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Antifungal Resistance in Asia: Mechanisms, Epidemiology, and Consequences

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Disclosure

- Research grands: Pfizer, Gilead
- Advisory boards: Pfizer, MSD, Gilead
- Speaker: Pfizer, MSD, Gilead

Contents

- What is meant by resistance?
- Is antifungal resistance in *Candida* and other yeasts a problem in Asia?
- Is antifungal resistance in *Aspergillus* and other molds a problem in Asia?
- Limitation of current published data
- Conclusion

What is meant by resistance?

Clinical failure	failure of drug therapy to resolve signs and symptoms of infection
Microbiological failure	failure of therapy to eradicate the organism
In vitro definition	based an minimum inhibitory concentrations and clinical breakpoints

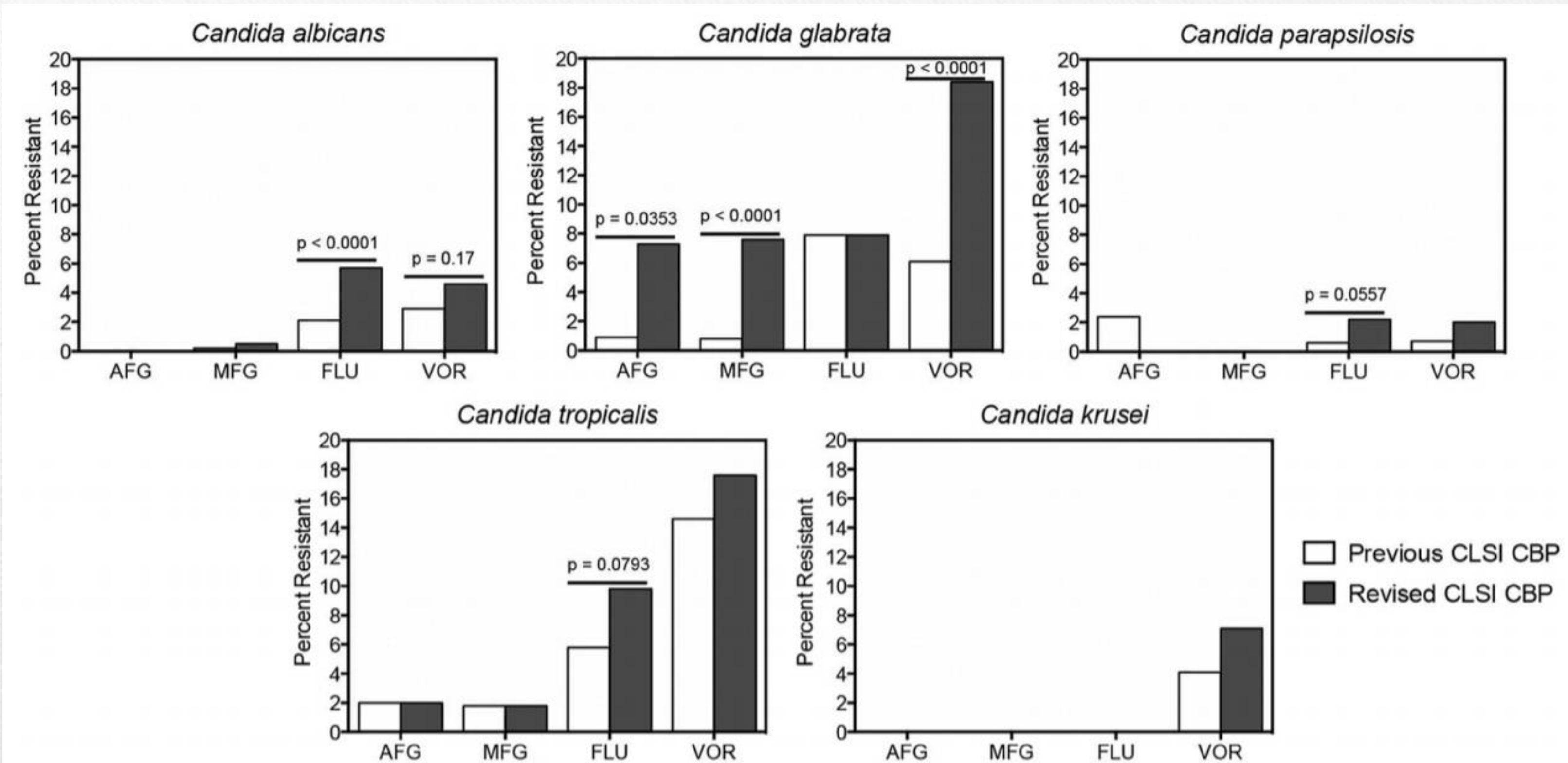
CLSI clinical breakpoints of antifungal resistance against *Candida* species

