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Research note

A prospective international *Aspergillus terreus* survey: an EFISG, ISHAM and ECMM joint study

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ABSTRACT

Objectives: A prospective international multicentre surveillance study was conducted to investigate the prevalence and amphotericin B susceptibility of *Aspergillus terreus* species complex infections.
Methods: A total of 370 cases from 21 countries were evaluated.
Results: The overall prevalence of *A. terreus* species complex among the investigated patients with mould-positive cultures was 5.2% (370/7116). Amphotericin B MICs ranged from 0.125 to 32 mg/L, (median 8 mg/L).
Conclusions: *Aspergillus terreus* species complex infections cause a wide spectrum of aspergillosis and the majority of cryptic species display high amphotericin B MICs. **B. Risslegger, Clin Microbiol Infect 2017;23:776.e1–776.e5**

Introduction

Aspergillus terreus species complex holds an exceptional position within the aspergilli, as it appears to be a rare pathogen of infection and displays polyene resistance [1–3]. *Aspergillus terreus* is a common cause of invasive aspergillosis at the M. D. Anderson Cancer Center in Houston, TX, USA, and the University Hospital of Innsbruck, Austria [3–5]. Almost no data are available on how frequently this species occurs elsewhere and whether differences within amphotericin B susceptibility exist. Our objective was to investigate the global prevalence of *A. terreus* species complex in fungal diseases and to survey amphotericin B susceptibility.

Materials and methods

An international surveillance network was established on behalf of the European Fungal Infection Study Group, the International Society for Human and Animal Mycology *Aspergillus terreus* working group, and the European Confederation of Medical Mycology. Thirty-eight centres from 21 countries participated. Each centre collected isolates and reported the number of *A. terreus* and fungal pathogens detected for 12 consecutive months (2014–2015). Patient characteristics, epidemiological data and antifungal treatment were documented through an online questionnaire using the www.clinicalsurveys.net online platform. Patients were classified according to the European Organization for the Research and Treatment of Cancer/Mycoses Study Group consensus definitions [6] by the participating centres. Unless otherwise noted, the isolation of *A. terreus* from sputa of non-neutropenic patients was categorized as colonization. Isolates were sent to the Division of Hygiene and Medical Microbiology for molecular species identification [7,8] and susceptibility testing according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) method [2]. *Aspergillus terreus* strains were identified to the cryptic species level by sequencing partial β-tubulin and applying a validated in-house database owned by Jos Houbraken, CBS Fungal Biodiversity Centre, Utrecht, the Netherlands. An amphotericin B epidemiological cut-off value of 4 mg/L was set for *A. terreus* [2].

This study was approved by the Ethics Commission of the Medical University of Innsbruck (UN4926).

Results

A total of 461 patients were enrolled, of which 91 were excluded because of insufficient patient documentation ($n = 45$) or lack of fungal isolates ($n = 46$) being available. Consequently, this survey comprises 370 eligible cases with an equal number of corresponding *A. terreus* isolates. Cases were derived from Europe ($n = 261$), followed by Middle East ($n = 70$), India ($n = 19$), South America ($n = 10$) and North America ($n = 10$) (Fig. 1). *Aspergillus terreus* sensu stricto ($n = 315$), *Aspergillus citrinoterreus* ($n = 36$), *Aspergillus alabamensis* ($n = 6$), *Aspergillus hortai* ($n = 10$), *Aspergillus floccosus* ($n = 1$) and *Aspergillus neoafricanus* ($n = 1$) were identified. One isolate (*A. terreus 1214*) was closest to *A. alabamensis* and might represent a new species. Hence, cryptic species accounted for 14.9% (55/370) with *A. citrinoterreus* (36/55, 65.5%) being dominant.

