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Analysis of Resistance In Antifungals (ARIA) - Surveillance of *Candida* spp. Isolates collected from Europe in 2019

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Introduction

ARIA is an new annual global surveillance initiative collecting yeast and fungal isolates from hospitals worldwide designed to determine resistance to antifungal agents and trends over time. The data presented here are specifically for *Candida* spp. collected from Europe in 2019.

Methods & Materials

Isolates (n=252) were collected from hospitals located in Europe, shipped to the IHMA Switzerland central laboratory, and re-identified by MALDI-TOF or molecular methods. The country of origin and number of each species collected is shown in Table 1.

MIC determinations were performed at a central laboratory following the Clinical and Laboratory Standards Institute (CLSI) broth microdilution method [1] using amphotericin B (AMB), anidulafungin (AFG), caspofungin (CFG), fluconazole (FLC), isavuconazole (IVC), micafungin (MFG), posaconazole (PSC) and voriconazole (VRC).

Percentage susceptibility (%S) or wild-type (%WT) were calculated according to CLSI breakpoints [2] or epidemiological cut-off values (ECVs) [3],

Table 1. Breakdown of *Candida* spp. collected by country

Species	ALL	Czech Republic	Germany	Italy	Turkey
C. glabrata	68	17	19	19	13
C. albicans	54	14	11	14	15
C. parapsilosis	45	2	1	21	21
C. tropicalis	38	8	3	19	8
C. krusei	21	3	8	2	8
C. lusitaniae	9	2		1	6
C. guilliermondii	8		1	7	
C. kefyr	7		4		3
C. dubliniensis	2		1		1
Grand Total	**252**	**46**	**48**	**83**	**75**

Results

Table 2. Summary MIC and susceptibility data for all countries combined.

		AFG	AMB	CFG	FLC	ISA	MFG	PSC	VRC
C. albicans (54)	MIC_{50}	0.03	0.5	0.03	0.25	0.008	0.015	0.06	0.008
	MIC_{90}	0.12	1	0.12	1	0.03	0.12	0.25	0.03
	%S (WT)	98.1	(100.0)	100.0	96.3	-	100.0	(68.5)	100.0
C. glabrata (68)	MIC_{50}	0.25	0.5	0.12	4	0.03	0.03	0.5	0.03
	MIC_{90}	0.5	1	0.25	32	0.25	0.12	1	1
	%S (WT)	42.6	(100.0)	89.7	-	-	86.8	(100.0)	(85.3)
C. guilliermondii (8)	MIC_{50}	1	0.25	0.5	4	0.25	0.25	0.25	0.12
	MIC_{90}	-	-	-	-	-	-	-	-
	%S (WT)	87.5	(100.0)	100	(87.5)	-	100	(100.0)	-
C. kefyr (7)	MIC_{50}	0.25	0.5	≤0.06	0.5	≤0.008	0.12	0.06	≤0.008
	MIC_{90}	-	-	-	-	-	-	-	-
	%S (WT)	(100.0)	(100.0)	-	(100.0)	-	(100.0)	(100.0)	-
C. krusei (21)	MIC_{50}	0.12	1	0.25	16	0.25	0.25	0.5	0.12
	MIC_{90}	0.25	1	0.5	32	0.25	0.5	0.5	0.25
	%S (WT)	100.0	(100.0)	81.0	-	-	85.7	(95.2)	100.0
C. lusitaniae (9)	MIC_{50}	0.5	0.25	0.25	≤0.25	≤0.008	0.12	0.06	≤0.008
	MIC_{90}	-	-	-	-	-	-	-	-
	%S (WT)	(100.0)	(100.0)	(100.0)	(100.0)	-	-	(88.9)	-
C. parapsilosis (45)	MIC_{50}	2	0.5	0.5	0.5	0.008	1	0.06	0.008
	MIC_{90}	2	1	0.5	16	0.06	2	0.25	0.5
	%S (WT)	91.1	(100.0)	100.0	66.7	-	95.6	(97.8)	80.0
C. tropicalis (38)	MIC_{50}	0.03	1	0.06	1	0.03	0.06	0.25	0.03
	MIC_{90}	0.06	1	0.12	2	0.12	0.12	0.5	0.12
	%S (WT)	100.0	(100.0)	100.0	92.1	-	100.0	(42.1)	94.7

MIC_{50}/MIC_{90} = concentration required to inhibit 50%/90% of population
Grey shading = <90% S or WT

Table 3. Breakdown of *Candida* spp. by resistance.

Species	Sum of NWT & RES				TOTAL
	0	1	2	3	
C. glabrata	49	14	5		68
C. albicans	37	16	1		54
C. parapsilosis	34	10		1	45
C. tropicalis	16	20	1	1	38
C. krusei	20	1			21
C. lusitaniae	8	1			9
C. guilliermondii	7	1			8
C. kefyr	7				7
C. dubliniensis	1	1			2
Grand Total	**179**	**64**	**7**	**2**	**252**

NWT, non-wild-type; RES, resistant

Figure 1. Antifungal % susceptibility of *C. albicans* by European country.

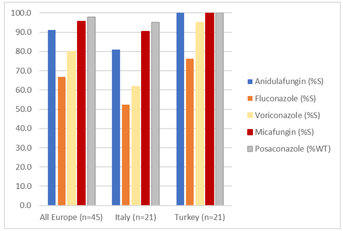

Figure 2. Antifungal % susceptibility of *C. glabrata* by European country.

