

Invasive Fusariosis in Patients with Hematologic Diseases

Subjects: **Allergy**

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Invasive fusariosis is a serious fungal disease affecting high-risk hematologic patients, especially AML patients receiving induction remission chemotherapy and allogeneic HCT recipients. The most frequent clinical presentation is disseminated disease, with fever, metastatic skin lesions, pneumonia, and positive blood cultures. The outcome is largely dependent on recovery of host defenses, with virtually a 100% death rate in persistently neutropenic patients, despite monotherapy or combination antifungal therapy.

fusariosis

fungal infection

fungemia

immunocompromised

neutropenic

1. Introduction

Invasive fungal disease (IFD) is a serious complication in patients with hematologic malignancies, with the highest incidence occurring in patients with acute leukemia and in hematopoietic cell transplant (HCT) recipients ^{[1][2]}. Until the 1980s, yeasts, particularly *Candida* species, were the most frequent agents of IFD. However, with the introduction of fluconazole prophylaxis, IFD caused by molds became more prevalent ^[3]. While *Aspergillus* species account for the majority of cases of IFD in hematologic patients, infection caused by other molds, such as *Fusarium* species, may occur, with a relatively high incidence in some areas of the globe ^[4].

2. Fungus

Fusarium species are ubiquitous filamentous fungi, commonly found in the soil, plants, and water ^[4]. They are important agents of disease in plants ^[5] and are part of water biofilms in hospital water systems worldwide ^{[6][7][8][9]}. In non-immunocompromised individuals, the most frequent infections caused by *Fusarium* species are onychomycosis and keratitis ^{[10][11]}. Immunosuppressed patients with hematologic diseases may develop invasive fusariosis, with disseminated skin lesions, positive blood cultures, and a poor outcome ^[12].

The genus *Fusarium* comprises more than 300 phylogenetically distinct species, grouped in more than 20 species complexes ^{[13][14]}. However, *Fusarium* species causing disease in humans are grouped into seven species complexes (**Table 1**): *Fusarium solani* species complex (FSSC) , *Fusarium oxysporum* species complex (FOSC), *Fusarium fujikuroi* species complex (FFSC), *Fusarium incarnatum-equiseti* species complex (FIESC), *Fusarium chlamidosporum* species complex (FCSC), *Fusarium dimerum* species complex (FDSC), and *Fusarium sporotrichoides* species complex (FSAMSC) ^[15]. Approximately 70% of cases of invasive disease occurring in

hematologic patients are caused by FSSC and FOSC [4], but there are geographic differences in species distribution [16][17][18].

Table 1. Most frequent species complexes of the genus *Fusarium* involved in human infections and their respective species within each complex.

Species Complex	Species Complex
<i>Fusarium solani</i> species complex	<i>Fusarium fujikuroi</i> species complex
<i>Fusarium falciforme</i>	<i>Fusarium acutatum</i>
<i>Fusarium keratoplasticum</i>	<i>Fusarium anthophilum</i>
<i>Fusarium lichenicola</i>	<i>Fusarium andiyazi</i>
<i>Fusarium petrophilum</i>	<i>Fusarium fujikuroi</i>
<i>Fusarium pseudensiforme</i>	<i>Fusarium nygamai</i>
	<i>Fusarium proliferatum</i>
	<i>Fusarium verticillioides</i>
<i>Fusarium oxysporum</i> species complex	<i>Fusarium incarnatum-equiseti</i> species complex
<i>Fusarium oxysporum</i>	<i>Fusarium incarnatum</i>
Unnamed	<i>Fusarium equiseti</i>
	Unnamed
<i>Fusarium sporotrichoides</i> species complex	<i>Fusarium dimerum</i> species complex
<i>Fusarium aereniacum</i>	<i>Fusarium dimerum</i>
<i>Fusarium brachygibbosum</i>	<i>Fusarium delphinoides</i>
<i>Fusarium langsethiae</i>	<i>Fusarium penzigii</i>
<i>Fusarium sporotrichioides</i>	
<i>Fusarium chlamidosporum</i> species complex	
<i>Fusarium chlamidosporum</i>	

