Fusarium in Clinical Practice

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In recent years, human infections by *Fusarium* have been rising worldwide, mostly involving immunocompromised hosts. To understand this infection clinicians must recognize the intersecting points between the patient, the environment, and the relationship among all the elements that affect fusariosis in agriculture, and human and animal diseases.

Fusarium, one health, infection

1. Introduction

One Health is a concept defined as a worldwide strategy for expanding interdisciplinary collaborations and communications in all aspects of health care for humans, animals, and the environment [1]. *Fusarium* has been described as a pathogen of humans, animals, and plants, a phenomenon known as trans-kingdom pathogenicity [2] [3]. In recent years, human infections by *Fusarium* have been rising worldwide, mostly involving immunocompromised hosts [3][4]. To understand these human infections, the dynamics among hosts (human/animal), pathogens, and the environment must be explored.

In humans, these fungi cause a broad spectrum of infections, including both superficial (onychomycosis and keratitis) and disseminated diseases (particularly in hematological cancer and neutropenic patients) [5]. Fungal keratitis is not only a common cause of corneal infection in developing countries but also a significant cause of ocular morbidity and blindness [6][7].

2. *Fusarium* in Human Diseases

In severely immunocompromised patients, fusariosis is the second most common mold infection in humans, right after aspergillosis [8]. These fungi cause superficial (such as onychomycosis and keratitis), locally invasive, and disseminated disease.

2.1. Onychomycosis

Onychomycosis is one of the most widely recognized finger and toenail infections with an overall prevalence of 5.5% [9]. This pathology can affect the physical, functional, psychosocial, and emotional state of the patient [10]. Even though it is not a life-threatening condition, numerous significant anatomical functions of the nail may be

affected, with difficulty in walking, embarrassment, and work-related challenges being the most commonly reported issues [10]. Recognized risk factors for onychomycosis are trauma, ageing, obesity, diabetes, participation in fitness activities, immunosuppression (HIV(human immunodeficiency virus), drug-induced), malignancies, sedentarism, and occlusive footwear [9][10][11]. People who have pedicure treatment are less likely to acquire onychomycosis [12].

Dermatophytes, mainly *Trichophyton rubrum*, are responsible for most fungal nail infections and about 30% to 40% of onychomycosis cases are caused by non dermatophyte molds (NDMs) and yeasts [9]. In South America, studies suggest that *Fusarium* may be the most common NDM [12][13]. Species identification has a crucial role in this disease, for example, *F. keratoplasticum* and *F. falciforme* are the most frequent species isolated in Colombia, and some of these isolates exhibited lower azole in vitro activity [12].

Fungal production of proteases that degrade keratin may facilitate invasion [12]. In addition, histological studies have revealed the capacity of *F. oxysporum* to invade human nails, including the firm attachment to the nail plate and the dissemination to deep layers, causing disorganization of nail structure [14]. Also, the formation of fungal biofilms is a contributor to persistent infection, which offers advantages such as antifungal resistance, protection against host defenses, increased virulence, communication, metabolism cooperation, and differential gene expression [15][16][17]. By viewing an infected nail through a scanning electron microscope (SEM) it can be seen that this fungus is able to form a biofilm, by penetrating unassisted nail layers to cause onychomycosis. It can also be seen that the ventral surface of the human nail is more vulnerable to infection than the dorsal surface [15].

2.2. Keratitis

Corneal disease is one of the leading causes of blindness worldwide. In 2001, trauma and corneal ulceration were reported as principal causes of unilateral blindness and the global estimate varies from 1.5 to 2 million cases per year [6]. Current epidemiological information proposes that microbial keratitis might be epidemic in South, South-East, and East Asia, and may exceed 2 million cases per year worldwide [18]. Furthermore, it has been demonstrated that fungal keratitis contrasted to bacterial keratitis can be progressively destructive. On the one hand, a retrospective analysis not only found that fungal keratitis was more likely to perforate the cornea than bacterial keratitis (OR (Odds ratio) = 5.86, 95% CI (confidence interval), 1.35–20.66), but also that it leads to an irreversible change [19]. Likewise, around 15–27% of patients with fungal keratitis require surgical intervention, such as corneal transplantation, removal of ocular contents, and enucleation, as a result of a failed pharmacological treatment [20].