		C. albicans	*C. glabrata*	*C. tropicalis*	*C. krusei*	*C. parapsilosis*
Anidulafungin	Old	≥4	≥4	≥4	≥4	≥4
	New	≥1	≥0.5	≥1	≥1	≥8
Micafungin	Old	≥4	≥4	≥4	≥4	≥4
	New	≥1	≥0.25	≥1	≥1	≥8
Fluconazole	Old	≥64	≥64	≥64	≥64	≥64
	New	≥8	≥64	≥8	≥8	≥8
Voriconazole	Old	≥4	≥4	≥4	≥4	≥4
	New	≥1	≥1 *	≥1	≥2	≥1

*epidemiologic cutoff value

Clinical and Laboratory Standards Institute (CLSI) **2008**, M27-A3; **2012**. M27-S4.

Impact of New Antifungal Breakpoints on Antifungal Resistance in *Candida*



Fothergill et al. J Clin Microbiol. 2014; 52:994

EUCAST Antifungal Clinical Breakpoint – Yeasts

v. 8.0 valid from 2015-11-16

Antifungal agent	MIC breakpoint (mg/L)													
	C. albicans		*C. glabrata*		*C. krusei*		*C. parapsilosis*		*C. tropicalis*		*C. guilliermondii*		Non-species related breakpoints[1]	
	S ≤	R >	S ≤	R >	S ≤	R >	S ≤	R >	S ≤	R >	S ≤	R >	S ≤	R >
Amphotericin B	1	1	1	1	1	1	1	1	1	1	IE	IE	IE	IE
Anidulafungin	0.03	0.03	0.06	0.06	0.06	0.06	0.002	4	0.06	0.06	IE[2]	IE[2]	IE	IE
Caspofungin	Note[3]	Note[3]	Note[3]	Note[3]	Note[3]	Note[3]	Note[3]	Note[3]	Note[3]	Note[3]	IE[2]	IE[2]	IE	IE
Fluconazole	2	4	0.002	32	-	-	2	4	2	4	IE[2]	IE[2]	2	4
Isavuconazole	IE	IE	IE	IE	IE	IE	IE	IE	IE	IE	IE	IE	IE	IE
Itraconazole	0.06	0.06	IE[2]	IE[2]	IE[2]	IE[2]	0.12	0.12	0.12	0.12	IE[2]	IE[2]	IE	IE
Micafungin	0.016	0.016	0.03	0.03	IE[4]	IE[4]	0.002	2	IE[4]	IE[4]	IE[4]	IE[4]	IE	IE
Posaconazole	0.06	0.06	IE[2]	IE[2]	IE[2]	IE[2]	0.06	0.06	0.06	0.06	IE[2]	IE[2]	IE	IE
Voriconazole	0.12[5]	0.12[5]	IE	IE	IE	IE	0.12[5]	0.12[5]	0.12[5]	0.12[5]	IE[2]	IE[2]	IE	IE

EUCAST Antifungal Clinical Breakpoint - Molds

v. 8.0 valid from 2015-11-16

Antifungal agent	MIC breakpoint (mg/L)											
	A. flavus		*A. fumigatus*		*A. nidulans*		*A. niger*		*A. terreus*		Non-species related breakpoints[1]	
	S ≤	R >	S ≤	R >	S ≤	R >	S ≤	R >	S ≤	R >	S ≤	R >
Amphotericin B	IE[2]	IE[2]	1	2	Note[3]	Note[3]	1	2	-	-	IE	IE
Anidulafungin	IE	IE	IE	IE	IE	IE	IE	IE	IE	IE	IE	IE
Caspofungin	IE	IE	IE	IE	IE	IE	IE	IE	IE	IE	IE	IE
Fluconazole	-	-	-	-	-	-	-	-	-	-	-	-
Isavuconazole	IE[2]	IE[2]	1	1	0.25	0.25	IE[2]	IE[2]	1	1	IE	IE
Itraconazole[4]	1	2	1	2	1	2	IE[2,5]	IE[2,5]	1	2	IE[5]	IE[5]
Micafungin	IE	IE	IE	IE	IE	IE	IE	IE	IE	IE	IE	IE
Posaconazole[4]	IE[2]	IE[2]	0.12[6]	0.25[6]	IE[2]	IE[2]	IE[2]	IE[2]	0.12[6]	0.25[6]	IE	IE
Voriconazole[4]	IE[2]	IE[2]	1	2	IE	IE	IE[2]	IE[2]	IE[2]	IE[2]	IE	IE

