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CLINICAL AND LABORATORY FEATURES OF INVASIVE ASPERGILLOSIS IN INTERNAL ORGAN TRANSPLANT RECIPIENTS: A CASE REPORT, REGISTRY ANALYSIS, AND LITERATURE REVIEW

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Internal organ transplantation is a high-tech medical intervention that significantly improves patient survival and quality of life. However, infections remain the leading cause of mortality in organ transplant recipients. Invasive aspergillosis (IA) is the second most common invasive fungal infection in this population and is associated with high mortality rates, reaching up to 90%. This article presents a clinical case of IA following heart transplantation (HT), along with an analysis of registry data and institutional experience in managing this serious complication based on registry data. Between September 2010 and October 2024, 23 adult patients with IA following an internal organ transplantation were included in the institutional registry. Most IA cases occurred after heart transplantation (65%), followed by kidney transplantation (31%), and, less commonly, lung transplantation (4%). The lungs were the primary site of IA (96% of cases). Diagnosis was confirmed through direct microscopy of clinical samples, such as bronchoalveolar lavage (BAL) fluid and tissue biopsies, in 50% of patients, while fungal cultures yielded positive results in 35% of cases. The predominant pathogen was *Aspergillus fumigatus* (73%), followed by *Aspergillus niger* (18%) and *Aspergillus flavus* (9%). A positive galactomannan test in BAL was detected in 85% of patients. All patients received targeted antifungal therapy, primarily with voriconazole (87%), while echinocandins and itraconazole were used in 17% and 4% of cases, respectively. Overall 90-day patient survival was 78%. The literature review outlines the main approaches to the diagnosis and management of invasive infections associated with *Aspergillus spp.*

Keywords: Aspergillus spp., aspergillosis, invasive aspergillosis, immunosuppressive therapy, organ transplantation, heart transplantation.

INTRODUCTION

Internal organ transplantation is a complex surgical procedure that requires long-term immunosuppressive therapy to maintain the viability and function of the transplanted organ. This therapy works by suppressing the recipient's immune system to prevent graft rejection. However, immunosuppression also reduces the body's ability to mount an adequate defense against infections [1–3].

Pathogens causing infectious complications may vary depending on the timing of transplantation. Early infections (within the first month) are typically caused by nosocomial pathogens and may also stem from donor-derived infections. Opportunistic infections usually develop within 3–12 months after transplantation, reflecting the substantial impact of immunosuppressive therapy. Late infections (after 12 months) may occur in patients requiring intensive ongoing immunosuppression or those exposed to additional environmental risk factors.

However, the nature and timing of infections are influenced by factors such as the choice of immunosuppressive agents and the duration of antimicrobial prophylaxis [1–3]. Among fungal pathogens, the most common are *Candida spp.*, *Aspergillus spp.*, *Cryptococcus neoformans*, and *Pneumocystis*.

Invasive aspergillosis (IA) is the second most common invasive fungal infection in organ transplant recipients and is associated with a high mortality rate, ranging from 30% to 90%, depending on the transplanted organ type, degree of immunosuppression, and clinical form of the disease [2, 3]. In the Russian Federation, the number of publications addressing this problem remains limited.

This article presents a clinical case of invasive pulmonary aspergillosis in a heart transplant (HT) recipient, an analysis of registry data on IA in organ transplant recipients, and a review of relevant literature.

Objective: to evaluate the risk factors, etiology, clinical features, diagnostic approaches, and treatment strategies for IA in internal organ transplant recipients.

MATERIALS AND METHODS

The diagnosis of invasive mycosis was established according to the 2020 EORTC/MSG criteria [4]. Risk factors, etiology, clinical features, diagnostic findings,

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and treatment outcomes were assessed using data from the registry of IA patients [5], maintained by the Department of Clinical Mycology, Allergology, and Immunology at the North-Western State Medical University, St. Petersburg. Statistical analysis was performed using Microsoft Office Excel 2010 and Statistica 13.5 (StatSoft, Inc., USA). Survival analysis was conducted using the Kaplan–Meier method.

A literature review was conducted using PubMed (as of December 2024), ClinicalKey (as of December 2024), and the Russian e-Library (as of December 2024). The search strategy employed the following keywords: *Aspergillus spp.*, aspergillosis, invasive mycoses, invasive aspergillosis, internal organ transplantation, lung transplantation, liver transplantation, heart transplantation, and kidney transplantation.

CLINICAL CASE

Patient Z., a 53-year-old female, was admitted to the mycology clinic of North-Western State Medical University with complaints of cough producing difficult-to-expectorate sputum and intermittent fever up to 37.8 °C.

Her medical history revealed a diagnosis of Hodgkin's lymphoma in 1991, for which she underwent four courses of polychemotherapy (PCT) according to the MOPP regimen (mustargen, vincristine, procarbazine, prednisolone) and 28 courses of radiation therapy. Following treatment, she achieved sustained remission, which has persisted to this day.

