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Antifungal Susceptibility and Species Distribution of 1,881 Candidaemia Isolates from Patients in Canadian Hospitals: CANWARD Study 2011-2016

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ABSTRACT

Background: CANWARD is a national surveillance program that characterizes pathogens causing infections in patients admitted to Canadian hospitals. The epidemiology of invasive *Candida* infections in Canada is not well characterized yet evidence of antifungal resistance in other countries increases. In this study, we present the species prevalence and antifungal susceptibility of candidaemia isolates recovered from hospitalized patients over a six year period.

Methods: *Candida* species causing bloodstream infections were collected (1 per patient) from participating hospital clinical laboratories from 2011 to 2016. Antifungal susceptibility was determined using the CLSI M27 broth microdilution method and interpretation guidelines (S4) for fluconazole (FLUC), voriconazole (VORI), caspofungin (CASP) and micafungin (MICA). Epidemiological cut-off values (ECV) of ≤ 1 mg/L for amphotericin B (AMB) against all species, and 0.5 mg/L for VORI against *C. glabrata* (CG) were used in the absence of M27 breakpoints.

Results: Isolates were submitted by 18 centres, 12 of which participated in ≥4 of the 6 study years and represented 8 of 10 provinces. Of 1881 *Candida* spp., *C. albicans* (CA), *C. glabrata* (CG), *C. parapsilosis* (CP) and *C. tropicalis* (CT) revealed an overall prevalence (%) of 49.8, 20.9, 11.8, and 5.2, respectively, with a temporal decrease of CA (60.9% to 42.7%, p<0.0001) and concomitant increase of CG (16.4% to 22.3%, p=0.023). The majority of patients were admitted to medicine (42.6%) and critical care wards (31.6%), followed by surgical wards (13.0%) and emergency departments (8.2%). The rates (%) of non-susceptibility (NS) to FLUC, VORI, and CASP, and MICA were 0.6, 0.4, 1.2, and 0.1 for CA (n=934), 5.4, 1.3, 0, 0 for CP (n=224), and 3.1, 3.1, 0, 0, for CT (n=98), respectively. CG (n=394) showed 1% resistance to FLUC, with no temporal change in the MIC distribution, 3.3% NS to MICA, and 3.6% of isolates had VORI MICs >ECV. None of the isolates showed AMB MICs >ECV. FKS point mutations known to confer echinocandin resistance were detected in 12 of 13 MICA NS CG isolates.

Conclusion: CANWARD surveillance of invasive *Candida* shows that the proportion of CA infection is decreasing over time while the proportion of CG infection is increasing over time. Evidence of acquired resistance is limited and azole MIC distributions for CG have not changed. Consistent with practice guidelines, these data demonstrate that cases of candidaemia in Canadian hospitals are often caused by CA, CG, and CP that are highly susceptible to existing antifungal agents.

BACKGROUND

The epidemiology of candidaemia in Canadian hospitals is informed by a limited number of publications. A recent surveillance study at two sites showed that *C. albicans* was the predominant cause of invasive candidiasis, followed by *C. glabrata* and *C. parapsilosis* [1].

Surveillance data from other countries have identified emergent resistance of *Candida* species to azole and echinocandin agents, most notably, *C. glabrata* [2,3,4].

Through the CANWARD surveillance program, we have characterized the species prevalence and antifungal susceptibility of candidaemia isolates recovered from hospitalized patients over a six year period.

MATERIALS & METHODS

Participating clinical microbiology laboratories collected up to ten *Candida* isolates per month, from January to October of each study year, from patients with incident candidaemia (1 per patient).

Demographic and hospital admission location were submitted with each isolate to a central laboratory that confirmed species identification and antifungal susceptibility.

Minimum inhibitory concentration (MIC) testing and clinical breakpoint (CBP) interpretation was performed as per CLSI M27 broth microdilution standards (A3, S4) using 24 h incubation and visual endpoint determination for AMB, FLUC, VORI, CASP, and MICA. We also applied ECVs of ≤ 1mg/L for AMB against all species and ≤0.5 mg/L for VORI against *C. glabrata*.

Echinocandin resistant MICs in *C. glabrata* isolates were confirmed by molecular analysis of FKS loci. Molecular confirmation of azole resistant MICs was not pursued.

RESULTS

Annual participation by study sites was relatively consistent and represented 8 of the 10 provinces; 12 of the 18 sites submitted isolates for ≥ 4 of the 6 study years. From 2011-16, annual isolate volumes were 238, 277, 347, 337, 332, and 350, respectively.

