

This case highlights the importance of a good clinical history and communication of relevant results between clinicians and pathologists. Without correlation of clinical, immunological, biochemical, and histological results the diagnosis could not be made and optimal management instituted. Throughout this patient's admission, the histological diagnosis evolved as more information became available.

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An insight into *in vitro* susceptibility of non-*albicans* *Candida* species from bloodstream infections to echinocandins in a Singapore cohort



Sir,

Initial therapy of candidaemic patients with echinocandins has been demonstrated to be a significant predictor of survival.¹ The echinocandins have been promulgated as front-line agents for *Candida* bloodstream infection (BSI) in all

patients, neutropenic or non-neutropenic.² In recent years, incidence of BSIs due to non-*albicans* species has surpassed those due to *Candida albicans* across many centres.³ *Candida albicans* is deemed typically susceptible to the commonly used antifungals while acquired echinocandin resistance is an emerging problem among non-*albicans* species like *Candida glabrata*.⁴ At the same time, other species, like *Candida parapsilosis* and *Meyerozyma guilliermondii*, are characterised by inherently raised minimum inhibitory concentrations (MICs) to echinocandins. Against the rising spectre of multidrug resistance, the Infectious Disease Society of America, in its recent guidelines on candidiasis, recommends susceptibility testing to echinocandins among those who have infections with *C. glabrata* or *C. parapsilosis* (strong recommendation; low-quality evidence).² Few studies in Singapore have evaluated resistance among non-*albicans* species to this class of drug. It was previously reported in 2016 that resistance to the echinocandins does not pose a major challenge across the Asia-Pacific region.⁵

At our 1600 bed tertiary care hospital, antifungal susceptibility testing is performed by the Sensititre YeastOne (TREK Diagnostic Systems, USA) on index isolates of *Candida* species from positive blood culture broths (BACTEC FX; Becton Dickinson, USA). The Laboratory Information System was used to interrogate the susceptibility profiles for all bloodstream isolates over a period of 3.5 years (February 2014–August 2017). The MICs were interpreted as per the recent Clinical and Laboratory Standards Institute species-specific clinical breakpoints.⁶

A total of 163 episodes of candidaemia were identified within this time period. Strains isolated from expired and discharged patients [*C. glabrata* ($n = 20$), *C. tropicalis* ($n = 11$), *Candida dubliniensis* ($n = 4$), *Candida orthopsilosis* ($n = 3$), *C. parapsilosis* ($n = 1$), *Candida duobushaemulonii* ($n = 1$)] were not subjected to susceptibility testing as per the laboratory policy and were excluded from the analysis.

Our hospital mainly deals with elderly patients. Patients in our study cohort had a median age of 69 years (interquartile range 61–79 years). In geriatric populations, infections due to *C. glabrata* typically eclipse those due to other non-*albicans* species.⁷ Not surprisingly, this species comprised 50.4% ($n = 62$) of all non-*albicans* ($n = 123$) isolates subjected to a susceptibility test at our centre (Table 1). Of note, *C. glabrata*, a species prone to echinocandin resistance due to its plastic and haploid genome, tested almost uniformly susceptible. Only one isolate tested non-susceptible with an anidulafungin MIC of 0.25 mg L⁻¹. This patient had been on 11 days of intravenous anidulafungin (100 mg once a day) prior to collection of blood cultures.

The near absence of resistance bodes well for our elderly patient population where the presence of co-morbidities would significantly curtail therapeutic options. Amphotericin B would be a likely candidate for this species given its innately high MICs to the azoles. However, nephrotoxic agents like polyenes may not find favour in a geriatric centre such as ours, with liposomal formulations being several-fold more expensive than conventional options. Further, widely preferred liposomal formulations share similar side effect profiles, albeit with a lower frequency. These adverse effects are pertinent in this geriatric cohort given their overall compromised renal function status.

Echinocandin resistance was absent in *C. tropicalis*, a species for which non-susceptibility to the triazoles

Table 1 *In vitro* susceptibility of blood isolates of various *Candida* species to the azoles and echinocandins