Amphotericin B MICs ranged from 0.125 to 32 mg/L for *A. terreus* sensu stricto; MICs for all cryptic species were consistently higher, ranging from 2 to 32 mg/L (see Table 1). According to the EUCAST

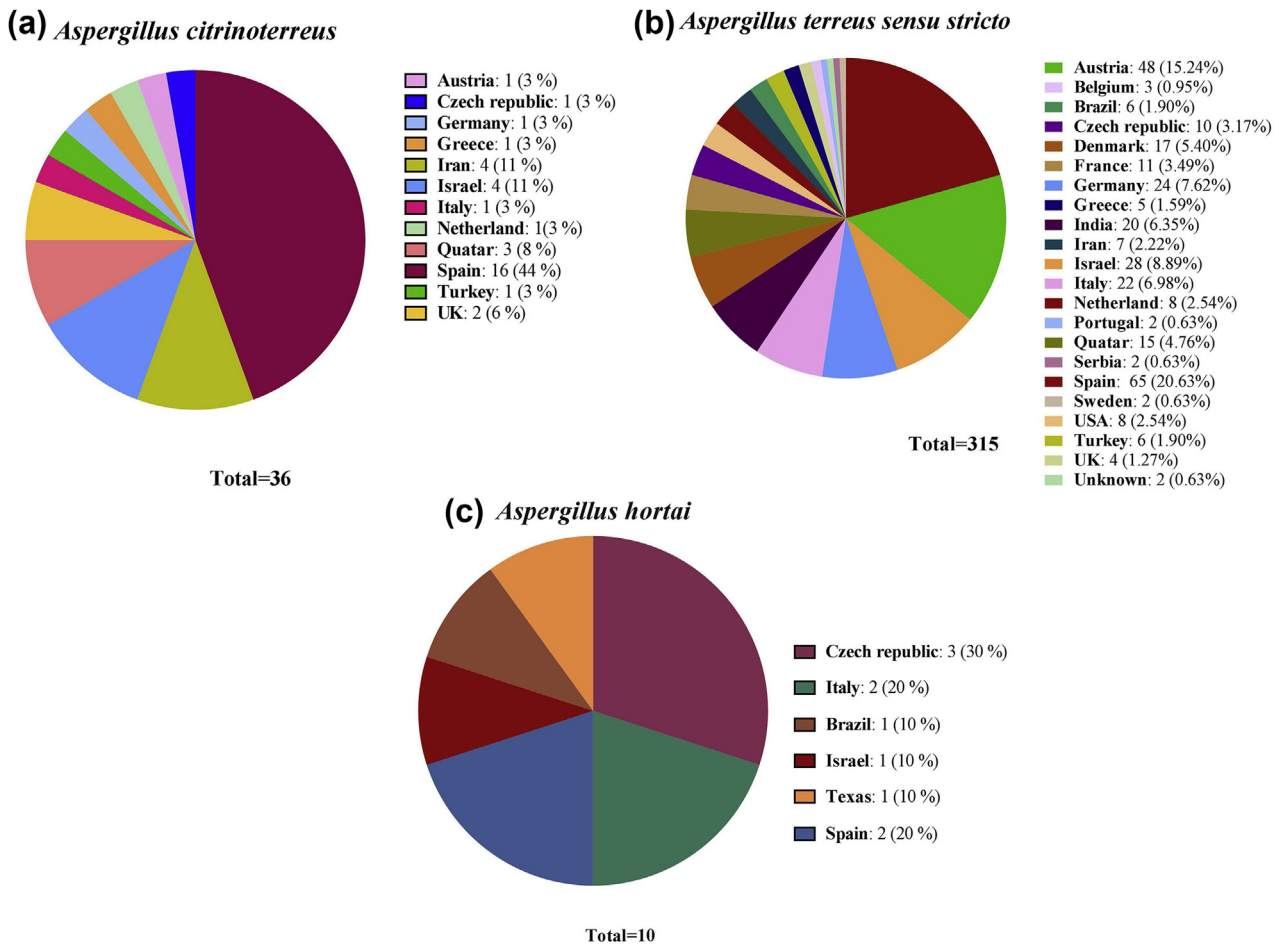

Fig. 1. Overview of countries and Aspergillus terreus species complex isolated numbers collected during the study period: (a) *Aspergillus citrinoterreus*, (b) *Aspergillus terreus* sensu stricto, (c) *Aspergillus hortai*.

cut-off values, 194 isolates (52.4%) were classified as non-wild types. A proportion of 6.3% ($n = 20$) of the *A. terreus* sensu stricto isolates displayed lower MICs, ranging from 0.25– to 0.5 mg/L. Isolates were predominantly acquired from Spain ($n = 85$) and Austria ($n = 49$) (Fig. 1).

