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Taxonomy and Clinical Spectra of *Fusarium* Species: Where Do We Stand in 2014?

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Abstract With the recent change of the botanical code for the names of algae, fungi, and plants, fungi are no longer allowed to have multiple names for their different reproductive stages. Here we discuss that under the new nomenclatural rules and for taxonomic stability, *Fusarium* is to be preferred above names for some of its known sexual stages like *Haemonectria* and *Gibberella*. The genus *Fusarium* contains emerging etiological agents of disease ranging from onychomycoses, skin and eye-infections, to deep localized and disseminated infections. Deep infections occur nearly exclusively in immunocompromised patients, while remaining infections primarily affect healthy individuals. Within the large genus, at least seven species complexes comprising multiple species have been implicated in human and animal infections. In this review we give an overview of currently known opportunistic *Fusarium* species and the infections they cause.

Keywords Disseminated infection · Emerging fungal pathogen · Fusarioses · *Fusarium avenaceum* · *Fusarium chlamydosporum* · *Fusarium dimerum* species complex · *Fusarium fujikuroi* species complex · *Fusarium incarnatum-equiseti* species complex · *Fusarium lateritium* · *Fusarium oxysporum* species complex · *Fusarium semitectum* · *Fusarium solani* species complex · *Fusarium sporotrichioides* · Incidence · Keratitis · Nomenclatural stability · Onychomycosis · Population studies

An Introduction to *Fusarium* Taxonomy

For centuries, systematics has been based on morphological characteristics, and hence fungi were grouped mostly according to visible (reproductive) structures. As many fungal species exhibit both asexual and sexual reproduction—which may occur independently from each other—they were

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allowed to carry separate names for different parts of the life cycle. DNA analysis has become indispensable, which has led to discoveries of genetic links between previously separated entities. Where in the past, anamorphic and teleomorphic names clarified relationships between species, they have become rather confusing today.

Due to recent changes in the International Code of Nomenclature for Algae, Fungi, and Plants, as of January 2013 every fungal species is allowed to have only a single name [1]. Furthermore, where formerly, preference would be given to the sexual name over the asexual one, exceptions are now allowed, e.g., for sake of preservation of older names, but also for widely used genus and species names. A huge task now lies in the determination of what is the best name for each species.

For *Fusarium*, a plea has been made to conserve the name *Fusarium* above all linked teleomorphic names like *Heamonectria* and *Gibberella* [2•]. For nomenclatural stability, assembled experts in the fields of plant pathology, mycotoxins, and human and animal pathology preferred to maintain the best known—or perhaps we should say, for its variety of deleterious effects, most infamously known—name: *Fusarium*. Hence, use of the name *Fusarium* is unproblematic, but generic borderlines are yet to be determined. For medically relevant fungi, an extra plea has been made to reduce the number of unnecessary name changes and to keep well-known names as stable as possible [3•].

In this era of genomics, it is well-accepted to use a multilocus sequence typing (MLST) approach in combination with the genealogical concordance phylogenetic species recognition (GCPSR) principle [4] rather than morphology to recognize species and to sort out their relationships. For many of the morphologically defined *Fusarium* species, we know from MLST-GCPSR that we are dealing with species complexes of morphologically (nearly) indistinguishable siblings rather than with single species. *Fusarium* was one of the first fungal groups where the term 'species complex' was commonly used for closely related species [e.g.,[7, 8]. Within such a species complex different MLST-haplotypes can be recognized that, after careful consideration, may be established as separate species. An example of this is the recent recognition of *F. keratoplasticum* and *F. petroliphilum*, two opportunistic pathogens in the *Fusarium solani* species complex [5].

Geiser et al. [2•] in their proposal to preserve the genus *Fusarium* in a robust way maintain a wide definition of the genus *Fusarium* (Fig. 1A; node F1 is the hypothetical ancestor for the entire genus). In this way, the terminal Fusarium clade comprises at least 20 strongly supported species complexes and nine monotypic lineages [6], including seven *Fusarium* species complexes associated with described cases of human infections: the *F. dimerum* species complex (FDSC), the *F. solani* species complex (FSSC), the *Fusarium oxysporum* species complex (FOSC), the *F. fujikuroi* species complex (FFSC, encompassing *F. proliferatum* and *F. verticillioides*), the *F. incarnatum-equiseti* species complex (FIESC), the *F. chlamydosporum* species complex (FCSC), and the complex including *F. sporotrichioides* (FSAMSC). Only a few other *Fusarium* species outside these species (complexes) have occasionally been implicated in human or mammal infections. In this review we will use this broadest definition (Fig. 1A-block A) of the genus *Fusarium*.

