Mini Review

Human fusariosis: An emerging infection that is difficult to treat

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Abstract

Fusarium spp. has been associated with a broad spectrum of emerging infections collectively termed fusariosis. This review includes articles published between 2005 and 2018 that describe the characteristics, clinical management, incidence, and emergence of these fungal infections. Fusarium solani and F. oxysporum are globally distributed and represent the most common complexes. Few therapeutic options exist due to intrinsic resistance, especially for the treatment of invasive fusariosis. Therefore, the use of drug combinations could be an important alternative for systemic antifungal resistance. Increase in the number of case reports on invasive fusariosis between 2005 and 2018 is evidence of the emergence of this fungal infection.

Keywords: Fusarium spp. Emerging fungal infection. Human fusariosis.

INTRODUCTION

Fusariosis is an infection that affects plants, animals, and humans, and is caused by various fungi of the genus Fusarium[12]. Fusarium spp. is responsible for significant economic losses in the agricultural field worldwide[3] due to difficulties in management of diseases caused by this species[4]. Similarly, in the medical field, different Fusarium species have been related to local or invasive infections in both immunodepressed and immunocompetent individuals[5,6,7].

However, infections are difficult to treat because of the lack of consensus regarding treatment protocols for fusariosis in humans caused by multi-drug resistant isolates[8,9]. In addition, it is possible that environmental isolates from Fusarium spp. acquire resistance due to previous exposure to fungicides that were used in the agricultural fields[10,11], and these isolates may disseminate and consequently infect humans[12,13]. Perhaps this process of infection may be avoided by implementing public control policies regarding the sale and use of fungicides.

As such, the aim of this study is to review the literature to demonstrate the characteristics, clinical management, incidence, and emergence of fungal infections caused by Fusarium species. The lack of attention on these cases by public health institutions and the insufficient research on the development of novel antifungal agents as therapeutic options emphasize the need to address the main factors involved in fusariosis, such as clinical forms, treatment, and lack of epidemiological control. To address this problem, articles published between 2005 and 2018 were analyzed, and 23 publications were obtained that included important conclusions regarding this proposition (Table 1).

EMERGENCE OF PATHOGENIC FUSARIUM SPECIES

Fusarium species exhibit global distribution, and it is believed that approximately ten complexes are related to human pathogens, including F. solani, F. oxysporum, F. fujikuroi, F. incarnatum-equiseti, F. clamydosporum, F. dimerum, F. sambucinum, F. concolor, and F. lateritium[14]. Among these complexes, members of the F. solani complex are the most common and virulent (comprising approximately 40-60% of infections), followed by F. oxysporum (~20%), F. fujikuroi and F. moniliforme (~10%)[5,14,15].
TABLE 1: Timeline of fusariosis: publication basis for the review study and conclusions of the last 15 years.

