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Low rates of voriconazole resistance and absence of cyp51A mutations among A. fumigatus recovered from lung transplant recipients receiving prophylaxis

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Background: We previously showed that voriconazole prophylaxis (VOR Px) for 3-6 months after lung transplant (LTx) reduced but did not eliminate fungal infection. Breakthrough (BT) infection was predominantly due to *Aspergillus* spp. other than *A. fumigatus* and other moulds. Infections off Px were predominantly due to *A. fumigatus*. Azole-resistant (R) *Af* with *cyp51A* mutations have emerged in Europe, Asia and the Middle East, largely due to agricultural fungicide use. The objectives of this study were to define the epidemiology of azole-R among lung transplant recipients who had received VOR Px, and to identify potential *cyp51A* mutations in R *A. fumigatus* isolates

Material/methods: From 2009-13, we collected *Aspergillus* isolates from LTx recipients. Antifungal susceptibility testing (AFST) against VOR, itraconazole (IT), and posaconazole (POS) was performed by microbroth dilution (CLSI M27-A3). After PCR amplification, the full sequence of the *cyp51A* gene and its promoter region was determined. Sequences were compared with those available through GenBank (accession #AF338659).

Results: *Aspergillus* spp. and R to agents are summarized in the Table. BT/non-BT isolates by spp. were *fumigatus* (9/12), *niger* (6/10), *flavus* (3/1), others (5/7). VOR (p=0.6), IT (p=0.4), POS (p=0.85) MICs did not differ between BT and non-BT isolates. IT and POS MICs were significantly lower against *A. fumigatus* than non-*fumigatus* isolates (p=0.04 and 0.05, respectively). 3 *A. fumigatus* isolates, all S, were 795 A>G mutants; none of *A. fumigatus* isolates R to an antifungal were mutants.

Conclusions: Routine VOR Px post-LTx was not associated with emergence of VOR-R *Aspergillus*. Taken with our previous data, the findings suggest that sub-therapeutic VOR concentrations rather than R are responsible for breakthrough *Aspergillus* infections. Therapeutic drug monitoring and interventions to optimize VOR pharmacokinetics may improve Px effectiveness. In contrast to VOR, IT and POS R rates were significant. Target mutations may exert differential effects on *Aspergillus* susceptibility to IT and POS, compared to VOR. *cyp51A* mutations do not appear to mediate R in *A. fumigatus* isolates from this population, but the sample size of azole-R isolates in the study was small.

Resistant isolates	**N=**	**Itraconazole**	**Posaconazole**	**Voriconazole**
All *Aspergillus* spp.	53	19% (10)	17% (9)	2% (1)
A. fumigatus	21	14% (3)	14% (3)	0% (0)
Non-*A. fumigatus*	32	22% (7)	19% (6)	3% (1)