Is antifungal resistance in *Candida* and other yeasts a problem in Asia?

Get ready for voting…

Go to webpage: **pollev.com/mmtn**

Voting question on the next slide

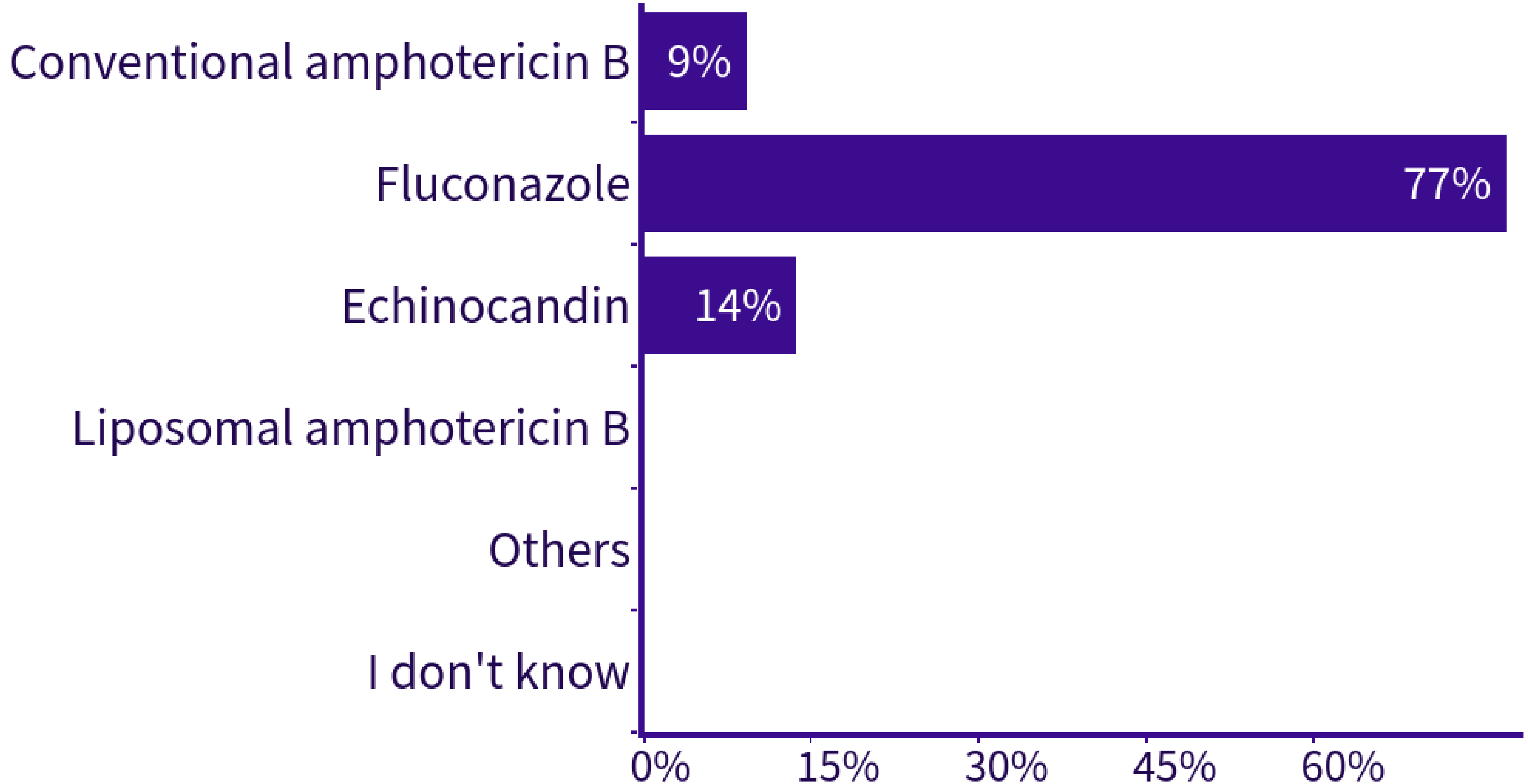
Wifi network: MMTN2016
Password: 2016mmtn