Species (n)	Antifungal	Number of isolates with MIC (mg L ⁻¹) of														
		≤0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	≥128
<i>C. glabrata</i> (62)	Fluconazole	—	—	—	—	—	—	—	—	2	13	17	22	1	4	3
	Voriconazole	1	—	—	2	10	22	18	3	4	2	—	—	—	—	—
	Anidulafungin	—	18	33	8	2	1	—	—	—	—	—	—	—	—	—
	Micafungin	9	41	12	—	—	—	—	—	—	—	—	—	—	—	—
<i>C. tropicalis</i> (33)	Fluconazole	—	—	—	—	—	—	—	8	19	1	1	—	2	1	1
	Voriconazole	—	—	—	4	10	14	1	—	3	—	1	—	—	—	—
	Anidulafungin	—	3	7	14	9	—	—	—	—	—	—	—	—	—	—
	Micafungin	1	8	21	3	—	—	—	—	—	—	—	—	—	—	—
<i>C. parapsilosis</i> (14)	Fluconazole	—	—	—	—	—	—	4	5	3	1	—	—	1	—	—
	Voriconazole	1	3	7	2	—	1	—	—	—	—	—	—	—	—	—
	Anidulafungin	—	—	—	—	—	—	4	10	—	—	—	—	—	—	—
	Micafungin	—	—	—	—	—	—	5	9	—	—	—	—	—	—	—
<i>C. orthopsilosis</i> (4)	Fluconazole	—	—	—	—	—	—	2	2	—	—	—	—	—	—	—
	Voriconazole	1	1	2	—	—	—	—	—	—	—	—	—	—	—	—
	Anidulafungin	—	—	—	—	—	1	3	—	—	—	—	—	—	—	—
	Micafungin	—	—	—	—	—	1	3	—	—	—	—	—	—	—	—
<i>P. kudriavzevii</i> (3) ^a	Fluconazole	—	—	—	—	—	—	—	—	—	—	—	—	—	—	3
	Voriconazole	—	—	—	—	—	1	2	—	—	—	—	—	—	—	—
	Anidulafungin	—	—	1	1	1	—	—	—	—	—	—	—	—	—	—
	Micafungin	—	—	—	—	3	—	—	—	—	—	—	—	—	—	—
<i>C. haemulonii</i> (2)	Fluconazole	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	Voriconazole	—	—	—	—	—	—	—	—	—	—	2	—	—	—	—
	Anidulafungin	—	—	—	—	1	—	1	—	—	—	—	—	—	—	—
	Micafungin	—	—	—	—	1	—	1	—	—	—	—	—	—	—	—
<i>M. guilliermondii</i> (1) ^b	Fluconazole	—	—	—	—	—	—	—	—	—	1	—	—	—	—	—
	Voriconazole	—	—	—	1	—	—	—	—	—	—	—	—	—	—	—
	Anidulafungin	—	—	—	—	—	—	1	—	—	—	—	—	—	—	—
	Micafungin	—	—	—	—	—	—	1	—	—	—	—	—	—	—	—
<i>C. dubliniensis</i> (1)	Fluconazole	—	—	—	—	1	—	—	—	—	—	—	—	—	—	—
	Voriconazole	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	Anidulafungin	—	—	—	—	1	—	—	—	—	—	—	—	—	—	—
	Micafungin	—	1	—	—	—	—	—	—	—	—	—	—	—	—	—
<i>C. duobushaemulonii</i> (1)	Fluconazole	—	—	—	—	—	—	—	—	—	1	—	—	—	—	—
	Voriconazole	—	—	1	—	—	—	—	—	—	—	—	—	—	—	—
	Anidulafungin	—	—	—	—	1	—	—	—	—	—	—	—	—	—	—
	Micafungin	—	—	—	1	—	—	—	—	—	—	—	—	—	—	—
<i>C. nivariensis</i> (1)	Fluconazole	—	—	—	—	—	—	—	—	—	1	—	—	—	—	—
	Voriconazole	—	—	—	—	1	—	—	—	—	—	—	—	—	—	—
	Anidulafungin	—	—	1	—	—	—	—	—	—	—	—	—	—	—	—
	Micafungin	—	1	—	—	—	—	—	—	—	—	—	—	—	—	—
<i>C. metapsilosis</i> (1)	Fluconazole	—	—	—	—	—	—	—	—	1	—	—	—	—	—	—
	Voriconazole	—	—	—	1	—	—	—	—	—	—	—	—	—	—	—
	Anidulafungin	—	—	—	—	—	1	—	—	—	—	—	—	—	—	—
	Micafungin	—	—	—	—	—	—	1	—	—	—	—	—	—	—	—

CLSI species-specific breakpoints⁶ are as follows.

Anidulafungin: *C. glabrata* S (≤0.12), I (0.25), R (≥0.5).

Micafungin: *C. glabrata* S (≤0.06), I (0.12), R (≥0.25).

Anidulafungin and micafungin: *C. tropicalis/P. kudriavzevii* S (≤0.25), I (0.5), R (≥1); *C. parapsilosis/M. guilliermondii* S (≤2), I (4), R (≥8).

Fluconazole: *C. glabrata* SDD (≤32), R (≥64); *C. tropicalis/C. parapsilosis* S (≤2), SDD (4), R (≥8).