In 2016, the patient was diagnosed with cancer of the left breast, stage IV (T4bN3M1). In 2017, she underwent a radical Madden mastectomy on the left side, followed by eight courses of PCT according to the FAC regimen (5-fluorouracil 500 mg/m^2, doxorubicin 50 mg/m^2, and cyclophosphamide 500 mg/m^2 intravenously, every 3 weeks, for a total of six cycles) and three courses of biological therapy with trastuzumab (2016–2017). The disease has since remained in remission.

In 2019, she developed mycotic keratouveitis caused by Fusarium spp., requiring inpatient care and systemic antifungal therapy with voriconazole (400 mg daily). She subsequently underwent penetrating keratoplasty and corneal transplantation of the right eye; however, these were complicated by total graft opacity, high myopia, and chorioretinal degeneration.

Following prior radiation therapy courses, the patient developed symptoms of chronic heart failure (CHF) and was diagnosed with radiation-induced heart disease and mixed cardiomyopathy.

The patient's condition progressively deteriorated, with increasing edema and more frequent episodes of chest pain. On subsequent examination, the following were noted: decreased ejection fraction (stage IIB), bilateral hydrothorax, mitral regurgitation grade 1–2, tricuspid regurgitation grade 1–2, pulmonary hypertension grade 2, paroxysmal unstable ventricular tachycardia, and coronary artery atherosclerosis with 70% stenosis of the right coronary artery. She remained under long-term cardiology follow-up.

Due to the lack of response to standard treatment regimens and worsening signs of CHF, heart transplantation (HT) was indicated. In October 2023, she underwent orthotopic HT using the bicaval technique.

Postoperatively, immunosuppressive therapy (IST) was initiated at standard doses for the prevention of graft-versus-host disease (GvHD), including mycophenolic acid 180 mg/day (later administered intermittently and eventually discontinued one month after initiation due to agranulocytosis), prednisolone up to 12 mg/day, and tacrolimus at ≥3 mg/day, titrated according to therapeutic blood concentration.

During a routine examination in December 2023, the patient again reported shortness of breath. Chest computed tomography (CT) revealed a solitary lesion in segment S4 of the right lung (9 mm in diameter, with indistinct margins) and bilateral hydrothorax. A course of antibiotic therapy was administered, resulting in complete regression of the S4 lesion and resolution of fluid accumulation in the right pleural cavity; the left-sided pleural effusion decreased in volume.

Evaluation at the local tuberculosis dispensary showed a positive Diaskintest, while sputum analysis revealed no acid-fast bacilli.

In May 2024, the patient developed recurrent low-grade fever, with body temperature rising to 37.8 °C. Repeat chest CT demonstrated new irregularly shaped infiltrates in segments S2 and S6 of the right lung, superimposed on interstitial changes. A 10-day course of levofloxacin was prescribed, leading to clinical improvement.

The patient was referred again to a phthisiatrician and underwent an inpatient evaluation at a tuberculosis hospital in June 2024. Microscopy of sputum and bronchial lavage fluid for mycobacteria was negative, and polymerase chain reaction (PCR) testing of both samples did not detect DNA of Mycobacterium tuberculosis complex.

Bronchoalveolar lavage (BAL) culture yielded Klebsiella pneumoniae (1×10^3 CFU/mL) and Aspergillus spp. (1×10^4 CFU/mL). A BAL galactomannan assay, performed at Kashkin Research Institute of Medical Mycology, was positive (optical density index: 1.99).

A transbronchial biopsy revealed lung tissue fragments with hemorrhages, focal deposits of brown pigment, and a small necrotic focus without accompanying cellular reaction; Ziehl–Neelsen staining did not detect acid-fast mycobacteria.

Given these findings, invasive pulmonary aspergillosis was suspected. The patient was subsequently hospitalized at the mycology clinic of North-Western State Medical University.

Upon admission to the mycology clinic, the patient's condition was satisfactory; consciousness was clear; skin showed no visible changes; focal alopecia was noted. Breathing was labored, without wheezing. Pulse was 75 beats/min, blood pressure 130/85 mm Hg. Heart sounds were rhythmic on auscultation, with no pathological murmurs.

Clinical blood test: Leukocytes – 3.3 × 10^9/L; erythrocytes – 3.68 × 10^{12}/L; hemoglobin – 118 g/L; platelets – 285 × 10^9/L; neutrophils – 0.8 × 10^9/L; lymphocytes – 2.2 × 10^9/L; ESR – 27 mm/h.

Biochemical blood test: ALT – 16 U/L; AST – 23 U/L; creatinine – 119 μmol/L; urea – 11.9 mmol/L; glucose – 6.3 mmol/L; total bilirubin – 10.9 μmol/L.

Electrocardiography: sinus rhythm with tachysystole, heart rate 90 bpm, horizontal electrical axis of the heart, left ventricular hypertrophy.

Chest CT: persistent hydrothorax (left – up to 10 mm, right – up to 5 mm). In the right lung, partial regression of infiltrative changes with residual ground-glass opacities; grouped foci present, some tending to merge with blurred contours; lower lobe shows multidirectional dynamics with regression of some foci and emergence of new ones. In the left lung, paramediastinal consolidation in the upper lobe shows moderate volume increase; regression of blurred foci in the upper lobe is also noted.

