Epidemiology of Aspergillus resistance in Belgium: results of the Belgian Mycoses Surveillance Network

(Leuven, Brussels, Bruges, Ghent, Roeselare, Antwerp, Aalst, BE)

Introduction: Triazoles are the mainstay of therapy in Aspergillus infections. However, reports of azole resistance have emerged. As high resistance percentages are reported in our neighbouring country the Netherlands, a national Aspergillus surveillance program was set up to map the situation in Belgium. Materials and Methods: Clinically relevant Aspergillus isolates were prospectively collected with concomitant patient data from April 2011 to April 2012, in 18 Belgian hospitals. All isolates (one isolate per patient per month) were sent to University Hospitals Leuven for susceptibility testing following the CLSI M38-A2 protocol. Resistance was defined as a minimal inhibitory concentration (MIC) to itraconazole >2 mg/L, MIC voriconazole >2 mg/L or MIC posaconazole >0.5 mg/L. Resistant isolates were identified to the species level by beta-tubulin sequencing. Resistant Aspergillus fumigatus isolates were subjected to cyp51A sequencing to clarify the resistance mechanism. Results and Discussion: 220 isolates (192 A. fumigatus complex (87%), 13 A. flavus complex (6%), 10 A. niger complex (4.5%) and 5 other Aspergillus species (2.3%)) were included. These belonged to 185 patients: 39 with allergic bronchopulmonary aspergillosis (ABPA) (52 isolates), 124 with invasive aspergillosis (IA) (133 isolates), 17 with chronic aspergillosis or Aspergillus bronchitis (29 isolates) and 6 with single aspergilloma (6 isolates). One patient known with ABPA developed IA later in the surveillance. In IA, the main underlying illness was chronic obstructive pulmonary disease (26%) followed by hematological disease (24%) and solid organ transplantation (17%). Of 192 A. fumigatus complex isolates, 7 (from 7 patients) were pan-azole resistant (3.6%). All 7 were confirmed to the species level as A. fumigatus. Cyp51A typing revealed the TR34/L98H mutation in 6 isolates (4 IA, 1 ABPA, 1 Aspergillus bronchitis) and TR46/Y121F/T289A in one (Aspergillus bronchitis). 4/7 patients with resistant isolates were azole-naïve. 9 A. niger complex isolates were cultured from patients with IA, of which 8 were identified as A. tubingensis, which is intrinsically azole-resistant. Conclusion: In a prospective surveillance of clinically relevant Aspergillus isolates in Belgium, 3.6% pan-azole resistance was found in A. fumigatus, with TR34/L98H as the predominant resistance mechanism. However, one isolate harboured the TR46/Y121F/T289A resistance mechanism, which was only recently described in the Netherlands.