

Emerging and Life-threatening Fungal Pathogens in the Immunocompromised Host

a report by

Gulsen Ozkaya Sahin and **Murat Akova**

Hacettepe University School of Medicine, Department of Medicine, Section of Infectious Diseases, Ankara



Gulsen Ozkaya Sahin



Murat Akova

Gulsen Ozkaya Sahin works in the Hacettepe University School of Medicine, Department of Medicine, Section of Infectious Diseases, in Ankara, Turkey. She has made numerous presentations internationally, and has written and translated many articles and book sections. Following post-graduate education at the Hacettepe University Department of Internal Medicine, worked with Dr Partice Nordmann on extended-spectrum beta-lactamase production in *Enterobacteriaceae* family.

Dr Murat Akova is Professor of Medicine in the Section of Infectious Diseases at the Hacettepe University School of Medicine, in Ankara, Turkey. He is a member of the Alliance for the Prudent Use of Antibiotics, American Society for Microbiology, European Organisation for Research and Treatment of Cancer (EORTC), the International Antimicrobial Therapy Cooperative Group (IATCG), the Invasive Fungal Infections Cooperative Group (IFICG), the European Society of Clinical Microbiology and Infectious Diseases Fungal Infections Study Group, the Immunocompromised Host Society, the International Society for Infectious Diseases and The Pathological Society of Great Britain and Ireland (1989–1994).

The incidence of invasive opportunistic fungal infections (IOFIs) has increased substantially over the past 30 years. Currently, IOFIs are important causes of morbidity and mortality among patients with haematological malignancies or those undergoing stem cell transplantation (SCT).¹ It is estimated that IOFIs develop in 10% to 25% of patients with acute leukaemia and those receiving SCT. The case fatality rate exceeds 50% and is approximately 100% in invasive aspergillosis (IA), especially in patients with persistent neutropaenia.² The role of neutropaenia for the development of IOFI has been well-known and the other risk factors include permissive environmental conditions, selective antifungal pressure and expanding population of immunocompromised host.¹ Increasing awareness of IOFIs, improved culture techniques and the advances in radiological imaging techniques have also been contributed to the increasing incidence of IOFIs.¹ *Candida* and *Aspergillus* species traditionally account for the majority of documented infections. However, recent epidemiological reports indicate a shift towards non-*Albicans Candida* (NAC) and other emerging yeasts and moulds such as *Trichosporon*, *Fusarium*, *Scedosporium* and *Zygomycetes*.³ This text aims to provide a general overview of emerging invasive fungal pathogens with a more detailed description of *Fusarium* species as an example of emerging mould infections.

Invasive NAC Infections

NAC species are responsible for 35% to 65% of all candidemias. They are seen most frequently in cancer patients, especially in those with haematological malignancies and SCT (40% to 70%). The proportion of NAC among *Candida* spp. is increasing – NAC species represented 10% to 40% of all causes of invasive candidiasis before 1990; but since then the incidence has increased by up to 65%. The most common NAC species are *C. parapsilosis* (20% to 40% of all NAC), *C. tropicalis* (10% to 30%), *C. krusei* (10% to 35%) and *C. glabrata* (5% to 40%), and less commonly *C. lusitaniae* (2% to 8%) and *C. guilliermondii* (1% to 5%).⁴ Specific risk factors for NAC include previous colonisation, leukaemia, SCT, prior surgery, renal failure, use of indwelling vascular catheter and prior azole therapy or prophylaxis.^{5–7}

NAC species differ from *C. albicans* by higher mortality rates and resistance to currently available antifungal agents. Fluconazole resistance could be observed in up to 95% of *C. krusei*, 35% of *C. glabrata* and 4% to 25% of *C. tropicalis* and *C. lusitaniae*.³ Amphotericin B resistance is also seen in a small proportion of species. However, this might be a significant problem in certain species such as *C. lusitaniae*, *C. nigosa*, *C. krusei* and *C. guilliermondii*.³ Therefore, species-directed therapy should be applied according to the isoletes identified.⁴