| Authors                  | Year | Journal                                    | Main conclusions                                                                 |
|--------------------------|------|--------------------------------------------|----------------------------------------------------------------------------------|
| Nucci and Anaissie       | 2007 | Clinical Microbiology Reviews              | Infections by the Fusarium species are superficial in healthy patients, and these patients tend to respond well to therapy. Disseminated fusariosis affects the immunocompromised host and is often fatal. |
| Katlyar and Edlind       | 2009 | Antimicrobials Agents and Chemotherapy     | Genetic mutations in Fks sequences result in decreased sensitivity of the Fusarium sp., rendering it difficult to treat human fusariosis. |
| Romani                   | 2011 | Nature Reviews Immunology                  | When the infective structures of Fusarium spp. reach the mucous membranes, the innate cellular immune response of the host is activated, which includes dendritic cells, macrophages, monocytes, neutrophils, and soluble mediators of the complement system. |
| Guarro et al.            | 2013 | European Journal of Clinical Microbiology & Infectious Diseases | Fusariosis is related to high mortality. Recovery from neutropenia remains the most important determinant of outcomes in such patients. |
| Nucci et al.             | 2014 | Clinical Microbiology and Infection        | Significant improvement in the results of invasive fusariosis in the last decade with changes in therapeutic practices, involving a decrease in the use of amphotericin B and increase in the use of voriconazole and combination therapy. |
| Spotl et al.             | 2014 | Plant Disease                              | Epidemic of fusariosis in plants can be harmful to humans and animal health, since the ingestion of cereals contaminated with mycotoxins can cause serious food poisoning. |
| van Diepeningen et al.   | 2014 | Current Clinical Microbiology Reports      | The use of molecular techniques is recommended to identify Fusarium species that cause infections. |
| Varon et al.             | 2014 | The Journal of Infection                  | Skin lesions may be considered entry points for Fusarium spp. Infections, especially in individuals that exhibit risk factors, such as high-risk hematological patients. |
| Price et al.             | 2015 | Pest Management Science                   | Fusarium sp. exhibits mechanisms that contribute to the acquisition of resistance to even the most diverse antifungal agents. These mechanisms include changes in the amino acid sequence, overexpression of the CYP51 gene, and overexpression of genes that encode efflux pumps. |
| van Diepeningen et al.   | 2015a| Current Fungal Infection Report           | Different Fusarium species have been associated with local or invasive infections in both immunosuppressed and immunocompetent individuals. |
| van Diepeningen et al.   | 2015b| Mycoses                                    | Members of the F. solani complex are the most common and virulent, followed by F. oxysporum, F. fujikuroi, and F. moniliforme. |
| Al-Hatmi et al.          | 2016a| Emerging Microbes & Infections            | Treatment given for Fusarium infections varies according to the site of infection. |
| Al-Hatmi et al.          | 2016b| The Journal of Antimicrobial Chemotherapy  | In vitro combined use of natamycin and voriconazole was found to be synergistic against most Fusarium strains, thereby significantly reducing the concentrations required to inhibit fungal growth. |
| Dalhoff                  | 2016 | Journal of Global Antimicrobial Resistance | Fusariosis is difficult to treat and the use of antimycotics in agriculture and horticulture facilitates the acquisition of antifungal resistance. |
| Espinel-Ingroff et al.   | 2016 | Antimicrobial Agents and Chemotherapy      | A cutoff point for minimum inhibitory concentration values for various Fusarium species was proposed based on laboratory results. |
| Ribas et al.             | 2016 | Brazilian Journal of Microbiology         | Environmental isolates of Fusarium spp. could acquire resistance due to previous exposure to fungicides that are used agriculturally in the field. |
| Al-Hatmi et al.          | 2017 | Journal of Fungi                          | No standardization is established regarding MIC cut points for Fusarium, which renders it difficult to classify the susceptibility profile of isolates. |
| Batista et al.           | 2017 | Chemistry Select                          | New chemical molecules exhibited low MICs (high potency) against Fusarium spp. and reduced toxicity with promising applicability in the biological and industrial fields. |
| Fuenteferia et al.       | 2017 | Letters in Applied Microbiology           | Combination therapy have been an important alternative for combating Fusarium species. |
| Kolar et al.             | 2017 | Investigative Ophthalmology & Visual Science | Declin-1 and TLR2 play an important role in the regulation of F. solani-induced AMP expression in corneal epithelial cells, facilitating the eradication of fungal pathogens. |
| Al-Hatmi et al.          | 2018 | International Journal of Antimicrobial Agents | New identification tools for Fusarium spp. to aid in selecting the most appropriate treatment. |
| Bashir et al.            | 2018 | Environmental Science and Pollution Research | Evaluated various concentrations of fungicides used to combat fusariosis in plant. The use of carbendazim significantly reduced the incidence of disease by 49.7% after 40 days of application. |
| Homa et al.              | 2018 | Frontiers in Microbiology                 | F. falciforme was the most prevalent species of FSSC in South India. Susceptibility and virulence of clinical and environmental isolates were similar. |
Despite global distribution, endemic regions are tropical and subtropical in nature. Although fusariosis is associated with specific climatic conditions, environmental and clinical isolates have been reported to cause infections outside previously established borders. This fungus has efficient mechanisms of dispersion, and its conidia reach considerable distances. Moreover, genetic similarities between clinical isolates and environmental isolates of the same species may be related to infections in patients by Fusarium spp. in the environment.

**CLINICAL ASPECTS OF FUSARIOSIS**

Fusarium species cause a wide spectrum of infections in humans, ranging from superficial and locally invasive to disseminated, with the most prevalent infections being onychomycosis, skin infections, and keratitis.

Invasive infections can be widespread involving the skin, brain, bloodstream, lungs, eyes, and bones. Patients with severe and prolonged neutropenia, especially those with hematological malignancies, are most susceptible to prevalent infections. Moreover, systemic antifungal agents usually lasting more than 4 or 6 months, even with the use of topical therapies, are often associated with paronychia and characterized by purulent periungual inflammation. The most commonly involved complexes are F. oxysporum and F. solani. Treatment is difficult and prolonged, usually lasting more than 4 or 6 months, even with the use of topical and systemic antifungal agents.