The requirement for prolonged and intensive treatment, resulting in negative ocular outcomes (loss of vision and/or loss of the eyeball), indicates that both the economic and medical implications are substantial [21]. In addition, a correlation between gross national income (GNI) and the etiology of microbial keratitis has been shown. Fungal keratitis is associated with countries with low GNI [22]. Moreover, there are numerous cases of fungal keratitis related to the utilization of contact lenses. Between 2004 and 2006, an outbreak of *Fusarium* fungal keratitis occurred in contact lens users worldwide, owing to a decrease in the disinfection capacity of contact lens solutions

[23]. Clinical signs of fungal keratitis include a sudden onset of pain along with photophobia, discharge with a reduced vision, and opacity on the surface of the cornea [24].

The common fungal causative agents are *Fusarium* spp., *Aspergillus flavus* and *A. fumigatus,* and *Candida albicans* (which is less common in tropical climates) [25]. *Fusarium* keratitis has increased over the last forty years and it is estimated that around half of all the cases of microbial keratitis in tropical countries are caused by this genus, probably on account of an increasing use of topical steroids and antibacterial agents, as well as a rise in surgical procedures, contact lens use, ocular trauma, chronic ocular surface diseases, and immunocompromised patients [26]. In Tunisia, fungal keratitis represents 83% of the cases, with *F. solani* being the most prevalent species (66%) [27]. In Brazil, 25% of fungal keratitis is caused by *Fusarium* [28], and in Mexico, *F. solani* was found in 37% of the patients [29]. Recent studies conducted in south India have shown that *F. keratoplasticum* and *F. falciforme* were the most prevalent species isolated from keratomycoses and environmental settings; in fact, agricultural workers in India often become infected after a corneal injury caused by plant or soil material [30].

The interaction of pathogenic fungi with host cells is the main factor in the pathogenesis of mycotic keratitis. The human central corneal temperature (32.6 ± 0.70 °C) is suitable for the development of *Fusarium* [31]. Adherence of microorganisms to host cells through an assortment of adhesins is essential for the initiation of the infection [24]. Consequently, *Fusarium* keratitis can invade the cornea and the anterior chamber of the eye. Here, in the pupillary area, it forms a lens-iris-fungal mass which affects the normal drainage of the aqueous humor and causes an increase in the intraocular pressure, leading to fungal malignant glaucoma [24][32]. Also, *Fusarium* mycotoxins can suppress immunity and break down tissues. Certain cytosolic proteins and peptide toxins can destroy corneal epithelial cells [33]. Proteases play an important role in fungal keratitis because they can cause corneal ulcers [24][34]. As described in onychomycosis, the formation of biofilm is another factor that contributes to the pathogenesis of keratitis as well as antifungal resistance [35][36]. Biofilm proteomics studies in *F. falciforme* have identified several proteins whose levels changed during the biofilm formation phases, as well as the enzymes involved in glycolysis/gluconeogenesis and pentose pathways. Some of the proteins involved could promote angiogenesis, adhesion/invasion, and immunomodulation [36].

2.3. Invasive Disease

Invasive fusariosis affects most patients with prolonged and profound neutropenia and/or severe T-cell immunodeficiency, acute leukemia, and hematopoietic cell transplant (HCT) recipients. Besides, it is not only the most frequent clinical form of fusariosis but also the most common challenging in immunocompromised patients, accounting for approximately 70% of all cases of fusariosis in this population [37]. A retrospective analysis of 233 cases (92% of them being patients with hematologic diseases) reported that the outcome is usually poor, with a 90-day probability of survival of 43% of the patients [37].

The typical clinical onset consists of a patient with prolonged (>10 days) and profound (<100 cells/mm^3) neutropenia who is persistently febrile and develops disseminated and characteristic skin lesions (papular or nodular erythematous lesions), with a positive blood culture [37][38]. *Fusarium solani* is the most common species

involved in fusariosis (50% of cases), followed by *F. oxysporum* (20%), and *F. verticillioidis* and *F. moniliforme* (10% each) [4].