Other Emerging Fungal Pathogens

A wide variety of previously uncommon opportunistic fungi are increasingly encountered as the causes of life-threatening infections in neutropaenic patients. These emerging fungal pathogens may be classified as hyaline septated moulds (*Aspergillus terreus*, *Aspergillus unguis*, *Fusarium* spp., *Acremonium* spp., *Pacilomyces* spp., *Trichoderma* spp. and dermatophytes, particularly *Microsporum* and *Trichophyton* spp.), dematiaceous septated moulds (*Scedosporium apiospermum*, *Bipolaris* spp., *Cladophialophora bantiana*), zygomycetes (*Rhizopus* spp., *Mucor* spp., *Absidia* spp.), yeasts (*Cryptococcus neoformans*, *Trichosporon* spp.) and dimorphic fungi (*Penicillium marneffei*, *Coccidioides immitis*). Infections by these pathogens have extraordinarily high-case fatality rates.^{8–10}

Henceforward, this article will focus on difficult-to-treat *Fusarium* species, which were recently demonstrated as a nosocomially transmissible fungus as an example for emerging moulds.^{11,12}

Fusarium Species

Fusarium spp. are cosmopolitan soil saprophytes and facultative plant pathogens. Since the early 1970s, disseminated infection with *Fusarium* spp. has become an increasingly common problem in immunosuppressed patients.

Soil contamination of the hands and feet, inhalation of the aerosolised conidia and, less commonly, ingestion of the conidia are the major routes of the acquisition.¹² A more recent study has supported the hospital water

supply system as a potential source of fusariosis.¹¹ Burns, corneal and skin trauma, sinusitis and the presence of any type of catheters breaching skin integrity may increase the risk of the fusariosis by overcoming the local host factors.^{13,14} However, fusariosis occurs most commonly in patients with acute leukaemia (70% to 80% of cases), prolonged neutropaenia (more than 90% of cases) and in patients who underwent SCT.¹⁵

After inoculation of *Fusarium spp.*, the toxins produced by this pathogen may enhance the breakdown of tissues and consequently facilitate entry of fusaria into the vascular structures and then dissemination. Like *Aspergillus spp.*, *Fusarium spp.* have a propensity for vascular invasion, resulting in thrombosis and tissue necrosis.¹⁶

Human diseases associated with toxigenic *Fusarium spp.* include alimentary toxic alukia, Kashin-Beck disease and scabby grain intoxication developing after ingestion of infected cereals and grain.¹⁷ Foreign bodies associated fusarial infections include keratitis in contact lens wearers, peritonitis following peritoneal catheter and central venous catheter-associated fungaemia.¹² *Fusarium spp.* may also cause diseases following single organ invasion such as keratitis, onychomycosis, skin infections, otitis, bone and joint infections, invasive intranasal infections, brain abscess and pneumonia. Disseminated multiorgan infection may occur in case of severe immunosuppression.

Disseminated infection commonly manifests itself with fever and myalgia that are unresponsive to broad-spectrum antibacterial chemotherapy during periods of neutropaenia. Skin lesions occur in two-thirds of cases, usually presenting as multiple erythematous subcutaneous nodules, painful erythematous macules and papules with progressive central infarction, or target lesions.¹⁸ Lesions are most commonly seen on the extremities but have also been reported on the trunk and face. Skin lesions, indicating dissemination, can occur within a day of the onset of fever. On the contrary, in disseminated aspergillosis, skin lesions develop in less than 10% of the patients.¹⁵

Isolation of the fungus from blood and biopsy from the skin lesions are the two most effective ways for the diagnosis.¹⁸ In sharp contrast to the rare isolation of *Aspergillus spp.* from the bloodstream, the rate of isolation of *Fusarium spp.* from the blood is more than 60%.^{15,18} Finding hyaline and septated hyphal elements in skin biopsy specimen should aid in making rapid therapeutic decisions. For the easy visualisation of the hyphae in skin biopsy, Gomori methenamine silver or periodic acid-Schiff stains should be used. In culture, rapid growing, pink/orange-coloured colonies and sickle-shaped macroconidia are the characteristic features of *Fusarium spp.*

Although the clinical significance of antifungal susceptibility and synergy testing and interpretative breakpoints have not yet been established, it is known that *Fusarium spp.* demonstrate high minimal inhibitory concentration (MIC) values for fluconazole, itraconazole, posaconazole and ravuconazole (MIC >8µg/ml) and high minimal effective concentration (MEC) values for caspofungin (MEC >8µg/ml). Amphotericin B demonstrates an MIC value between 1-4µg/ml. Voriconazole is a promising antifungal in the treatment of fusarium infections, with an MIC value of 0.25-4µg/ml.¹⁹⁻²¹

Because the treatment of disseminated fusariosis is plagued by high failure rates, alternative agents for therapy have been sought. Some of the published *in vitro* studies and case reports are summarised below.

