Review Article

Fusarium: The Versatile Pathogen

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Abstract

Fusarium is an emerging human opportunistic pathogen of growing importance, especially among immunosuppressed haematology patients due to an increased incidence of disseminated infections over the past two decades. This trend is expected only to continue due to the advances in medical and surgical technologies that will prolong the lives of the severely ill, making these patients susceptible to rare opportunistic infections. Production of mycotoxins, enzymes such as proteases, angio-invasive property and an intrinsically resistant nature, makes this genus very difficult to treat. *Fusarium* is frequently isolated from the cornea and less commonly from nail, skin, blood, tissue, Continuous Ambulatory Peritoneal Dialysis (CAPD) fluid, urine and pleural fluid. Conventional microscopy establishes the genus, but accurate speciation requires multilocus sequence typing with housekeeping genes such as internal transcribed spacer, translation elongation factor-1α and RPB1 and 2 (largest and second largest subunits of RNA polymerase), for which expansive internet databases exist. Identifying pathogenic species is of epidemiological significance, and the treatment includes immune reconstitution by granulocyte–colony-stimulating factor, granulocyte macrophage–colony-stimulating factor and a combination of the most active species – specific antifungals, typically liposomal amphotericin-B and voriconazole. However, patient outcome is difficult to predict even with *in vitro* susceptibility with these drugs. Therefore, prevention methods and antifungal prophylaxis have to be taken seriously for these vulnerable patients by vigilant healthcare workers. The current available literature on PubMed and Google Scholar using search terms '*Fusarium*', 'opportunistic invasive fungi' and 'invasive fusariosis' was summarised for this review.

Keywords: Amphotericin B, *Fusarium,* keratitis, multilocus sequence typing, opportunistic fungi, voriconazole

Introduction

Fusarium sp. are hyaline filamentous fungi found everywhere – in air, water, soil, on plants and organic substrates. This widespread distribution of *Fusarium* is due to its ability to withstand a wide range of conditions and to grow on a broad range of substrates and their efficient mechanisms for dispersal. Often regarded as soil-borne fungi, because of their abundance in soil and frequent association with plant roots, they are also present in water as components of water biofilms.[1] Being common colonisers of aerial plant parts, they form either part of the normal mycoflora or act as plant pathogens on horticultural crops and cereal grains, rendering these unfit for consumption – causing huge economic losses to the agricultural industry aside from posing a threat to human and animal health.[2-4] *Fusarium* sp. have recently been implicated in the low hatch success of endangered sea turtles.[5] The incurable Panama disease (*Fusarium* wilt) of banana caused the Gros Michel cultivar variety of the Cavendish banana to perish in the 1950s.[6]

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Conventionally, *Fusarium* has been more of an agronomic threat than a medical one, but over the last three decades, owing to a variety of contributing factors, this scenario has undergone a radical change, with *Fusarium* sp. emerging as major opportunistic human pathogens, causing an expansive range of superficial and systemic infections with high morbidity in the former and extreme mortality in the latter.[4,7] The current available literature on PubMed and Google Scholar using search terms '*Fusarium*', 'opportunistic invasive fungi' and 'invasive fusariosis' was summarised for this review.

Epidemiology of Human Disease

Fusarium causes a wide spectrum of infections in humans, termed fusarioses, including superficial (keratitis, onychomycosis), locally invasive (cellulitis, intertrigo, sinusitis), deep or disseminated infections, the last occurring

