Resistance in human pathogenic yeasts and filamentous fungi: prevalence, underlying molecular mechanisms and link to the use of antifungals in humans and the environment.

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Abstract: Antifungal drug resistance is a multifaceted clinical challenge, and when present, a primary cause of treatment failure in patients with severe fungal infections. Changing epidemiology, increasing resistance rates and a narrow antifungal armamentarium may further underline the required attention on resistance particularly within the most prevalent invasive fungal infections caused by Candida yeasts and Aspergillus moulds. In Denmark, the resistance epidemiology remains to be fully elucidated. This thesis sought to address this demand as well as provide insight into the landscape of underlying molecular resistance mechanisms. Paper I and II both contributed to the understanding of FKS (ß-glucan synthase) mediated echinocandin resistance in Candida species. Paper I covered a unique stepwise acquisition of a homozygous mutation in FKS1 of Candida tropicalis leading to an amino acid change corresponding to a well-known S645P in Candida albicans. Paper II presented a failure case due to Candida krusei displaying high-level echinocandin resistance likely attributable to an acquired D662Y amino acid substitution in FKS1. Intrinsic differences in FKS1 among Candida species may explain why the level of resistance both depends on the mutation as well as the species and cannot be easily translated to the level of clinical resistance. Intrinsic fluconazole resistance in C. krusei further substantiated the clinical implications of acquired echinocandin resistance. Paper III presented a rare multidrug resistance case in a series of isogenic C. albicans isolates, almost covering the entire spectrum of known resistance mechanisms in Candida and involved the proposal of novel resistance mutations. An A61E change in ERG11 was potentially involved in reduced susceptibility to long-structured azoles. Increased expression levels of azole efflux pumps were probably accredited to novel gain-of-function variants in the transcription factor TAC1 (R688Q and R673L). Echinocandin resistance was induced by the well-known S645P variant of FKS1 and polyene resistance was likely inflicted by a frameshift mutation in ERG2 leading to loss of function of the encoded protein and subsequent ergosterol depletion. The number of acquired resistance cases is increasing in our settings and Paper IV sought to illuminate whether antifungal resistance is overlooked in the current fungaemia programme. This involved the acquisition of post-treatment oral isolates from 193 candidaemia patients among which 114 received azoles (primarily fluconazole) and 85 received an echinocandin (and some both). Azole-exposed patients carried a significantly higher proportion of species less susceptible to fluconazole (primarily Candida glabrata) among colonising Candida compared to baseline blood isolates (p50% of all our azole-resistant isolates. The genotyping data of resistant and a selection of susceptible A. fumigatus showed high identity to foreign isolates (>15%). This could argue for the hypothesis on clonal expansion, which has previously been suggested for TR34/L98H clones in the Netherlands and India, but could also indicate an insufficient discriminatory power of such analysis. Still, a proposed A. fumigatus outbreak in a haematology ward was unresolved since no genetically identical isolates were recovered from patients and air samples, illustrating the ubiquitous nature of this organism. Overall, the main concerns are a changing Candida epidemiology towards species less susceptible to fluconazole combined with the rapid acquisition of echinocandin resistance, especially among C. glabrata isolates. For A. fumigatus, the concern is the emergence of azole resistant strains in the environment, displaying cross-resistance to clinical azoles, and thus posing unforeseen clinical challenges in the management of invasive aspergillosis. Collectively, these findings call for an increased awareness especially at clinical microbiology laboratories, which ideally would lead to susceptibility testing of all clinically relevant isolates by reference or validated methods. Moreover, novel diagnostic approaches for non-culturable pathogens are warranted and especially DNA-based detection by PCR may serve as a solid complimentary tool for improved diagnostics of invasive fungal infections.

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