The detection of the growth of *Fusarium* in clinical specimens is not difficult in a routine mycology laboratory. *Fusarium* species grow rapidly on many media without cycloheximide. The colonies in potato dextrose agar are pink, red, gray, or yellow, with velvety to cottony surfaces. The genus is easily identified by the typical banana-shaped macroconidia. However, species identification requires molecular methods [19] or mass spectrometry using

matrix-assisted laser desorption–ionization flight time (MALDI-TOF). The latter has been evaluated in both pure colonies and blood culture bottles, and is the easiest method for species identification [19][20]. Adventitious sporulation is characteristic of *Fusarium*, and the yeast-like structures, called aleuroconidia, are responsible for the frequent occurrence of positive blood cultures and metastatic skin lesions [12]. In tissue, the hyphae of *Fusarium* are hyaline, septate with acute-angle branching, with an appearance similar to *Aspergillus*. Sometimes aleuroconidia are found in tissue together with hyphae, which is suggestive of *Fusarium*. However, since the appearance of these hyaline hyphae in tissue is quite similar among different fungi, the term hyalohyphomycosis is more appropriate when the genus is not identified. This underscores the importance of culture of tissue biopsy, together with histopathology. If culture is not available or does not grow the fungus, in-situ hybridization in paraffin-embedded tissue may help to define the genus [21].

3. Diagnosis of Invasive Fusariosis

The confirmation of the diagnosis of invasive fusariosis depends on the growth of the organism in culture of biologic materials and/or the demonstration of tissue invasion by hyphae. As mentioned above, the sole demonstration of septate, acute-branching, and hyaline hypha in tissue is not enough to establish the diagnosis of invasive fusariosis as other hyaline molds have the same histopathologic picture. In such circumstances, the most appropriate diagnosis is hyalohyphomycosis.

The most frequent sources of diagnosis are the blood and skin biopsy. Among 84 hematologic patients with invasive fusariosis, the diagnosis was made by culture in 65 patients (77.4%): blood culture (26 cases), culture of a fragment of skin biopsy (18 cases), culture of blood and skin biopsy (12 cases), culture of sinus tract (eight cases), and culture of a bronchoalveolar lavage (BAL) fluid (one case). In the remaining 19 cases, the diagnosis was made by culture and histopathology (blood and skin in 18, and sinus in one) [22]. In another series with 233 cases of invasive fusariosis, detailed information about the diagnosis was available in 224 cases: culture alone in 138 (61.6%), culture and histopathology in 83 (37.0%), and histopathology alone in three. The skin was the main source of diagnosis in 100 cases, followed by blood (85 cases) [23].

Although considered specific for aspergillosis, serum galactomannan, as detected by the Platelia *Aspergillus* enzyme immunoassay (BioRad), may be positive in infection caused by other fungi, including *Fusarium* species [24]. We evaluated the performance of serum galactomannan in hematologic patients with invasive fusariosis diagnosed in three centers in Brazil. Among 18 patients, 15 (83%) had at least one positive serum galactomannan test (median of 4 positive tests). Serum galactomannan was positive before the first clinical manifestation of invasive fusariosis in 8 patients, and in 11 before the diagnosis of fusariosis [25]. In other study, we compared the characteristics of 36 patients with invasive aspergillosis with 26 patients with invasive fusariosis. Serum galactomannan was positive in 88.6% and 73.3% of patients with aspergillosis and fusariosis, respectively, with no differences in the median number of positive tests and galactomannan values [26]. Therefore, in regions where invasive fusariosis is more frequent, patients with lung nodules and positive serum galactomannan may have either aspergillosis or fusariosis.