Given the patient's risk factors – IST (continuous tacrolimus use), GvHD, and prolonged glucocorticosteroid (GCS) therapy – together with the examination findings (neutropenia, positive BAL galactomannan test, Aspergillus spp. culture from BAL, and focal "ground-glass" infiltrative changes on chest CT), a diagnosis of invasive pulmonary aspergillosis was established. Antifungal therapy with voriconazole at standard doses was initiated, with blood tacrolimus levels monitored.

Concomitant therapy included: fosinopril 10 mg daily, torasemide 2.5 mg daily, amlodipine 2.5 mg daily, atorvastatin 10 mg daily, folic acid 10 mg daily, iron sulfate 80 mg daily, calcium-D_3 2 tablets daily, magnesium B_6 1 tablet three times daily, prednisolone 7.5 mg daily, and tacrolimus 3 mg daily.

Tacrolimus blood levels were assessed once every three days. When the level reached 17.1 ng/mL, the daily dose was reduced to 2 mg. After 24 hours, the concentration rose to 19.2 ng/mL, necessitating a further reduction to 1 mg/day. Three days later, the tacrolimus level decreased to 9.2 ng/mL.

On the 14th day of hospitalization, follow-up chest CT imaging revealed regression of infiltrative changes in the right lung, reduced inflammatory changes in segments S2, S4–S5, S6, and S8 on the right, and decreased pleural effusion volume in the left pleural cavity (Fig. 2).

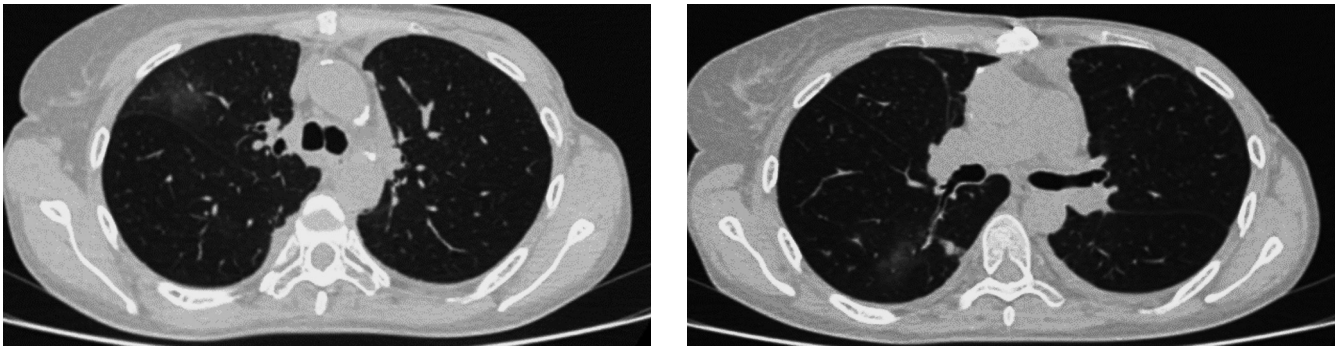

Fig. 1. Chest CT scan showing "ground-glass" opacities and confluent foci in the right lung; the left lung demonstrates a region of consolidation with moderate volume enlargement

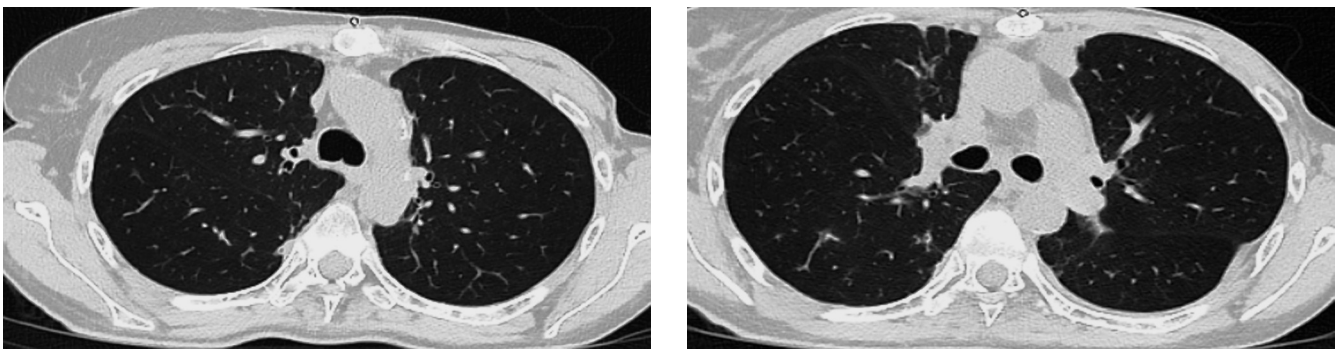

Fig. 2. Chest CT scan 14 days after initiation of therapy: regression of infiltrative changes in the right lung; decreased inflammatory involvement in segments S2, S4–5, S6, and S8 on the right; reduced pleural effusion in the left pleural cavity

The patient's condition was deemed stable, and she was discharged for outpatient follow-up. Given the persistence of risk factors, continuation of voriconazole therapy for at least two months was recommended, with regular monitoring of liver function and assessment for potential drug interactions. Outpatient follow-up at a mycology clinic was also advised.