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almost exclusively in severely immunocompromised patients.[2] With the utilization of fluconazole prophylaxis in transplant recipients and other immune suppressed patients came a change in the epidemiology of fungal infections – incidence of candidiasis reduced and by contrast, invasive mould infections increased, especially in patients receiving large doses of corticosteroids and who had prolonged or profound neutropenia and/or severe T-cell immunodeficiency. Fusariosis is now the third most common cause of mould infections after aspergillosis and zygomycosis, with an increasing incidence in patients with haematological malignancies and haematopoietic stem cell transplantation (HSCT). Persistent or profound neutropenia has been proven to be the single most predisposing factor towards disseminated *Fusarium* infections.[4,8] *Fusarium* from soil or water gains entry inside the body through contact with minute breaks in the skin or mucous membranes, causing onychomycosis or locally invasive skin infections (cellulitis, paronychia and interdigital intertrigo), the latter seen more commonly in diabetics. These sites serve these organisms as cutaneous portals of systemic entry during periods of immunosuppression, allowing for dissemination of infection.[9] Infection may occur as a result of extensive skin breakdown, such as in burns and wounds, wherein even air-borne conidia may be the source[10] or due to presence of foreign bodies, such as keratitis in contact lens wearers or peritonitis in patients receiving continuous ambulatory peritoneal dialysis (CAPD). *Fusarium* sp. have been isolated from public swimming pools, shower drains and hospital water systems.[11-15] *Fusarium keratoplasticum*, a member of the *Fusarium solani* species complex (FSSC), is recognised as a plumbing inhabiting pathogen.[16] Outbreaks and pseudo-outbreaks of fusariosis have occurred in the hospital as well as in the community, due to contamination of a common source such as water or disinfecting solutions.[17] *Fusarium* sp. may cause allergic diseases (e.g. sinusitis) in immunocompetent individuals.[18] The distinct mycotoxins (secondary metabolites) produced by some species are associated with a variety of human and animal health problems. *Fusarium* mycotoxins include trichothecenes, fumonisins, moniliformins and the fungal oestrogen, zearalenone. Mycotoxicosis is seen in humans and animals following ingestion of food contaminated by mycotoxin-producing *Fusarium* spp. (*Fusarium langsethiae*, *Fusarium sporotrichioides*, *Fusarium poae*, *Fusarium avenaceum*, *Fusarium tricinctum*, *Fusarium graminearum* and *Fusarium culmorum*).[2,19] Mycoproteins derived from a soil-inhabiting *Fusarium* sp. (*Fusarium venenatum*) are commercially manufactured as high-protein meat-substitute foods and marketed by the brand name 'Quorn', which have been proven to cause severe allergic reactions in sensitive individuals.[20]

Taxonomy

Genus *Fusarium* is classified as belonging to the Order *Hypocreales* of Phylum *Ascomycota*.[21] The taxonomy of *Fusarium* species has been controversial. Earlier work on *Fusarium* systematics was done before pleomorphism and variation in fungi were recognised, which led to the naming of numerous separate species based on superficial observations. The necessity for a precise and reliable system of classification became clear when it became evident that *Fusarium* species cause serious diseases. The name *Fusarium* had been used to denote the asexual ('anamorph') stage of the fungus, and the rarely encountered sexual ('teleomorph') stage was recognised by the names *Gibberella*, *Nectria, Neocosmospora* and *Haematonectria.* However, under the new nomenclatural rules and for taxonomic stability (one fungus one name, 2013),[22] *Fusarium* is to be preferred above all other names for the genus. This effort is to simplify the already complicated taxonomy of *Fusarium* and greatly improve the state of the molecular databases such as GenBank, MycoBank and *Fusarium*-ID that are currently available, wherein the confused state of Dual Nomenclature associated with *Fusarium* is reflected plainly. At present, GenBank accessions from the FSSC are deposited under four different genus names (i.e., *Fusarium*, *Nectria*, *Neocosmospora* and its later synonym *Haematonectria*).[22,23] The genus *Fusarium* currently comprises at least 200 species, grouped into approximately 10 phylogenetic species complexes.[24] *Fusarium* was one of the first fungal groups where the term 'species complex' was commonly used for closely related species. Most of the identified opportunistic *Fusarium* pathogens belong to FSSC, (*F. keratoplasticum*, *Fusarium falciforme, Fusarium lichenicola* and *Fusarium petroliphilum*); *Fusarium oxysporum* species complex (FOSC) and *Fusarium fujikuroi* (previously *Gibberella fujikuroi*) species complex (FFSC, *Fusarium napiforme, Fusarium temperatum, Fusarium guttiforme, Fusarium verticillioides, Fusarium thapsinum, Fusarium nygamai, Fusarium acutatum, F. fujikuroi, Fusarium proliferatum, Fusarium sacchari, Fusarium ananatum* and *Fusarium subglutinans*). Less frequently observed are members of *Fusarium incarnatum-equiseti* species complex (*Fusarium lacertarum, Fusarium scirpi, Fusarium equiseti*, i.e. haplotypes 1–14, *Fusarium incarnatum* or *Fusarium semitectum*); *Fusarium dimerum* species complex (FDSC, *Fusarium delphinoides*, *Fusarium penzigii*, *F. dimerum*); *Fusarium chlamydosporum* species complex; *Fusarium sambucinum* species complex (including *F. sporotrichioides*) and *F. tricinctum* species complex.[3,21,25] *Fusarium moniliforme* has now been renamed *F. verticillioides*. Some members of the species-rich FSSC have now been named: *F. petroliphilum* (FSSC 1), *F. keratoplasticum* (FSSC 2) and *F. falciforme* (FSSC 3 + 4).[26]

