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P1767 EUCAST susceptibility testing of isavuconazole: MIC data for contemporary Danish clinical mould isolates

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Background: Isavuconazole is the newest medical azole and has activity against various yeasts and moulds. We investigated EUCAST MICs for isavuconazole and comparators against 429 mould isolates obtained during 2016-2017.

Materials/methods: E.Def 10.1 azole-R screening of *Aspergillus fumigatus* followed by E.Def 9.3.1 testing of non-S *A. fumigatus* and all other moulds were performed for isavuconazole, voriconazole, posaconazole, itraconazole, amphotericin B and terbinafine. MICs are expressed in mg/L throughout. EUCAST ECOFFs/breakpoints were adopted for wild-type/susceptibility classification. *CYP51A* sequencing was performed for non-wild-type/resistant *A. fumigatus* and *A. terreus*. QC isavuconazole MIC ranges were: *A. flavus* ATCC204304: 1-2 and *A. fumigatus* ATCC204305 0.5-2, respectively.

Results: *Aspergillus* accounted for 90% of the isolates (Table). Overall, 24/387 (6.2%) *Aspergillus* isolates were non-wild-type. Among non-aspergillus moulds, low MICs (≤0.25) were observed against *M. canis, T. rubrum, T. interdigitale, Circinella muscae* and *Saprochaete capitata,* and low activity (MIC ≥16) against *S. apiospermum, Fusarium* spp. and 4/16 Mucorales isolates (*Mucor circinelloides* (n=2), *Rhizopus oryzae* and Mucorales species).

Among *A. fumigatus,* 10/322 (3.1%) were resistant and 30/322 (9.3%) non-wild-type, whereas 6/12 (50%) *A. terreus* were isavuconazole resistant and non-wild-type.

Among *A. fumigatus* isolates with an MIC=2, 17/20 (85%) were susceptible to itraconazole, posaconazole and voriconazole, whereas three (15%) were itraconazole (MIC>16) and posaconazole (MIC>4) resistant, including one also voriconazole intermediate. Two had Cyp51A alterations (M220K and G54A). Among *A. fumigatus* with MIC>2, 8/10 had Cyp51A alterations (TR34/L98H (n=3), TripR34/L98H (n=1), TR120/F46Y/M172V/E427K (n=1), G432S (n=1), G448S (n=2)) and all were non-susceptible to itraconazole, posaconazole and voriconazole. Thus, 13/322 (4%) *A. fumigatus* were unlikely good targets for isavuconazole, including 4/13 due to an environmental resistance mechanism.

Among *A. terreus* isolates with MIC=2, 4/4 had wild-type *CYP51A* and susceptibility to the other three azoles. In contrast, 2/2 with MIC>2 harboured an M217I alteration and were unlikely good targets for isavuconazole (2/12=17% of all *A. terreus*).

Conclusions: Acquired isavuconazole resistance was infrequent except in *A. terreus* and was, when present, associated with cross-resistance to other azoles. Resistant *A. fumigatus* were of environmental origin in one-third of the cases. Isavuconazole displayed activity against several other species including *Trichophyton,* a species with increasing terbinafine resistance.

Table. Susceptibility to isavuconazole among 429 mould isolates. Bold indicates isolates with non-wt susceptibility, grey shading indicates resistant.

	N	*N%*	S	MIC (mg/L)									Range	Modal MIC
				≤0.125	0.25	0.5	1	2	4	8	16	>16		
Aspergillus all	387	90%	232	1	4	25	53	38	13	14	7		≤0.125-16	
Most common *Aspergillus*														
A. flavus complex	16	4%				2	7	6	**1**				0.5-4	1
A. fumigatus	322	75%	232	1	1	18	40	20	**1**	**5**	**4**		≤0.125-16	1
A. nidulans complex	1	0%			1								0.25	
A. niger complex	25	6%					2	7	9	**6**	**1**		1-16	4
A. terreus	12	3%				3	3	**4**			**2**		0.5-16	2
Other *Aspergillus*	11	3%			2	2	1	1	2	3			0.25-8	
Fusarium	14	3%									1	13	16->16	
Dermatophytes	9	2%		5	2		1	1					≤0.125-2	
Mucorales	16	4%			1		1	4	3	3	4		0.25-16	
Other moulds	3	1%		1							2		≤0.125-16	

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