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Current Status of *Fusarium* Infection in Human and Animal

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ABSTRACT

Fungi are extremely versatile class of organisms comprised mostly of saprophytes, grows on dead organic material. A relatively small number of fungal species have developed a parasitic lifestyle, associated with the ability to recognize and penetrate a specific host, exploit its nutrient reserves, overcome its innate defense responses and cause disease. Many organisms attacked by fungi encompasses evolutionary distinct groups from lower to higher eukaryotes, most prominently plants, insects and mammals, including humans. To cause disease, fungal pathogens rely on an arsenal of pathogenicity and virulence factors, which's spatially and temporally correct deployment determines the basic pathogenic potential and the extent of infection, respectively. Being a common contaminant and a well-known plant pathogen, *Fusarium* sp. may cause various infections in humans. *Fusarium* is one of the emerging causes of opportunistic mycoses to human and animal. Up to date, approximate 15 species had been reported to cause human and animal diseases. Common species includes species are *F. Solani* (commonest), *F. oxysporum, F. verticoides, F. proliferatum* and *F. anthophilum.*

Key words: *Fusarium* sp., mycoses, human and animal infection

INTRODUCTION

Fusarium species are widely distributed in soil, subterranean and aerial plant parts, plant debris and other organic substrates (Nelson *et al*., 1994) and are present in water worldwide as part of water structure biofilms (Elvers *et al*., 1998). The genus *Fusarium* has been commonly associated with many crop diseases such as ear and kernel rot of corn, scab of rice and wheat and stalks rot and grain mold infection of sorghum (Williams and McDonald, 1983). A number of species, e.g., *Fusarium roseum* (Morooka *et al*., 1972), *F. graminearum* (Vesonder *et al*., 1973), *F. culmorum, F. tricinctum* (Vesonder *et al*., 1981) and *F. nivale* (Betina, 1984), have been reported to produce deoxynivalenol (DON), a trichothecene mycotoxin. The DON causes feed refusal and vomiting when ingested by swine (Ueno, 1983). Recently, a disease in humans affecting a large segment of the population in the subtropical Kashmir Valley in India was found to be caused by the consumption of wheat and wheat products contaminated with DON (Bhat *et al*., 1989). *Fusarium* species are common hyaline soil saprophytes and plant pathogens which have frequently been reported as etiologic agents of opportunistic infections in humans. These infections have usually been limited to superficial mycoses, but recently the number of infections of deep tissues and disseminated infections has greatly increased, especially in patients with an underlying

immunosuppressive condition. The characteristic signs of these infections are disseminated skin nodules, fungemia and multiorgan involvement. Frequently, myalgia is also present. Skin involvement occurred in over 80% of cases of disseminated infections. These lesions are significant because they are readily accessible for biopsy and culture, thus permitting an early diagnosis. The therapy and outcome are dependent on the degree of invasion of the organisms and the status of the host. Identification of the pathogen to genus level is not difficult, but identification to species level requires a greater degree of expertise. Up to now, 15 species of *Fusarium* have been reported to cause infections in humans and animals. Few patients with disseminated fusarial infections have survived, even after receiving an adequate dosage of amphotericin B, the only antifungal agent that has some effect against these fungi. *In vitro* susceptibility to amphotericin B is a poor predictor of the clinical outcome of invasive fungal infections. Recovery of the phagocytic mechanisms in the form of rising neutrophil counts appears to be mandatory for clinical resolution. The resolution of neutropenia may be aided by the use of exogenous growth factors. Outside the USA, the majority of cases of disseminated fusarial infection have been reported from Mediterranean or tropical countries (Guarro and Gené, 1995).

The widespread distribution of *Fusarium* species may be attributed to their ability to grow on a wide range of substrates and their efficient mechanisms for dispersal (Burgess, 1981). Invasive fungal infections are a major medical problem, particularly among immunocompromised hosts such as patients with hematological malignancies and those who have undergone stem cell or solid organ transplantation (Krcmery *et al*., 1996; Boutati and Anaissie, 1997; Marr and Bowden, 1999; Sampath and Paya, 2001; Fleming *et al*., 2002; Marr *et al*., 2002). Some fungal species, including *Fusarium* sp., rarely cause disease but are considered emerging pathogens (Fleming *et al*., 2002; Marr *et al*., 2002). *Fusarium* species are plant pathogens, but increasingly they have been described as a cause of infections in patients with leukemia and stem cell transplant recipients (Boutati and Anaissie, 1997). *Fusarium* is a filamentous fungus widely distributed on plants and in the soil. It is found in normal mycoflora of commodities, such as rice, bean, soybean and other crops (Pitt *et al*., 1994). While most species are more common at tropical and subtropical areas, some inhabit in soil in cold climates. Some *Fusarium* species have a teleomorphic state (Larone, 1995; Sutton *et al*., 1998). *Fusarium* and a few other genera of molds actually sporulate *in vivo*, a phenomenon that allows them to grow in cultures taken from blood. *Fusarium* species disseminate through the bloodstream after entry through the lungs or through a cutaneous source, such as a simple paronychia. Painful nodular skin lesions occur frequently with hematogenous spread.

The fungi belonging to the genus *Fusarium* are well-known plant pathogens and food contaminants that also cause superficial and subcutaneous infections, such as onychomycosis and keratomycosis, in humans (Nelson *et al*., 1994). Head scab of wheat caused by *Fusarium* species is characterized by bleaching of the wheat spike; shriveled kernels and accumulation of mycotoxins which may cause various ailments in humans and animals. They have recently emerged as major opportunistic agents in immunocompromised hosts, especially in patients with hemopathy (Boutati and Anaissie, 1997; Hennequin *et al*., 1997). Four species account for more than 95% of human infections: *Fusarium solani*, *Fusarium moniliforme* (*Fusarium verticilloides*) and *Fusarium oxysporum* are each responsible for about 30% of the cases, whereas *Fusarium dimerum* is involved in 5% of the cases (Guarro and Gené, 1992; Hennequin *et al*., 1997). The most common and important *Fusarium* toxins include deoxynivalenol (DON/vomitoxin), diacetoxyscirpenol (DAS) HT-2, T-2 and nivalenol, which are classified under trichothecenes and zearalenone (Ueno, 1983). There were frequent reports of outbreaksof *Fusarium* toxinsin several parts of the world. In India,

a well known outbreak involving *Fusarium* species among humans is the scabby grain intoxication reported from Kashmir (Bhat *et al*., 1989). Fumonisins are a family of mycotoxins produced by the *Fusarium* and related fungi that primarily contaminate maize and it is from this source that the major health threats emerge, although other commodities may be affected (Marasas, 2001; Voss *et al*., 2007; Stockmann-Juvala and Savolainen, 2008). Fumonisins contamination of maize occurs in many parts of the world with reported levels >100 ppm in some regions (IARC, 2002; Placinta, *et al*., 1999). The determinants of contamination include location, climate and susceptibility of the plants to fungal invasion, insect damage and crop stress (De la Campal *et al*., 2005). Fumonisins were first isolated and their structure was identified in 1988 (Gelderblom *et al*., 1988). Fumonisins consist of a long hydroxylated hydrocarbon chain with added tricarballylic acid, methyl and amino groups. Diagnosis of *Fusarium* at the species level is based on conventional methods, which include the description of colonies on appropriate media (texture, color and pigment etc.) and microscopic description of conidiogenous cells and conidia. This can be best observed after 2 weeks of incubation, lengthening the time for a definitive diagnosis. Because of important variations of characters, such as pigmentation and growth rate, is often seen within a given species, only well-trained mycologists are able to ensure the diagnosis (Guarro and Gené, 1992).

