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Multiple-triazole-resistant aspergillosis. — Source link

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Retraction: Hussain HM, Hotopf M, Oyebode F. Atypical Antipsychotic Drugs and Alzheimer's Disease. N Engl J Med 2007;356:416.

TO THE EDITOR: A letter that I submitted to the *Journal* was published in the January 25 issue.[1] Because there has been concern about the provenance and authorship of that letter, I request that it be retracted.

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1. Hussain HM, Hotopf M, Oyebode F. Atypical antipsychotic drugs and Alzheimer's disease. N Engl J Med 2007;356:416.

Multiple-Triazole–Resistant Aspergillosis

TO THE EDITOR: The use of voriconazole has become common for the management of invasive aspergillosis. However, therapy with voriconazole still sometimes fails, more often because of unresponsive underlying disease than because of resistance of the fungus. Since the first description of itraconazole resistance in *Aspergillus fumigatus*,[1] three amino acid substitutions in the 14α-sterol demethylase *cyp51A* gene, which is the target site for azole drugs, have been described.[2]

Our laboratory receives fungal isolates for identification and susceptibility testing from throughout the Netherlands. Since 2002, using Clinical and Laboratory Standards Institute methodology, we have observed an increase in the number of *A. fumigatus* isolates with elevated minimum inhibitory concentrations of voriconazole (2 to >16 mg per liter), itraconazole (>16 mg per liter), the investigational azole ravuconazole (4 to >16 mg per liter), and posaconazole (0.5 to 1.0 mg per liter). Thirteen isolates were cultured from nine patients from six hospitals in the Netherlands (Table 1). Primary aspergillosis was diagnosed in four patients, and five patients presented with breakthrough invasive aspergillosis.

A new mechanism of resistance, consisting of a Cyp51A amino acid substitution at codon 98 (L98H) together with a tandem repeat in the gene promoter, was found to be responsible for the azole-resistant phenotype. This resistance mechanism was present in 12 of the 13 isolates. Genotyping of the isolates showed no evidence for clonal spread of a single *A. fumigatus* genotype.

The prevalence of multiple-triazole resistance was compared with a previously conducted nationwide survey of 170 *A. fumigatus* isolates collected from 114 patients from 21 Dutch hospitals between 1945 and 1998.[4] In this period, no patients with multiple-triazole–resistant isolates were found as compared with 10 of 81 patients in the period since 2002 ($P<0.001$).

Although the emergence of this new resistance mechanism coincides with the approval of voriconazole, the factors that may explain this phenomenon remain unclear. Four patients became infected with a multiple-triazole–resistant strain during long-term prophylaxis with itraconazole, a drug that has been widely available for clinical use since 1991. The recovery of multiple-triazole–resistant strains in patients who had not been previously treated with azoles suggests that alternative sources of azoles, such as the use of azole compounds in agricultural environments, might play a role.[5]

Our observation underscores the need to make an etiologic diagnosis of invasive mold infection

Table 1. Characteristics of Nine Patients from Whom *A. fumigatus* Resistant to Multiple Triazoles Was Cultured.

Sex	Yr of Age	Underlying Disease	Date of Isolation	Site of Isolation	Disease Classification*	Previous Azole Exposure	Treatment	Outcome
Male†	15	X-linked chronic granulomatous disease	April 4, 2002	Sputum	Breakthrough invasive pulmonary aspergillosis, proven	Prophylaxis with itraconazole (for 6 yr)	Voriconazole (high-dose)	Survived
Male	73	None	Dec. 3, 2003	Ear swab	Invasive aspergillosis of mastoid cavity, proven	None	Surgery and topical therapy	Survived
Male	16	Hyper-IgE syndrome	Nov. 19, 2004	Bronchoalveolar-lavage fluid	Breakthrough invasive pulmonary aspergillosis, proven	Treatment with voriconazole (for 2 yr)	Surgery and posaconazole	Survived
Female	76	Pulmonary fibrosis	June 26, 2005	Sputum	Invasive pulmonary aspergillosis, possible	None	Voriconazole	Survived
Male	31	Chronic granulomatous disease	Nov. 1, 2005	Lung aspirate	Breakthrough invasive pulmonary aspergillosis, probable	Prophylaxis with itraconazole (for >10 yr)	Caspofungin and posaconazole	Survived
Female	68	Acute myeloid leukemia	Feb. 14, 2006	Bronchoalveolar-lavage fluid	Disseminated invasive aspergillosis, probable	None	Voriconazole	Died
Female	62	Chronic obstructive pulmonary disease	April 5, 2006	Bronchoalveolar-lavage fluid	Invasive pulmonary aspergillosis, possible	None	Voriconazole, amphotericin B, and posaconazole	Survived
Male	19	Chronic granulomatous disease	April 15, 2006	Bone	Breakthrough aspergillus osteomyelitis, proven	Prophylaxis with itraconazole (for >2 yr)	Voriconazole, caspofungin, and posaconazole	Survived
Male	45	Acute myeloid leukemia and allogeneic hematopoietic stem-cell transplantation	May 11, 2006	Nose swab	Breakthrough aspergillus sinusitis, proven	Prophylaxis with itraconazole (for 4 wk)	Posaconazole	Died

* Diseases were classified according to consensus criteria defined by the European Organisation for Research and Treatment of Cancer and the National Institute of Allergy and Infectious Diseases Mycoses Study Group.
† Information about this patient is from Warris et al.[3]

and to determine antifungal drug activity in clinically relevant *A. fumigatus* isolates. Furthermore, international surveillance programs are warranted to investigate the spread of resistance in *A. fumigatus*.

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