Alternatively, a more narrow definition of the genus *Fusarium* could be made, placing the border of the genus, for instance, at nodes F2 or F3 in Fig. 1A. Under these scenarios there are two species complexes that include human opportunists and that would then need reallocation into new genera: The first group would be FDSC (Fig. 1A-block D), including *F. dimerum*, *F. delphinoides*, and others. The other option would exclude also the FSSC (Fig. 1A-block C), which would exclude the largest and most important group with respect incidence: best known as *F. solani sensu lato*, leaving everything linked with a *Gibberella*-like teleomorphic stage (Fig. 1A-block A) as core-*Fusarium* species. Nodes F1, F2, and F3 receive different levels of support based on phylogenetic analyses like maximum likelihood, maximum parsimony, and Bayesian analysis, but as none of these are 100 % conclusive, the definition of *Fusarium* is kept as broad as possible [2•, 6].

Identification of *Fusarium* Species

The most typical feature of the genus *Fusarium* is its unique spindle- or canoe-shaped, multicellular macroconidia. However, these macroconidia are not always present, and differently shaped, single-celled or multicellular micro- and/or mesoconidia may also be formed as well as (pseudo-)chlamydospores. The shape of conidiophores, i.e., the structures on which conidia are formed, may differ between species. Some species are homothallic and produce fruiting bodies with ascospores, while heterothallic species need a suitable partner to produce such structures [7]. Keys have been published for the recognition of clinical *Fusarium* species [e.g.,[4, 83]. These keys are based on morphological structures and require expert training. Fungi have to be grown on standardized, specialized media, and the formation of distinguishing features may require up to 6–8 weeks, rendering precise identification clinically redundant. Besides, morphological recognition of *Fusarium* species in a hospital setting is often impossible by degeneration of colony morphology or by conversion to a 'pionnotal' phenotype [8].

For DNA-based identification of fungi in general, the barcoding and recognition region is the internal transcribed sequence (ITS) region. However, for *Fusarium* spp. this region is too conserved and may not even distinguish between species complexes, let alone down to the species level. For