Among the more than 50 *Fusarium* species identified, 12 have been described as causes of human infection. Traditional identification is based on morphological methods, is cumbersome and requires adequate training. As a consequence, the identification of 33 to 50% of *Fusarium* isolates is erroneous or missed (Healy *et al*., 2005; Nucci and Anaissie, 2007). *Fusarium solani* is the most frequently reported species and causes approximately 50% of infections; the next most prevalent species are *F. oxysporum* (20%), *F. verticillioides* (10%) and *Fusarium moniliforme* (now classified as *F. verticillioides*; 10%) (Seifert *et al*., 2003; Nucci and Anaissie, 2007). The fungus *Fusarium verticillioides*, a toxigenic isolate is capable of synthesizing mycoferritin only upon induction with iron in yeast extract sucrose medium (Vakdevi *et al*., 2009).

Deoxynivanol (DON, also known as vomitoxin) is a type B trichothecene that occurs predominantly in grains such as wheat, barley, oats, rye and maize and less often in rice, sorghum and wheat. In India DON has been implicated in a human mycotoxicosis in combination with T-2 toxin and other trichothecenes when a considerable population in the subtropical Kashmir valley was affected by a gastrointestinal disorder (Bhat *et al*., 1989). The occurrence of DON is associated primarily with *Fusarium graminearum* (*Gibberella zeae*) and *Fusarium culmorum*, both of which are important plant pathogens which cause *Fusarium* head blight in wheat and *Gibberella* ear rot in corn. A direct relationship between the incidence of *Fusarium* head blight and contamination of wheat with DON has been established (McMullen *et al*., 1997). The incidence of *Fusarium* head blight is strongly associated with moisture at the time of flowering (anthesis) rather than the amount of rainfall. The geographical distribution of the two species appears to be related to temperature, though *F. graminearum* being the common species and occurring in warmer climates. DON has been implicated in incidents of mycotoxicoses in both humans and farm animals.

There may be geographic variability in the prevalence of specific *Fusarium* species. As an example, in a study of 75 patients in Italy, *F. verticillioides* is the most frequently isolated species (41%), followed by *F. solani* (25%) (Tortorano *et al*., 2008). In Northern Italy, more than 50% of the cases of deep infection are caused by *F. verticillioides*, whereas *F. solani* accounted for most of the superficial infections. This may be due to the various geographic distributions of the species or may be a result of the more accurate identification obtained by molecular methods (Tortorano *et al*., 2008).

Being common plant pathogens, *Fusarium* sp. are causative agents of superficial and systemic infections in humans. Infections due to *Fusarium* sp. are collectively referred to as fusariosis. The most virulent *Fusarium* sp. is *Fusarium solani* (Mayayo *et al*., 1999).

Fusarium species are hyaline filamentous fungi that cause a broad spectrum of infections in humans, including superficial (such as keratitis and onychomycosis), locally invasive, or disseminated infections, with the last occurring almost exclusively in severely immunocompromised patients (Nucci and Anaissie, 2002). *Fusarium* species may also cause allergic diseases (sinusitis) in immunocompetent individuals (Wickern, 1993) and mycotoxicosis in humans and animals following ingestion of food contaminated by toxin-producing *Fusarium* sp. (Nelson *et al*., 1994). The clinical presentation of fusariosis largely depends on the immune status of the host and the fungal portal of entry (Nucci and Anaissie, 2007). Superficial infections, such as keratitis and onychomycosis, are usually observed in immunocompetent individuals, whereas invasive infections occur in immunocompromised patients, mainly in association with prolonged and profound neutropenia or severe T-cell immunodeficiency (Nucci and Anaissie, 2002).

Fusarium infections are an important problem worldwide, commonly affecting immunocompromised individuals. It has emerged as an important cause of infection in immunosuppressed patients. The extent to which infection mechanisms are conserved between both classes of hosts is unknown. *Fusarium oxysporum* is the causal agent of vascular wilt disease in plants and an emerging opportunistic human pathogen. Knockout mutants in genes encoding a mitogen-activated protein kinase, a pH response transcription factor, or a class V chitin synthase previously shown to be implicated in virulence on tomato plants were tested in the mouse model (Ortoneda *et al*., 2004). The results indicate that some of these virulence factors play functionally distinct roles during the infection of tomato plants and mice. Thus, a single *F. oxysporum* strain can be used to study fungal virulence mechanisms in plant and mammalian pathogenesis. Findings are consistent with the fact that systemic infections in humans caused by *F. oxysporum* are predominantly reported in immunocompromised individuals (Vartivarian *et al*., 1993; Ponton *et al*., 2000; Nucci and Anaissie, 2002). The presence of germinating microconidia in different organs suggests that this strain can grow actively on mammalian tissue and may also undergo cycles of conidiation in the host, as reported previously for pathogenic *Fusaria* (Liu *et al*., 1998).

Taxonomy, biology and clinical aspects of *Fusarium* species: There are several taxonomic systems available for identifying *Fusarium* species. The identification of fungal species and determination of their significance in the clinical laboratory is complex practices that help establish or exclude a fungal cause of disease. In the past, the clinical mycologist utilized a limited array of phenotypic measurements for categorizing isolates to the species level. This scenario is shifting in favor of molecular identification strategies largely due to a combination of several factors: (1) The changing landscape of epidemiology of medically important fungi, in which novel organisms never before implicated in human infection are being reported from clinical samples (Balajee *et al*., 2009); (2) reports of species-specific differences in antifungal susceptibilities of these newly recognized fungi (Balajee *et al*., 2009); (3) numerous studies demonstrating that morphology alone may not be a sufficiently objective method for species determination (Alcazar-Fuoli *et al*., 2008) and (4) a growing scarcity of bench scientists and microbiologists trained in traditional mycology. With the increasing incidence of fungal infections and reports of invasive fungal infections in nontraditional populations, such as patients with critical illnesses, the onus is on the clinical microbiologist/mycologist to return a timely and accurate identification. Molecular methods are

rapid with a turnaround time of about 24 h from the time of DNA extraction, yield results that are objective with data portable between labs and could be more economical in the long run.

The field of medical mycology has embraced molecular methods of identification, resulting in the exploration of numerous potential targets, an explosion in the number of sequences from these loci and recognition of previously unknown fungal species adding to the already staggering fungal diversity. On the other hand, this practice may have opened up a number of possibilities, at least from the perspective of a mycologist in a routine microbiology laboratory, resulting in considerable uncertainty about the best possible molecular method to obtain a species identification. Realizing this, a consortium of international experts was assembled as an International Society for Human and Animal Mycology (ISHAM; www.isham.org) working group on fungal molecular identification. With the goal of supporting clinical laboratories in their efforts to identify fungal species from culture by using molecular methods, the ISHAM working group agreed to begin by focusing on molecular strategies available for medically important fungi of the genera *Aspergillus* and *Fusarium* and the order *Mucorales* (Zygomycota) (Balajee *et al*., 2009).

Identification strategy based on comparative sequence analysis: Today, comparative sequence-based identification strategies can be considered the new gold standard for fungal species identification (Poirot *et al*., 1985). This method is based on PCR amplification of a selected region of genomic DNA (target locus), followed by sequencing of the resulting amplicon(s). Once a consensus sequence is obtained, it can be queried against a database library and evaluation for species identification can be performed by generating dendrograms, examining percent similarity/percent dissimilarity, or executing more sophisticated phylogenetic analyses. The current approach in clinical laboratory practice is to interpret sequence comparison results by generating a percent identity score, which is a single numeric score determined for each pair of aligned sequences and which measures the number of identical nucleotide matches in relation to the length of the alignment. Cutoff scores for species identification are arbitrary and the scores can vary depending on numerous factors including the quality of the sequence, the number and accuracy of existing database records from the same species and locus, the length of the sequence fragment and the software program employed. At present, there is no definitive study describing an absolute cutoff for same-species identity across the fungal kingdom and no consensus definition exists on how to define a species using such comparative sequence methodologies (Balajee *et al*., 2009).