Q. Which is your most commonly used empirical antifungal agent for invasive candidiasis?

A. Conventional amphotericin B
B. Fluconazole
C. Echinocandin
D. Liposomal amphotericin B
E. Others
F. I don’t know

Which is your most commonly used empirical antifungal agent for invasive candidiasis?

When poll is active, respond at **PollEv.com/mmtn**



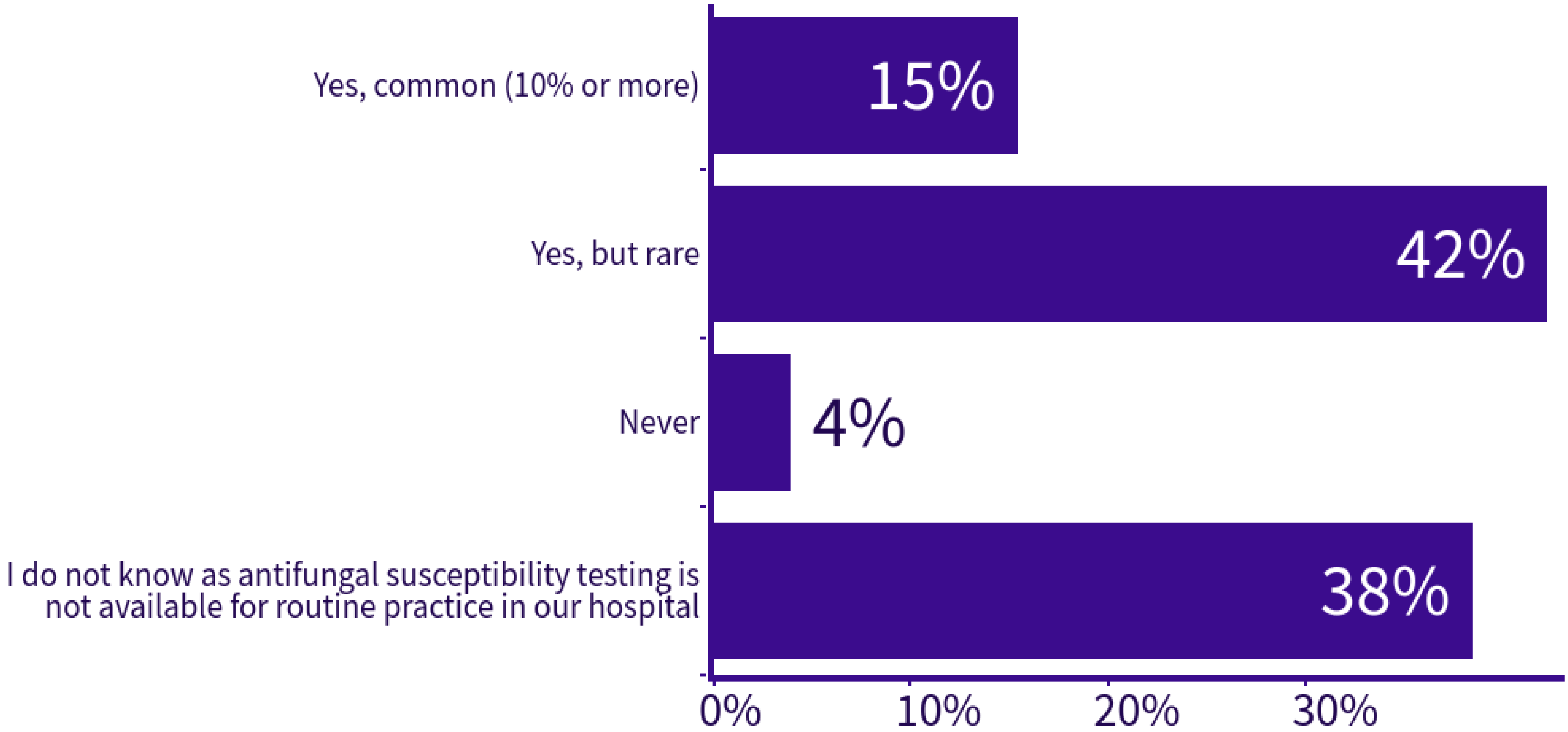
Total Results: 22

Q. Does antifungal resistance compromise the use of current empirical antifungal agent for invasive candidiasis in your hospital?