Underlying diseases are described in Table 2. Species distribution did not differ per underlying disease and specimen investigated (Table 2). Diseases comprised invasive aspergillosis (25.1%), allergic bronchopulmonary aspergillosis (12.4%), chronic aspergillosis (11.4%), chronic obstructive pulmonary disease exacerbation (5.5%), aspergilloma (3.7%), otitis externa (2.5%) and wound infections (0.7%). In all, 25.1% and 27.3% of the patients suffered from proven and probable invasive aspergillosis, 28.6% were colonized, 10.1% had onychomycosis and 8.9% had mycological documented diseases such as otitis externa or aspergilloma.

Using a random effects model the pooled estimated proportion was 5.6% (95% CI 3.8–7.7) with $I^2 = 92\%$ ($p < 0.0001$) and the proportions ranged from 0.0% to 58.3%. These calculations were

Table 1
Distribution of amphotericin B MICs against *Aspergillus terreus* species complex isolates collected during the study period and tested according to EUCAST methodology

Aspergillus species	Amphotericin B MICs, mg/L								
	0.125	0.25	0.5	1	2	4	8	16	32
A. terreus sensu stricto	3	7	10	14	36	81	86	55	23
A. citrinoterreus					3	13	8	7	5
A. hortai					1	2	5	2	
A. alabamensis					2	3	1		
A. floccosus						1			
A. neoafricanus									1
Potential new species							1		

Table 2
Species distribution of Aspergillus terreus species complex isolated from the various human specimens

Aspergillus species	Specimens, total numbers						
	Sputa	Bronchoalveolar lavages and tracheal secretions	Body fluids	Biopsies	Swabs	Others[a]	Total
A. terreus sensu stricto	126	65	53	33	17	21	315
A. citrinoterreus	14	7	3	5	3	4	36
A. hortai	4	2			1	3	10
A. alabamensis	3	2			1		6
A. floccosus					1		1
A. neoafricanus						1	1
Potential new species				1			1
Total	147	76	56	39	23	29	370

[a] Aspirates, wound secretions, nails.

performed with MedCalc 16.8.4. Four reference centres and one centre dealing with onychomycosis only were excluded from the analysis.

A total of 68 patients received antifungal treatment at the time of fungal diagnosis, 12 were treated with amphotericin B or liposomal amphotericin B. The remaining 56 received combinations of azoles and echinocandins and improved. Only one patient died due to the *A. terreus* infection. No information on outcome was available in 13 patients.

Discussion

Infections due to *A. terreus* species complex were detected in 21 countries and 38 centres with an overall prevalence of 5.2% among mould infections. High amphotericin B MICs were frequently observed and crossed all cryptic species. Infections were reported from all over the world with three main specific findings. First, Spain and Austria were the countries with the highest density of *A. terreus* isolates collected. Second, the number of *A. terreus* cases enrolled varied from centre to centre, and displayed a broad range from zero to several cases per country. Third, it seems that few susceptible amphotericin B variants exist within *A. terreus* sensu stricto.

Taking into account the differences in the environmental conditions, host-related characteristics, and the use of antifungal agents, it is not possible to conclude on the particular biogeography of *A. terreus* species complex. In addition, one has to be aware that data collected may depend on the quality of care, patient demographics, infection control practices, frequency of specimen collection and laboratory methodology. Hence, further studies are needed to determine whether specific risk and/or environmental factors are associated with infections by *A. terreus.*

It was notable that *Aspergillus* section *Terrei* was most commonly isolated from patients suffering from chronic lung diseases (39.2%). No similar data have been reported [9] and it remains to be seen whether *A. terreus* reflects an emerging pathogen of this disease entity.

Aspergillus terreus is a poor target for amphotericin B and hence is reported as resistant [2]. The role of isolates with MICs <0.5 mg/L needs further evaluation. The pharmacodynamic target may be attained with the standard amphotericin B dose for isolates with MICs $\leq$0.25 mg/L [10] and infections were successfully treated with high-dose liposomal amphotericin B [11].