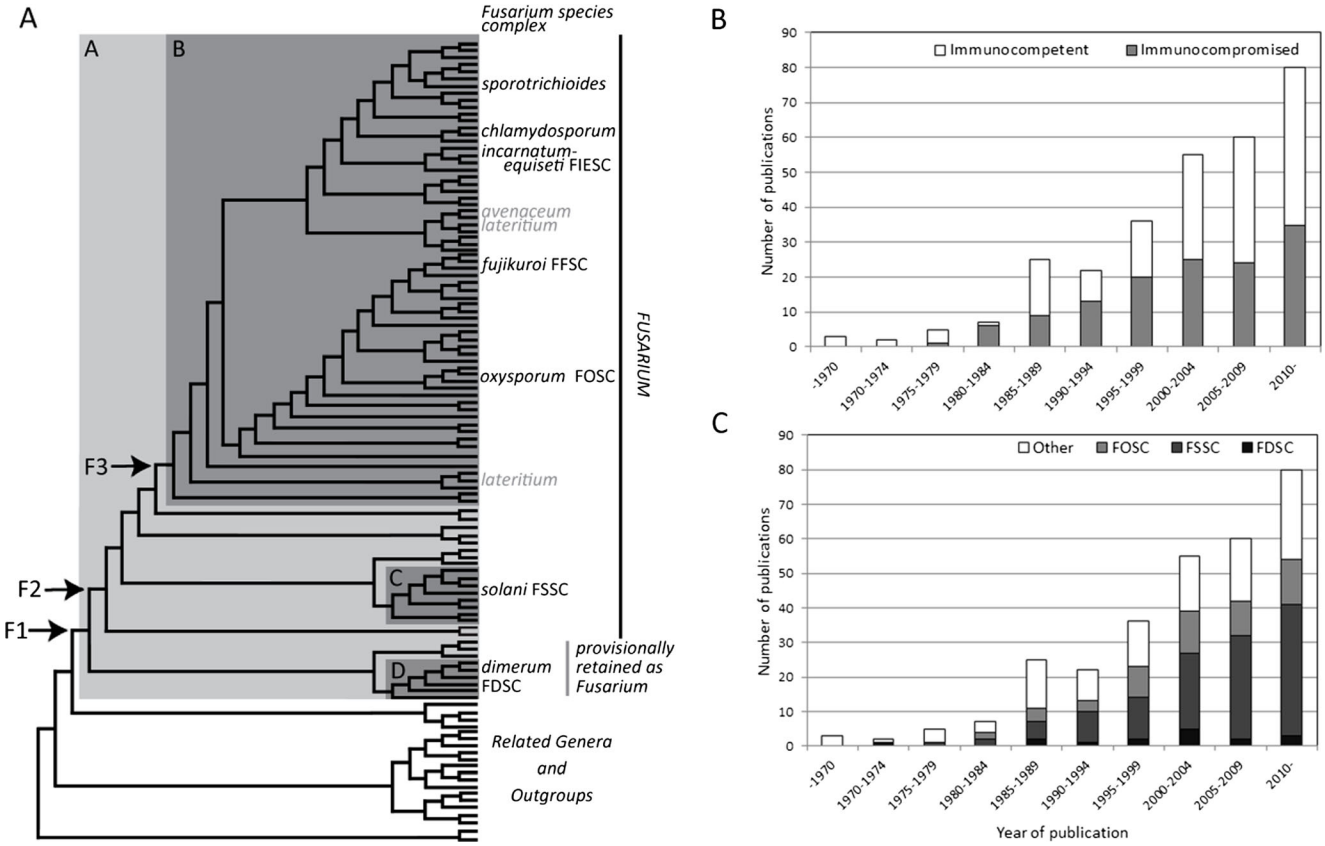

Fig. 1 *a* Cladogram representation of the (provisional) genus Fusarium [2•, 6] with the location of Fusarium species (complexes) reported multiple times to have been involved in human infections (*black*) or just once (*grey*). *b-c* These Fusarium spp. are emerging fungal pathogens indicated by the increasing number of case reports on fusarioses over the years (Pubmed http://www.ncbi.nlm.nih.gov/pubmed data until October 2013). *b* Both the numbers of infections in healthy individuals as well as in immunocompromised patients have increased. *c* The majority of case reports were caused by members of the Fusarium solani species complex, followed by members of the Fusarium oxysporum species complex and other species

identification of molecular siblings, the Translation elongation factor 1-alpha (*TEF-1α*) region, or RNA polymerase II subunits 1 and 2 (*RPB1* and *RPB2*) are especially recommended [9]. A curated database allows for the comparison of found sequences with well-identified *Fusarium* isolates (http://www.cbs.knaw.nl/fusarium/) [9].

Molecular identification techniques of *Fusarium* based on DNA polymorphisms have been developed for use on pure cultures. Direct sequencing of DNA in patient samples also provides an option [10]. Detection techniques include reverse line blotting (RLB) [11], loop-mediated isothermal amplification (LAMP) [12], or rolling circle amplification (RCA) [13]. Besides, multiplex DNA screenings have been developed. These methods may combine (tandem) polymerase chain reactions (PCR) reactions with flow cytometry and/or microarrays [14–18].

Other diagnostic tools in development focus on specific peptides or other metabolites produced by fungi. In particular, matrix-assisted laser desorption ionization time-of-flight (Maldi-TOF) mass spectrometry is being explored [19–21]. This technique is still restricted to the identification of pure cultures, while patient samples are still problematic.

Emerging Opportunists—now and in the Future

Members of the genus *Fusarium* have been involved in infections ranging from localized (nail, skin, eye, or other location), mainly in immunocompetent hosts, to disseminated infections in immunocompromised patients (for a review see e.g., [8] and below). Over the years, the number of case reports on fusarioses both in immunocompetent and compromised hosts has steadily increased (Fig. 1B; data until October 2013 from PubMed http://www.ncbi.nlm.nih.gov/pubmed). About 40 % of these reports were due to members of the FSSC, while the FOSC was involved in approximately 20 % of these reports (Fig. 1C).

Species distributions in the different types of fusarioses have to be concluded from the few population studies done so far. Three studies focused on onychomycoses and skin infections in Italy [22], Switzerland [23], and Colombia

[24], respectively (Table 1). Etiological agents belonged to FSSC causing 31–82 % and FOSC 4–56 % of infections, while members of the FFSC caused 2–37 %; only in one study a single member of the FDSC was found. The prevalence of onychomycoses in humans lies in the range of 5–15 % of the adult population [29–31]. Many of these are caused by *Candida* or dermatophytes, but some studies indicate that *Fusarium* spp. can make up to 10–15 % of the cases [van Diepeningen unpublished results, 20]. Suggested predisposing factors for onychomycosis in general include increasing age, but also immunosuppression, poor peripheral circulation, trauma, and tinea pedis [29].