A. Yes, common (10% or more)
B. Yes, but rare
C. Never
D. I do not know as antifungal susceptibility testing is not available for routine practice in our hospital

Does antifungal resistance compromise the use of current empirical antifungal agent for invasive candidiasis in your hospital?

Poll is full and no longer accepting responses



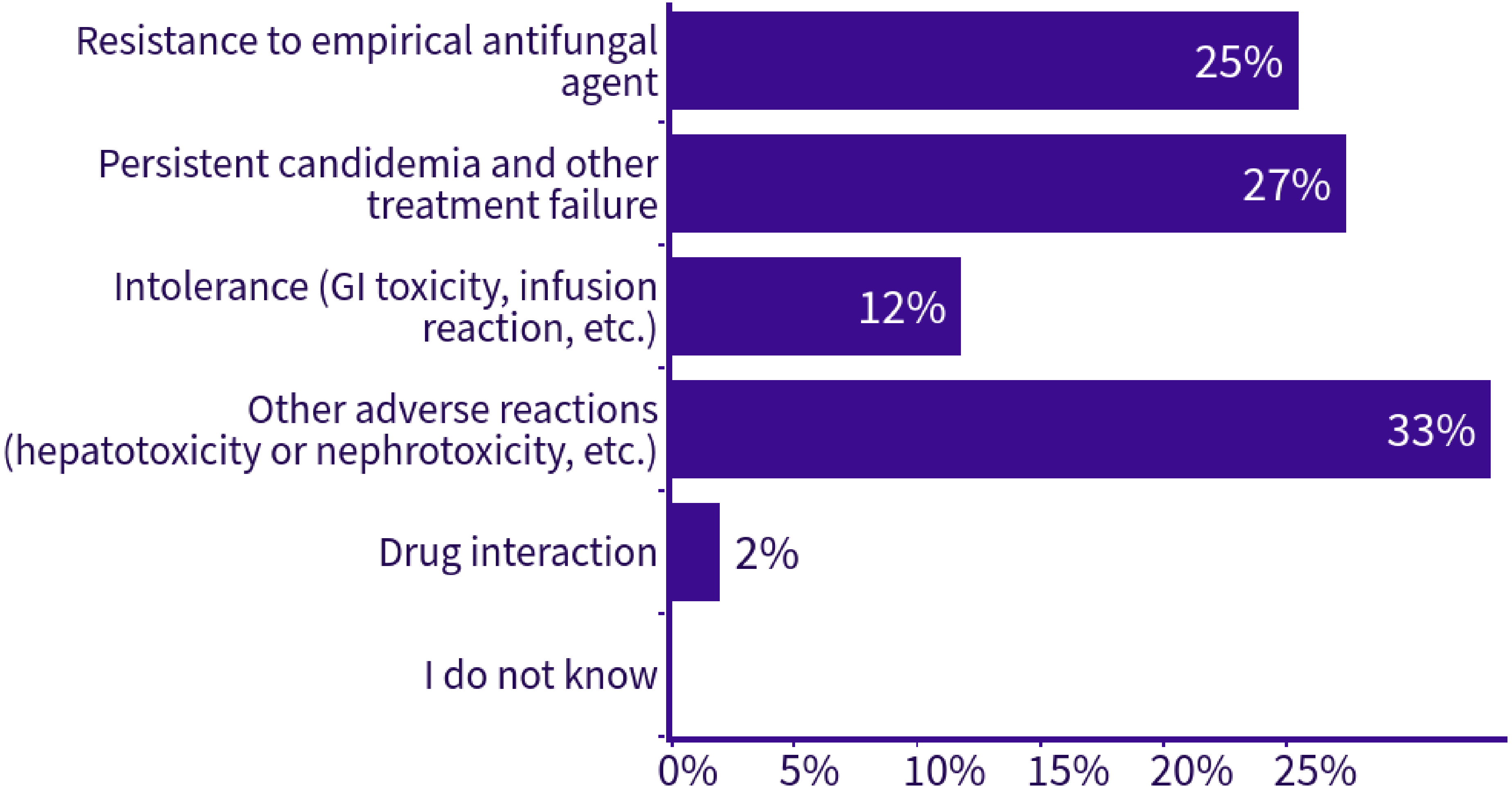
Total Results: 26

Q. The most common two reasons of modification of therapeutic agents for invasive candidiasis? (Select two choices)

A. Resistance to empirical antifungal agent
B. Persistent candidemia and other treatment failure
C. Intolerance (GI toxicity, infusion reaction, etc.)
D. Other adverse reactions (hepatotoxicity or nephrotoxicity, etc.)
E. Drug interaction
F. I do not know