Multiple studies have demonstrated that comparative sequence-based identification using the nuclear ribosomal Internal Transcribed Spacer (ITS) region (ITS1, 5.8S rRNA and ITS2) located between the nuclear small- and large-subunit rRNA genes (White *et al*., 1990) could be employed for species complex-level identification of *Aspergillus* (Hinrikson *et al*., 2005) and most *Mucorales* (Schwarz *et al*., 2006) species and for identification within some species complexes of *Fusarium* (Zhang *et al*., 2006; O'Donnell *et al*., 2008). The ITS region satisfies most of the aforementioned requirements of a universal marker since this region can be reliably amplified for most fungi, is conserved, is present as multiple copies in the fungal genome, yields sufficient taxonomic resolution for most fungi and has the additional advantage that the GenBank (http://www.ncbi.nlm.nih.gov), European Molecular Biology Laboratory nucleotide sequence database (http://www.ebi.ac.uk/embl/) and DNA Data Bank of Japan (http://www.ddbj.nig.ac.jp/) contain a large number of sequences from this locus, enabling a ready comparison of the sequence from an unknown isolate (Balajee *et al*., 2009).

Significant disadvantages of the ITS region include (1) insufficient hypervariability to distinguish the various species in the *Aspergillus* sections and *Fusarium* species complexes; (2) its failure to distinguish between closely related species (sibling species) because of insufficient nucleotide differences, for example, *Aspergillus lentulus* and *Aspergillus fumigatus* and (3) problems with the reliability of the ITS sequences deposited in the reference databases (e.g., GenBank/EMBL/DDBJ) (Nilsson *et al*., 2006).

Comparative sequence-based identification strategies can be meaningful only with the availability of well-curated, robust and reliable databases that are populated with sequence data from type or reference strains (where possible), have been rigorously validated in terms of their nomenclature and include sequences from a wide variety of target species. The most widely used database is GenBank, which contains a huge number of sequences, but these are combined with unedited and nonvalidated information, which may be updated and corrected only by the original submitter. Errors in fungal sequences within GenBank have been found to be as high as 20% (Nilsson *et al*., 2006). Despite calls for the process to be changed, to allow for third-party revision, there seems little prospect of this in the near future (Pennisi, 2008). On the other hand, smaller databases, such as those provided with commercial sequence-based identification systems, are often inadequate because of their lack of breadth (omitting many, often important species) and depth (containing few representatives of the same species) (Hall *et al*., 2004). To overcome these problems, specific sequence databases for particular groups of fungi, based on quality-controlled sequences, have been created mainly for plant-pathogenic, industrially important and ectomycorrhizal ascomycete and basidiomycete fungi, e.g., *Fusarium* sp. (Geiser *et al*., 2004).

Clinical importance of *Fusarium* sp.: The most frequent species causing fusariosis are *Fusarium solani*, *Fusarium oxysporum* and *Fusarium verticillioides* (Guarro and Gené, 1995; Alastruey-Izquierdo *et al*., 2008; Tortorano *et al*., 2008), but several other species are also found to cause human infections, although less frequently. Some of these species are *Fusarium chlamydosporum*, *Fusarium dimerum*, *Fusarium incarnatum* and the following other species that are included into the *Gibberella fujikuroi* species complex: *Fusarium napiforme*, *Fusarium nygamai*, *Fusarium proliferatum* and *Fusarium sacchari* (Nirenberg and O'Donnell, 1998; Nucci and Anaissie, 2007). These species have been associated with different types of infection, in particular with keratomycoses and other ocular infections (De Hoog *et al*., 2000) and with disseminated infections in immunocompromised patients (Kiehn *et al*., 1985; Poirot *et al*., 1985; Richardson *et al*., 1988; Summerbell *et al*., 1988; Helm *et al*., 1990; Barrios *et al*., 1990; Krulder *et al*., 1996; Segal *et al*., 1998; Austen *et al*., 2001; Letscher-Bru *et al*., 2002; Guarro *et al*., 2003). The real incidence of these species is unknown since they are poorly known and laboratorians and clinical microbiologists are not generally aware of their possible presence in human infections (Azor *et al*., 2008).

Since, the species of *Fusarium* are generally resistant to all the available antifungal drugs (Pujol *et al*., 1997), it could be considered that speciation of *Fusarium* is necessary only for epidemiological purposes. However, some *in vitro* data concerning particular species seem to be very promising and deserve to be investigated clinically. For instance, *F. verticillioides* isolates were susceptible to posaconazole and terbinafine and *Fusarium thapsinum* isolates to terbinafine (Azor *et al*., 2008). The identification of fusaria to the species level is not easy and in numerous clinical cases the etiological agent is reported as being a *Fusarium* sp. However, several recent studies have demonstrated the usefulness of molecular methods for the identification of those

Fusarium species that are difficult to distinguish morphologically (Alastruey-Izquierdo *et al*., 2008; Azor *et al*., 2008; Tortorano *et al*., 2008). In recent years, the *in vitro* antifungal susceptibilities of the most frequent species of *Fusarium* have been evaluated (Pujol *et al*., 1997; Azor *et al*., 2007, 2008; Alastruey-Izquierdo *et al*., 2008; Tortorano *et al*., 2008) but only a few isolates of the less-common species have been studied. Azor *et al*. (2008) studied to (1) evaluate the correlation between the morphological and the molecular identification of less-frequent *Fusarium* species isolates received by our laboratory and (2) determined the antifungal susceptibilities of isolates representative of those less-common *Fusarium* species of clinical interest identified molecularly.

For the phylogenetic analysis, sequencing of the TUB region of the β-tubulin gene has proven to be highly phylogenetically informative in different molecular studies of the genus *Fusarium* (O'Donnel *et al*., 1998, 2000; O'Donnel and Cigelnik, 1997). For DNA extraction, amplification and sequencing, we followed the procedures previously described by Gilgado *et al*. (2005), with some modifications.

The use of the internal transcribed spacer rRNA gene sequences has proven to be useful for the identification of numerous fungal pathogens. However, this marker has been used only for the recognition of species complexes in the genus *Fusarium* (Balajee *et al*., 2009). *Fusarium sacchari, F. subglutinans* and other related species constitute a morphologically similar group of species that can be differentiated practically only by the use of mating tests or molecular markers (Leslie and Summerell, 2006). Although, several human infections have been attributed to *F. subglutinans* (De Hoog *et al*., 2000; Leslie and Summerell, 2006), the identification of the case isolates is questionable. None of the clinical isolates included in this study was molecularly identified as *F. subglutinans*. Our study confirmed that *F. chlamydosporum* and, especially, *F. dimerum* represent complexes of species (O'Donnell *et al*., 2007), as has occurred in other more common species of *Fusarium*, such as *F. solani*, *F. oxysporum* and *F. verticillioides* (O'Donnell *et al*., 1998, 2000, 2004; Azor *et al*., 2007, 2008).