Figure 1 shows the annual prevalence of common species. CA was the most common cause of candidaemia but its prevalence decreased significantly from 2011 to 2016 (p<0.0001). The prevalence of CG (2nd most common) increased significantly (p=0.023). Esoteric species comprising 2.4% of total isolates are not shown.

The relative proportion of candidaemia patients admitted to Medicine, Critical Care, Surgical, and Emergency wards did not change over time. The male to female ration was ~1:1 and the mean patient age was 55; patients aged 18 to 65 and >65 years represented 57% and 36% of cases, respectively.

Table 1 illustrates the antifungal MIC distribution and percent of isolates that are Not Susceptible (NS) or Non Wild-Type (NWT). Notable findings included MICA NS isolates of CG and FLUC NS isolates of CP, which were not associated with a specific year or study site. For CG, the annual FLUC mode ranged from 1 to 4 mg/L and the MIC_{90} ranged from 4 to 16 mg/L; there we no temporal trends.

The percent annual MIC distribution of MICA against CG is shown in **Figure 2**, with the susceptible (S) and resistant (R) breakpoints depicted by red and blue lines, respectively. All NS isolates were confirmed to harbour point mutations in the FKS hot spot 1 and 2 regions known to confer echinocandin resistance (data not shown).

RESULTS

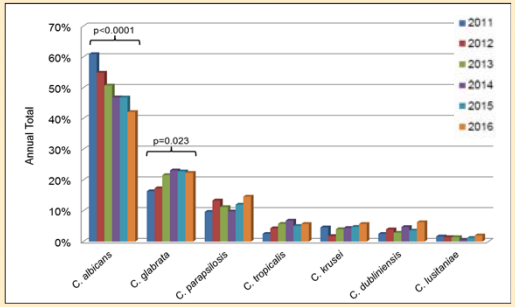

Figure 1. Temporal distribution of *Candida* species causing candidaemia in hospitalized patients.

Table 1. Antifungal Susceptibility and MIC Distribution of Common *Candida* Species Causing Candidaemia.

Organism (no.)	Agent	Mode	MIC_{90}	CBP/ECV	%NS	%NWT
C. albicans (934)	AMB	0.25	0.5	≤1	-	0
	FLUC	0.12	0.25	≤2	0.6	-
	VORI	≤0.015	≤0.015	≤0.12	0.4	-
	CASP	≤0.008	0.12	≤0.25	1.2	-
	MICA	≤0.008	≤0.008	≤0.25	0.1	-
C. glabrata (394)	AMB	0.5	0.5	≤1	-	0
	FLUC	2	8	≤32	1.0	-
	VORI	0.06	0.25	≤0.5	-	3.8
	MICA	≤0.008	0.015	≤0.06	3.3	-
C. parapsilosis (224)	AMB	0.5	1	≤1	-	0
	FLUC	0.5	1	≤2	5.4	-
	VORI	≤0.015	0.03	≤0.12	1.3	-
	CASP	0.5	1	≤2	0.0	-
	MICA	0.5	1	≤2	0.0	-
C. tropicalis (98)	AMB	0.5	1	≤1	-	0
	FLUC	0.25	0.5	≤2	3.1	-
	VORI	≤0.015	0.06	≤0.12	3.1	-
	CASP	0.12	0.25	≤0.25	1.0	-
	MICA	≤0.008	0.015	≤0.25	0.0	-

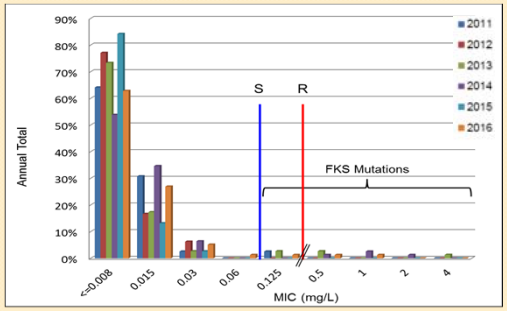

Figure 2. Micafungin MIC distribution against 394 *C. glabrata* isolates.

CONCLUSIONS

Candidaemia in Canadian hospitals is most often caused by *C. albicans*, *C. glabrata*, and *C. parapsilosis*. From 2011 to 2016, the proportion of bloodstream infections caused by *C. albicans* has significantly decreased, while the proportion of *C. glabrata* bloodstream infections has significantly increased, albeit, more stable over the most recent years.

Acquired resistance to the azoles and echinocandins is uncommon across all species.

Guideline-concordant empiric therapy decisions are appropriate for candidaemia patients in Canadian hospitals.

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