC) and the Mycoses Study Group (MSG) which are made for immunosuppressed patients, but not for patients in ICU. These criteria allow stratifying the diagnosis into three categories: possible, probable or proven (table 1).

Laboratory techniques such as serum galactomannan (GM) measurement are useful in acute infections, with a sensitivity of about 70% (in patients with hematological malignancies). However, the optimal value for a diagnosis is not defined; the U. S. Food and Drug

Administration (FDA) has defined values higher than one to make the diagnosis and for some authors values higher than 0.5 should be considered positive<sup>20-22</sup>. The 1,3-beta-D-glucan (BDG) can be used to diagnose acute events in patients with hematological malignancies; however, the tests sensitivity in solid organ transplant patients can decrease up to 20%, therefore, its use is not recommended in these patients. The culture of this microorganism is made in a medium rich in glucose

**Table 1. Diagnostic Criteria for Invasive Pulmonary Aspergillosis**

Diagnosis	Criteria
Proven	Specimen obtained in tissue or culture positive for <i>Aspergillus spp</i>
Probable	<p>Fullfilment with at least one criterion of each category</p> <p>Host Criteria</p> <ul style="list-style-type: none"> <li>• Recent history of neutropenia</li> <li>• Receipt of stem cell transplantation</li> <li>• Prolonged use of corticosteroids</li> <li>• Treatment with T-cell immunosuppressants</li> <li>• Inherited severe immunodeficiency</li> </ul> <p>Clinical Criteria</p> <ul style="list-style-type: none"> <li>• Dense, well-circumscribed lesion(s) with or without a halo sign</li> <li>• Air-crescent sign</li> <li>• Cavity</li> </ul> <p>Micological Criteria</p> <ul style="list-style-type: none"> <li>• Direct detection (citology, culture, bronchoalveolar lavage, bronchial brush)</li> <li>• Indirect detection (presence of fungal elements indicating a mold)</li> </ul>
Possible	Presence of risk factors in the patient with clinical suspicion, in the absence mycological test or with negative results

**Table 2. Antifungal treatment for invasive pulmonary aspergillosis**

Drug	Doses	
Voriconazole	Children 2-12 years old:	IV: 7 mg/kg/dose/12 h or PO: 200 mg/12 h
	Children 12-16 years old:	IV: 6 mg/kg/dose/12 h (first day); then 4 mg/kg/12 h
	Children < 40 kg:	PO: 200 mg/12 h (first day); then 100 mg/12 h
	Children ≥ 40 kg:	PO: 400 mg/12 h (first day); then 200 mg/12 h
Liposomal Amphotericin B	IV: 3-5 mg/kg/d	
Posaconazole	Children < 15 kg	PO: 6 mg/kg/12 h
	Children 15-19,9 kg:	PO: 100 mg/12 h
	Children 20-33,9 kg:	PO: 200 mg/12 h
	Children ≥ 34 kg:	PO: 400 mg/12 h
Caspofungin	IV: 75 mg/m <sup>2</sup> /dose (first day); then 50 mg/m <sup>2</sup> /día	
Itraconazole	Children 1 month-18 years old: 2.5-5 mg/kg/12 h	
Isavuconazole	< 18 years old: Safety and Efficacy not established	

\*IV: Intravenous PO: Per Oris.

such as Sabouraud Agar, at temperatures between 28 and 30°C, without the need for CO<sub>2</sub>. Cultures such as Mycosel inhibit their growth<sup>23</sup>.

Flexible bronchoscopy (FB) with BAL, is the cornerstone for microbiological detection of *Aspergillus spp*, primarily in cases of consolidations, tree-in-bud pattern, and pulmonary infiltration<sup>24</sup>. In patients with abdominal organs transplantation, the positive finding of *Aspergillus spp* in BAL is infrequent up to 1.5%, although the positive predictive value is 72%<sup>23</sup>. The risks associated with the technique range from 0.08 to 0.5% with mortality rates of 0 to 0.04%. Limitations of FB with BAL are lesions located in the periphery of the pulmonary parenchymal region, in case of severe hypoxia or hemorrhagic diastasis<sup>20</sup>. BAL culture limitations include oropharyngeal contamination (epithelial cells >1%) and the lack of differentiation between fungal infection and colonization (10<sup>4</sup> CFU/mL)<sup>25,26</sup>.

The treatment of IPA patients includes the use of antifungals, where the first option is voriconazole, which has shown greater effectiveness compared to other alternatives such as liposomal amphotericin B, isavuconazole, posaconazole, caspofungin and itraconazole<sup>27</sup>. A duration of six to twelve weeks is recommended, depending on the degree of immunosuppression and the extent of disease<sup>20,28</sup>. The surgical management is an option in case of limited infections and therapeutic failure<sup>29</sup>; it is considered in case of a single lesion, lesions close to large vessels, pleural invasion or chest wall injury<sup>30</sup>.

The prophylaxis includes inhaled amphotericin B or micafungin. It is recommended for use in the liver transplant patient with, at least, three criteria such as prolonged steroid use before transplantation, acute renal failure on hemodialysis, acute liver failure, retransplantation or high rate of intraoperative transfusion<sup>31</sup>.

## Conclusion

The IPA is a clinical entity with high mortality, which may occur more frequently in transplant patients, therefore, the suspicion must be considered for a timely diagnosis and treatment. Currently, there are limitations due to the lack of information in the pediatric population, which opens a new path for the research world.

## Ethical Responsibilities

**Human Beings and animals protection:** Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

**Data confidentiality:** The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

**Rights to privacy and informed consent:** The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author. recorded in the respective form

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Authors state that no economic support has been associated with the present study.

## Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

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