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Candida and Candidaemia. Susceptibility and Epidemiology

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Abstract

In our part of the world invasive fungal infections include invasive yeast infections with Candida as the absolutely dominating pathogen and invasive mould infections with Aspergillus as the main organism. Yeasts are part of our normal micro-flora and invasive infections arise only when barrier leakage or impaired immune function occurs. On the contrary, moulds are ubiquitous in the nature and environment and their conidia inhaled at a daily basis. Hence invasive mould infections typically arise from the airways whereas invasive yeast infections typically enter the bloodstream causing fungaemia. Candida is by far the most common fungal blood stream pathogen; hence this genus has been the main focus of this thesis. As neither the Danish epidemiology nor the susceptibility of fungal pathogens was well described when we initiated our studies we initially wanted to be able to include animal models in our work. Therefore, a comprehensive animal study was undertaken comparing the virulence in a haematogenous mouse model of eight different Candida species including the five most common ones in human infections (C. albicans, C. glabrata, C. krusei, C. parapsilosis and C. tropicalis and in addition three rarer species C. guilliermondii, C. lusitaniae and C. kefyr). We found remarkable differences in the virulence among these species and were able to group the species according to decreasing virulence in three groups I: C. albicans and C. tropicalis, II: C. glabrata, C. lusitaniae and C. kefyr, and III: C. krusei, C. parapsilosis and C. guilliermondii. Apart from being necessary for our subsequent animal experiments exploring in vivo antifungal susceptibility, these findings also helped us understand at least part of the reason for the differences in the epidemiology and the pitfalls associated with the establishment of genus rather than species specific breakpoints. In example, it was less surprising that C. albicans has been the dominant pathogen and associated with a significantly higher mortality than C. parapsilosis and that C. glabrata and C. krusei mainly emerged in the post fluconazole era and in settings with azole selection pressure. Moreover, it was less surprising that infections due to mutant C. albicans isolates with echinocandin MICs of 1-2 mg/l were not good targets for the echinocandins despite the fact that the outcome for infections involving wild type C. parapsilosis for which similar echinocandin MICs were similar was not inferior. This last observation highlights the importance of providing optimal, reproducible and sensitive reference susceptibility testing methods and notably accompanied by appropriate breakpoints that allow a separation and

detection of susceptible and resistant isolates against which the commercial tests can be validated. Correct detection of resistant isolates is for obvious reasons crucial in order to avoid inappropriate treatment. And if the test method cannot correctly identify resistant isolates it makes little sense performing susceptibility testing at all. On the other hand misclassification of susceptible isolates as resistant is also an issue as the patient is thereby deprived an appropriate treatment option among the few available. These comments may seem very basic; nevertheless, it has taken a lot of effort and patience to optimise the susceptibility tests, understand the variability issue for caspofungin testing, to provide appropriate breakpoints that reduced misclassifications to a minimum and not the least to facilitate a harmonisation of breakpoints across the Atlantic sea. We initially realised that the CLSI method and echinocandin breakpoint misclassified resistant isolates. This was due to the endorsement of a single susceptibility breakpoint across all Candida species and the three echinocandins and therefore set as high as 2 mg/l in order to include and not bisect the C. parapsilosis population. Through our comprehensive comparisons of echinocandin susceptibility testing using EUCAST, CLSI, Etest, disk diffusion and agardilution with different media with and without the supplementation of bovine serum albumin we provided data that supported the current reference methodologies, provided that drug and species specific breakpoints were selected. Moreover, the issues of caspofungin variability and of overlap between micafungin MICs for wild type and mutant C. glabrata populations were handled and understood. Anidulafungin EUCAST breakpoints are now published and publically available at the www.eucast.org website and anidulafungin testing recommended as a marker for the echinocandin class. Our antifungal EUCAST breakpoint setting approach has been adopted by the CLSI leading to revision and harmonisation of breakpoints for the three echinocandins, fluconazole and voriconazole. Our epidemiological studies developed gradually over the years following our observation of a notably high incidence rate of fungaemia compared to our Nordic neighbours. Initially, we anticipated that our high incidence was at least in part related to the fact that the capture area for our initial studies was skewed with dominance of university hospitals and inclusion of all centres performing solid organ or bone marrow transplantation. However, when the surveillance was extended to the entire country, the high incidence remained a consistent finding and we even demonstrated that the incidence rate is still increasing. Additionally we demonstrated a changing epidemiology as a high and increasing proportion of the cases involved fluconazole resistant isolates and that this proportion also was significantly higher than in the other Nordic countries. This appears to be related to a significantly higher and increasing fluconazole use in Denmark than in the other Nordic countries. Exploring the incidence rate for the individual hospitals and age groups we demonstrated not unexpectedly that the incidence rate was highest at the university centres, but also that whereas the age specific incidence rate was comparable in children and the younger adults with that in the other Nordic countries it was notably higher in the elderly population. This in combination with the fact that it is increasing specifically in the elderly men and that the incidence rates in the Nordic countries were comparable two decades back suggest that host specific factors including antifungal consumption rather than genetic differences in susceptibility to fungaemia account for the differences, and hence that it is possibly modifiable by implementing relevant measures. Hence, it was important to investigate the underlying clinical conditions and diagnostic factors and the outcome in Danish patients with fungaemia. In this study we demonstrated that two thirds of the patients had received abdominal surgery or intensive care treatment prior to the development of the fungaemia, a proportion that is higher than in most other studies. We also demonstrated that unless surveillance cultures are handled with careful attention the detection of non-C. albicans may go unnoticed which imply a risk of inappropriate treatment in cases involving intrinsically resistant species. Finally, we demonstrated the necessity of using a fungal blood culture flask in addition to the conventional aerobic and anaerobic ones if all C. glabrata infections (BACTEC) and all polymicrobial infections (BacT/ALERT) are to be diagnosed. Hence close monitoring with the use of improved diagnostic options (such as frequent BC including a mycosis bottle, surveillance cultures and mannan antigen and antibody screening) of particularly ICU and abdominal surgery patients may help better identify patients with fungaemia and allow early treatment. With respect to treatment and outcome we found that the fluconazole resistant species C. glabrata, C. krusei and S. cerevisiae were significantly more common in patients exposed to at least 7 days of antifungal prophylaxis (mainly fluconazole). We also demonstrated that a significant proportion of the patients initially received inappropriate antifungal treatment and that the outcome was significantly improved when patients with C. glabrata received caspofungin as their first line

agent. This has today been incorporated in the Danish and international treatment guidelines. The prevalence of acquired antifungal resistance remained very low throughout the study period, however, we may only have detected the tip of the resistance iceberg due to the study design, where for epidemiological purposes only the initial isolate was included with the lowest antifungal exposure, and as the susceptibility tests and breakpoints were not optimal for the detection of resistance at all centres. Most Danish laboratories either do not susceptibility test or use commercial tests such as the Etest and later the VITEK system. These are FDA approved with the CLSI breakpoints which, as we have shown, have been far too high to reliably detect resistance and which despite having now been revised and harmonised are not yet in formal CLSI print and hence not incorporated in the product inserts for the commercial tests on the market. Finally, even for laboratories aware of these issues challenges are still ahead as the official breakpoints not always lead to a correct classification for MIC endpoints obtained using the commercial systems or as the commercial tests do not include a relevant concentration range for all drug bug combinations. I thus believe, the studies included in this thesis have contributed significantly to the understanding of the interplay between the Candida virulence, epidemiology and susceptibility and the importance of appropriate diagnostics and treatment choice. It is my hope that we thereby have contributed to the improved options and outcome for patients with candidaemia.

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