The most common two reasons of modification of therapeutic agents for invasive candidiasis? (Select two choices)

Poll is full and no longer accepting responses



Total Results: 51

Incidence and species distribution of candidaemia in Asia: a laboratory-based surveillance study

B. H. Tan[1], A. Chakrabarti[2], R. Y. Li[3], A. K. Patel[4], S. P. Watcharananan[5], Z. Liu[6], A. Chindamporn[7], A. L. Tan[8], P.-L. Sun[9], U.-I. Wu[10] and Y.-C. Chen[11,12], on behalf of the Asia Fungal Working Group (AFWG)

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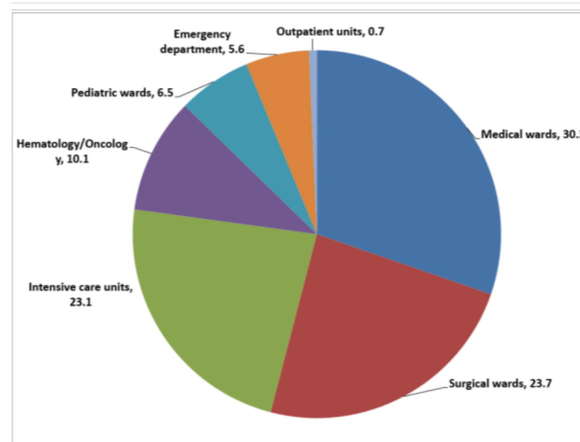
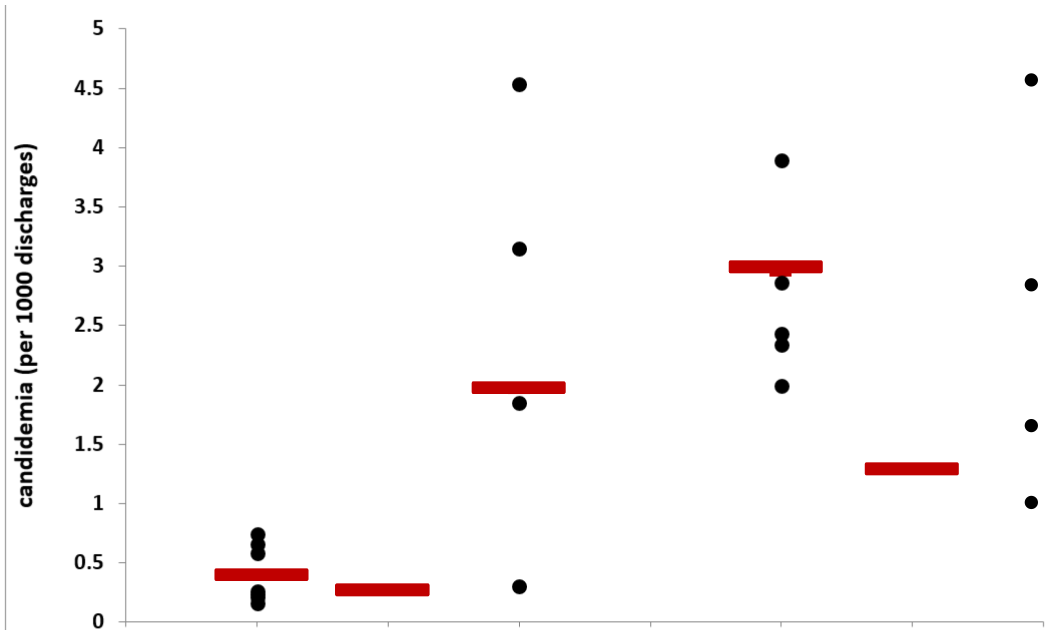