Cryptic species accounted for 14.8%, with *A. citrinoterreus* being the most prevalent. Although the clinical implications of sibling species of *A. terreus* are less well understood, our study confirms that these species are generally resistant to amphotericin B and are causing a wide spectrum of invasive and non-invasive aspergillosis. Guinea et al. [12] observed *A. citrinoterreus* acting mainly as a co-pathogen with *Aspergillus fumigatus*.

Our study has some limitations. We do not have a comprehensive worldwide *A. terreus* survey network and some countries are missing for a variety of reasons. Also, generally, the diagnosis of fungal infections is difficult to obtain and may often be based on detection of biomarkers rather than on isolation of the infecting organism. Hence, some cases may have been missed and chronic lung diseases were not specified in more detail. Further, we have no data available on co-infections that may complicate diseases. The centres included represent a convenience sample. However, this is the largest and geographically most diverse study on the contemporary epidemiology of *A. terreus* species complex infections worldwide.

Our study shows that *A. terreus* sensu stricto is widely distributed in climatically divergent countries, and that cryptic species display high amphotericin B MICs. The *A. terreus* species complex was most commonly isolated from patients suffering from chronic lung diseases (39.2%).

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Transparency declaration

We declare that we have no conflicts of interest related to this study. CLF received research grants, travel grants or honoraria as a speaker or advisor from Gilead Sciences, Pfizer, Schering Plough, MSD and Basilea. VAA received research grants or honoraria as a speaker or advisor from Astellas, Pfizer and Schering Plough, MSD. WB received honoraria as a speaker from Pfizer, Schering Plough and MSD. CF received research grants or honoraria as a speaker or advisor from Astellas, Gilead Sciences, MSD and Basilea. AH received travel grants from Astellas and served on the advisory board of Gilead. EJ received travel grants or honoraria as a speaker or advisor from Bio-Rad, Gilead Sciences, Pfizer, Schering Plough and MSD. DPK has received research support from Pfizer, Astellas Pharma, honoraria from Astellas, Merck, Pfizer and he serves on the advisory boards of Merck, Amplyx, Cidara and F2G. JFM received grants from Astellas, Basilea and Merck. He has been a consultant to Astellas, Basilea and Merck and received speaker's fees from Merck, United Medical and Gilead. ALC received educational grants from Pfizer, Gilead and United Medical and research grant from Pfizer, Astellas. MCA received research grants/contract work (paid to SSI) from Amplyx, Basilea, Cidara, F2G, Gilead, Pfizer & T2Candida, speaker honoraria from Astellas, Basilea, Gilead, MSD, Novartis, Pfizer and T2Candida. NK has received research support from Pfizer, honoraria from Astellas, Merck and Pfizer, and he serves on the advisory boards of Merck and Pfizer. OAC is supported by the German Federal Ministry of Research and Education, has received research grants from Actelion, Aranis, Astellas, AstraZeneca, Basilea, Bayer, Cidara, Duke University (NIH UM1AI104681), F2G, Gilead, GSK, Leeds University, MedPace, Melinta Therapeutics, Merck/MSD, Miltenyi, Pfizer, Rempex, Roche, Sanofi Pasteur, Scynexis, Seres Therapeutics, The Medicine Company, is a consultant to Anacor, Amplyx, Actelion, Astellas, Basilea, Cidara, Da Volterra, F2G, Gilead, Inositec AG, Janssen Pharmaceuticals, Matinas, Menarini, Merck/MSD, Paratek Pharmaceuticals, Scynexis, Seres, Summit, Vical, Vifor and received lecture honoraria from Astellas, Basilea, Gilead and Merck/MSD. BW received research support from Pfizer, travel grants or honoraria as a speaker or advisor from Gilead Sciences, Pfizer, Astellas, MSD and Basilea. LK received a grant from Gilead and has been an adviser to Astellas, Gilead, Schering-Plough, has received research grants from Gilead, Merck, Sharpe & Dohme, Schering-Plough and has received honoraria for educational lectures from Gilead, Pfizer, Merck, Sharpe & Dohme, Schering-Plough and Janssen. AMT received research support from Gilead Sciences, travel grants or honoraria as speaker from Gilead Sciences, Pfizer, Astellas. KL has received research grants from Gilead, MSD and Pfizer, received travel support from MSD, Pfizer and Gilead and received lecture honoraria from Gilead, MSD and Pfizer. SAA received Investigator Initiated Research grant support from Pfizer and speaker honoraria or travel grants from Astellas, Gilead, Merck and Pfizer. SO received research grants from Pfizer and Astellas, honoraria as advisor from MSD, Astellas Pharma and Gilead Sciences. ER reports grants, and non-financial support from Astellas, Pfizer, Gilead and Merck, outside the submitted work. AAI received