Detailed molecular studies employing sequences of multiple loci such as elongation factor 1α (EF-1α) (Guarro *et al*., 2000), β-tubuhn (β-TUB), calmodulin (CAM) and RNA polymerase II second largest subunit (RPB2) and subsequent phylogenetic analyses of medically important fusaria have revealed the presence of multiple cryptic species within each morphologically recognized morphospecies. For instance, *Fusarium solani* actually represents a complex (i.e., *F. solani* species complex) of over 45 phylogenetically distinct species of which at least 20 are associated with human infections (Summerbell *et al*., 1988; Nucci and Anaissie, 2007). Similarly, members of the *Fusarium oxysporum* species complex are phylogenetically diverse (Summerbell *et al*., 1988; Nucci and Anaissie, 2007), as are members of the *Fusarium incarnatum-equiseti* species complex and *Fusarium chlamydosporum* species complex (Nirenberg and O'Donnell, 1998). Cases involving the latter two complexes are typically reported as the polytypic morphospecies *F. incarnatum*/*Fusarium semitectum*/*F. equiseti* and *F. chlamydosporum*, respectively (Pastor and Guarro, 2007). Available data clearly demonstrate that sequences from the nuclear ribosomal ITS region and domains D1 and D2 of the 28S ribosomal DNA (rDNA) large subunit are too conserved to resolve most clinically important fusaria at the species level (Summerbell *et al*., 1988; Nucci and Anaissie, 2007), despite reports to the contrary (Helm *et al*., 1990; Guarro and Gené, 1995). Moreover, use of the ITS rDNA within the *Gibberella fujikuroi* species complex and *F. oxysporum* species complex (Neuburger *et al*., 2008) and β-tubulin within the *F. incarnatum-equiseti* species complex and *F. solani* species complex should be avoided due to paralogous or duplicated divergent alleles (O'Donnell, 2000).

Mycological methods and culture characteristics of *Fusarium* sp.: It grows well at 37°C, reaching a diameter of 4.5 cm in 7 days on potato dextrose agar. On a cornmeal agar slide culture, the isolate produced numerous one-to two-celled, clavate, oblong to fusiform microconidia (2.5 to 4 μm by 8 to 12 μm) directly on short and narrow phialides (denticles) on sympodially proliferating conidiophores. Canoe-shaped macroconidia of four or more cells, characteristic of the genus *Fusarium*, measuring 3 by 30 μm observed only rarely on the cornmeal agar slide culture and were not observed on the other culture media. Intercalary, smooth or slightly rough, brown-walled chlamydospores abundantly produced on cultures in 7 to 10 days. The gibberellins are one of the major groups of growth promoting hormones and are secondary metabolites of the fungus *Fusarium moniliforme* (Mitter *et al.*, 2002). The chlamydospores were mostly globose (6 to 15 μm in diameter) and formed in short chains, but some produced cross septae and became muriform. The colony reverse was faintly brown in the beginning but became dark brown as the culture aged due to the increasingly abundant, darkly pigmented chlamydospores (Segal *et al.*, 1998).

The clinical manifestations and histological appearance of *Fusarium* sp. is indistinguishable from those of organisms causing invasive aspergillosis. Both genera infect profoundly immunocompromised patients and both are associated with vascular invasion, tissue infarction and hemorrhage. Recently, Liu *et al.* (1998) and Groll *et al.* (2005) reviewed biopsy and cytology specimens from culture-confirmed hyalohyphomycosis caused by *Fusarium*, *Paecilomyces*, or *Acremonium* species to identify histologic features that distinguish these molds from *Aspergillus* species. Sporadic phialide-and phialoconidium-like structures were present in 16 of 19 cases, including 7 of 10 cases of infection by a *Fusarium* species (Groll *et al.*, 2005). Phialoconium-like structures seen in tissue were spherical, oval, curved, or elliptical. These specialized structures may be helpful in alerting the pathologist to the possibility of a non-*Aspergillus* species but are not readily detected unless inspected with a 100x oil immersion lens (Groll *et al.*, 2005). This is point out that the presumptive histologic diagnosis should be confirmed by culture whenever possible (Groll *et al.*, 2005). In the absence of definitive identification by culturing, the likelihood of infection with a *Fusarium* species is substantially increased if either widespread cutaneous dissemination or the isolation of the mold from a blood culture occurs (Balajee *et al.*, 2009).

The identification of a *Fusarium* species in a culture is difficult if macroconidia are not present (CLSI, 2008). In these instances confusion with other genera, such as *Acremonium*, *Cylindrocarpon*, or *Verticillium*, may occur (CLSI, 2008). Rarely, infection of the nasopharynx and sinuses by a *Fusarium* species may resemble rhinocerebral zygomycosis (Melcher *et al.*, 1993). Usually the distinction between these two molds can be made histologically because the hyphae of zygomycetes are wider, branch at right angles and demonstrate a paucity of septations (Melcher *et al.*, 1993).

Typically, *Fusarium* sp. is not confused with dematiaceous molds. Masson-Fontana staining for fungal cells was introduced by Gilgado *et al.* (2005) in an attempt to discern melanin formation by *Cryptococcus neoformans* in brain tissue. They observed that though Masson-Fontana staining was not specific for melanin, it was useful in differentiating cryptococcal cells from other yeast-like pathogens. The Masson-Fontana reagent stains any phenolic compound, including melanin. Since then, the staining has been frequently used for fungal histopathology to detect melanin-like pigment when the pathogen is suspected to be a dematiaceous mold that fails to produce brown-walled hyphae in tissue (Guarro and Gené, 1995; Azor *et al.*, 2008; Neuburger *et al.*, 2008). It must be emphasized that Masson-Fontana staining is not specific for melanin and that hyphae without melanin can produce positive results as long as phenol compounds are present.

Fusarium species grow easily and rapidly in most media without cycloheximide. Although, the genus *Fusarium* can be identified by the production of hyaline, banana-shaped, multicellular macroconidia with a foot cell at the base, species identification is difficult and may require molecular methods. Recently, a commercially available PCR-based method was tested with 21 clinical isolates of *Fusarium* species and 5 ATCC isolates. Using sequencing identification as a gold standard, seven of nine different species were identified (Swofford, 2001).

Pathogenicity of *Fusarium* sp.: The soil-borne fungus *Fusarium oxysporum* is the known as a serious emerging pathogen of humans due to the increasing number of severe cases reported and to its broad resistance to the available antifungal drugs (Krulder *et al*., 1996; Austen *et al*., 2001). *Fusarium* now represents the second most frequent mold causing invasive fungal infections in immunocompromised patients, frequently with lethal outcomes (Melcher *et al*., 1993; Jessup *et al*., 2000; O'Donnell *et al*., 2004). *Fusarium oxysporum*, together with *F. solani* and *F. verticillioides*, are responsible for practically all of the cases of invasive fusariosis in humans (Groll *et al*., 2005). Given the dual ability to cause disease both on plants and on humans reasoned that *F. oxysporum* could serve as a universal model for studying fungal virulence mechanisms found that strain 4287 is able to produce systemic infections in immunodepressed mice, resulting in a high death rate. By applying the mouse model to a number of knockout mutants previously shown to exhibit altered virulence on tomato plants, Ortoneda *et al*. (2004) showed that specific virulence factors in a single fungal strain play distinct functional roles in plant and animal pathogenesis. *Fusarium solani* is one of the most frequently isolated fungi from soil and plant debris and is also associated with serious invasive mycoses in immunocompromised and immunosuppressed patients (Azor *et al*., 2007). This species, as defined based on morphology, is actually a diverse complex of over 45 phylogenetic and/or biological species (Gilgado *et al*., 2005), termed the *Fusarium solani* species complex (FSSC). These morphologically similar species are generally identified broadly under the name *F. solani*. They are ubiquitous in soil and decaying plant material, where they act as decomposers, but they are also host-specific pathogens of a number of agriculturally important plants, including pea, cucurbits and sweet potato. Moreover, they are increasingly associated with opportunistic infections of humans and other animals, causing systemic infections with a high mortality rate (CLSI, 2008), as well as localized infections in the skin and other body parts (Barrios *et al*., 1990; Balajee *et al*., 2009). In immunocompetent patients, FSSC isolates are mainly known from mycotic keratitis subsequent to traumatic introduction of inoculum. Neutropenic patients, a category of particularly strongly immunocompromised patients, are susceptible to dissemination of infection from superficial or subcutaneous initiation; such infections are usually fatal (Barrios *et al*., 1990; Cruse *et al*., 2002; Balajee *et al*., 2009). Members of the *Fusarium solani* Species Complex (FSSC) are increasingly implicated as the causative agents of human mycoses, particularly in the expanding immunocompromised and immunosuppressed patient populations. Best known as ubiquitous plant pathogens and saprotrophs, the FSSC comprises over 45 phylogenetically distinct species distributed among three major clades.

