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◀ [1] ▶

Record 1 of 1

Title: Susceptibility and Diversity in the Therapy-Refractory Genus *Scedosporium*

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Abstract: *Scedosporium* species show decreased susceptibility to the majority of systemic antifungal drugs. Acquired resistance is likely to disseminate differentially with the mode of exchange of genetic material between lineages. Inter- and intraspecific diversities of *Scedosporium* species were analyzed for three partitions (rDNA internal transcribed spacer gene [ITS], partial beta-tubulin gene, and amplified fragment length polymorphism profiles), with the aim to establish distribution of resistance between species, populations, and strains. Heterogeneity of and recombination between lineages were determined, and distances between clusters were calculated using a centroid approach. Clinical, geographic, and antifungal data were plotted on diversity networks. *Scedosporium minutisporum*, *Scedosporium desertorum*, and *Scedosporium aurantiacum* were distinguished unambiguously in all partitions and had differential antifungal susceptibility profiles (ASP). *Pseudallescheria fusoidea* and *Pseudallescheria ellipsoidea* were indistinguishable from *Scedosporium boydii*. *Pseudallescheria angusta* took an intermediate position between *Scedosporium apiospermum* and *S. boydii*. *Scedosporium boydii* and *S. apiospermum* had identical ASP. Differences in (multi)resistance were linked to individual strains. *S. apiospermum* and *S. boydii* showed limited interbreeding and were recognized as valid, sympatric species. The *S. apiospermum/S. boydii* group, comprising the main clinically relevant *Scedosporium* species, consists of separate lineages and is interpreted as a complex undergoing sympatric evolution with incomplete lineage sorting. In routine diagnostics, the lineages in *S. apiospermum/S. boydii* are indicated with the umbrella descriptor "*S. apiospermum* complex"; individual species can be identified with rDNA ITS with 96.3% confidence. Voriconazole is recommended as the first-line treatment; resistance against this compound is rare.

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