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Azole-resistant Aspergillus fumigatus at a university hospital in Belgium: a laboratory-based surveillance

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Background: Azole-resistant *Aspergillus fumigatus* is an emerging worldwide problem with major clinical implications. A clinical case of *A. fumigatus* containing the TR_{46}/Y121F/T289A mutation in the *cyp51A* gene was detected in 2013 at Hôpital Erasme in Brussels. A laboratory-based surveillance of unselected *A. fumigatus* was set up in order to determine the azole-resistance frequency and resistance mechanisms.

Material/methods: From June 2015 to October 2016, 212 *A. fumigatus* isolated from 109 patients hospitalized at Hôpital Erasme were screened by VIPcheck™ azole-resistance detection 4 wells-plates containing voriconazole, itraconazole and posaconazole. All isolates able to grow on any one of the azole-containing wells were further investigated for their minimal inhibitory concentrations (MICs) by Sensititre YeastOne, as well as by *cyp51A*, *cyp51B* and *hapE* sequencing. Epidemiological cutoff's based on CLSI guidelines were used for interpretation of the MIC values (0.5 µg/mL for posaconazole, and 1 µg/mL for voriconazole and itraconazole). Demographic and clinical data were collected from patient's charts.

Results: Twenty-two *A. fumigatus* isolates (10%) from 14 patients (13%) were azole-resistant by VIPcheck™. All isolates showed MICs higher than the epidemiological cut-off values for at least one of the three triazoles tested (**Table 1**). *cyp51A* mutations were observed in 20 *A. fumigatus* isolates from 12 patients (11%). The TR_{34}/L98H was the most prevalent, followed by TR_{46}/Y121F/T289A. The N248K mutation was observed in one strain. One patient harboured *A. fumigatus* isolates with two different mutations: TR_{34}/L98H and G448S. No mutations were observed in two cases. An isolate with TR_{34}/L98H showed also a deletion in the *cyp51B* promotor. No isolates showed mutations at *hapE*.

All patients but one harboring azole-resistant *A. fumigatus* were colonized: 30% cystic fibrosis patients and 30% lung transplant patients. One heart transplant patient was diagnosed for invasive aspergillosis, and treated with voriconazole. Six-weeks after the treatment, *Aspergillus* with TR_{46}/Y121F/T289A was detected in this patient. Similarly, four other patients were exposed to azoles treatment or prophylaxis before resistant strains were detected. These patients carried *A. fumigatus* isolates with TR_{46}/Y121F/T289A, TR_{34}/L98H, TR_{34}/L98H and G448S, or N248K mutations.

Table 1. Mutations at *cyp51A* in azole-resistant *A. fumigatus.*

***cyp51A* mutations (n)**	**MIC range (µg/mL)**			**Number of patients**
	Voriconazole	**Itraconazole**	**Posaconazole**	
TR_{46}/Y121F/T289A (7)	8	0.5	0.25-0.5	4
TR_{34}/L98H (11)	1-2	0.5-16	0.5-1	7[a]
G448S (1)	1	0.5	0.25	1[b]
N248K (1)	8	0.5	0.5	1
No mutations (2)	1-2	0.5-1	0.25-0.5	2

[a] One patient had also a 8 nucleotide deletion at the *cyp51B* promotor.

[b] This patient harbored also TR_{34}/L98H *A. fumigatus.*

n, number of isolates.

Conclusions: This laboratory-based surveillance of unselected *A. fumigatus* showed a high prevalence (13%) of azole-resistance in *A. fumigatus* in our hospital in comparison with other studies. However, only 1 of 109 patients was suffering from azole-resistant invasive aspergillosis.