In recent years, there have been an increasing number of reports of human infection due to *Fusarium* species, mostly involving immunocompromised hosts (Guarro and Gené, 1995; De Hoog *et al*., 2000; Azor *et al*., 2007). It causing localized infection, deep-seated skin infections and disseminated disease. Reports of infection in nonimmunocompromised hosts are infrequent and usually involve dialysis-related, burn wound, or ocular infections (Nelson *et al*., 1983; O'Donnell, 2000; Austen *et al*., 2001; Letscher-Bru *et al*., 2002; Dignani and Anaissie, 2004; Nucci and

Anaissie, 2007; O'Donnell *et al.*, 1998, 2000, 2004, 2007; Alastruey-Izquierdo *et al.*, 2008; Balajee *et al.*, 2009), although it has been suggested recently that, among these patients, the most frequent site of infection is the skin (Melcher *et al.*, 1993).

Reports of fusarial infection in immunocompetent patients are sparse. These include mostly infection of the eyes, skin and nails, peritoneum, or lungs (Nelson *et al.*, 1983; Melcher *et al.*, 1993; O'Donnell, 2000; Austen *et al.*, 2001; Letscher-Bru *et al.*, 2002; Dignani and Anaissie, 2004; Herbrecht *et al.*, 2004; Nucci and Anaissie, 2007; O'Donnell *et al.*, 1998, 2000, 2004, 2007; Neuburger *et al.*, 2008; Alastruey-Izquierdo *et al.*, 2008; Balajee *et al.*, 2009).

Nir-Paz *et al.* (2004) found several risk factors for higher in-hospital mortality among patients with fusarial infections; chronic renal failure, hematological malignancy and burns were associated with increased odds (by multiple logistic regression analysis) for death during hospitalization (odds ratio, ≥15.0), as was disseminated infection (odds ratio, 8.7). Fleming *et al.* (2002) and Azor *et al.* (2007) have also commented on dissemination being associated with higher mortality.

Fusarium solani is more frequently associated with disseminated disease than other *Fusarium* species. It is a similar tendency, which may reflect the greater pathogenic potential in a murine model (Krulder *et al.*, 1996). However, since the species of most of our isolates were not determined, no firm conclusion can be drawn. Fusarial infection has a tendency for seasonal variation. The infection is most prevalent in autumn in France (Guarro and Gené, 1995) and in Summer in Texas and Italy (Nirenberg and O'Donnell, 1998; De Hoog *et al.*, 2000; Azor *et al.*, 2007). In Israel, the highest incidence of *Fusarium* species isolation was in the summer, particularly among patients from rural areas and was associated with ocular and respiratory tract infections (Barrios *et al.*, 1990; Nirenberg and O'Donnell, 1998). This may reflect sporulation of *Fusarium* sp. during this season. Interestingly, in Israeli agricultural practice, *Fusarium* sp. is usually considered pathogens of various field and vegetable crops during the summer (Guarro *et al.*, 2000). However, two agriculturally significant *F. oxysporum* forms that are considered winter pathogens (Guarro *et al.*, 2000; Cruse *et al.*, 2002). Moreover, in Israel, fusarial infections are unrelated to rain and wind, in contrast to previous reports from other countries (Nirenberg and O'Donnell, 1998; De Hoog *et al.*, 2000; Azor *et al.*, 2007), since Israeli summers are rainless and hot (around 30°C). It is conceivable that the humidity, which is high in the coastal plain in the summer (55 to 70%) and low in the mountains (40 to 55%) (Azor *et al.*, 2008), may partly explain the differences between these regions, as presented by more cases per 1,000 admissions in Sheba Medical Center, which is located in the coastal plain, than in the Hadassah University Hospital, located in the mountains of Jerusalem (Nir-Paz *et al.*, 2004).

The frequency of isolation of *Fusarium* species varies between different countries (De Hoog *et al.*, 2000; Guarro *et al.*, 2000; Azor *et al.*, 2007). Such variation was also observed between two different geographical regions within a same country. The major differences between the hospitals that Reference studied are their location and elevation we can consider that *Fusarium* species are emerging pathogens in the mountainous area and possibly to a lesser extent in the coastal plain as well.

F. oxysporum f. sp. *lycopersici* causes systemic infection and death in immunodepressed mice. *F. oxysporum* strains have been reported either as plant or human pathogens. Ortoneda *et al.* (2004) tested the hypothesis that a single strain of *F. oxysporum* can produce disease both on plant and mammalian hosts. As candidate strains of *F. oxysporum* f. sp. *lycopersici* race 2 is well characterized (Nucci and Anaissie, 2007; Alastruey-Izquierdo *et al.*, 2008). *F. oxysporum* strain 4287 has been used in numerous molecular studies, resulting in the availability of genomic and cDNA libraries and optimized plant infection assays (De Hoog *et al.*, 2000).

The most frequent species of *Fusarium* causing keratitis are *Fusarium solani* and *Fusarium oxysporum* (Zapater, 1986; Vismer *et al*., 2002). More rarely, *Fusarium dimerum* (Vismer *et al*., 2002), *Fusarium verticillioides*, *Fusarium sacchari* (Zapater, 1986) and very recently, *Fusarium polyphialidicum* (Guarro *et al*., 2003) have also been reported. Keratitis is more common in tropical and subtropical areas. Its incidence correlates with harvest time and seasonal increases in temperature and humidity (Behrens-Baumann, 1999).

Fusarium solani is clearly the most common fungus causing keratitis. Despite the high incidence of *Fusarium* and although its ability to infect the eye has been demonstrated in numerous studies (Behrens-Baumann, 1999; Thomas, 2003), it is unknown whether only a few strains have this ability for eye invasion or whether this is a general feature of all strains of *F. solani*. This issue is the key to determining the epidemiology of these infections. At least at the morphological and cultural levels, no differences are observed between environmental and corneal isolates of *F. solani* (Thomas, 2003).

The two different strains of the same species can infect the same eye concomitantly, especially if they belong to ubiquitous genera such as *Aspergillus*, *Candida*, or *Fusarium*. More than one colony should be collected from cultures derived from corneal samples, even if they are morphologically similar, to type them (if possible) and to avoid problems with treatment when multiple strains with different antifungal susceptibilities are present (Godoy *et al*., 2004). Although, molecular epidemiological studies have been completed for nosocomial fusariosis (Anaissie *et al*., 2001; Ortoneda *et al*., 2004), most of the analyses were conducted on members of the *F. solani* species complex. Nevertheless, a relationship between an environmental isolate and a patient isolate was determined in one case of infection due to a member of the FOC (Anaissie *et al*., 2001).

Guarro *et al*. (2000) reported on a case of mixed infection caused by two species of *Fusarium* in a human immunodeficiency virus-positive patient with lymphoma who was neutropenic due to chemotherapy. The patient showed the typical signs of a disseminated fusarial infection, with *Fusarium solani* isolated from skin lesions and *F. verticillioides* isolated from blood. The report discusses how difficult it is to make an accurate diagnosis when an immunosuppressed patient is infected with more than one fungal species, especially when the species are morphologically very similar.