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References

[1] Perkhofer S, Lass-Flörl C, Hell M, Russ G, Krause R, Hönigl M, et al. The Nationwide Austrian *Aspergillus* Registry: a prospective data collection on epidemiology, therapy and outcome of invasive mould infections in immunocompromised and/or immunosuppressed patients. Int J Antimicrob Agents 2010;36:531–6.

[2] Arendrup MC, Cuenca-Estrella M, Lass-Flörl C, Hope WW. European Committee on Antimicrobial Susceptibility Testing Subcommittee on Antifungal Susceptibility Testing (EUCAST-AFST). EUCAST technical note on *Aspergillus* and amphotericin B, itraconazole, and posaconazole. Clin Microbiol Infect 2012;18:E248–50.

[3] Lass-Flörl C, Grif K, Mayr A, Petzer A, Gastl G, Bonatti H, et al. Epidemiology and outcome of infections due to *Aspergillus terreus*: 10-year single center experience. Br J Haematol 2005;131:201–7.

[4] Lass-Florl C, Grif K, Kontoyiannis DP. Molecular typing of *A. terreus* isolates collected in Houston, Texas and Innsbruck, Austria: evidence of great genetic diversity. J Clin Microbiol 2007;45:2686–90.

[5] Lackner M, Coassin S, Haun M, Binder U, Kronenberg F, Haas H, et al. Geographically predominant genotypes of *Aspergillus terreus* species complex in Austria: a microsatellite typing study. Clin Microbiol Infect 2016;22:270–6.

[6] De Pauw B, Walsh TJ, Donnelly JP, Stevens DA, Edwards JE, Calandra T, et al. Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. Clin Infect Dis 2008;46:1813–21.

[7] Balajee SA, Baddley JW, Peterson SW, Nickle D, Varga J, Boey A, et al. ISHAM Working Group on *A. terreus*. *Aspergillus alabamensis*, a new clinically relevant species in the section *Terrei*. Eukaryotic Cell 2009;8:713–22.

[8] Kathuria S, Sharma C, Singh PK, Agarwal P, Agarwal K, Hagen F, et al. Molecular epidemiology and in-vitro antifungal susceptibility of *Aspergillus terreus* species complex isolates in Delhi, India: evidence of genetic diversity by amplified fragment length polymorphism and microsatellite typing. PLoS One 2015;10:e0118997.

[9] Denning DW, Cadranel J, Beigelman-Aubry C, Ader F, Chakrabarti A, Blot S, et al. Chronic pulmonary aspergillosis: rationale and clinical guidelines for diagnosis and management. Eur Respir J 2016;47:45–68.

[10] Elefanti A, Mouton JW, Verweij PE, Zerva L, Meletiadis J. Susceptibility breakpoints for amphotericin B and *Aspergillus* species in an in vitro pharmacokinetic-pharmacodynamic model simulating free-drug concentrations in human serum. Antimicrob Agents Chemother 2014;58:2356–62.

[11] Lewis RE, Albert NP, Liao G, Wang W, Prince RA, Kontoyiannis DP. High-dose induction liposomal amphotericin B followed by de-escalation is effective in experimental *Aspergillus terreus* pneumonia. J Antimicrob Chemother 2013;68:1148–51.

[12] Guinea J, Sandoval-Denis M, Escribano P, Peláez T, Guarro J, Bouza E. *Aspergillus citrinoterreus*, a new species of section Terrei isolated from samples of patients with non-hematological predisposing conditions. J Clin Microbiol 2015;53:611–7.