In relation to pathogenesis, animal models of fusariosis showed that mortality was correlated with inoculum size [37]. In nonneutropenic mice, the disease was described by necrotizing abscesses with hyphae, hemorrhage, and neutrophil and macrophage infiltration [39]. Paradoxically, neutropenic mice did not exhibit an inflammatory cellular reaction and had a significantly higher fungal burden [39]. A murine model of intratracheal inoculation of *F. solani* was recently used to investigate its spread to different organs in immunocompetent animals within 24 h after inoculation. Results showed that a 1×10^8 conidia/animal inoculum followed a 100% death rate of immunocompetent mice in 24 h [40].

3. Fusariosis Treatment

Before reviewing any human fusariosis treatment, we must discuss a frequently forgotten issue in clinical practice: the role of the environment and fungicides in the patient response to antifungal drugs. Fungicides are chemical agents utilized for control and treatment of fungal infections in plants. They exhibit a variety of mechanisms of action, such as effects on respiration, signal transduction, mitosis cell division, membrane, and cell wall [41]. Also, azole fungicides, which include tebuconazole, propiconazole, and epoxiconazole, also called demethylation inhibitor (DMI), are the most widespread treatment in agriculture due to their low cost and broad-spectrum [42]. For example, tebuconazole is generally used to control FHB (*Fusarium* head blight) [43]. Tebuconazole demonstrated various effects on *Fusarium culmorum* (a common pathogen of cereals), including morphological changes at the ultrastructural level such as considerable thickening of the hyphal cell walls, excessive septation, the formation of the incomplete septa, extensive vacuolization, accumulation of lipid bodies, and progressing necrosis or degeneration of the hyphal cytoplasm [44]. Moreover, *F. culmorum* is capable of adapting to triazole pressure by overexpressing a drug resistance transporter [45].

As referenced before, the overuse of fungicides in crops and flower fields becomes imperative for the identification of *Fusarium* to the species level (some species have higher MIC values than others), not only from an epidemiological viewpoint but also for choosing the appropriate antifungal treatment [46].

3.1. Localized Infection

There are currently no available antifungal recommendations in accordance with *Fusarium* isolation. Treatment with nail lacquers and systemic treatment is usually used; unfortunately, *Fusarium* onychomycosis and keratitis are difficult to eradicate. Onychomycosis systemic treatment with itraconazole or terbinafine is usually effective, but relapses are very common [47] Some *Fusarium* strains isolated from nail samples have also demonstrated in vitro susceptibility to amphotericin B (which binds to ergosterol in the cell membrane) [12]. Additionally, treating fungal keratitis represents a challenge because of the limited and variable susceptibility of *Fusarium* to antifungal agents, the poor tissue penetration of topical antifungal agents, resulting in low drug bioavailability, and the absence of a routine determination of antifungal susceptibility [48]. First-line therapy for *Fusarium* keratitis includes a topical

antifungal agent either alone or in combination with systemic antifungal medication. Natamycin (which inhibits fungal growth by binding to sterols) has been the traditional drug of choice for topical treatment; however, amphotericin B drops (1.5 mg/mL) and voriconazole have also been used [49]. A randomized trial comparing topical 5% natamycin with topical voriconazole 1% for the treatment of fungal keratitis (24.6% of which were caused by *Fusarium*), suggested that natamycin may be more effective in healing corneal ulcers and improving visual acuity [50].

3.2. Invasive Infection

There is a variable susceptibility of *Fusarium* spp. to antifungal agents. The empirical treatment for invasive fusariosis infections is either voriconazole (VRC) (which inhibits the ergosterol production by binding and inhibiting the lanosterol-14alpha-demethylase), or liposomal amphotericin B (L-AMB), surgical debridement (if conceivable), and posaconazole (which inhibits the ergosterol production by binding and inhibiting the lanosterol-14alpha-demethylase) for salvage therapy [51]. If possible, neutropenia recovery and surgical debridement could be disease management tools. Information displays a 90-day survival rate of 42% in patients treated with voriconazole and showed that combined therapy does not work better than voriconazole alone [52]. In patients with acute leukemia, L-AMB or VCR are preferred. The ending point of invasive infection greatly depends on persistent neutropenia and or corticosteroid-induced immunosuppression [53]. In vitro synergism between antifungals and antimicrobials or non-antifungal agents have been studied, and percentages of synergism were as high as 80% for amiodarone (AMD) + VRC, of 75% for moxifloxacin and AMB, and of 65% for AMD + AMB [54].

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