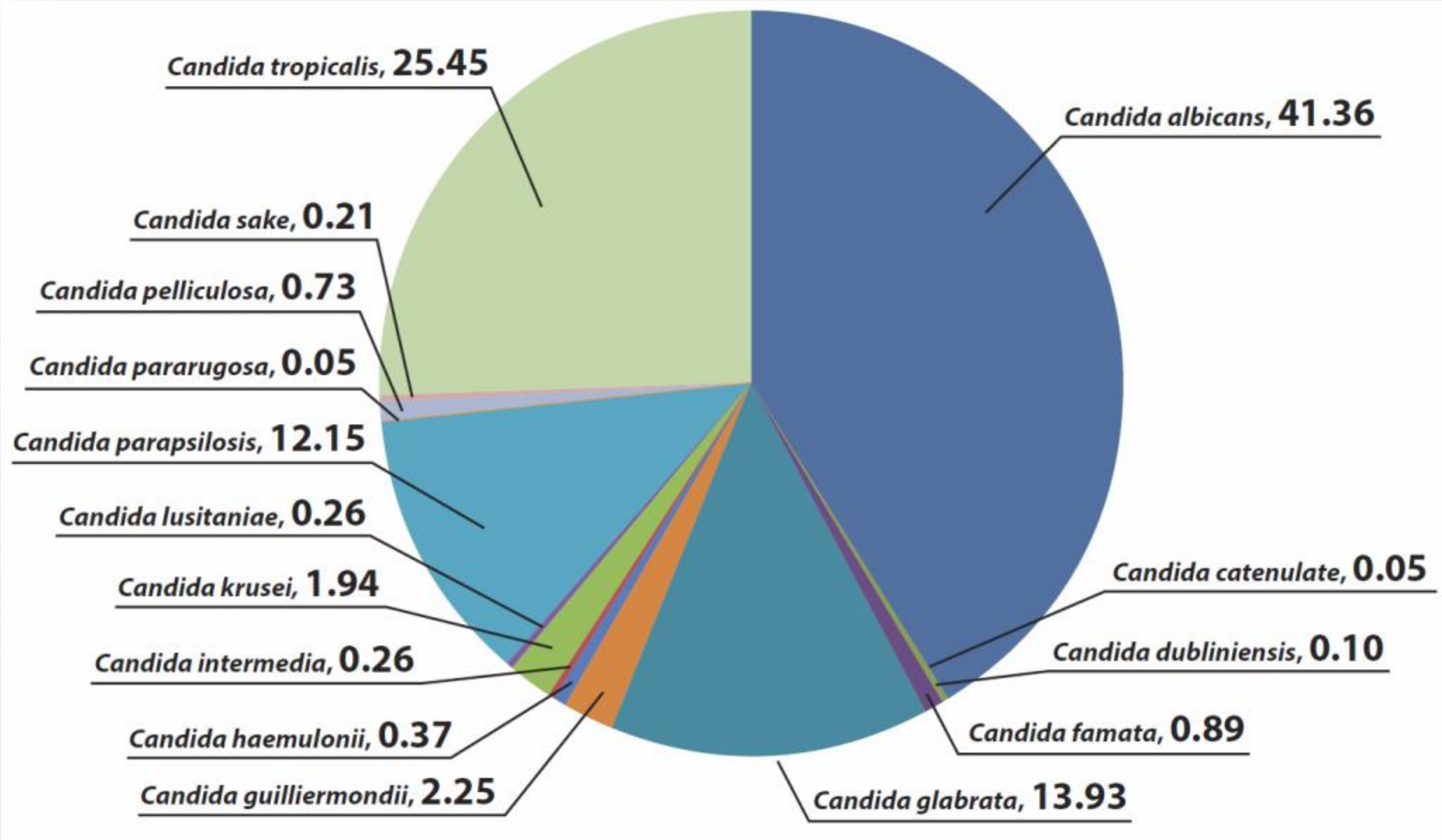
	China	HK	India	Singapore	Taiwan	Thailand
No. of hospitals	9	1	3	1	6	3
No. of episodes	310	30	330	73	1104	130

- The overall incidence was **1.22** episodes per 1,000 discharges or 0.15 episodes/1000 patient-days
- Varied among the hospitals and countries.
- ICU: **11.7** per 1000 discharges
- There was a moderate correlation between incidence of candidemia and the ICU/total bed ratio (R^2=0.47)