Another fungal biomarker that has potential in the diagnosis of invasive fusariosis is serum 1,3- β -D-glucan. We evaluated the performance of 1,3- β -D-glucan in 13 patients with invasive fusariosis. Twelve of the thirteen patients (92.3%) had at least one positive 1,3- β -D-glucan serum level (median of four). The test was positive before the diagnosis of invasive fusariosis in 11 of the 12 patients, at a median of 10 days. Comparing this group with a control group of hematologic patients with similar underlying diseases and treatments, the sensitivity, specificity, and positive and negative predictive values of two consecutive positive beta-glucan tests were 85%, 69%, 7%, and 99%, respectively. We concluded that, while the test is positive in the majority of patients with invasive fusariosis, the low positive predictive value strongly limits its usefulness in the diagnosis [24].

4. Management of Invasive Fusariosis

In contrast with the lack of correlation between antifungal susceptibility tests and the outcome, there is a close relationship between immunity and survival. Analyzing prognostic factors in 84 hematologic patients with invasive fusariosis, the 90-day probability of survival was 0% if patients had persistent neutropenia and were receiving corticosteroids, 4% in those with persistent neutropenia only, 30% in patients receiving corticosteroids but not neutropenic, and 67% in patients without any of these two factors [22]. In our analysis of the outcome of 233 cases of invasive fusariosis (215 with hematologic diseases), variables associated with poor outcome (90-day mortality) were again receipt of corticosteroids (HR 2.11), neutropenia at the end of treatment (HR 2.70), and primary treatment with deoxycholate amphotericin B (HR 1.83) [23].

Primary anti-mold prophylaxis is usually indicated in hematologic patients at high risk to develop invasive fusariosis, including AML in induction remission [27] and allogeneic HCT [28]. In patients receiving anti-mold prophylaxis, breakthrough infection may occur, including fusariosis [29][30][31].

Patients with a prior history of invasive mold disease and who will subsequently be exposed to a period of immunosuppression may theoretically be at risk to present with recurrence of the fungal infection. The use of secondary prophylaxis in such circumstances has been well established in invasive aspergillosis [32][33][34], but there is limited data in other mold infections. We evaluated the usefulness of secondary prophylaxis for invasive fusariosis in a multicenter retrospective study of 40 patients who were successfully treated for invasive fusariosis and were exposed to subsequent periods of immunosuppression (neutropenia in 35 and graft versus host disease in 5). Relapse of invasive fusariosis occurred in 2 of 8 patients (25%) who were not on prophylaxis and in 3 of 32 (9.4%) who received secondary prophylaxis (mostly voriconazole). Considering only patients who had prior disseminated fusariosis, relapse occurred in 2 of 2 (100%) not on secondary prophylaxis and in 3 of 26 (11.5%) who received secondary prophylaxis ($p = 0.03$) [35]. In light of these data, we believe that secondary prophylaxis (voriconazole or a lipid preparation of amphotericin B) should be strongly considered in patients with prior invasive fusariosis who will be exposed to subsequent periods of immunosuppression, especially if the disease was disseminated.

