O083
Oral Session
Emerging resistance in fungi

POST TREATMENT ANTIFUNGAL RESISTANCE AMONG COLONISING CANDIDA ISOLATES IN CANDIDAEMIA PATIENTS: PRELIMINARY RESULTS FROM A SYSTEMATIC MULTICENTRE STUDY

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Objectives Acquired antifungal resistance in *Candida* is an uncommon finding in most candidaemia surveys. Hypothetically, this may in part be due to the typical study design, i.e. only the initial isolate is included representing a lower level of antifungal exposure. As invasive infections arise from the colonising flora, and as the level of antifungal exposure for mucosa isolates may facilitate selection of resistance we decided to determine the level of antifungal resistance in oral *Candida* isolates from candidaemia patients post treatment.

Methods Patients with candidaemia were enrolled from the on-going national surveillance study. Culturing of post treatment oral swabs (CHROMagar), species identification (MALDI-TOF) and susceptibility testing (EUCAST E.def7.2 (azoles, anidulafungin and micafungin) and Etest (amphotericin B)) was compared to the same data from corresponding blood isolates to study the differences in the two populations. Only cases with culture positive oral swabs were included. *FKS1* was sequenced for isolates for which anidulafungin MIC was above the EUCAST breakpoint (*C. albicans*: >0.03; *C. glabrata, C. tropicalis, C. krusei*: >0.06 µg/mL). The study is a 1-year on-going study (March 2013 - February 2014).

Results Oral swabs were obtained from 164 candidaemia episodes (159 patients) of which 116 (70.7 %) were culture positive (111 patients) yielding 175 *Candida* isolates (table). In azole treated patients, a significant difference in species distribution was observed with fewer *C. albicans* (p<0.01), more *C. glabrata* (p<0.01) and slight increase of *S. cerevisiae* (p=0.057). In the echinocandin treated group we observed insignificant changes in species distribution but the *C. albicans* fraction still decreased (table). No blood isolates but nine oral isolates displayed elevated anidulafungin MICs, five of which harboured well-described resistance mechanisms (table). MIC_{50}/MIC_{90} values were as follows (µg/mL) for *C. albicans* (blood vs. oral isolates respectively): ANI: 0.008/0.03 vs. 0.015/0.03, FLU: 0.125/0.25 vs. 0.125/0.25 and for *C. glabrata* ANI: 0.06/0.06 vs. 0.06/0.125 and FLU: 2/8 vs. 2/32, respectively.

Conclusion: These preliminary findings suggest that isolates with intrinsic or acquired resistance are present at notable levels in the post-treatment colonising flora in candidaemia patients. The most pronounced difference between blood and post treatment mucosal isolates were found in the azole treated patients and linked to both an emergence of intrinsically fluconazole resistant species but also an increase in fluconazole MICs for *C. glabrata*. Acquired azole resistance needs further investigation. However, of note 8% (5/65) echinocandin treated patients harboured *fks1* mutants after treatment. This may constitute a risk population for subsequent invasive echinocandin resistant infection and underscores the need for close monitoring of resistance. Considering the challenges any clinician encounters regarding therapeutic management of *Candida* infections, knowledge on the dynamics of antifungal resistance development is essential to limit the evolutionary inevitability of resistance and improve the management of invasive candidiasis.

			No. of patients in three treatment groups**								
			Azole		Echinocandin		Polyene				
			FLU 55 cases VORI 4 cases		CAS 54 cases ANI 10 cases MICA 1 case		AMB 9 cases STAT 3 cases		No. of isolates with elevated anidulafungin MIC	FKS genotypes	
Species	No. of blood isolates (%)	No. of oral isolates (%)	Blood	Swab	Blood	Swab	Blood	Swab		FKS1	FKS2
C. albicans	53 (45.7)	62 (35.4)^{NS}	37 (62,7)	20 (33.9)^{PP}	20 (30.8)	13 (20)^{NS}	5 (41.7)	4 (33.3)^{NS}	2	F641L, D648V	
C. glabrata	42 (36.2)	71 (40.6)^{NS}	11 (18.6)	25 (42.4)^{PP}	31 (47.7)	34 (52.3)^{NS}	4 (33.3)	3 (25)^{NS}	3	WT	F659L, S663P F659-del
C. krusei	6 (5.1)	8 (4.6)^{NS}	4 (6.8)	4 (6.8)^{NS}	5 (7.7)	6 (9.2)^{NS}	2 (16.7)	3 (25)^{NS}	1	WT	WT
C. tropicalis	4 (3.4)	9 (5.1)^{NS}	1 (1.7)	1 (1.7)^{NS}	3 (4.6)	2 (3.1)^{NS}	0 (0)	0 (0)			
C. parapsilosis	4 (3.4)	3 (1.7)^{NS}	2 (3.4)	1 (1.7)^{NS}	1 (1.5)	2 (3.1)^{NS}	0 (0)	0 (0)			
S. cerevisiae	2 (1.7)	8 (4.6)^{NS}	0 (0)	5 (8.5)$^{p=0.057}$	2 (3.1)	4 (6.2)^{NS}	1 (8.3)	1 (8.3)^{NS}			
Other *Candida*/yeast*	5 (9,1)	14 (8)^{NS}	4 (6.8)	3 (5.1)^{NS}	3 (4.6)	4 (6.2)^{NS}	0 (0)	1 (8.3)^{NS}			
Total	116	175	59	59	65	65	12	12	6	NA	NA
Intrinsic resistance***	55 (47.4)	95 (54.2)^{NS}	16 (27.1)	35 (59.3)^{PP}	1 (1.5)	3 (4.6)^{NS}	0 (0)	0 (0)	NA	NA	NA

**C. guilliermondii, C. lusitaniae, C. dubliniensis, C. utilis, C. kefyr, C. pulcherrima, C. neoformans*

***If treated with more than 1 drug, patient was registered twice. Conversely, if multiple isolates, only the most intrinsically resistant species was counted.*

****C. glabrata, C. krusei, S. cerevisiae, C. guilliermondii, C. neoformans* (reduced FLU susceptibility), *C. parapsilosis, C. guilliermondii* (reduced echinocandin susceptibility), *C. lusitaniae* (reduced AMB susceptibility).*

P Significant change from left to index column, (p < 0.05), calculated by Fischer's exact test. PP p<0.01. NS Non-significant change