Fusarium-Culture

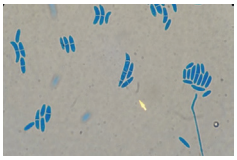
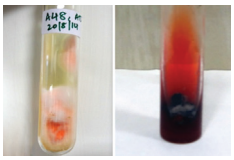
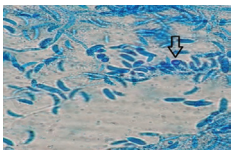
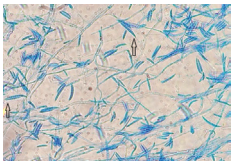
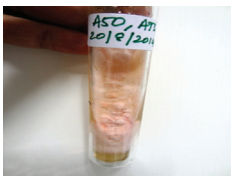
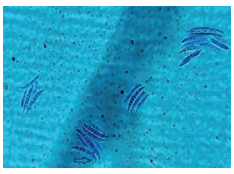
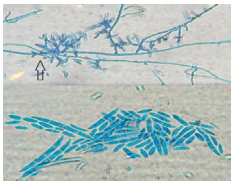
Typically, the genus is rapidly growing in culture media without cycloheximide although some species within FDSC and FFSC are slow growing.[3] They vary in colour and many yield a diffusible violaceous pigment (e.g. FSSC). In potato dextrose agar, *Fusarium* colonies grow with a velvety or cottony surface and are white, yellow, pink, purple, salmon or grey on the surface, with a pale, red, violet, brown or sometimes blue reverse.[4] The pionnotal type (moist and slimy) may

mislead identification.[27] Microscopically, they may produce different types of spores called macroconidia, microconidia, mesoconidia and chlamydospores. The macroconidia are produced on monophialides and polyphialides in the aerial mycelium[2] or in specialised structures called sporodochia in which the spore mass is supported by a superficial cushion-like mass of short monophialides bearing the macroconidia. The shape of these conidiophores (the specialised hyphae from which conidia arise) may differ between species and aid genus-level identification.[21] Macroconidia are hyaline, formed holoblastically and singly, banana/canoe-shaped, multicellular/multiseptate with a foot cell at the base and differ among genus/species.[2] Morphological keys for species recognition are available in published literature.[28,29] Species identification however is difficult, requires expert training and use of standardised media and may require molecular methods. Table 1 summarises the morphological features of a few common clinical *Fusarium* species.