Arikan et al.²² evaluated the *in vitro* interactions for caspofungin and amphotericin B alone and in combination against six isolates of *Fusarium spp.* Combination of caspofungin plus amphotericin B resulted in a synergistic effect in three isolates, additive effect in one isolate and indifferent effect in two. Notably, no antagonism was observed. Clancy et al.²³ demonstrated synergistic effect of amphotericin B plus azithromycin in 26 isolates of *Fusarium spp.*

Anecdotal data indicated that in *Fusarium solani* infections, amphotericin B alone demonstrated <50% success and all of the cases responded successfully when treated with amphotericin B plus 5-flucytosine, or amphotericin B plus voriconazole or voriconazole alone.^{24,25}

However, in all reported cases, survival is almost always associated with the recovery from neutropaenia.²⁶ Other adjunctive therapeutic measures that may affect the success of antifungal treatment include the removal of indwelling catheters and the addition of colony-stimulating factors or granulocyte transfusions.^{27,28}

Conclusions

Fungi as opportunistic pathogens in immunocompromised patients have become a serious health threat over the last 30 years. Nowadays, while the patients face more severe immunosuppression as a part of treatment for their underlying diseases, and several antifungal agents have become available to treat common infections (such as those caused by *C. albicans* and *Aspergillus spp.*), the less virulent yeasts and moulds with increased antifungal resistance emerge as important pathogens. Clinicians are challenged to diagnose and treat those infections by applying alternative diagnostic measures and using new antifungal agents, if necessary, in combination. ■