ANALYSIS OF REGISTRY DATA

Between September 2010 and October 2024, 23 adult patients with invasive aspergillosis (IA) following internal organ transplantation were included in the registry. Of these, 48% were male, with a median age of 55.5 years (range: 19–67; Q1: 49, Q3: 61).

RESULTS

In most cases, IA developed after heart transplantation (65%), followed by kidney transplantation (31%), and less frequently after lung transplantation (4%). The predominant risk factors were the use of immunosuppressive agents – tacrolimus, sirolimus, and mycophenolate mofetil – in 96% of patients, and systemic glucocorticosteroids in 89%. Additional predisposing factors included lymphocytopenia (35%; median duration 20 days [Q1: 15; Q3: 30]) and agranulocytosis (10%; median duration 7 days [Q1: 1; Q3: 14]). Severe bacterial infections, such as pneumonia or sepsis, preceded IA in 63% of cases, while viral pneumonia was noted in 35%. At the time of IA onset, 37% of patients were in the intensive care unit (ICU).

The lungs were the primary site of IA localization (96%). Extrapulmonary involvement (13%) included lesions of the paranasal sinuses, soft tissues of the face, central nervous system aspergillosis, and abdominal organ involvement.

The clinical picture of invasive pulmonary aspergillosis (IPA) was dominated by nonspecific symptoms: fever (65%), respiratory failure (56%), and cough (41%). In isolated cases, hemoptysis was noted (4%). Radiological signs were mainly characterized by infiltrative-focal lung lesions (67%) with a predominance of bilateral processes (76%). In 46% of cases, IPA was accompanied by the appearance of hydrothorax, and in 12.5% of cases, cavities of lung tissue destruction were noted. In patients with viral co-infection or those in the period of agranulocytosis, the "ground glass" symptom was noted (31%).

The diagnosis was established on the basis of direct microscopy of biosubstrates (bronchoalveolar lavage (BAL) and biopsies) in 50% of patients, and in 35% the pathogen was isolated in culture. The main pathogen in IA was *Aspergillus fumigatus* (73%), less commonly *Aspergillus niger* (18%) and *Aspergillus flavus* (9%). A positive galactomannan test in BAL was detected in 85% of patients with IPA. Histological examination revealed characteristic thin hyaline filaments of mycelium branching at an angle of 450 in 13% of patients. A combination of IA with other invasive mycoses (cryptococcosis, pneumocystosis, and candidiasis) was observed in 17%.

Prior to the diagnosis of IA, empirical antifungal therapy with agents active against mold microfungi was administered to 30% of patients. All patients (100%) subsequently received targeted antimycotic therapy. The agents used included voriconazole (87%), echinocandins (17%), and itraconazole (4%). Combination antifungal therapy was required in one patient (4%). Median duration of IA treatment was 96 days [Q1 – 38; Q3 – 150]. Overall 90-day survival rate was 78%.

LITERATURE REVIEW

The first year after transplantation carries the highest risk for invasive fungal infections (IFI), which may result from surgical complications, donor-derived infections, or pre-existing infections in the recipient [6]. The incidence of infectious complications is higher among recipients of heart, lung, and liver transplants compared to kidney transplants. On average, the prevalence of invasive mycoses in organ transplant recipients is approximately 5%, varying by transplant type [7]. The highest rates are observed in small intestine (11.6%) and lung (8.6%) transplants, followed by liver (4.7%), heart (4%), pancreas (3.4%), and kidney (1.3%) transplants [7, 8].

Aspergillosis is the most common invasive fungal infection in this population, while mucormycosis occurs less frequently [9, 10]. In Russia, the number of IA cases has been steadily increasing. In 2024, Khostelidi et al. reported registry data on 17 patients with IA following organ transplantation [11]. By 2025, the number of recorded cases had increased by nearly 30%.

IA typically shows up 3–6 months after organ transplantation [6]. One important risk factor is fungal colonization, with cumulative airway mold colonization rates ranging from 20% to 50% [12]. *Aspergillus spp.* are the most frequent respiratory tract colonizers among potentially pathogenic microfungi. The colonization rate is notably higher in patients with cystic fibrosis. Luong M.L. et al. (2014) reported detection of *Aspergillus spp.* in 70% of cystic fibrosis patients prior to transplantation [12].

Several additional factors contribute to the risk of invasive mycosis, including prolonged ICU stay, renal replacement therapy, concurrent generalized bacterial infection, mechanical ventilation, diabetes mellitus, viral infections, and donor genetic polymorphisms [2, 6]. While all these factors play a role, the use of immunosuppressive agents to prevent transplant rejection remains the predominant risk factor.

Pathogens responsible for invasive mycoses in transplant recipients can affect virtually any organ; however, distinct clinical patterns are typically associated with specific pathogens. In the case of Aspergillus species, the predominant clinical forms are invasive pulmonary aspergillosis (74%–78%) and aspergillus tracheobron-

chitis (5%–25%) [8], with less common manifestations involving the paranasal sinuses (PNS), central nervous system (CNS), and other sites. The clinical presentation of invasive pulmonary aspergillosis is nonspecific, often including cough, dyspnea, and fever [13].