Fusarium-Genome

Polymerase chain reaction (PCR) followed by DNA sequencing allows unambiguous identification of *Fusarium* sp. However, the most often used pan-fungal molecular marker the internal transcribed spacer region of fungal rDNA has considerable overlap among the various *Fusarium* species and is not recommended as a target for DNA sequencing and molecular identification. Partial regions of translation elongation factor 1 alpha gene and the second largest subunit of RNA polymerase II gene (RPB2) genes have been found to be better discriminatory and are useful in determining the species and also for phylogenetic analysis of isolates (e.g. multilocus sequence typing [MLST]).[26] *Fusarium*-specific primers targeting these regions for both PCR and DNA sequencing are available in the literature.[24,30] Species identification requires matching the DNA sequences using Basic Local Alignment and Search Tool (BLAST) in the *Fusarium*-ID (http://isolate.fusariumdb.org/blast.php),[31] NCBI GenBank (http://blast.ncbi.nlm.nih.gov/Blast.cgi) and CBS-KNAW (http://www.cbs.knaw.nl/fusarium/) databases. Using curated databases that accept only verified sequences gives accurate results and minimises errors and misidentification. The *Fusarium*-ID and CBS-KNAW are growing databases which contain only vouchered sequences attached to publicly available cultures. During BLAST analysis, looking specifically for matches with reference strains will give better and more accurate results.

Table 1: Macroscopic and microscopic morphology of some common clinical *Fusarium* species

Species	Culture	Microscopy
Fusarium keratoplasticum Range of shades in culture Up to 3-septate macroconidia and microconidia on long monophialides, produced in false heads		
Fusarium falciforme Range of shades in culture One type of conidia predominantly observed, generally 1-2 septate Chlamydospores seen		
Fusarium incarnatum Grow rapidly, white at first, later becoming brown Loosely branching conidiophores, abundant polyphialides, macroconidia 3-7 septate, slightly curved, with foot cell Microconidia, Chlamydospores sparse		
Fusarium equiseti Grow rapidly, white to peach Loosely branching, monophialidic conidiophores Macroconidia falcate, 3-5 septate, with a distinct pedicellate basal cell (arrow) Microconidia usually absent Chlamydospores in singles, pairs or chains if present		
Fusarium sporotrichioides Shades white to buff to brown Short, branching, polyphialidic conidiophores (arrow) Macroconidia needle-like, lightly curved in some places Microconidia oval		

Fusarium and Human Disease

Ocular infection

Keratitis

FSSC members are now proven to be the most common etiologic agent of fungal keratitis.[32-34] Most commonly occurring agents within this complex are *F. keratoplasticum* and *F. falciforme*.[16] In tropical countries such as Tanzania, the incidence of *Fusarium* keratitis is 75%.[34] Predisposing factors to fungal keratitis include ocular trauma (injury by vegetative matter/nail/flying insect/cow tail/soil/dirty water leading to fungal inoculation), topical antibiotic and corticosteroid use, diabetes mellitus, exposure keratitis, tear insufficiency, nasolacrimal duct blockage and contact lens use.[2,32,35] Local trauma such as foreign body trauma or surgery helps fungal spores or mycelial fragments to overcome the natural skin or the mucosal barrier.[36] Farmers suffering vegetative trauma and contact lens wearers, who are otherwise immunocompetent, form majority of those affected.[2,37]

2005–2006 outbreak

In 2005–2006, an unprecedented outbreak of contact lens-associated *Fusarium* keratitis occurred with >250 cases reported worldwide including countries such as India, China, United States,[38] Hong Kong and Singapore.[39] Cases were primarily soft hydrophilic contact lens wearers who used Bausch and Lomb ReNu with MoistureLoc and Bausch and Lomb ReNu MultiPlus multipurpose contact lens disinfecting solutions which contained the antimicrobial agent alexidine dihydrochloride (0.00045%), a new ingredient in the contact lens solution market at the time. At least 10 different *Fusarium* species were identified among the isolates, including *F. solani*, comprising 19 unique multilocus genotypes.[40] It was proven that the lack of temperature control during storage of lens solution bottles in closed shelves of retail shops allowed alexidine to permeate into the walls of the containing plastic bottles by heat acceleration, thus decreasing the effective concentration of the biocide and resulting in an unusual mechanism of drug failure, which allowed *Fusarium* introduced by the user from the environment while lens handling to multiply and infect the wearers.[41] The manufacturing company Bausch and Lomb was cited by the Food and Drug Administration for inadequate temperature control of their products and ReNu with MoistureLoc was ultimately withdrawn from the world market on 15 May 2006.[40]

