

**Azole resistance in *Aspergillus fumigatus* complex isolates causing aspergillosis in Madrid**

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**Objectives:** *Aspergillus fumigatus* complex comprises *A. fumigatus* sensu stricto (AfSS) and other morphologically indistinguishable species (cryptic species). Although azole-resistant AfSS isolates are increasingly reported in Europe, their frequency is unknown in Spain. We assessed the azole resistance rate in clinically significant *A. fumigatus* complex isolates collected from patients admitted to a tertiary hospital in Madrid. **Methods:** We studied *A. fumigatus* complex isolates from 150 patients with proven/probable invasive aspergillosis or aspergilloma (n=23/121/6) from 1999 to 2011. Isolates were from the lower respiratory tract (n=306), biopsy specimens (n=16), wounds (n=23), and other sites (n=8). In samples yielding multiple colonies, isolates were identified using beta-tubulin gene sequencing; only 1 isolate per species identified was selected. The antifungal susceptibility of 362 *A. fumigatus* complex isolates to itraconazole, voriconazole, and posaconazole was obtained using CLSI M38-A2. *cyp51A* was sequenced in AfSS isolates with high itraconazole, voriconazole, or posaconazole minimum inhibitory concentrations (MICs) (>2/>2/>0.5 µg/ml). **Results:** The species were distributed as follows: AfSS (n=343), *A. lentulus* (n=9), *A. novofumigatus* (n=6), *A. viridinutans* (n=2), and *Neosartorya udagawae* (n=2). Most of the patients were infected by only 1 species (AfSS [n=143] or *A. lentulus* [n=2]). However, the remaining 5 patients were co-infected with multiple *A. fumigatus* complex species (2-4 species), and AfSS was always involved. Most patients infected by cryptic species were diagnosed from 2009 onward. Cryptic species isolates were less susceptible to azoles than AfSS (Table). In contrast, resistance in AfSS was rare; only 1/6 AfSS isolates in which *cyp51A* was sequenced had a mutation conferring resistance (G448). When AfSS with the mutation at G448 and isolates belonging to cryptic species were considered to be azole-resistant, 5.3% of patients were infected by azole-resistant isolates. This rate was even lower in patients infected only by AfSS (0.7%). **Conclusion:** Azole resistance was very low in AfSS isolates from patients with aspergillosis in Madrid. In contrast, the increasing frequency of *A. fumigatus* cryptic species from 2009 warrants further resistance monitoring.

		<b>Itraconazole</b>	<b>Voriconazole</b>	<b>Posaconazole</b>
	<b>N</b>	<b>MIC<sub>90</sub> (range)</b>	<b>MIC<sub>90</sub> (range)</b>	<b>MIC<sub>90</sub> (range)</b>
<b>Total</b>	362	1 (0.25-16)	1 (0.25-16)	0.5 (0.06-1)
<b><i>A. fumigatus</i> sensu stricto (AfSS)</b>	343	1 (0.25-4)	1 (0.25-16)	0.5 (0.06-1)
<b>Cryptic species</b>	19	16 (1-16)	8 (1-16)	1 (0.25-1)