Members of the phylogenetically diverse monophyletic *Fusarium oxysporum* Complex (FOC) are best known as cosmopolitan soilborne plant pathogens that are responsible for economically devastating vascular wilts of an enormous range of agronomically important plant hosts (Di Pietro *et al*., 2003). Members of the FOC are also frequently isolated from nonplant sources, particularly from the soil but also from air and animals. Over the past 2 decades, however, fusaria have emerged as opportunistic pathogens causing life-threatening disseminated infections in immunocompromised patients (Boutati and Anaissie, 1997). In patients who are persistently neutropenic, deeply invasive fusarial infections cause 100% mortality (Nucci and Anaissie, 2002). Most localized and disseminated cases of fusariosis are caused by members of the *Fusarium solani* species complex, followed by members of the FOC (Anaissie *et al*., 2001). Fortunately, the recent development of one strain of *F. oxysporum* as a model system greatly facilitates the molecular genetic dissection of fungal virulence determinants during plant and animal pathogenesis (Ortoneda *et al*., 2004).

***Fusarium* infections and immunity:** The innate immunity plays a major role in the defense against mold infections (Shoham and Levitz, 2005). Macrophages and neutrophils damage fusarial

hyphae and their effect is primed by gamma interferon, granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF) (Gaviria *et al*., 1999) and interleukin-15 (Winn *et al*., 2005). The effect of interleukin-15 is mediated by the release of interleukin-8 and by direct stimulation of hyphal damage. More recently, the role of Toll-like receptors in the innate immune recognition of fungi has been recognized (Romani, 2004) and although little is known about fusariosis and Toll-like receptors, this system is likely important in invasive fusariosis as well. The importance of immunity in the pathogenesis of fusariosis is supported by *in vitro* and *in vivo* experimental studies (Gaviria *et al*., 1999; Legrand *et al*., 1991; Romani, 2004; Winn *et al*., 2005), the unique susceptibility of severely immunocompromised patients to disseminated fusariosis (Boutati and Anaissie, 1997) and the strong correlation between immune reconstitution and outcome (Nucci *et al*., 2003).

The importance of T-cell defenses against *Fusarium* is illustrated by the occurrence of disseminated fusariosis in nonneutropenic Hematopoietic Stem Cell Transplant (HSCT) recipients (Nucci *et al*., 2004) patients have severe T-cell immunodeficiency caused by multiple therapies for their underlying disease and for Graft-versus-Host Disease (GvHD). Further supporting the importance of T-cell immunity and phagocytes is the major impact of corticosteroid therapy on the outcome of fusariosis, as shown by the much higher death rate among recipients of such therapy than among patients who were not receiving corticosteroids (Nucci *et al*., 2003).

Fusarium species possess several virulence factors, including the ability to produce mycotoxins, including trichothecenes, which suppress humoral and cellular immunity and may also cause tissue breakdown (Nelson *et al*., 1994). The first outbreak of trichothecene poisoning in humans was reported from Kashmir, India in 1987 and attributed to the consumption of bread made from mouldy flour (Bhat *et al*., 1989). In addition, *Fusarium* species have the ability to adhere to prosthetic material and to produce proteases and collagenases (Kratka and Kovacikova, 1979).

Genetic virulence determinants of *Fusarium oxysporum* have been recently studied in immunosuppressed mice. Nucci and Anaissie (2007) recorded animals inoculated with microconidia of a well-characterized tomato-pathogenic isolate (wild type), which resulted in disseminated infection and death. Inoculation of mutants with knockout mutations in genes encoding three known virulence factors for tomato plants (a mitogen-activated protein kinase, a pH response transcription factor, or a class V chitin synthase) led to discrepant results regarding pathogenicity for plants and animals. The mitogen-activated protein kinase gene, which is essential for virulence in fungal plant pathogens, was not necessary for virulence of *F. oxysporum* in this model. Conversely, the pH response transcription factor was required for animal virulence but not for plant virulence. Most mice infected with the chitin synthase knockout mutant isolates died within 24 h, as opposed to 5-to 12-day survival with the wild-type strain. Postmortem studies suggested that these animals died of respiratory insufficiency, probably as a result of severe lung damage, rather than the usual pattern of more generalized lesions seen in the other experiments. This unusual fast-killing effect was thought to be due to the presence of numerous large (30×25 μm) lemon-shaped or irregularly swollen mutant conidia, causing physical obstruction to lung interstitial capillaries. These morphological alterations in conidia of the chitin synthase knockout mutants are caused by defects in cell wall integrity (Ortoneda *et al*., 2004).

Immunocompromised patients at high risk for fusariosis are those with prolonged and profound neutropenia and/or severe T-cell immunodeficiency (Boutati and Anaissie, 1997). Unlike infection in the normal host, fusariosis in the immunocompromised population is typically invasive and disseminated (Nucci and Anaissie, 2002). Nucci and Anaissie (2007) recorded in a study of

84 patients with hematologic diseases, the infection occurred more frequently in patients with acute leukemia (56%) and most patients (83%) were neutropenic at diagnosis (Nucci *et al*., 2003). Airborne fusariosis is thought to be acquired by the inhalation of airborne fusarial conidia, as suggested by the occurrence of sinusitis and or pneumonia in absence of dissemination. The role of skin as a portal of entry is supported by the development of infection following skin breakdowns due to trauma (automobile accidents, bamboo), burns or onychomycosis in normal hosts (Nucci and Anaissie, 2002) and the development of cellulitis (typically at sites of tissue breakdown such as toes and fingers), which may remain localized or lead to disseminated infection in immunocompromised patients (Boutati and Anaissie, 1997; Nucci *et al*., 2003).

Given the ubiquity of *Fusarium* species in the environment, fusariosis may potentially be acquired in the community, as suggested by the presence of airborne fusarial conidia in outdoor air samples (Boutati and Anaissie, 1997; Anaissie *et al*., 2001; Raad *et al*., 2002). In a prospective study, *Fusarium* species were recovered from a hospital water system (water, water storage tanks, shower and sink drains, shower heads and sink faucet aerators) and from hospital air and other environments (Anaissie *et al*., 2001).

Endophtalmitis: While fusarial endophtalmitis in immunocompetent individuals usually occurs as a complication of advanced keratitis (Dursun *et al*., 2003) or ocular surgery, such as cataract extraction (Ferrer *et al*., 2005), fusarial endophtalmitis in the immunocompromised host more commonly results from hematogenous seeding in the setting of disseminated infection (Tiribelli *et al*., 2002; Rezai *et al*., 2005).

DISEASES OF *FUSARIUM* IN HUMANS AND ANIMALS

Sinusitis: In the immunocompetent host, *Fusarium* sp. may cause allergic sinusitis (Wickern, 1993) or chronic noninvasive or invasive sinusitis (Kurien *et al*., 1992).

Pneumonia: Lung involvement is common in invasive fusariosis (114 of 294 cases (39%)) and almost always occurs among immunocompromised (109/114) patients with disseminated infection. Isolated fusarial pneumonia was reported in 14 patients (11 immunocompromised), usually manifesting as nodular and cavitary lesions. As expected, lung involvement is associated with higher mortality, even after controlling for immune status (Nucci and Anaissie, 2007).

In a series of 84 patients with fusariosis and an underlying hematologic disease, lung infiltrates (proven or presumed to be due to fusariosis) were present in 54% of patients and, like in aspergillosis, consisted of nonspecific alveolar or interstitial infiltrates, nodules and cavities. The clinical presentation was nonspecific, with some presenting with a chinical picture similar to invasive aspergillosis, with dry cough, pleuritic chest pain and shortness of breath (Nucci *et al*., 2003).

Skin involvement: Among immunocompromised patients, skin lesions are also be localized, usually as a result of skin breakdown caused by trauma, or may lead to disseminated infection. Among 16 patients with metastatic skin lesions, a recent history of cellulitis at the site of onychomycosis (11 patients), local trauma (3 patients), or an insect bite (2 patients) was reported (Nucci and Anaissie, 2002).