References

1. Pagano, L.; Caira, M.; Candoni, A.; Offidani, M.; Fianchi, L.; Martino, B.; Pastore, D.; Picardi, M.; Bonini, A.; Chierichini, A.; et al. The epidemiology of fungal infections in patients with hematologic malignancies: The SEIFEM-2004 study. *Haematology* 2006, 91, 1068–1075.
2. Kontoyiannis, D.P.; Marr, K.A.; Park, B.J.; Alexander, B.D.; Anaissie, E.J.; Walsh, T.J.; Ito, J.; Andes, D.R.; Baddley, J.W.; Brown, J.M.; et al. Prospective Surveillance for Invasive Fungal Infections in Hematopoietic Stem Cell Transplant Recipients, 2001–2006: Overview of the Transplant-Associated Infection Surveillance Network (TRANSNET) Database. *Clin. Infect. Dis.* 2010, 50, 1091–1100.
3. Nucci, M.; Marr, K.A. Emerging Fungal Diseases. *Clin. Infect. Dis.* 2005, 41, 521–526.
4. Nucci, M.; Anaissie, E. *Fusarium* Infections in Immunocompromised Patients. *Clin. Microbiol. Rev.* 2007, 20, 695–704.
5. Sáenz, V.; Alvarez-Moreno, C.; Le Pape, P.; Restrepo, S.; Guarro, J.; Ramírez, A.M.C. A One Health Perspective to Recognize *Fusarium* as Important in Clinical Practice. *J. Fungi* 2020, 6, 235.
6. Balmas, V.; Fancellu, F.; Sanna, S.; Scherm, B.; Migheli, Q.; Malbrán, I. Water distribution systems in Sardinian hospitals host invasive clonal lineages of the *Fusarium oxysporum* and *Fusarium solani* species complexes. *Mycologia* 2021, 113, 725–733.
7. Litvinov, N.; da Silva, M.T.N.; van der Heijden, I.M.; Graça, M.G.; de Oliveira, L.M.; Fu, L.; Giudice, M.; de Aquino, M.Z.; Odone-Filho, V.; Marques, H.H.; et al. An outbreak of invasive fusariosis in a children's cancer hospital. *Clin. Microbiol. Infect.* 2015, 21, 268.e1–268.e7.
8. Scheel, C.M.; Hurst, S.F.; Barreiros, G.; Akiti, T.; Nucci, M.; Balajee, S.A. Molecular analyses of *Fusarium* isolates recovered from a cluster of invasive mold infections in a Brazilian hospital. *BMC Infect. Dis.* 2013, 13, 49.
9. Anaissie, E.J.; Kuchar, R.T.; Rex, J.; Francesconi, A.; Kasai, M.; Müller, F.C.; Lozano-Chiu, M.; Summerbell, R.C.; Dignani, M.C.; Chanock, S.J.; et al. Fusariosis Associated with Pathogenic *Fusarium* Species Colonization of a Hospital Water System: A New Paradigm for the Epidemiology of Opportunistic Mold Infections. *Clin. Infect. Dis.* 2001, 33, 1871–1878.
10. Homa, M.; Shobana, C.S.; Singh, Y.R.B.; Manikandan, P.; Selvam, K.P.; Kredics, L.; Narendran, V.; Vágvolgyi, C.; Galgóczy, L. *Fusarium* keratitis in South India: Causative agents, their antifungal susceptibilities and a rapid identification method for the *Fusarium solani* species complex. *Mycoses* 2013, 56, 501–511.
11. Ranawaka, R.R.; Nagahawatte, A.; Gunasekara, T.A. *Fusarium* onychomycosis: Prevalence, clinical presentations, response to itraconazole and terbinafine pulse therapy, and 1-year follow-