Two studies focused on eye infections caused by *Fusarium* in India [25] and Mexico [26] reported that 75–82 % of the infections are caused by FSSC, 9–12 % by FDSC, and then occasionally by members of FOSC, FFSC, and FIESC. Fungal keratitis is often linked with trauma, especially with vegetable or other organic matter. The infection is more common in tropical areas and in areas with a relatively large agrarian population. However, prevalence data are still approximate.

Lortholary et al. [27] focused on disseminated fusarioses in the immunocompromised host, where approximately one-third is caused by FSSC, another third by FFSC, and the remainder by FOSC, FDSC, or rarely by FIESC. Limited data exist on the prevalence of each species. Girmenia et al. [32] estimated a prevalence of 0.06 % of fusarioses in patients with acute leukemia in Italy, while Nucci et al. [33] noted an increase in Brazil from 0.86 to 10.23 cases of fusariosis/1,000 hospital admissions in haemato-oncology wards. The one-year cumulative incidence of fusariosis in AML/MDS, allogeneic HCT, and autologous HCT patients proved to be 5.2, 3.8, and 0.6 % (p=0.01), respectively [34]. Disseminated infection in general seems to occur especially in haemato-oncological patients (Table 2). The numbers of cases in patients after a solid-organ transplant, HIV, or other reasons for immunodeficiency are much lower. Fusarioses in SOT recipients tend to remain localized, occur later in the post-transplantation period, and have a better outcome [86].

With ever-rising numbers of immunocompromised patients due to better treatment and survival rates, and also through better prophylaxis against *Candida* and *Aspergillus*, the prevalence of invasive fusariosis may rise further in the future. Primary cutaneous infections often prove to be the portal of entry for a disseminated fusariosis [33, 87]. In return, disseminated infections lead to secondary cutaneous lesions [e.g., [88].

From a global comparison of the different studies of fusarioses, it can be deduced that there are regional differences in prevalent etiological agents (Table 1). For example, in Colombia the numbers of onychomycoses caused by FSSC are higher than in Europe [22–24]. Furthermore, some species complexes seem to be more often involved in certain types of infections; for instance, members of FFSC are relatively often involved in disseminated infections [27]. While members of FDSC seem to be more often involved in eye and disseminated infections than in onychomycoses.

Clinical Spectra of *Fusarium* Species

The *Fusarium solani* species complex (FSSC) globally is the most common group encountered in human infections. It contains sixty or more haplotypes, some of which are predominant in patients [28, 89]. Of these, *F. falciforme*, *F. keratoplasticum*, *F. lichenicola*, and *F. petroliphilum* have been treated as separate species within FSSC, capable of human infection. Reported cases by members of FSSC range from onychomycosis to disseminated infection (see Table 2 for references). However, in most of the published cases no FSSC haplotypes were mentioned and sequences were not available. For this reason, they are listed in Table 2 as infections by *F. solani sensu lato*. Disseminated infections in patients with underlying diseases other than haemato-oncological disorders are rare, although a few cases of infection after solid organ transplant [40, 41] or in patients with auto-immune disorders [45] have been described.

At least 26 of the at least 256 DNA Sequence Types recognized within the cosmopolitan *Fusarium oxysporum* species complex (FOSC) have been involved in human infection [90]. Recognition of subgroups within FOSC has been restricted to *formae speciales* based on host plant specificity. The generalized name *Fusarium oxysporum sensu lato* has been used for the

Table 1 Incidence of the different *Fusarium* species (complexes) in different types of fusarioses, based on different population studies

Geographic location Type of fusariosis	**Italy**[22] Skin/Nail	**Switzerland**[23] Nail	**Colombia**[24] Nail	**India**[25] Eye	**Mexico**[26] Eye	**France**[27] Disseminated	**USA**[28] All
Species complexes							
F. solani SC - FSSC	31 %	33 %	65 %	75 %	82 %	36 %	60 %
F. oxysporum SC - FOSC	34.5 %	56 %	33 %	4 %	6 %	16 %	10 %
G. fujikuroi SC - GFSC	34.5 %	9 %	2 %	9 %	0	37 %	10 %
F. dimerum SC - FDSC	0	2 %	0	9 %	12 %	9 %	5 %
F. chlamydosporum SC - FCSC	0	0	0	0	0	0	15 %
F. incarnatum-equiseti SC - FIESC	0	0	0	3 %	0	2 %	