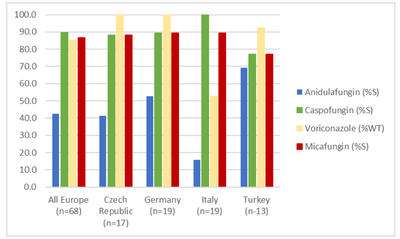

Figure 3. Antifungal % susceptibility of *C. parapsilosis* by European country.

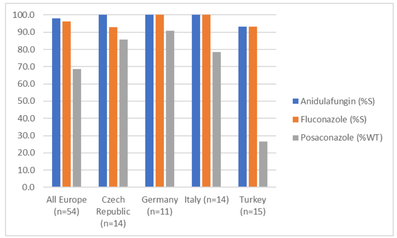

Figure 4. Antifungal % susceptibility of *C. tropicalis* by European country.

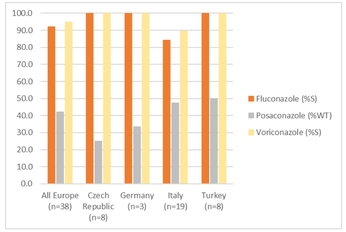

Table 4. Isolates resistant or non-wild-type to two or more antifungals.

Species	Country	AMB	MFG	AFG	FLC	PSC	VRC	CFG	RES/NWT count
C. glabrata	Italy	WT	SUS	INT	RES	WT	NWT	SUS	2
	Italy	WT	SUS	RES	INT	WT	NWT	SUS	2
	Italy	WT	SUS	RES	INT	WT	NWT	SUS	2
	Italy	WT	SUS	RES	INT	WT	NWT	SUS	2
	Turkey	WT	SUS	RES	INT	WT	NWT	SUS	2
C. albicans	Czech Republic	WT	SUS	SUS	RES	NWT	SUS	SUS	2
C. tropicalis	Italy	WT	SUS	SUS	RES	NWT	RES	SUS	3
	Italy	WT	SUS	SUS	RES	NWT	INT	SUS	2
C. parapsilosis	Italy	WT	SUS	SUS	RES	NWT	RES	SUS	3

RES, resistant; INT, intermediate; SUS, susceptible; NWT, non-wild-type; WT, wild-type

Results summary

- All isolates tested had WT MICs for AMB (Table 2).
- Breakpoints or ECVs are not available for IVC but MIC_{90} values were 0.25 mg/L or lower against all *Candida* spp.
- Only *C. kefyr* (n=7) was 100% S or WT to all antifungals tested (Table 2).
- *C. albicans* (n=54) were >90% S or WT to all antifungals except PSC where 68.5% were WT overall (Table 1). PSC WT varied by country ranging from 26.7% in Turkey to 90.9% in Germany (Fig. 1).
- *C. glabrata* (n=68) were 100% WT to PSC but <90% S or WT to AFG, CFG and VRC (Table 2). AFG %S was low in all countries, especially Italy, and %S to VRC and MFG was lower in Turkey than other countries (Fig. 2).
- *C. parapsilosis* (n=45) were 100% S to CFG (Table 2) but <90% S to FLC or VRC. Only a small number of isolates were collected from the Czech Republic and Germany (Table 1) and all were fully S or WT. Only 52.4 % and 66.7% of isolates from Italy were susceptible to FLC or VRC, respectively. In contrast, isolates from Turkey were 95.2% S to VRC but 76.2% S to FLC (Fig. 3).
- *C. tropicalis* (n=38) were 100% S to AFG, CFG and MFG, >90% WT to FLC and VRC but only 42.1% WT to PSC (Table 2). The %S to FLC and VRC was 100% in each country except Italy where S was 84.2% and 89.5%, respectively. The %WT to PSC was low in all countries ranging from 25.0% in the Czech Republic to 50.0% in Turkey (Fig. 4).
- All *C. krusei* (n=21) were >95% S or WT to AFG, PSC and VRC (Table 2). Insufficient isolates were collected to analyse by country.
- The number of *C. guilliermondii* (n=8), *C. lusitaniae* (n=9), and *C. dubliniensis* (n=2) collected were small (Table 1) and insufficient to analyse by country. All except 1 *C. guilliermondii*, 1 *C. lusitaniae* and 1 *C. dubliniensis* were fully S or WT.
- Within the Europe collection 179 isolates (71.0%) were S or WT to all antifungals tested and a further 64 (25.4%) were resistant (RES) or non-WT to 1 antifungal only (Table 3). The remaining 9 isolates were RES or non-WT to 2 or 3 antifungals (Table 3). These isolates are listed in Table 4.
- The majority of the more resistant isolates (7 of 9) were from Italy (Table 4).

Conclusions

- Most *Candida* spp. were highly susceptible to the antifungal agents tested, but some non-susceptibility was apparent - especially in Italy.
- These data are important to help clinicians make informed choices for antifungal agent therapy.
- As ARIA evolves it will become an essential tool to monitor and assess changes in antifungal resistance (for *Candida* spp., other yeasts and filamentous fungi) by geography and over time.

References and Acknowledgements

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