Keratitis is one of the most common infections caused by Fusarium spp. and primarily develops from trauma to the eye, contact lens wear, and use of corticosteroids. Trauma is the key predisposing factor and occurs in 40–60 % of patients.

Skin infections are the result of dissemination of the fungus primarily in immunocompromised patients. The most common pattern of disseminated disease is the combination of multiple painful erythematous papules or nodules, commonly with central necrosis. Such occurrences spread throughout the body and continuously release fungal cells, thereby resulting in a positive blood culture, and often pulmonary involvement, with or without involvement at other sites.

The immune system impedes the establishment of invasive infections by various species of fungi as high mortality is seen in immunosuppressed individuals. However, in terms of the emerging pathogenic species of the genus Fusarium, the lymphocyte response via Th2 may facilitate the invasiveness of this disease and explain the self-limiting difficulty related to its complex mycosis.

When the infective structures of Fusarium spp. reach the mucous membranes, the innate cellular immune response of the host is activated, which includes dendritic cells, macrophages, monocytes, neutrophils, and soluble mediators of the complement system. These responses are initiated by pattern recognition receptors (PRRs), which recognize a series of common and constant molecular patterns that are present in nearly all microorganisms, denominated as pathogen-associated molecular patterns (PAMPs). The activation of PRRs plays a dual role: it initiates processes of the innate immune system, such as phagocytosis, and establishes a link between innate and adaptive immunity via MHC type I and type II expressions.

The most important PAMPs in filamentous fungi are mannann, β-glucan, and chitin. The primary soluble PRR is pentraxin-3, whereas cellular PRRs are lectins, Toll-like-receptors, and NOD receptors. Fusarium species are recognized by type 2 Toll-like-receptors, which are generated in response to the production of anti-inflammatory cytokines (IL4 and IL10), and thus promote an adaptive immune system response that is mediated by Th2 lymphocytes. Th2-type lymphocyte response, in which anti-inflammatory cytokines are produced, thereby leading to an inadequate response by the host to the infection and high morbidity and mortality.

Despite their minor importance, various humoral factors also participate in the innate response, as the complement is activated by their associated classical and alternative pathways. However, the predisposing factors of invasive mycoses relate to the dysfunction of the immune system of phagocytosis, rather than defects in humoral immunity. More knowledge on humoral immunity activity in response to fungal infections is required, although some studies have attempted to demonstrate a specific marker of invasive diseases caused by Fusarium spp.

**ANTIFUNGAL RESISTANCE AND THERAPEUTIC OPTIONS**

Fusarium spp. exhibit intrinsic resistance to echinocandins. Moreover, some isolates exhibit resistance to azoles that are associated with a third analogue of the CYP51 gene. On the other hand, the intrinsic resistance of echinocandins is linked to the Y639 region of the FKS1 gene, which is responsible for encoding the catalytic subunit of β-1-3 glucan synthase. These fungi also exhibit mechanisms that contribute to acquiring resistance to most antifungal agents, such as changes in amino acid sequences, overexpression of the CYP51 gene, and overexpression of genes that encode efflux pumps.

Minimal inhibitory concentrations and minimum effective concentrations have not been established for Fusarium species. To present this missing knowledge, Espinel-Ingroff defined the epidemiological breakpoints for amphotericin B, posaconazole, and itraconazole in relation to the main Fusarium species that cause fusariosis. In this scenario, a few options exist to combat this infection, and the frequently used antifungal agents include natamycin, amphotericin B, and voriconazole. Therefore, depending on the clinical case, amphotericin B and voriconazole are the drugs of choice. In vitro and in vivo tests also reveal natamycin and voriconazole as drugs of choice to treat keratitis induced by Fusarium spp.
In the case of resistance, the use of combinations of drugs may be an important alternative to combat various *Fusarium* species, increase the efficacy and spectrum of action of antifungal agents, and lower drug dosage and thus reduce toxic side effects\(^{34,35}\). Moreover, *in vitro* drug combinations have demonstrated the ability to control fungal biofilms in other fungal species\(^{36}\), and studies focused on *Fusarium* sp. remain scarce. Combinations of antifungal and non-antifungal agents have also been tested *in vitro* and the results are promising, especially in fusariosis, as a strong association with the inflammatory response has been found\(^{37,38}\). Despite promising results in an *in vitro* context, the use of combinations requires clinical studies to verify its effectiveness *in vivo*. A few reports have been conducted on treating patients with fusariosis using more than one drug. Tortorano et al. (2014) have reported an association between the use of lipid-based amphotericin B and voriconazole, as well as the use of up to three antifungals in the same patient\(^{39}\).