Table 2 Clinical spectrum and the geographical occurrence of the different etiological agents found within the genus *Fusarium*, based on case report and population study data. In *light grey* are infections that have only been described in a single case report or single population study; in *dark grey* are the more frequent infections

Species Complex	Species	Clinical spectrum							Occurrence in Nature		
		Onychomycosis	Skin infection	Keratitis +endophthalmitis	Deep, localized	Disseminated			Spread [#25; unless stated otherwise]	Reported Clinical cases	Main habitat [#25; unless stated otherwise]
						Haemato/onco	SOT	other			
FSSC	*F. solani sensu latu*	[30]	[69]	[47]	[72]	[70](involvi	[64],[67],		Worldwide	Worldwide	soil & plant spp.
	F. falciforme	Pers. Obs	Pers. Obs	[13]	[56]	[82]		[57]	Worldwide #63	Worldwide	Soil, human #63
	F. keratoplasticum	Pers. Obs	[58]	[58]	[58]	[58]			Worldwide #7,#58	Worldwide	Diverse: soil, human,
	F. lichenicola		[60]	[59]	[61]	[62]			Worldwide #63	Worldwide	Soil, human #63
	F. petroliphilum			[58]	[58]	Pers. Obs			Worldwide #7,#58	Worldwide	(Oil-poluted) soil, plants,
FOSC	*F. oxysporum sensu latu*	[10],[11], [40]	[73]	[34],[47]	[53],[74]	[75],[76]	[67]	[65],[66]	Worldwide	Worldwide	Soil& plant wilt pathogen
FDSC	*F. dimerum*	[40],[51]	[52]	[47],[34]	[53]	[54]			Worldwide	Worldwide	Soil
	F. delphinoides			[51]		[51]			Worldwide #51	Worldwide	Soil, plant pathogen chick
	F. penzigii			[51]					England, Sri Lanka #51	Sri Lanka #51	Wood/*Fagus* associated #51
FCSC	*F. chlamydosporum*	[40]	[8]	[34]	[55]	[8]			(Semi)arid regions	USA, South Africa, Brazil	Soil, saprophyte
FIESC	*F. incarnatum*	[40]	[78]	[34]	[79]	[8]			Worldwide	Worldwide	Soil, plants
	F. equiseti	[80]	[52]	[8]	[8]	[81]			Worldwide	Worldwide	Soil, plants, secondary
FFSC	*F. acutatum*				[26]				India, Pakistan	Qatar	*Cajanus* and wheat (aphids)
	F. anthophilum				Gangrenous)	[27]			Cosmopolitan (temperate)	Japan	Various plant spp.
	F. andiyazi					[28]			America, Africa, Asia	Turkey	Sorghum, rice, figs
	F. napiforme				[29]	[30]			Africa, Argentina, Australia	USA, South Korea	Soil, sorghum, millet and
	F. nygamai	[31]			[32]				Hot, arid locations	Colombia, NL/Egypt	Sorghum, cotton, cereal
	F. proliferatum	[31]		[37]	[38]	#39			Worldwide	Worldwide	Many substrates, maize,
	F. sacchari	[40]	[10]	[41]	[42]				Asia, America	Brazil, Europe, India	Sugar cane, sorghum, maize
	F. subglutinans			[43]	[44]				Cooler regions	China, Europe	Especially on maize
	F. thapsinum			[83]		[84]			Warmer climates worldwide	Turkey, China	Sorghum
	F. verticillioides	[40]	[10]	[47]	[85]	[14]			Worldwide	Americas, Europe	Especially on maize
FSAMSC	*F. sporotrichioides*		[49]		[50]				Widespread, temperate	Japan, Turkey	Diverse substrates
FASC	*F. avenaceum*	[36]			[36]				Temperate regions	Japan	Soil, different plant species
FLSC	*F. lateritium*			[34]				[35]	Worldwide	South Africa, Brazil	Soil, woody plants
FFSC	*F. polyphialidicum*			[33]					Europe, Africa, Australia	Spain	Soil, sorghum

aggregate. Also, fusarioses caused by members of the FOSC range from onychomycosis to disseminated infection, but the latter occurred not only in haemato-oncological [e.g., [57, 58], but also in SOT [41] and HIV [59] patients, as well as in an individual suffering from a heatstroke [60].