References

1. Vento S, Cainelli F, "Infections in patients with cancer undergoing chemotherapy: aetiology, prevention, and treatment", *The Lancet Oncology* (2003);4: pp. 595–604.
2. Sahin G O, Akova M, "Invasive fungal infections", *Business Briefing: European Pharmacotherapy* (2005);pp. 131–132.
3. Pfaller M A, Diekema D J, "Rare and emerging opportunistic fungal pathogens: concern for resistance beyond *Candida albicans* and *Aspergillus fumigatus*", *J. Clin. Microbiol.* (2004);42: pp. 4,419–4,431.
4. Krcmery V, Barnes A J, "Non-albicans *Candida* spp. causing fungaemia: pathogenicity and antifungal resistance", *J. Hosp. Infect.* (2002);50: pp. 243–260.
5. Viscoli C, Girmenia C, Marinus A, Cllette L, Martin P, Vandercam B, Doyen C, Lebau B, Spence D, "Candidemia in cancer patients: a prospective, multicenter surveillance study by the Invasive Fungal Infection Group (IFIG) of the European Organization for Research and Treatment of Cancer (EORTC)", *Clin. Infect. Dis.* (1999);28: pp. 1,071–1,079.
6. Groll A H, Shah P M, Menzel C, Schneider M, Just-Muebling G, Hubner K, "Trends in the postmortem epidemiology of invasive fungal infections at a university hospital", *J. Infect.* (1996);33: pp. 23–32.
7. Rees J R, Pinner R W, Hajjeh R A, Brandt M E, Reingold A L, "The epidemiological features of invasive mycotic infections in the San Francisco Bay area, 1992–1993: results of population-based laboratory active surveillance", *Clin. Infect. Dis.* (1998);27: pp. 1,138–1,147.
8. Walsh T J, Groll A, Hiemenz J, Fleming R, Roilides E, Anaissie E, "Infections due to emerging and uncommon medically important fungal pathogens", *Clin. Microbiol. Infect.* (2004);10 (Suppl 1): pp. 48–66.
9. Marr K, Carter R A, Crippa F, Wald A, Corey L, "Epidemiology and outcome of mould infections in hematopoietic stem cell transplant recipients", *Clin. Infect. Dis.* (2002);34: pp. 909–917.
10. Chamilos G, Marom E M, Lewis R E, Lionakis M S, Kontoyiannis D P, "Predictors of pulmonary zygomycosis versus invasive pulmonary aspergillosis in patients with cancer", *Clin. Infect. Dis.* (2005);41: pp. 60–66.
11. Anaissie E J, Stratton S L, Dignani M C, Lee C K, Summerbell R C, Rex J H, Monson T P, Walsh T J, "Pathogenic molds (including *Aspergillus* species) in hospital water distribution systems: a 3-year prospective study and clinical implications for patients with hematologic malignancies", *Blood* (2003);101: pp. 2,542–2,546.
12. Dignani M C, Anaissie E, "Human fusariosis", *Clin. Microbiol. Infect.* (2004);10 (Suppl 1): pp. 67–75.
13. Girmenia C, Arcese W, Micozzi A, Martino P, Bianco P, Morace G, "Onychomycosis as a possible origin of disseminated *Fusarium solani* infection in a patient with severe aplastic anemia", *Clin. Infect. Dis.* (1992);14: p. 1,167.
14. Kiehn T E, Nelson P E, Bernard E M, Edwards F F, Koziner B, Armstrong D, "Catheter-associated fungemia caused by *Fusarium chlamyosporum* in a patient with lymphocytic lymphoma", *J. Clin. Microbiol.* (1985);21: pp. 501–504.
15. 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: pp. 999–1,008.
16. Lopes Bezerra L M, Filler S G, "Interactions of *Aspergillus fumigatus* with endothelial cells: internalization, injury, and stimulation of tissue factor activity", *Blood* (2004), 103: pp. 2,143–2,149.
17. Nelson P E, Dignani M C, Anaissie E J, "Taxonomy, biology, and clinical aspects of *Fusarium* species", *Clin. Microbiol. Rev.* (1994), 7: pp. 479–504.
18. Nucci M, Anaissie E, "Cutaneous infection by *Fusarium* species in healthy and immunocompromised hosts: implications for diagnosis and management", *Clin. Infect. Dis.* (2002), 35: pp. 909–920.
19. Rotowa N A, Shadomy H J, Shadomy S, "In vitro activities of polyene and imidazole antifungal agents against unusual opportunistic fungal pathogens", *Mycoses* (1990), 33: pp. 203–211.
20. Arkan S, Lozano-Chiu M, Paetznick V, Nangia S, Rex J H, "Microdilution susceptibility testing of amphotericin B, itraconazole, and voriconazole against clinical isolates of *Aspergillus* and *Fusarium* species", *J. Clin. Microbiol.* (1999); 37 (12): pp. 3,946–3,951.
21. Arkan S, Lozano-Chiu M, Paetznick V, Rex J H, "In vitro susceptibility testing methods for caspofungin against *Aspergillus* and *Fusarium* isolates", *Antimicrob. Agents Chemother.* (2001);45: pp. 327–330.
22. Arkan S, Lozano-Chiu M, Paetznick V, Rex J H, "In vitro synergy of caspofungin and amphotericin B against *Aspergillus* and *Fusarium* species", *Antimicrob. Agents Chemother.* (2002);46: pp. 245–247.
23. Clancy C J, Nguyen M H, "The combination of amphotericin B and azithromycin as a potential new therapeutic approach to fusariosis", *J. Antimicrob. Chemother.* (1998);41: pp. 127–130.
24. Vincent A L, Cabrero J E, Greene J N, Sandin R L, "Successful voriconazole therapy of disseminated *Fusarium solani* in the brain of a neutropenic cancer patient", *Cancer Control* (2003);10: pp. 414–419.
25. Patterson T S, Barton L L, Shebab Z M, Hutter J J, "Amphotericin B lipid complex treatment of a leukemic child with disseminated *Fusarium solani* infection", *Clin. Pediatr. (Phila)*. (1996);35: pp. 257–260.
26. Rodriguez C A, Lujan-Zilbermann J, Woodard P, Andreansky M, Adderson E E, "Successful treatment of disseminated fusariosis", *Bone Marrow Transplant* (2003);31: pp. 411–412.
27. Raad I, Hachem R, "Treatment of central venous catheter-related fungemia due to *Fusarium oxysporum*", *Clin. Infect.*

Dis. (1995);20: pp. 709–711.

28. Spielberger R T, Falleroni M J, Coene A J, Larson R A, “Concomitant amphotericin B therapy, granulocyte transfusions, and GM-CSF administration for disseminated infection in a granulocytopenic patient”, Clin. Infect. Dis. (1993);16: pp. 528–530.