Factors that contribute to the severity of fusariosis include increased incidence of multidrug resistance to *Fusarium* spp.\(^ {39}\) and the lack of research relating to the development of new therapeutic options for treatment. In general, these infections progress with a severe prognosis, especially in terms of ophthalmology, in which cases of fungal keratitis led to negative outcomes, such as loss of vision, in affected individuals. Currently, isavuconazole, characterized as a second generation triazole antifungal, is being studied as an alternative for its potential treatment of fungal diseases in patients with hematological diseases\(^ {40}\).

**FUNGICIDES AND RESISTANCE IN PHYTOPATHOGENIC FUSARIUM SPECIES**

Fungicides are specific substances that are used in the agricultural field to combat and prevent fungal diseases. Waste from the use of these substances is considered a pollutant with potential risk to the human body, as well as more commonly to the environment\(^ {41}\). Demethylation inhibitors are abundantly used in the agricultural field. Moreover, demethylation inhibitors change the fungal population after multiple applications, thus requiring the application of new fungicides. A substitute used is triazole, and its time of permanence in the soil depends on the concentration used and generally ranges from 67 days to more than 1688 days, with a trend of accumulation based on the frequency of use\(^ {42}\).

A risk factor that may be associated with fungicides in the environment is the development of microbial resistance\(^ {43}\) similar to that associated with the overuse of antifungals in humans\(^ {44}\). Azoles are the most commonly used of all groups for both pest control and treatment of human infections. Therefore, the potential development of resistance to this specific class is of increasing concern\(^ {4}\). Some benefits of theazole class include low cost and high efficacy, thereby rendering it the first-choice antifungal for use as a fungicide agent in crops since the 1970s\(^ {45}\).

Proper fungicide management in agricultural fields is a current demand in terms of the economics related to agricultural practices, as well as in terms of negative environmental impact\(^ {46}\).

**INCIDENCE OF HUMAN FUSARIOSIS**

Cutaneous lesions have been observed due to the spread of fungi in patients with hematological diseases. In Brazil, from 2007 to 2009, invasive fusariosis was proved to be the most frequent or probable invasive fungal disease, with 23 episodes among 937 patients with hematologic diseases\(^ {49}\). Based on the information discussed thus far, a bibliographical search was conducted on the PubMed and Science Direct platforms using the term “fusariosis in human,” including case reports published between 2005 and 2018. In this review, we included data from articles published only in 2005 and 2018, comprising 14 publications, with the aim to observe possible changes in both the etiology of infections and treatment (Table 2). The factors for inclusion of the case reports involve the presence of relevant information on etiological agents, predisposing factors, and treatments. The exclusion factor was defined as the lack of any required information, as previously cited.

We observed that *F. solani* prevails as the etiological agent of fusariosis. The treatment also did not change over the years, indicating that amphotericin B, voriconazole, and posaconazole are prophylactic agents and treatment options for fusariosis\(^ {48}\). The clinical forms of the disease in the case reports focused more on infections that present cutaneous lesions, which is characterized by the spread of the disease in patients with hematological dysfunctions.

The increased incidence of fusariosis from 2005 to 2018 can be observed in Figure 1 (A-B), which graphically shows the increase in the number of articles published on the PubMed and Science Direct platforms in this time period.

**CONCLUSION**

The efficient mechanisms of the dispersion of *Fusarium* spp. have led to the global distribution of clinical and environmental isolates. *F. solani* and *F. oxysporum* are the most common complexes. Infections in humans range from superficial to disseminated, and patients with hematological malignancies are the most susceptible. Dissemination of the fungus is seen mainly in immunocompromised patients because of the ease of infection related to the portal of entry of the fungus in the host, such as via the airways or the rupture of tissues and mucous membranes.