- up in nine cases. *Int. J. Dermatol.* 2015, 54, 1275–1282.
12. Boutati, E.I.; Anaissie, E.J. *Fusarium*, a significant emerging pathogen in patients with hematologic malignancy: Ten years' experience at a cancer center and implications for management. *Blood* 1997, 90, 999–1008.
 13. O'Donnell, K.; Al-Hatmi, A.M.S.; Aoki, T.; Brankovics, B.; Cano-Lira, J.F.; Coleman, J.J.; de Hoog, G.S.; Di Pietro, A.; Frandsen, R.J.N.; Geiser, D.M.; et al. No to *Neocosmospora*: Phylogenomic and Practical Reasons for Continued Inclusion of the *Fusarium solani* Species Complex in the Genus *Fusarium*. *mSphere* 2020, 5.
 14. O'Donnell, K.; Rooney, A.P.; Proctor, R.H.; Brown, D.W.; McCormick, S.P.; Ward, T.J.; Frandsen, R.J.; Lysøe, E.; Rehner, S.A.; Aoki, T.; et al. Phylogenetic analyses of RPB1 and RPB2 support a middle Cretaceous origin for a clade comprising all agriculturally and medically important fusaria. *Fungal Genet. Biol.* 2013, 52, 20–31.
 15. Van Diepeningen, A.D.; Al-Hatmi, A.M.S.; Brankovics, B.; De Hoog, G.S. Taxonomy and Clinical Spectra of *Fusarium* Species: Where Do We Stand in 2014? *Curr. Clin. Microbiol. Rep.* 2014, 1, 10–18.
 16. Herkert, P.F.; Al-Hatmi, A.M.S.; Salvador, G.L.D.O.; Muro, M.D.; Pinheiro, R.L.; Nucci, M.; Queiroz-Telles, F.; De Hoog, G.S.; Meis, J.F. Molecular Characterization and Antifungal Susceptibility of Clinical *Fusarium* Species from Brazil. *Front. Microbiol.* 2019, 10, 737.
 17. Lortholary, O.; Obenga, G.; Biswas, P.; Caillot, D.; Chachaty, E.; Bienvenu, A.-L.; Cornet, M.; Greene, J.; Herbrecht, R.; Lacroix, C.; et al. International Retrospective Analysis of 73 Cases of Invasive Fusariosis Treated with Voriconazole. *Antimicrob. Agents Chemother.* 2010, 54, 4446–4450.
 18. Tortorano, A.M.; On the behalf of the ECMM Working Group; Prigitano, A.; Esposto, M.C.; Arsenijevic, V.A.; Kolarovic, J.; Ivanovic, D.; Paripovic, L.; Klingspor, L.; Nordøy, I.; et al. European Confederation of Medical Mycology (ECMM) epidemiological survey on invasive infections due to *Fusarium* species in Europe. *Eur. J. Clin. Microbiol. Infect. Dis.* 2014, 33, 1623–1630.
 19. De Carolis, E.; Posteraro, B.; Lass-Flörl, C.; Vella, A.; Florio, A.R.; Torelli, R.; Girmenia, C.; Colozza, C.; Tortorano, A.M.; Sanguinetti, M.; et al. Species identification of *Aspergillus*, *Fusarium* and *Mucorales* with direct surface analysis by matrix-assisted laser desorption/ionization time-of-flight mass spectrometry. *Clin. Microbiol. Infect.* 2012, 18, 475–484.
 20. Walsh, T.J.; McCarthy, M.W. The expanding use of matrix-assisted laser desorption/ionization-time of flight mass spectroscopy in the diagnosis of patients with mycotic diseases. *Expert Rev. Mol. Diagn.* 2019, 19, 241–248.
 21. Hayden, R.T.; Isotalo, P.A.; Parrett, T.; Wolk, D.M.; Qian, X.; Roberts, G.D.; Lloyd, R.V. In Situ Hybridization for the Differentiation of *Aspergillus*, *Fusarium*, and *Pseudallescheria* Species in

