O081
Oral Session
Emerging resistance in fungi

INTRA-ABDOMINAL CANDIDIASIS IS AN IMPORTANT RESERVOIR FOR THE EMERGENCE OF FKS MUTATIONS AMONG CANDIDA GLABRATA AND CANDIDA ALBICANS

R.K. Shields[1], M.H. Nguyen[1], **C.J. Clancy**[1]

[1]Medicine, University of Pittsburgh, Pittsburgh PA, USA

Objectives: *Candida* echinocandin (EC) resistance is attributed to *FKS* mutations. Our objectives were to define the incidence of *FKS* mutations for different types of invasive candidiasis (IC), and identify associations between *FKS* mutations and EC treatment responses.

Methods: Isolates were collected from pts with bloodstream or intra-abdominal infections (BSI, IAC). Caspofungin (CSP) minimum inhibitory concentrations (MICs) were determined by broth microdilution. Prior EC exposure was defined as ≥3d of CSP before IC, and breakthrough (BT) as receipt of CSP at onset of IC. *FKS1* (all spp.) and *FKS2* (*C. glabrata* [Cg]) hot spots were PCR-amplified.

Results: 256 isolates causing unique episodes of IC were tested; 54% (139), 20% (52), 17% (44), 4% (11), and 4% (10) were Cg, *C. albicans* (Ca), *C. parapsilosis* (Cp), *C. tropicalis* (Ct), and *C. krusei* (Ck), respectively. 56% (144/256) of isolates (90 Cg, 27 Ca, 16 Cp, 8 Ck, 3 Ct) were from patients (pts) without prior EC exposure; none harbored *FKS* mutations. Median EC exposure was 21.5d (range 3 – 438) for the remaining 112 isolates (83 BSI, 29 IAC; 49 Cg, 25 Ca, 28 Cp, 8 Ct, 2 Ck); 27% (30) were BT (11 Cg, 9 Cp, 7 Ca, 2 Ct, 1 Ck) and 13% (15) *FKS* mutants (12 Cg [4 *FKS1,* 8 *FKS2*], 3 Ca). BT was more common for IAC than BSI (45%, 13/29 *vs* 20%, 17/83; p=0.015). Rates of *FKS* mutations were 24% and 12% for Cg and Ca. 73% (8) and 14% (1) of BT Cg and Ca were mutants, respectively. *FKS* mutations were absent among other spp. 21% (6) and 11% (9) of isolates from IAC and BSI were mutants, respectively (p=0.21). 83% (5/6) of BT Cg from pts with IAC were *FKS* mutants. Median CSP MICs were higher (2 *vs* 0.5; p=0.0002) and prior EC exposure longer (68 *vs* 20d; p=0.002) in *FKS* mutants versus wild-type (WT). 61% (157) of pts were treated with an EC; 41% (64) failed therapy, including 93% (13/14) with IC due to *FKS* mutants compared to WT (36%; p<0.0001). Failure rates were 51% (19/37), 50% (3/6), 40% (11/27), 38% (3/8), and 35% (28/79) for Cp, Ck, Ca, Ct, and Cg, respectively. Failure was more common with IAC than BSI (71%, 20/28 *vs* 34%, 44/129; p= 0.0005), and with prior EC exposure (58%, 46/80 *vs* 23%, 18/77; p<0.0001). Median CSP MICs did not differ among pts who failed or responded to ECs (p=0.11).
Conclusions: *FKS* mutations were seen in Cg and, to a lesser extent, Ca isolates after prolonged EC exposure. Mutations were not detected in other spp., even during BT infections. Risks for treatment failure included *FKS* mutations, prior EC exposure, and IAC. IAC was an important reservoir for emergence of EC resistance.