The *Fusarium dimerum* species complex (FDSC) contains at least 12 lineages, of which at least *F. dimerum sensu stricto*, *F. delphinoides*, and *F. penzigii* have been involved in human infection [61]. Most case reports on *F. dimerum* were published prior to its recognition as a species complex. Also, in this species complex the infections range from onychomycoses, keratitis, and other localized infections to disseminated infections in haemato-oncological patients.

Fusarium chlamydosporum has been named after its fast and abundant production of thick-walled chlamydospores in mycelium as well as in macroconidia [7]. The *Fusarium chlamydosporum* species complex (FCSC) (*F. chlamydosporum sensu lato*) contains at least four distinct species [28]. The complex has only once been implicated in a keratitis [54], but more often in onychomycoses, cutaneous and deep localized infections, and in disseminated infections in haemato-oncological patients [28, 35, 64].

Within the *Fusarium incarnatum-equiseti* species complex (FIESC) and using four loci, at least 28 species can be recognized, which are organized into two main clades [28]. Haplotypes 1−14 [28] are molecular siblings of *F. equiseti*, while the remaining species are grouped as '*F. incarnatum*' or '*F. semitectum*' [7, 28]. Representatives of the two groups have repeatedly been involved in onychomycoses, skin, eye, and deep localized and disseminated infections, especially in leukemic patients.

The two members of the *Fusarium fujikuroi* species complex (FFSC) that are most commonly observed in human infections are *F. proliferatum* and *F. verticillioides*. However, members of FFSC are increasingly identified in especially invasive and disseminated infections in haemato-oncological patients (Table 2). Many environmental *Fusarium* species and the human infections they cause have a worldwide distribution (Table 2). However, some species of FFSC species, e.g., *F. acutatum*, *F. anthophilum*, *F. andiyazi*, *F. nygamai*, and *F. sacchari* have a limited geographic distribution and/or are associated with specific climatic conditions. For some of the species, distributions

of environmental and clinical strains are concordant (e.g., *F. andiyazi*, *F. subglutinans*, and *F. thapsinum*), whereas in others the reported clinical cases indicate an expansion outside previously known borderlines (e.g., *F. acutatum* and *F. napiforme*). *Fusarium nygamai*, known from hot and arid climates, caused a disseminated infection in a patient from The Netherlands in Northern Europe, but this infection was presumably contracted during a recent holiday in Egypt [75].

Fusarium sporotrichioides is closely related to *Fusarium poae* and *F. langsethiae* and is located in the *Gibberella*-clade of *Fusarium* [91]. The species is known to produce T-2 and HT-2 mycotoxins [91], and thus far, two localized infections have been described: an ulcerative dermatitis [92], and a pedal lesion in a diabetic [93].

Outside the above-described species complexes, a few other *Fusarium* species have been implicated in humans and other mammals. A strain of *F. avenaceum* caused an infection of the claw of a dog, finally leading to osteomyelitis [94]. Both *F. lateritium* and *F. polyphialidicum* were recorded causing keratitis [54, 95], while *F. lateritium* also caused a disseminated infection in an HIV-patient [96].

Conclusions

Within the group of fungi we elect to call *Fusarium*, many species and species complexes have been involved in opportunistic human infections. Species recognition by morphological characters is difficult, as strains may be slow in forming distinguishing structures and in particular, clinical isolates may be pionnotal. Observed fusarioses range from onychomycoses, skin infections and keratitis, mainly in healthy individuals, to deep local and disseminated infections in the immunocompromised. The disseminated infections predominately occur especially in leukemic patients and have a high mortality rate. Many of the opportunistic species complexes seem, in principle, able to cause the whole range of fusariosis types. However, significant differences exist in the main species complexes in classes of infections observed locally (Table 1).

An important question is whether we need to identify the etiological agent of a fusariosis to the species level. In general, as many other members of the order Hypocreales, *Fusarium* species are highly refractory to antifungal therapy. Only few antifungal drugs—amphothericin, voriconazole and terbinafine—seem effective [89], and variation can be observed between and within species and species complexes [e.g., [25, 29, 48, 67]. To reveal small differences in susceptibility between clinically relevant *Fusarium* species, precise identification of siblings is recommended.

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Compliance with Ethics Guidelines

Conflicts of Interest Anne D. van Diepeningen, Abdullah M.S. Al-Hatmi, Balázs Brankovics, and G. Sybren de Hoog have declared no conflicts of interest.

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