In our registry, heart transplantation was the most frequent procedure among patients with IA (65%). This contrasts with literature data indicating that mycotic lesions of the respiratory tract caused by Aspergillus species occur primarily in lung transplant recipients [8]. In such patients, bronchoscopy may reveal ulcerative or necrotic bronchial lesions, pseudomembranes that slough to form ulcerative defects, and damage often localized around the anastomotic suture line. Central airway obstruction may be the initial manifestation of fungal tracheobronchitis, with bronchoscopy demonstrating fibrinous mucosal plugs containing *Aspergillus* hyphae [8].

The necrotizing pseudomembranous form of invasive fungal tracheobronchitis represents the most severe presentation, characterized by detachment of the necrotic epithelium and submucosal layer. Importantly, invasive tracheobronchial aspergillosis (ITBA) can be asymptomatic and detected incidentally during routine bronchoscopy. Early detection through surveillance bronchoscopy facilitates diagnosis before symptom onset, allowing timely initiation of antifungal therapy. The main complications of tracheobronchial aspergillosis include bronchomalacia, bronchial stenosis, suture dehiscence, bleeding, and extension into the lung parenchyma with subsequent dissemination [8].

Thus, when clinical symptoms of lung injury appear, recipients of internal organ transplants (lungs, heart, liver, kidneys) should undergo fiberoptic bronchoscopy with BAL to test for pathogenic microorganisms, including fungi, as well as a galactomannan assay for *Aspergillus spp.* antigen (AG).

The diagnostic criteria for these patients include identifying risk factors for mycotic infection in combination with clinical findings, CT imaging features, and laboratory results [14]. On lung CT scans, early manifestations (within the first 3–5 days) most commonly present as perivascular "ground-glass" opacities (50–60%). These lesions often progress to dense foci and infiltrates, with eventual formation of areas of destruction. A surrounding "halo" of perifocal inflammation is seen in 19%–53% of cases [13, 15].

When the paranasal sinuses (PNS) are involved, CT imaging typically reveals areas of osteodestruction. In cases of central nervous system involvement, focal brain lesions are visualized [15].

The main diagnostic methods include: microscopy of material from the lesion site, which detects thin septate mycelium branching at approximately 45°; culture testing, positive in 40–50% of cases; detection of galactomannan (GM) in BAL fluid, with a sensitivity of about 60% and specificity of 95–98% [16–18]; PCR testing for *Aspergillus* DNA [17].

Microscopy is performed on both native and stained preparations, most commonly using Gram, hematoxylin–eosin, Ziehl–Neelsen, India ink, or calcofluor white stains. Given the rapid progression of the infection, direct microscopy with calcofluor white staining under a fluorescent microscope is the fastest diagnostic approach [19, 20].

The presence of characteristic fungal mycelium in normally sterile biosubstrates or BAL fluid, combined with relevant risk factors, clinical signs, and imaging findings, is a key diagnostic criterion. Notably, refrigerating the specimen or homogenizing it prior to culture may reduce the likelihood of recovering microfungi.

Cultures are identified based on macromorphological and micromorphological features, as well as molecular methods. Histological examination using specific stains – such as Grocott's methenamine silver (GMS) and the periodic acid–Schiff (PAS) reaction – enables visualization of fungal elements within tissues and assessment of the degree of invasion, including associated inflammation and necrosis [14].

The detection of GM is one of the key diagnostic tests. According to a meta-analysis by Gavaldà et al. (2014), the sensitivity of the GM test in the blood of solid organ transplant recipients is approximately 30% [21]. The specificity of the assay is reduced due to the possibility of false-positive results; therefore, GM determination in blood is not recommended for routine diagnosis or treatment monitoring.

The most diagnostically valuable application of the GM test is in BAL samples, where sensitivity reaches 60% and specificity 95–98% [22, 23].

PCR assays have been developed for the amplification of *Aspergillus* DNA, typically performed on blood and BAL specimens. It is important to recognize that a positive PCR result from a respiratory sample may indicate either airway colonization or an invasive process [24]. Current international clinical guidelines from the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and the European Organisation for Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG) do not recommend the use of PCR as a stand-alone diagnostic tool, since these systems have not yet been standardized or validated in independent studies [25].

Microfungal pathogens can be identified using matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF) [24, 26]. The most common IA pathogens are *Aspergillus fumigatus* (73%), A. flavus (14%), and A. terreus (8%), although rare *Aspergillus* species are also occasionally encountered [26]. These findings are consistent with our own observations.

STRATEGIES FOR THE TREATMENT OF INVASIVE MYCOSES IN ORGAN TRANSPLANT RECIPIENTS

The main management approach in organ transplant recipients largely parallels established treatment strategies for other groups of immunocompromised patients [27].

Primary antifungal prophylaxis is indicated for all patients with extensive colonization of the respiratory and gastrointestinal tract mucosa by micromycetes in the postoperative period. Empirical antifungal therapy is recommended when clinical manifestations of localized or systemic infection are present and there is no improvement following 96 hours of standard antibacterial treatment. Etiotropic therapy should be initiated once diagnostic test results are available, with treatment tailored to the specific pathogen identified and the corresponding nosological form [28].