Ophthalmitis

Resistant *Fusarium* keratitis progressing to endophthalmitis has been recorded,[42,43] and failure of treatment with topical, intravitreal and systemic antifungals necessitates enucleation of affected eye. Exogenous *Fusarium* post-surgical endophthalmitis can complicate cataract surgery and has poor patient outcome.[44]

Onychomycosis

Fusarium is the major non-dermatophyte mould causing nail infections, leading to onychomycosis with highly characteristic milky lesions or onychogryphosis,[2] almost always involving the great toenails (very rarely, the fingernails), especially those affected by traumatic and dystrophic abnormalities, and/or nails already infected by dermatophytes. Increasing age, male gender, close contact with soil, trauma, poor peripheral circulation (due to smoking or peripheral vascular disease), pre-existing tinea pedis, the habit of walking barefoot/wearing sandals or the habit of frequenting swimming pools are predisposing factors to the development of onychomycosis and intertrigo due to *Fusarium*.[21,45-47] Among diabetics, onychomycosis represents an independent and important predictor for the development of diabetic foot syndrome and foot ulcer.[48] Although usual presentation is of a localised infection in immunocompetent individuals, these infections require more attention because of the angio-invasive potential of *Fusarium*, which can manifest when host immune responses are impaired.[49-52]

Skin and soft tissue infections

Localised primary skin infections present as paronychia, interdigital intertrigo[53] or cellulitis and can occur in immunocompetent patients with a pre-existing onychomycosis, recent history of skin breakdown from local trauma, plant puncture[54] or insect bite. Diabetes mellitus,[55-57] burns and excessive moisture are other predisposing factors.[58] Some patients present with ulcerated lesions resembling chromoblastomycosis. *Fusarium* also causes mycetoma[59,60] and haemodialysis graft rejection.[61] These localised lesions need aggressive treatment as they are ports of systemic entry for angio-invasive *Fusarium* during periods of immunosuppression.[50,62-64] Chronic infection may mimic lupus vulgaris and escape detection.[65]

Development of papules, nodules or characteristic 'target' lesions (rarely bullae or vesicles) is sometimes the only diagnostic sign of disseminated multi-organ *Fusarium* infection in the immunosuppressed individuals.[66,67] Most commonly involved body sites are the extremities, but lesions can occur at any site and evolve rapidly over a few days. Multiple lesions at different stages of evolution can exist in one patient at a single time. Skin biopsy is indicated and can be used for rapid molecular diagnosis. Material from skin lesions are valuable clinical specimen and grow *Fusarium* in culture.[68]

Sinusitis

Fusarium sinusitis may present as allergic,[18] chronic, non-invasive[69] (with symptoms of nasal obstruction/discharge) or even invasive type in the immunocompetent,[70] whereas in the immunocompromised (largely acute myeloid leukaemia patients), it is always of the invasive type, accompanied by mucosal necrosis (characteristic of the angio-invasive nature of *Fusarium*), periorbital/paranasal cellulitis and serves as portal for systemic dissemination.[71]

Deep systemic and invasive disseminated fusariosis

Fusarium osteomyelitis,[72] septic arthritis,[73,74] pneumonia,[75] brain[76-79] and vertebral[72] abscesses are documented with the occasional positive outcome. Route of *Fusarium* entry in these cases was traumatic inoculation or inhalation. Disseminated