Voriconazole: *C. tropicalis/C. parapsilosis* S (≤0.12), I (0.25–0.5), R (≥1); *P. kudriavzevii* S (≤0.5), I (1), R (≥2).

I, intermediate; R, resistant; S, susceptible; SDD, susceptible dose dependent.

^a Formerly *C. krusei*.

^b Formerly *C. guilliermondii*.

hovers in the vicinity of 24% in the Asia-Pacific region.⁵ This is particularly relevant as 18% of our isolates tested resistant to fluconazole. This yet again underscores the important role that the echinocandins play in our local context. Echinocandins have been a part of our formulary since 2007. Caspofungin constituted the empirical antifungal of choice for *Candida* BSI at our centre until March 2015 when it was duly substituted by the less expensive anidulafungin. Increasing echinocandin consumption also serves as a harbinger of *C. parapsilosis* infections.⁸ Remarkably, only 14 episodes of BSI attributed to this species have been documented at our centre in the past 4

years. Of particular note, two strains of *C. parapsilosis* were non-susceptible to their antifungal of choice, the azoles. Importantly, *in vitro* resistance to the echinocandins was not detected for any of these strains against a background of inherently high MICs.

Despite the reports of outbreaks due to *C. auris* documented across the globe, no strains of this particular species were isolated from our centre during the study period.^{9,10} However, we did isolate two strains of *C. haemulonii*, a phylogenetically related drug-resistant *Candida* species.¹¹ One of these strains was characterised by raised MICs to the echinocandins (Table 1).

Prior antifungal exposure is instrumental in driving resistance. In the face of cumulative clinical experience with the echinocandins, uniformly low MICs were observed for the non-*albicans* species, save one strain each of *C. glabrata* and *C. haemulonii*. This lends credence to our institutional antifungal policies, despite the absence of a formal antifungal stewardship program. The uniform susceptibility pattern observed may also be attributable in part to it being a predominantly geriatric centre, which does not share the vulnerable population of haematopoietic stem cell transplant patients where empirical and prophylactic usage is widely prevalent.

The epidemiology in North America is unlike that of the Asia-Pacific region, where alarming rates (~12%) of echinocandin resistance have been encountered in *C. glabrata*.¹² Many strains were simultaneously non-susceptible to the azoles, effectively rendering them multidrug resistant.

Formalisation of the stewardship program at our tertiary care centre would enable longitudinal monitoring of known risk factors for emerging resistance. The microbiology laboratory is in an ideal position to support this by continuing surveillance of susceptibility patterns. Although resistance to the echinocandins may eventually be inevitable, this class of antifungals currently holds promise as the mainstay for therapy of *Candida* BSI.

Our study adds to the growing knowledge on antifungal resistance in geriatric cohorts as the average life expectancy steadily rises across the developed world. A similar study in elderly patients from Italy documented uniform susceptibility among non-*albicans* species to caspofungin.¹³ Close to home, in China, rates of non-susceptibility to echinocandins were nil from an independent geriatric cohort.¹⁴ This study reaffirms the position of the laboratory as the sentinel site for detecting acquired antifungal resistance, long before clinical failure is documented. It also emphasises the developing role of antifungal stewardship across particularly vulnerable patient groups.

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Detection of OXA-carbapenemase-producing Enterobacteriaceae with chromID CARBA SMART screening plate



Sir,

Carbapenemase-producing Enterobacteriaceae (CPE) have disseminated worldwide and become a global health threat. Various carbapenemase genes have been detected, with significant differences in epidemiology between different geographical locations. In Singapore, OXA-48-like carbapenemases along with NDM and KPC are the three most common carbapenemase genes identified.¹ Phenotypic detection of OXA-48 CPE is fraught with limitations due to relative weaker carbapenemase activity and lower minimum inhibitory concentration (MIC) compared to other carbapenemases. Nonetheless, they are clinically significant. Therefore, the identification and isolation of patients colonised with CPE are integral components of infection control to prevent their spread in both routine and outbreak settings.

The chromID CARBA SMART (bioMérieux, France) is a screening biplate composed of chromID CARBA and chromID OXA-48 agar. The chromID CARBA is a selective agar for CPE with reported sensitivity and specificity of >90% for various non-OXA CPE.² Sensitivity as low as 22.8% of the chromID CARBA for detection of OXA CPE has been reported.³ Girlich *et al.*³ showed that chromID OXA-48 agar improved the detection of OXA-48-like carbapenemases with a lower limit-of-detection (LOD) of 10 colony forming units (cfu) per plate while the chromID CARBA agar had a LOD of 10⁵ cfu per plate for OXA-48 CPE. We report the 2 year experience at a tertiary hospital following implementation of the chromID CARBA SMART.