Senoner et al. (2023) showed that antifungal prophylaxis in liver transplantation significantly reduces the risk of proven invasive mycosis (OR 0.37; 95% CI: 0.19–0.72; p = 0.003). The use of antifungal prophylaxis in specialized departments is also associated with a marked reduction in mortality attributable to fungal infections (OR 0.32; 95% CI: 0.10–0.83; p = 0.02), although it does not significantly influence all-cause mortality (OR 0.87; 95% CI: 0.54–1.39; p = 0.55). In the absence of antifungal prophylaxis, invasive fungal infections (IFIs) develop in approximately 36% of transplant recipients [29].

Therefore, targeted prophylaxis with antifungal agents active against *Aspergillus spp.* is recommended in lung transplant recipients with documented pre-transplant colonization of the respiratory tract by *Aspergillus spp.* While the optimal duration of such prophylaxis remains undefined, it is typically administered for an average of 2–3 weeks [30].

Current clinical consensus identifies voriconazole and isavuconazole as the first-line agents for the treatment of IA (Table). Given the difficulty of conducting clinical trials specifically in organ transplant recipients, therapeutic recommendations are largely extrapolated from experience in other patient populations [14, 31, 32].

Voriconazole undergoes extensive metabolism via the cytochrome P450 enzyme system, which limits its use in transplant recipients due to the potential for significant drug–drug interactions, particularly with immunosuppressive agents. Therapeutic drug monitoring is an essential component of the management strategy in patients with multiple drug interactions [14].

Nevertheless, voriconazole has been successfully used as first-line therapy for IA in heart, lung, and liver transplant recipients [14]. Isavuconazole offers a more favorable safety profile [14, 33] and may be prescribed in cases where voriconazole is not effective.

Liposomal amphotericin B (L-AMB) represents an alternative agent for IA therapy, demonstrating *in vitro* activity against most mold species [14, 32, 34]. However, resistance has been documented in certain *Aspergillus* species, notably *Aspergillus terreus*. Echinocandins (caspofungin, micafungin, anidulafungin) are not recommended as monotherapy for IA, as they exert only fungistatic rather than fungicidal activity against *Aspergillus spp*. Their role is primarily as part of combination therapy, administered alongside voriconazole, isavuconazole, or L-AMB in selected cases [14, 32, 34].

The recommended duration of IA therapy is typically 12 weeks but may range from 6 to >50 weeks [14, 35]. Key determinants include initial therapeutic response, immune status, and activity of the underlying disease. Treatment should be maintained until all clinical manifestations and radiological abnormalities have resolved, and mycological tests yield negative results.

In organ transplant recipients, an essential component of management is to reduce the dose of immunosuppressive drugs and monitor graft function [36]. Patterson et al. (2016) and other expert groups advise a minimum treatment duration of 6–12 weeks, depending on the site

Table

Therapeutic approaches to invasive aspergillosis

Antifungal drug	Strength of recommendation and level of evidence	
Voriconazole 6 mg/kg IV twice daily on day 1, then 4 mg/kg IV twice daily; or 400 mg PO twice on day 1, then 200 mg PO twice daily (with or without food)	**A**	**I**
Isavuconazole 200 mg PO/IV three times daily for 2 days, then 200 mg once daily	**A**	**I**
Liposomal amphotericin B 3 mg/kg/day IV by infusion	B	II
Caspofungin 70 mg IV on day 1, then 50 mg/day IV	C	II
Micafungin 100 mg/day IV	C	III
Itraconazole 200 mg PO twice daily (suspension or tablets)	C	III
Lipid complex AmB 5 mg/kg/day IV	C	III
Combination: anidulafungin 200 mg IV on day 1, then 100 mg/day + voriconazole at standard dosing	C	I
Other combinations as initial therapy	C	III
Amphotericin B deoxycholate	D	I

and extent of IA, as well as the degree and persistence of immunosuppression [20].

FINDINGS

Our data indicate that IA can occur in recipients of internal organ transplants during immunosuppressive therapy. According to our registry, IA developed most frequently after heart transplantation (65%), followed by kidney transplantation (31%) and lung transplantation (4%). The predominant clinical manifestation was pulmonary involvement (96%). The most effective diagnostic method was galactomannan detection in BAL fluid, with a sensitivity of 85%. The leading causative agent was *Aspergillus fumigatus* (73%). The overall 12-week survival rate in our cohort was 78%.

CONCLUSION

The presented clinical case, combined with registry analysis and literature review, underscores that diagnosing and treating IA in organ transplant recipients remains a major challenge for clinicians and microbiologists. Advances in modern diagnostic methods facilitate early detection, which is crucial in immunocompromised patients who require lifelong immunosuppression. Timely and appropriate selection of antifungal therapy significantly improves survival and recovery outcomes in this patient population.

The authors declare no conflict of interest.