Invasive *Fusarium* infections stimulate an inadequate response by the host towards the infection, which accounts for the high mortality caused by this fungus. As such, biofilm formation renders treatment more difficult. *Fusarium* spp. exhibit intrinsic resistance to echinocandins, and some isolates exhibit resistance to azoles. In this scenario, the drugs of choice are amphotericin B and voriconazole, and drug combinations are an important means to combat multi-drug resistance. Just as the determination of the minimum inhibitory concentration provides an overview on *in vitro* resistance, it can also be considered strong evidence for selecting an antifungal treatment. Low investment by the pharmaceutical industry towards developing drugs to combat these infections was observed.

Risk factors of individuals contribute to the occurrence of new cases and *F. solani* continues to be the main etiological agent of fusariosis. Treatment also has not changed over the years, because of the lack of research in the development of new therapeutic options for the treatment of this infection. The increased incidence of fusariosis, as reported in the articles published between 2005 to 2018, is evidence of the emergence of this fungus.
TABLE 2: The symptoms of patients, treatments, etiological agents, and risk factors for patients described in articles published in 2005 and 2018.

| Author            | Year | Symptoms of Patients                  | Treatment                  | Etiological Agent | Risk Factors                          |
|-------------------|------|---------------------------------------|----------------------------|-------------------|----------------------------------------|
| Hayashida et al.  | 2018 | Erythematous nodules                  | Amphotericin B and voriconazole | F. solani        | Acute myeloid leukemia                 |
| Simon et al.      | 2018 | Pain and decreased vision             | Amphotericin B and voriconazole | F. dimerum        | Acute myeloid leukemia                 |
| Boral et al.      | 2018 | Blurred vision                        | Voriconazole               | F. solani        | Ocular trauma                          |
| Combalia et al.   | 2018 | Lesions on the eyebrow                | Complete excision of the lesions | F. solani        | Diabetes mellitus                      |
|                   |      |                                       |                            |                   | Kidney transplant                      |
|                   |      |                                       |                            |                   | Immunosuppress treatment               |
| Okada et al.      | 2018 | Lesions forming an ulcer              | Liposomal amphotericin B   | F. solani        | Neutropenia                            |
|                   |      |                                       |                            |                   | Varicella zoster virus                  |
| Puapatanakul et al| 2018 | Peritonitis and septicemia            | Amphotericin B             | Fusarium spp.    | Diabetes mellitus                      |
|                   |      |                                       |                            |                   | Hypertension                           |
|                   |      |                                       |                            |                   | End-stage kidney disease               |
| Borges et al.     | 2018 | Lesion                                | Amphotericin B and itraconazole | F. solani        | Acute myeloid leukemia                 |
|                   |      |                                       |                            |                   | Neutropenia                            |
| Arnoni et al.     | 2018 | Nodules on the chest                  | Amphotericin B and voriconazole | F. oxysporum   | Acute lymphocytic leukemia             |
| Kumari et al.     | 2018 | Lesions with pus discharge            | Itraconazole               | F. solani        | HIV positive                           |
| Yoshida et al.    | 2018 | Blurred vision                        | Amphotericin B and voriconazole | F. solani        | Acute myeloid leukemia                 |
| Rizzello et al.   | 2018 | Pain on eye                           | Amphotericin B and voriconazole | F. solani        | Acute lymphoblastic leukemia           |
|                   |      |                                       |                            |                   | Neutropenia                            |
| Anandi et al.     | 2005 | Breast abscess                        | Ketoconazole               | F. solani        | Diabetes mellitus                      |
| Gardner et al.    | 2005 | Pruritic plaque on forearm            | Amphotericin B and voriconazole | F. solani | Neutropenia                            |
| Karam et al.      | 2005 | Cutaneous nodules                     | Voriconazole               | F. moniliforme   | Myeloblastic leukemia                  |

FIGURE 1 - (A): Case reports of fusariosis published on the Pubmed Plataform between 2005 and 2018. (B): Case reports of fusariosis published on the Science Direct platform between 2005 and 2018
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AUTHORS’ CONTRIBUTIONS

BGB: Investigation, Methodology, Project administration, Supervision, Writing-Reviewing & Editing the final draft; MAC: Investigation, Methodology, Writing-Reviewing & Editing the final draft; PR: Investigation, Methodology, Writing-Reviewing & Editing the final draft; OJS: Writing-Reviewing & Editing the final draft; AMF: Methodology, Project administration, Supervision, Writing-Reviewing & Editing the final draft.

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CONFLICT OF INTEREST

The authors declare no competing interests.

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