infection, first reported in 1973, is characterised by persistent fever refractory to broad-spectrum antibiotic treatment and by skin lesions with a central necrosis.[3] In contrast to other fungi such as *Aspergillus*, disseminated *Fusarium* infections yield higher number of positive blood cultures. Multiple organ systems can be involved. Source of infection is often *Fusarium* from the external environment (soil, indoor plants, shower drains) or nosocomial sources such as water.[4,8] Thus, infection can be community acquired or hospital acquired. Conidia enter through minute breaks in the skin and mucous membranes or inhalation (rare). Endogenous sources include pre-existing localised infections (sinusitis/onychomycosis/cellulitis/ interdigital intertrigo/abscess) spreading systemically due to *Fusarium* angio-invasion during prolonged or even short[80] periods of neutropenia.[3,62,63,81-84] Disseminated fusariosis is commonly observed in patients with haematologic malignancies and HSCTs,[27,85-91] including autologous transplants,[80] and rarely even in HIV-patients[92] and solid organ transplant recipients including liver,[93] lung[94,95] and kidney.[96] Their true incidence may very well be underestimated and invasive fusariosis needs to be ruled out in all cases of febrile neutropenia.

Foreign body-associated *Fusarium* infection

Soft contact lenses with high water content can be *Fusarium* colonised.[97] Their proficiency to adhere, infiltrate and thrive within the interior lens matrix can cause fungal keratitis.[98] The ability of *Fusarium* species to adhere and invade the silastic wall of CAPD catheters and occlude them has been demonstrated by electron microscopy.[99] *Fusarium* peritonitis following CAPD has been reported on several occasions and outcome of the cases was uniformly good after removal of the catheter alone or in combination with antifungal therapy.[99,100] An electron microscopic picture of the central venous catheter in case of catheter-associated fusaremia reveals plugging of the catheter with masses of fungal hyphae and invasive destruction of the catheter wall. Recovery may follow catheter removal alone, but bloodstream infections require antifungal chemotherapy.[101] In these examples of foreign body-associated *Fusarium* infections, favourable outcomes may be due to the presence of a removable focus of infection. A point of note is that there are no reports so far of infections of implants made of hard materials (titanium and platinum).[2]

Fusarium mycotoxicoses

Consumption of food prepared from overwintered cereals colonised by T-2 toxin producing *F. sporotrichioides* and *F. poae* leads to alimentary toxic aleukia affecting the haematopoietic system. The disease occurs in three progressively worse clinical stages and is more severe in the malnourished and fatal if diagnosed late. Historically, it was observed on a big scale in USSR in the immediate post WW2 era when 100,000 people died from being forced to consume infected grain due to severe food shortage.[102] Kashin–Beck disease is a chronic dystrophic osteoarthritis of the peripheral joints and spine which starts in childhood and worsens to severe disability, occurring endemically in regions of Siberia (Urov River Valley), China and North Korea where climatic factors are conducive to high level of *Fusarium* infection in harvested grains. Another example of human mycotoxicosis are the sporadic epidemics of akakabi-byo (red mould disease/ scab) that occur in Japan, caused by contamination of cereal grains with mycotoxins produced by *F. graminearum* and *F. sporotrichioides*.[2]

Virulence Factors of *Fusarium*

Fusarium sp. possess several virulence factors, including the ability to produce mycotoxins, such as trichothecenes, which suppress humoral and cellular immunity and aided by production of adventitious yeast-like propagules, cause tissue breakdown and angio-invasion.[2] They have the capacity to adhere to prosthetic material and produce proteases and collagenases.[103] Proteases produced by species such as FSSC might have a role in the pathogenesis of *Fusarium* keratitis, and FSSC are the most virulent species as shown in a murine model of fusariosis in immunocompetent animals.[4] A fungal transcriptional regulator *PacC* was found to allow fungal adaptation to the ocular surface, promoting hyphal penetration of the cornea in FOSC.[104] Morphological changes *in vivo* with thickening of cell walls may protect *Fusarium* from the neutrophil assault. Keratitis-associated fusaria form robust biofilms as compared to wild-type strains.