REFERENCES

1. *Khostelidi SN.* Invasive mycoses in recipients of solid organ transplants (literature review). *Problems in Medical Mycology*. 2023; 25 (4): 3–14. (In Russ). doi: 10.24412/1999-6780-2023-4-3-14. EDN YHAXVI.
2. *Pata R, Kristeva J, Kosuru B.* Pneumonia in Transplant Recipients: A Comprehensive Review of Diagnosis and Management. *Cureus.* 2024 Nov 14; 16 (11): e73669. doi: 10.7759/cureus.73669.
3. *Neofytos D, Chatzis O, Nasioudis D et al.* Epidemiology, risk factors and outcomes of invasive aspergillosis in solid organ transplant recipients in the Swiss transplant cohort study. *Transpl Infect Dis*. 2018; 20 (4): e12898. doi: 10.1111/tid.12898.
4. *Donnelly JP, Chen SC, Kauffman CA, Steinbach WJ et al.* Revision and update of the consensus definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium. *Clin Infect Dis*. 2020; 71: 1367–1376. doi: 10.1093/cid/ciz1008.
5. Certificate of state registration of the database No. 2023620879 Russian Federation. "Invasive aspergillosis in adult patients" ("Database on the results of consultations at the P.N. Kashkin Research Institute of Medical Mycology"): *O.V. Shadrivova, S.N. Hostelidi, N.N. Klimko;* applicant Federal State Budgetary Educational Institution of Higher Education "North-Western State Medical University named after I.I. Mechnikov" of the Ministry of Health of the Russian Federation. EDN VPJAHY.
6. *Dorschner P, McElroy LM, Ison MG et al.* Nosocomial infections within the first month of solid organ transplantation. *Transpl Infect Dis Off J Transplant Soc*. 2014; 16: 171–187. doi: 10.1111/tid.12203.
7. *Patel MH, Patel RD, Vanikar AV et al.* Invasive fungal infections in renal transplant patients: a single center study. Ren Fail. 2017 Nov; 39 (1): 294–298. doi: 10.1080/0886022X.2016.1268537.
8. *Samanta P, Clancy CJ, Nguyen MH et al.* Fungal infections in lung transplantation. *J Thorac* Dis. 2021 Nov; 13 (11): 6695–6707. doi: 10.21037/jtd-2021-26.
9. *Khostelidi SN, Shadrivova OV, Shagdileeva EV et al.* Invasive mycoses caused by filamentous fungi in patients after internal organ transplantation. *Russian Journal of Transplantology and Artificial Organs.* 2024; 26 (S): 219–220. doi: 10.15825/1995-1191-2024-S-219-220.
10. *Khostelidi SN, Kozlova OP, Shagdileeva EV et al.* Invasive mycoses caused by filamentous fungi in patients after internal organ transplantation. *Russian Journal of Transplantology and Artificial Organs.* 2024; 26 (3): 56–65. doi: 10.15825/1995-1191-2024-3-56-65. EDN HNPVRD.
11. *Khostelidi SN, Kozlova OP, Shadrivova OV et al.* Invasive fungal infections after solid organ transplantation (St. Petersburg, Russia). *ABSTRACT BOOK: 3rd Balkan Conference on Medical Mycology and Mycotoxicology, Belgrade, Serbia, October 10–12, 2024. Belgrade: Serbian Society of Medical Mycology*, 2024: 89. EDN HZYZTU.
12. *Luong ML, Chaparro C, Stephenson A, Rotstein C et al.* Pretransplant Aspergillus colonization of cystic fibrosis patients and the incidence of post-lung transplant invasive aspergillosis. *Transplantation.* 2014 Feb 15; 97 (3): 351–357. doi: 10.1097/01.TP.0000437434.42851.d4.
13. *Khostelidi SN.* Clinical and laboratory features of nosocomial invasive aspergillosis: Abstract of the dissertation for the degree of candidate of medical sciences. St. Petersburg, 2010; 22. EDN QHFIBR.
14. *Ullmann AJ, Aguado JM, Arikan-Akdagli S, Denning DW, Groll AH et al.* Diagnosis and management of Aspergillus diseases: executive summary of the 2017 ESCMID-ECMM-ERS guideline. *Clin Microbiol Infect.* 2018 May; 24 Suppl 1: e1–e38. doi: 10.1016/j.cmi.2018.01.002.
15. *Varotto A, Orsatti G, Crimì F et al.* Radiological Assessment of Paediatric Fungal Infections: A Pictorial Review with Focus on PET/MRI. *In vivo*. 2019; 33 (6): 1727–1735. doi: 10.21873/invivo.11663.
16. *Husain S, Sole A, Alexander BD et al.* The 2015 International Society for Heart and Lung Transplantation guidelines for the management of fungal infections in mechanical circulatory support and cardiothoracic organ transplant recipients: executive summary. *J Heart Lung Transplant*. 2016; 35 (3): 261–282. doi: 10.1016/j.healun.2016.01.007.
17. *Imbert S, Meyer I, Palous M, Brossas JY et al.* Aspergillus PCR in bronchoalveolar lavage fluid for the diagnosis