- Tissue Section. *Diagn. Mol. Pathol.* 2003, 12, 21–26.
22. Nucci, M.; Anaissie, E.J.; Queiroz-Telles, F.; Martins, C.A.; Trabasso, P.; Solza, C.; Mangini, C.; Simoes, B.D.; Colombo, A.L.; Vaz, J.; et al. Outcome predictors of 84 patients with hematologic malignancies and *Fusarium* infection. *Cancer* 2003, 98, 315–319.
 23. Nucci, M.; Marr, K.; Vehreschild, M.; de Souza, C.; Velasco, E.; Cappellano, P.; Carlesse, F.; Queiroz-Telles, F.; Sheppard, D.; Kindo, A.; et al. Improvement in the outcome of invasive fusariosis in the last decade. *Clin. Microbiol. Infect.* 2014, 20, 580–585.
 24. Cummings, J.R.; Jamison, G.R.; Boudreaux, J.W.; Howles, M.J.; Walsh, T.J.; Hayden, R.T. Cross-reactivity of non-*Aspergillus* fungal species in the *Aspergillus* galactomannan enzyme immunoassay. *Diagn. Microbiol. Infect. Dis.* 2007, 59, 113–115.
 25. Nucci, M.; Carlesse, F.; Cappellano, P.; Varon, A.G.; Seber, A.; Garnica, M.; Nouér, S.A.; Colombo, A.L. Earlier Diagnosis of Invasive Fusariosis with *Aspergillus* Serum Galactomannan Testing. *PLoS ONE* 2014, 9, e87784.
 26. Nucci, F.; Nouér, S.; Capone, D.; Nucci, M. Invasive mould disease in haematologic patients: Comparison between fusariosis and aspergillosis. *Clin. Microbiol. Infect.* 2018, 24, 1105.e1–1105.e4.
 27. Cornely, O.A.; Maertens, J.; Winston, D.J.; Perfect, J.; Ullmann, A.J.; Walsh, T.J.; Helfgott, D.; Holowiecki, J.; Stockelberg, D.; Goh, Y.-T.; et al. Posaconazole vs. Fluconazole or Itraconazole Prophylaxis in Patients with Neutropenia. *N. Engl. J. Med.* 2007, 356, 348–359.
 28. Ullmann, A.J.; Lipton, J.H.; Vesole, D.H.; Chandrasekar, P.; Langston, A.; Tarantolo, S.R.; Greinix, H.; De Azevedo, W.M.; Reddy, V.; Boparai, N.; et al. Posaconazole or Fluconazole for Prophylaxis in Severe Graft-versus-Host Disease. *N. Engl. J. Med.* 2007, 356, 335–347.
 29. Biehl, L.M.; Vehreschild, J.J.; Liss, B.; Franke, B.; Markiefka, B.; Persigehl, T.; Bucker, V.; Wisplinghoff, H.; Scheid, C.; Cornely, O.A.; et al. A cohort study on breakthrough invasive fungal infections in high-risk patients receiving antifungal prophylaxis. *J. Antimicrob. Chemother.* 2016, 71, 2634–2641.
 30. Fernández-Cruz, A.; Semiglia, M.A.; Guinea, J.; Martínez-Jiménez, M.D.C.; Escribano, P.; Kwon, M.; Rodríguez-Macías, G.; Chamorro-De-Vega, E.; Rodríguez-González, C.; Navarro, R.; et al. A retrospective cohort of invasive fusariosis in the era of antimould prophylaxis. *Med. Mycol.* 2019, 58, 300–309.
 31. Lerolle, N.; Raffoux, E.; Socie, G.; Touratier, S.; Sauvageon, H.; Porcher, R.; Bretagne, S.; Bergeron, A.; Azoulay, E.; Molina, J.-M.; et al. Breakthrough invasive fungal disease in patients receiving posaconazole primary prophylaxis: A 4-year study. *Clin. Microbiol. Infect.* 2014, 20, O952–O959.

32. El-Cheikh, J.; Castagna, L.; Wang, L.; Esterni, B.; Faucher, C.; Fürst, S.; Pierre, B.; Mohty, M.; Blaise, D. Impact of prior invasive aspergillosis on outcome in patients receiving reduced-intensity conditioning allogeneic hematopoietic stem cell transplant. *Leuk. Lymphoma* 2010, 51, 1–6.
33. Kikuchi, M.; Nakasone, H.; Mitani, K.; Gotoh, M.; Kobayashi, A.; Kurita, N.; Saito, T.; Sato, K.; Kanda, Y. Japan Hematology and Oncology Clinical Study Group Retrospective assessment of secondary prophylaxis for invasive aspergillosis in neutropenic hematology patients and identification of risk factors for relapse of fungal disease. *Scand. J. Infect. Dis.* 2013, 45, 531–536.
34. Cordonnier, C.; Rovira, M.; Maertens, J.; Olavarria, E.; Faucher, C.; Bilger, K.; Pigneux, A.; Cornely, A.O.; Ullmann, A.J.; Bofarull, R.M.; et al. Voriconazole for secondary prophylaxis of invasive fungal infections in allogeneic stem cell transplant recipients: Results of the VOSIFI study. *Haematology* 2010, 95, 1762–1768.
35. Nucci, M.; Shoham, S.; Abdala, E.; Hamerschlak, N.; Rico, J.C.; Forghieri, F.; Nouér, S.A.; Cappellano, P.; Solza, C.; Gonzaga, Y.; et al. Outcomes of patients with invasive fusariosis who undergo further immunosuppressive treatments, is there a role for secondary prophylaxis? *Mycoses* 2019, 62, 413–417.

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