Host Response to *Fusarium*

Innate immunity plays a major role in resisting mould infections. Toll-like receptors,[105] T-cell defences[8] and phagocytes[106] play crucial roles in progression of invasive fusariosis. The occurrence of disseminated *Fusarium* in non-neutropenic HSCT recipients having severe T-cell immunodeficiency (caused by multiple

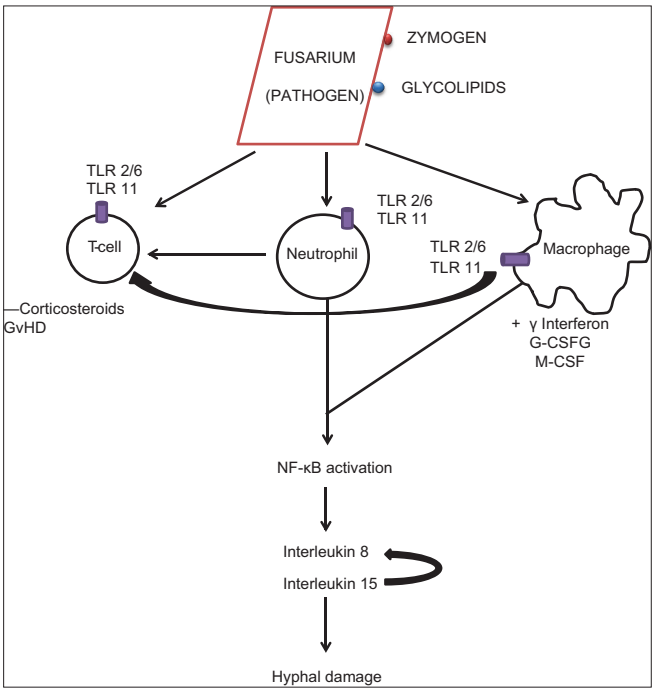


Figure 1: The innate immune response in *Fusarium* infection

therapies for their underlying disease and for graft-versus-host disease) and the major adverse impact of corticosteroid therapy on the outcome of fusariosis[82] support the importance of T-cell immunity. Macrophages and neutrophils damage *Fusarium* hyphae, and their effect is primed by √-interferon, granulocyte–colony-stimulating factor, granulocyte macrophage–colony-stimulating factor[107] and interleukin-15.[108] The effect of interleukin-15 is mediated by the release of interleukin-8 and by direct stimulation of hyphal damage.[4] There is a strong relationship between immune reconstitution and patient outcome which highlights the importance of the immune response in the pathogenesis of *Fusarium* infection[82,109] [Figure 1].

Diagnosis

Culture is the gold standard for diagnosis, but morphology-based identification has severe limitations for *Fusarium* species and cannot be used successfully without other approaches.

In keratitis, direct microscopy and culture of corneal scrapings are the usual method. Using a cost-effective assembly of smartphone and LED-integrated pocket magnifier was recently described, which can be useful in resource-limited or point-of-care settings.[110] *In vivo* confocal microscopy of infected eye is another rapid, non-invasive method.[111]

Blood tests are helpful in disseminated infections – the *Aspergillus* serum galactomannan tests cross-react with *Fusarium* infections due to similar cell wall structure. The Platelia *Candida* antigen detection enzyme immunoassay directed against mannan has been reported to give cross-reactions with *F. verticillioides* but not with *F. solani* or *F. oxysporum*[112] Enzyme immunoassay tests to detect mycotoxins produced by *Fusarium* also exist although these are used more in the field of phytopathology.[68] Radiological techniques such as early chest computed tomographic imaging can aid diagnosis. Histopathology, whenever viable, is highly recommended by experts.[113] Alternately, immunochemistry and *in situ* hybridisation methods are employed.[38,114,115]

DNA-based identification involves PCR assays that need adequate pure fungal DNA and procedures using whole-blood and tissue specimen have been described.[116] Furthermore, loop-mediated isothermal amplification assays have been established for *Fusarium*.[117] In the current era of genomics, DNA sequencing and use of MLST approach in combination with the genealogical concordance phylogenetic species recognition principle is a far better tool to recognise species and to sort out their relationships rather than relying alone on the phenotypic characters.[21] Genotyping in cases of outbreaks can be done by AFLP (Amplified Fragment Length Polymorphism) fingerprinting. Furthermore, progress is being made in peptide-based identification using matrix-assisted laser desorption/ionisation time-of-flight mass spectrometry[118,119] systems.

