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Fungal epidemiology

Surveillance, molecular identification and antifungal susceptibility of *Aspergillus* species in Madrid (Madrid *Aspergillus* resistance [MAR] study)

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Objectives: The emergence of *Aspergillus* species that are intrinsically resistant or have acquired resistance to antifungals was recently described, mainly in central Europe. Data regarding the incidence of these species, in other areas of the world, are scarce. We present the distribution of *Aspergillus* species and their antifungal resistance in a large collection of clinical isolates from patients colonized or infected with invasive aspergillosis (IA) in Spain.

Methods: Clinical *Aspergillus* species from 11 hospitals participating in an ongoing multicenter project (Madrid *Aspergillus* Resistance [MAR] study) were included. Isolates were screened for azole resistance using 4-well agar dilution plates. Patient information was collected and the azole-resistance was analyzed using standardized susceptibility testing (CLSI methodology), PCR amplification and gene sequencing. The prevalence of cryptic species and mixed IA was also assessed.

Results: A total of 497 isolates from 423 patients were tested (305 colonized and 118 with IA). *Aspergillus* species distribution in colonized patients/patients with IA was as follows: A. section *Fumigati* (59%/60%), A. section *Flavi* (13%/16%), A. section *Terrei* (9%/9%), A. section *Nigri* (9%/8%), A. section *Nidulantes* (8%/5%), A. section *Usti* (1%/1%) and A. section *Versicolores* (1%/1%).

The percentage of cryptic species was similar in both groups (5.2% in colonized patients and 6.5% in patients with IA). The 36 cryptic species identified were as follows: A. section *Fumigati* (*A. lentulus* [13], *Neosartorya udagawae* [1], *A. fumigatiaffinis* [1], *A. novofumigatus* [1], *A. felis* [1]). A. section *Usti* (*A. calidoustus* [5], *A. puniceus* [1], *A. egyptiacus* [1]). A. section *Flavi* (*A. tamari* [1]). A. section *Nigri* (*A. tubingensis* [5]). A. section *Nidulantes* (*E. quadrilineata* [1], *E. nidulans* [3]). A. section *Terrei* (*A. citrinoterreus* [1]). A. section *Versicolores* (*A. creber* [1]).

Among the 118 total patients with IA, 85 (72%) were caused by a single *Aspergillus* species and 33 (28%) by mixed infection. The percentage of mixed IA in all the hospitals varied from 0% to 53.3%. The 4 fungal combinations most frequently involved in mixed IA were *A. fumigatus* + A. section *Flavi* (27.7% of cases), *A. fumigatus* + A. section *Nigri* (18.2%), *A. fumigatus* + A. section *Nidulantes* (15.2%) and *A. fumigatus* + A. section *Terrei* (12.1%).

Six patients, from different hospitals, were infected by multi-azole-resistant *A. fumigatus* 'sensu stricto' (5 had the TR34/L98H mutation in the *cyp51A* gene and 1 the Y121F point mutation (first report in Spain to our knowledge).

Conclusion: In the Madrid region, a 6.5% of cases of IA were caused by cryptic species showing high *in vitro* MICs to antifungal agents. Of note, a high percentage of patients with IA due to mixed infection generally had a worse prognosis.

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