Fungmia: *Fusarium* species have emerged as a major cause of invasive disease and mortality among neutropenic patients (Anaissie *et al*., 1986, 1988, 1989; Vartivarian *et al*., 1993; Martino *et al*., 1994; Nelson *et al*., 1994; Boutati and Anaissie, 1997). Most cases of invasive

fusariosis are caused by *Fusarium solani*, *Fusarium oxysporum* and *Fusarium moniliforme*, but in about one-third the species is not identified. Disseminated fusariosis commonly manifests with cutaneous lesions, pulmonary infiltrates and, less often, sinusitis and involvement of the nasal cavity (Martino *et al*., 1994). In about one-half of cases of dissemination, *Fusarium* sp. is isolated from blood culture (Guarro and Gené, 1995; Boutati and Anaissie, 1997). Opportunistic fusarial infections in humans (Kiehn *et al*., 1985), Catheter-associated fungemia caused by *Fusarium chlamydosporum* in a patient with lymphocytic lymphoma (Martino *et al*., 1994). To our knowledge, the only reported case of human infection by *Fusarium chlamydosporum* was catheter-related fungemia in a patient with lymphoma (Kiehn *et al*., 1985).

In patients with severe and prolonged neutropenia, early diagnosis of infection by a *Fusarium* species is important because of the high risk of dissemination. *Fusarium* species, cosmopolitan soil saprobe, can cause systemic infection in humans. Increased incidence, often with fatal outcome, has been seen in neutropenic patients with hematological malignancies and in patients with bone-marrow and solid-organ transplantation (Guarro and Gené, 1995). Other rare systemic infections are reported due to fungi belonging to genera *Scedosporium*, *Pseudallescheria*, *Acremonium*, *Lecythophora*, *Phialemonium*, *Phaeoacremonium*, *Paecilomyces* and *Emmonsia*. Disseminated fusariosis in this population is associated with a high mortality and survival is dependent on the rapid recovery of the neutrophil count (Martino *et al*., 1994). As in our patient, localized disease may be cured with excision alone; however, we believe that in neutropenic patients, systemic antifungal therapy is warranted because of the high risk of clinically inapparent disseminated disease (Nucci *et al*., 1992).

In a review of nasopharyngeal and sinus infection caused by *Fusarium* sp., Lopes *et al*. (1995) reported that of 19 patients, 14 had a hematologic malignancy, 1 had aplastic anemia, 1 had diabetes and 3 had no risk factors. Disseminated fusariosis occurred in all patients with a hematologic malignancy as well as the patient with aplastic anemia; 10 (67%) of these 15 patients died. In contrast, among the immunocompetent patients, *Fusarium* disease was localized and surgery, with or without systemic antifungal therapy, was curative (Kurien *et al*., 1992). A single outbreak of acute foodborne disease possibly caused by *Fusarium* sp. has been reported in 27 villages of the Deccan plateau in southern India during October 1995 affecting 1,424 people (Bhat *et al*., 1989).

The optimal selection of antifungal therapy for fusariosis is not well defined in the literature. Despite the poor response, high-dose amphotericin B (1 to 2 mg/kg/day) or a lipid formulation of amphotericin is considered standard therapy. Numerous case studies and small-scale studies have investigated various combinations of antifungal regimens (Merz *et al*., 1988; Rabodonirina *et al*., 1994; Guarro and Gené, 1995) and the use of cytokine therapy and granulocyte transfusions (Spielberger *et al*., 1993) in neutropenic patients with infection by *Fusarium* sp. In a retrospective study of 43 patients with hematologic malignancy and fusariosis treated at the M.D. Anderson Cancer Center, use of transfusions with granulocyte colony-stimulating factor-elicited granulocytes appeared to be associated with a positive response (Boutati and Anaissie, 1997). However, the responders in this study also tended to be in remission from the underlying malignancy, to have already recovered their neutrophil counts and to have localized fusariosis; thus, the independent contribution of the granulocyte transfusions was uncertain (Boutati and Anaissie, 1997). No controlled studies of treatment of fusariosis have been published.

Fumonisins are a group of secondary metabolites produced by *Fusarium moniliforme* (Gelderblom *et al*., 1988). Fumonisin B1 (FB1) is the major metabolite and FA1 and FA2 are produced in trace amounts on maize culture and are non-toxic (Gelderblom *et al*., 1992). The

fungus, *Fusarium moniliforme* occurs worldwide on a variety of plant hosts and is the most prevalent fungi of corn (Jindal *et al*., 1999). This fungus was found to be the causative agent of equine leucoencephalomalacia (ELEM), a fatal disease of horses (Marasas *et al*., 1976). Fumonisin B1 either in purified form or in naturally contaminated corn or corn-based feeds has been reported to cause the diseases ELEM and Porcine Pulmonary Edema (PPE) (Harrison *et al*., 1990). Fumonisin B1 also causes liver toxicity and liver cancer in rats, atherosclerosis in monkeys and immunosuppression in poultry (Norred, 1993). An outbreak of fumonisin toxicosis in a poultry farm in Andhra Pradesh State, India was reported (Prathapkumar *et al*., 1997). In this outbreak, a total of 6,700 hens aged 64 weeks and 3,000 hens aged 36 weeks were affected with 10% mortality. The disease was characterized by sticky diarrohea, severe reduction in food intake, egg production and body weight followed by lameness and death. Analysis of the feed indicated contamination with FB1 up to 8.5 mg kg^{-1}. The disease was reproduced in day old cockerels by feeding suspect diet containing 8.5 mg kg^{-1} fumonisin and in laying hens by feeding a normal diet spiked with FB1 of 8 and 16 mg kg^{-1}. The outbreak in poultry coincided with that occurred in humans. The number of patients with fusariosis is likely to increase in the future as more patients receive intensive immunosuppressive therapy. Our purposes here are to report the first known case of tissue disease caused by *F. chlamydosporum* and to alert the clinician and pathologist to the varied histologic appearance of *Fusarium* sp. Rapid diagnostic methods for mold identification from histologic specimens would increase our diagnostic precision. To this end, immunohistologic techniques which can rapidly identify a number of medically important fungal genera, including *Fusarium*, have been introduced in a few specialized laboratories (Fukuzawa *et al*., 1995; Sekhon *et al*., 1995; Kaufman *et al*., 1997). Moreover, given the dismal prognosis of fusariosis in neutropenic patients, more effective antifungal therapy and reliable fungal susceptibility testing methods are urgently needed.

A striking characteristic of fusariosis, as opposed to aspergillosis, is the high frequency of positive blood cultures, mostly in the context of disseminated disease. Occasionally fungemia is the only manifestation of fusariosis, usually in absence of neutropenia, among patients with central venous catheters. Antifungal treatment and catheter removal result in cure in most such cases (Kiehn *et al*., 1985; Ammari *et al*., 1993; Castagnola *et al*., 1993; Raad and Hachem, 1995; Velasco *et al*., 1995; Eljaschewitsch *et al*., 1996; Musa *et al*., 2000).

Disseminated infection: Disseminated disease is the most frequent and challenging clinical form of fusariosis in immunocompromised patients, accounting for approximately 70% of all cases of fusariosis in this population. Patients at risk for disseminated fusariosis include those with acute leukemia and prolonged and profound neutropenia and patients undergoing HSCT (Nucci and Anaissie, 2007).

DIAGNOSIS OF *FUSARIUM* DISEASES

The diagnosis of fusariosis depends on the clinical form of the disease. The clinical picture is not of help in the diagnosis of keratitis, since the clinical manifestations are similar regardless of etiology (bacteria or fungi). Culture of corneal scrapings (most frequent) or tissue biopsy is usually required for a definitive diagnosis (Nucci and Anaissie, 2007). Confirmatory diagnosis of fusariosis is required histopathology. In tissue, the hyphae are similar to those of *Aspergillus* species, with hyaline and septate filaments that typically dichotomize in acute and right angles. However, adventitious sporulation may be present in tissue and the finding of hyphae and yeast-like

structures together is highly suggestive of fusariosis in the high-risk population. In the absence of microbial growth, distinguishing fusariosis from other hyalohyphomycoses may be difficult and requires the use of in situ hybridization in paraffin-embedded tissue specimens (Summerbell *et al.*, 1988).