Although a preliminary genus-level identification gives healthcare workers enough information to start patient treatment, it is immensely useful to further characterise these clinical *Fusarium* and understand the epidemiological significance of the strains causing human infections.

Susceptibility Profiles of *Fusarium* Species

Antifungal susceptibility testing is done following the broth microdilution method as per the CLSI M38-A2[120] or the EUCAST 9.3.1 guidelines (http://www.eucast.org/ast_of_fungi/methodsinantifungalsusceptibilitytesting/susceptibility_testing_of_moulds/). *Fusarium* sp. show typically high minimum inhibitory concentrations (MICs) on testing. Members of the FSSC are intrinsically resistant to fluconazole and show higher MICs to other azoles and amphotericin B,[121] whereas FOSC show lower MICs to voriconazole and posaconazole.[123] Susceptibility profiles differ within species complexes too – e.g. *F. verticillioides*[73] shows the lowest MICs and *F. nygamai* shows the highest MICs[122] within the FFSC. Espinel-Ingroff *et al*.[123] have gathered MIC distributions for the common human pathogens FSSC, FOSC and *F. verticillioides* with three triazoles and amphotericin B and proposed epidemiological cut-off value for them. E-test could be used as an alternative to broth microdilution for susceptibility testing of amphotericin B, voriconazole and posaconazole against clinical *Fusarium* isolates.

Treatment

Treatment of *Fusarium* infections is difficult owing to the intrinsic multidrug-resistant nature exhibited by members of the genus, some of them being pan resistant. Amphotericin B, natamycin and newer azoles such as voriconazole are the most active agents and can be used in combination. Posaconazole has been used for salvage therapy.[124] However, *in vitro* susceptibility or resistance to these agents may not predict the *in vivo* response in *Fusarium* infection. Antifungal susceptibility testing on individual strains allows for species-specific treatment and may result in considerable improvement in patient outcome. Topical 5% natamycin hourly is the treatment of choice for *Fusarium* keratitis along with systemic voriconazole and early keratectomy when indicated.[125] The new topical azole efinaconazole (10% solution) seems promising in the treatment of *Fusarium* onychomycosis.[126-128] Surgical debridement when required and prompt therapy with a combination of appropriate antifungals along with use of colony stimulating factors for immune reconstitution help improve outcome of invasive fusarioses.[7,82,109,129-131]

Prevention

Prevention of contact lens-related keratitis includes avoidance of mouldy environments and of non-sterile or reusable-cleaning solutions. Hand washing before lens manipulation and frequent cleaning and sterilisation of the lens paraphernalia are recommended.[40,132,133] Agriculturists and outdoor workers are urged to use protective eye wear. Footwear should be worn when in damp public places; toenails should be kept clean and trimmed to avoid trauma; feet should be dried completely

immediately after bathing; socks should be made of absorbent material (e.g., cotton) and changed immediately if wet.[134] Symptoms of tinea pedis should be addressed without delay. Immunosuppressed patients, especially in haematology, need primary or secondary voriconazole prophylaxis, hospital wards with high efficiency particulate arrestance filtered air and without indoor plants. They are advised boiled food over other diet and sponge baths over showers during their period of susceptibility. Aerosolised amphotericin B deoxycholate is recommended for lung-transplant recipients.[94]

Conclusion

Due to medical and surgical treatment advances taking place in this century, the susceptible patient pool for *Fusarium* is set to rise and its role as an opportunistic human pathogen will increase in prominence. There is an urgent need for increasing our knowledge base regarding this genus, for epidemiology and treatment. Owing to the difficulties in the management of established infection, prevention is deemed better than cure and demands the focus of healthcare workers.

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Conflicts of interest

There are no conflicts of interest.

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