and prognosis of aspergillosis in patients with hematological and non-hematological conditions. *Front Microbiol*. 2018; 9: 1877. doi: 10.3389/fmicb.2018.01877.
18. *Ignatieva SM, Shadrivova OV, Shurpitskaya OA et al.* Determination of galactomannan from *Aspergillus spp.* In patients with COVID-associated invasive aspergillosis. *Problems of medical mycology*. 2023; 25 (2): 115. EDN UKTCPI.
19. *Terrero-Salcedo D.* Updates in Laboratory Diagnostics for Invasive Fungal Infections. *J Clin Microbiol*. 2020; 58 (6): e01487-19. doi: 10.1128/JCM.01487-19.
20. *Patterson TF, Thompson GR, Denning DW, Fishman JA et al.* Practice guidelines for the diagnosis and management of aspergillosis: 2016 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2016; 63 (4): e1–e60. doi: 10.1093/cid/ciw326.
21. *Gavaldà J, Meije Y, Fortún J, Roilides E et al.* ESCMID Study Group for Infections in Compromised Hosts. Invasive fungal infections in solid organ transplant recipients. *Clin Microbiol Infect.* 2014 Sep; 20 Suppl 7: 27–48. doi: 10.1111/1469-0691.12660.
22. *Boch T, Buchheidt D, Spiess B, Miethke T, Hofmann WK, Reinwald M.* Direct comparison of galactomannan performance in concurrent serum and bronchoalveolar lavage samples in immunocompromised patients at risk for invasive pulmonary aspergillosis. *Mycoses*. 2016; 59 (2): 80–85. doi: 10.1111/myc.12434.
23. *Singh N, Winston DJ, Limaye AP, Pelletier S, Safdar N, Morris MI et al.* Performance characteristics of Galactomannan and beta-d-Glucan in high-risk liver transplant recipients. *Transplantation*. 2015; 99 (12): 2543–2550. doi*:* 10.1097/TP.0000000000000763.
24. *Haidar G, Falcione BA, Nguyen MH.* Diagnostic modalities for in- vasive mould infections among hematopoietic stem cell transplant and solid organ recipients: performance characteristics and prac- tical roles in the clinic. *Journal of Fungi.* 2015; 1 (2): 252–276. doi: 10.3390/jof1020252.
25. *Imbert S, Gauthier L, Joly I, Brossas JY et al.* Aspergillus PCR in serum for the diagnosis, follow-up and prognosis of invasive aspergillosis in neutropenic and nonneutropenic patients. *Clin Microbiol Infect*. 2016; 22 (6): 562e1–562e8. doi: 10.1016/j.cmi.2016.01.027.
26. *Neofytos D, Garcia-Vidal C, Lamoth F, Lichtenstern C, Perrella A, Vehreschild JJ.* Invasive aspergillosis in solid organ transplant patients: diagnosis, prophylaxis, treatment, and assessment of response. *BMC Infect Dis.* 2021 Mar 24; 21 (1): 296. doi: 10.1186/s12879-021-05958-3.
27. *Andreev SS, Bronin GO, Epifanova NYu et al.* Advantages of early administration of antimycotic therapy in hematological patients. *Oncohematology.* 2024; 19 (1): 99–112. doi: 10.17650/1818-8346-2024-19-1-99-112. EDN NOYKAI.
28. *Bitterman R, Marinelli T, Husain S.* Strategies for the Prevention of Invasive Fungal Infections after Lung Transplant. *J Fungi.* 2021; 7: 122. doi: 10.3390/jof7020122.
29. *Senoner T, Breitkopf R, Treml B, Rajsic S.* Invasive Fungal Infections after Liver Transplantation. *J Clin Med.* 2023; 12: 3238. doi: 10.3390/jcm12093238.
30. *Husain S, Camargo JF.* Invasive Aspergillosis in solid-organ transplant recipients: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. *Clin Transplant.* 2019; 33: e13544. doi: 10.1111/ctr.13544.
31. *Klimko NN, Khostelidi SN, Borzova YuV et al.* Nosocomial invasive aspergillosis in hematological oncology patients. *Clinical oncohematology*. Basic research and clinical practice. 2011; 4 (3): 228–234. EDN QALBGP.
32. *Klyasova GA.* New possibilities for the treatment of invasive aspergillosis. *Oncohematology.* 2021; 16 (4): 31–39. doi: 10.17650/1818-8346-2021-16-4-31-39. EDN LIRRGQ.
33. *Veselov AV.* Isavuconazole is a new antifungal drug of the triazole class. *Problems of medical mycology.* 2015; 17 (4): 18–24. EDN VEDMSV.
34. *Shadrivova OV.* Clinical and immunological features of invasive aspergillosis: Dissertation for the degree of Candidate of Medical Sciences. 2015; 126. EDN TYJMMI.
35. *Richardson M, Bowyer P, Sabino R.* The human lung and Aspergillus: You are what you breathe in? *Medical Mycology.* 2019; 57 (Suppl. 2): S145–S154. doi: 10.1093/mmy/myy149.
36. *Singh NM, Husain S,* The AST Infectious Diseases Community of Practice. Aspergillosis in solid organ transplantation. *American Journal of Transplantation*. 2013; 13: 228–241. doi: 10.1111/ajt.12115.

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