Two characteristics suggest the diagnosis of disseminated fusariosis in the severely immunocompromised host: skin lesions (either cellulitis or metastatic lesions) and positive blood cultures for mold. Unlike in aspergillosis, blood cultures are frequently positive in fusariosis. This is possibly due to the fact that *Fusarium* species produce yeast-like structures (adventitious sporulation) that facilitate their dissemination and growth in the blood (Liu *et al.*, 1998).

The 1,3-β-D-glucan test is usually positive in invasive fusarial infections but cannot distinguish *Fusarium* from other fungal infections (*Candida*, *Aspergillus*, *Trichosporon* and others) which are also detected by the assay (Odabasi *et al.*, 2004; Ostrosky-Zeichner *et al.*, 2005).

Nucci and Anaissie (2007), a PCR technique was developed for the detection of *Fusarium* species in blood and tissues. Two primers were developed and tested in a mouse model of disseminated fusariosis, as well as in human blood inoculated with fusarial mycelia. The primers were highly specific for 11 medically important *Fusarium* species and the method was able to detect *Fusarium* species in all blood samples.

TREATMENT OF *FUSARIUM* DISEASES

Fusarium species are relatively resistant to most antifungals. Ether and chloroform extracts and oil of *C. longa* have antifungal effects (Arikan *et al.*, 2000). Crude ethanol extract also possesses antifungal activity 120. Turmeric oil is also active against *Fusarium moniliforme* (Arikan *et al.*, 2000). However, different species have different susceptibility patterns (Bigley *et al.*, 2004). Therefore, reliable species identification is important for epidemiologic and clinical purposes. *Fusarium* sp. grow easily and rapidly within two to five days on Sabouraud dextrose agar producing downy, cottony colonies that are lavender to purple-red in color. In tissues, its hyphae is colorless, have septae and branch at acute angles and it is very difficult to differentiate these organisms from each other. Microscopically, the characteristic feature is sickle-or banana-shaped multicelled macroconidia (Azor *et al.*, 2008; Balajee *et al.*, 2009). It can be grow in 3 to 10 days of incubation at 30°C. The typical appearance and morphology of colonies (usually a loose cottony texture) and microscopic features and arrangement of macroconidia (usually hyaline, multiseptate, fusiform to sickle-shaped, mostly with an elongated apical cell and pedicellate basal cell), shape and mode of formation of microconidia, nature of the conidiogenous cell bearing microconidia and presence or absence of chlamydoconidia (Barrios *et al.*, 1990; Groll *et al.*, 2005).

Antifungal susceptibility: The typical antifungal susceptibility profile of *Fusarium* sp. is that of relative resistance to most antifungal agents. However, different species may have different patterns of susceptibility. *Fusarium solani* and *Fusarium verticillioides* are usually resistant to azoles and exhibit higher amphotericin B MICs than other *Fusarium* sp. By contrast, *Fusarium oxysporum* and *Fusarium moniliforme* is susceptible to voriconazole and posaconazole (Szekely *et al.*, 1999; Meletiadis *et al.*, 2000; Espinel-Ingroff *et al.*, 2002; Paphitou *et al.*, 2002; Espinel-Ingroff, 2003; Pfaller and Diekema, 2004; Cuenca-Estrella *et al.*, 2005, 2006).

Clinical experience: Because of a lack of clinical trials and the critical role of immune reconstitution in the outcome of fusariosis, the optimal treatment strategy for patients with severe

fusarial infection remains unclear. The outcome was very poor among the 45 patients who underwent HSCT, regardless of the receipt of deoxycholate amphotericin B (30 patients), a lipid formulation of amphotericin B (14 patients), or caspofungin (1 patient) (Nucci *et al*., 2004).

Combination therapy: Data on combination therapy for fusariosis are limited to a few case reports: caspofungin plus amphotericin B (Makowsky *et al*., 2005), amphotericin B plus voriconazole (Durand-Joly *et al*., 2003; Guzman-Cottrill *et al*., 2004), amphotericin B and terbinafine (Rothe *et al*., 2004) and voriconazole plus terbinafine (Howden *et al*., 2003). Given the scarcity of data and the potential publication bias, no solid recommendations can be provided.

Adjunctive therapies: In addition to antifungal treatment, the optimal management of patients with fusariosis includes surgical debulking of infected tissues (Lupinetti *et al*., 1990) and removal of venous catheters in the occasional patient with confirmed catheter-related fusariosis (Valenstein and Schell, 1986). The role of G-CSF or GM-CSF, G-CSF-stimulated granulocyte transfusions and gamma interferon in the adjuvant treatment of fusariosis is not established. However, given the poor prognosis of fusariosis, especially in persistently neutropenic patients, G-CSF and granulocyte transfusions are frequently used. In support, there are isolated case reports of the successful treatment of invasive fusariosis with a combination of medical treatment and some of these measures (Rodriguez *et al*., 2003).

PREVENTION OF *FUSARIUM* DISEASES

Because of the poor prognosis associated with fusariosis and the limited susceptibility of *Fusarium* sp. to antifungal agents, prevention of infection remains the cornerstone of management. In severely immunocompromised patients, every effort should be made to prevent patient exposure e.g., by putting high-risk patients in rooms with HEPA filters and positive pressure, avoiding contact with reservoirs of *Fusarium* sp. such as tap water (Anaissie *et al*., 2001) and/or cleaning showers prior to use by high-risk patients (Anaissie *et al*., 2002).

Infections by *Fusarium* species can be superficial or limited to single organs in otherwise healthy patients. Such infections are rare and tend to respond well to therapy. By contrast, disseminated fusariosis affects the immunocompromised host, especially HSCT recipients and patients with severe and prolonged neutropenia. Infection in this setting is frequently fatal and successful outcome is determined largely by the degree and persistence of immunosuppression and the extent of infection, with virtually a 100% death rate for persistently neutropenic patients with disseminated disease. These infections may be clinically suspected on the basis of a constellation of clinical and laboratory findings, which should lead to prompt therapy (Nucci and Anaissie, 2007).

CONCLUSIONS

The widespread distribution of *Fusarium* species may be attributed to their ability to grow on a wide range of substrates and their efficient mechanisms for dispersal. Invasive fungal infections are a major medical problem, particularly among immunocompromised hosts such as patients with hematological malignancies and those who have undergone stem cell or solid organ transplantation. Some fungal species, including *Fusarium* sp., rarely cause disease but are considered emerging pathogens. *Fusarium* is a filamentous fungus widely distributed on plants and in the soil. It is found in normal mycoflora of commodities, such as rice, bean, soybean and other crops. While most species are more common at tropical and subtropical areas like Asian region, some inhabit in soil

in cold climates. *Fusarium* species are plant pathogens, but increasingly they have been described as a cause of infections in patients with leukemia and stem cell transplant recipients. Some *Fusarium* species have a teleomorphic state. *Fusarium* and a few other genera of molds actually sporulate *in vivo*, a phenomenon that allows them to grow in cultures taken from blood. *Fusarium* species disseminate through the bloodstream after entry through the lungs or through a cutaneous source, such as a simple paronychia. Painful nodular skin lesions occur frequently with hematogenous spread. Therefore, this review article will certainly provide an brief idea on *Fusarium* infection to human and animal either the *Fusarium* isolates are originated from animal source (animal or human pathogenic) or plant source (plant pathogenic) in nature.

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