Clin Microbiol Infect 2015; 21: 946

Candida tropicalis was the leading non-*albicans* species

Species distribution in Asia ,1910 non-duplicate blood Candida isolates



Clin Microbiol Infect 2015; 21: 946–953

Both geographic and healthcare contribute to the variation of species distribution of candidemia

- *C. tropicalis* was more likely to be isolated at neutropenic patients than others (39% vs 17%).[1]
- *C. tropicalis* was more likely to be isolated at hemato-oncolgy wards than others (34.0% vs 24.5%).[2]
- The proportions of *C. tropicalis* among blood isolates were higher in tropical areas (India, Thailand and Singapore) than other geographical regions (46.2% versus 18.9%).[2]

1. Hung et al. J Formos Med Assoc 1996;95:19
2. Tan et al. Clin Microbiol Infect 2015; 21: 946

Candida bloodstream isolates, Asia-Pacific region

Species	Antifungal name	%I	%S	MIC50 (mg/l)	MIC90 (mg/l)
Candida albicans	Anidulafungin	0	100	0.016	0.064
	Caspofungin	0	100	0.064	0.064
	Fluconazole*	0	99.7	0.25	0.5
	Micafungin	0	100	0.008	0.016
	Voriconazole*	0	100	0.008	0.008
Candida tropicalis	Anidulafungin	0.4	99.2	0.032	0.125
	Caspofungin	0.4	99.6	0.064	0.125
	Fluconazole*	6.1	75.8	2	32
	Micafungin	0	100	0.032	0.032
	Voriconazole*	16.7	69.3	0.125	1
Candida parapsilosis	Anidulafungin	0	100	0.5	2
	Caspofungin	0	100	0.25	0.5
	Fluconazole*	3.0	94.8	0.5	2
	Micafungin	0.8	99.2	1	2
	Voriconazole*	0.8	99.2	0.008	0.032
Candida glabrata	Anidulafungin	0	99.1	0.032	0.064
	Caspofungin	5.2	93.1	0.125	0.125
	Fluconazole*	94.8	n/a	8	32
	Micafungin	1.7	98.3	0.016	0.016

861 isolates from 13 centers, 2014
Sensititre YeastOne YST-010, Thermofisher, United Kingdom
Tan TY, et al. Med Mycology 2016:54, 471

Candida bloodstream isolates, Asia-Pacific region

Species	Antifungal name	Brunei %I	Brunei %S	Korea %I	Korea %S	Philippines %I	Philippines %S	Taiwan %I	Taiwan %S	Thailand %I	Thailand %S	Singapore %I	Singapore %S	Vietnam %I	Vietnam %S
Candida albicans	Anidulafungin	0	100	0	100	0	100	0	100	0	100	0	100	0	100
	Caspofungin	0	100	0	100	0	100	0	100	0	100	0	100	0	100
	Fluconazole*	0	100	0	97.4	0	100	0	100	0	100	0	100	0	100
	Micafungin	0	100	0	100	0	100	0	100	0	100	0	100	0	100
	Voriconazole*	0	100	0	100	0	100	0	100	0	100	0	100	0	100
Candida tropicalis	Anidulafungin	0	100	0	100	0	100	0	96.6	0	100	2.3	97.7	0	100
	Caspofungin	0	100	0	100	0	100	0	100	0	100	2.3	97.7	0	100
	Fluconazole*	14.3	85.7	0	100	0	100	6.9	82.8	9.5	70.3	6.8	72.7	3.3	61.7
	Micafungin	0	100	0	100	0	100	0	100	0	100	0	100	0	100
	Voriconazole*	7.1	92.9	0	100	3.8	96.2	13.8	82.8	16.2	64.9	25	63.6	25	46.7
Candida parapsilosis	Anidulafungin	0	100	0	100	0	100	0	100	0	100	0	100	0	100
	Caspofungin	0	100	0	100	0	100	0	100	0	100	0	100	0	100
	Fluconazole*	11.1	83.3	3.8	96.2	4.2	87.5	9.0	91.0	0	100	0	95	0	100
	Micafungin	5.6	94.4	0	100	0	100	0	100	0	100	0	100	0	100
	Voriconazole*	0	100	0	100	4.2	95.8	0	100	0	100	0	100	0	100
Candida glabrata	Anidulafungin	0	100	0	100	0	100	0	100	0	96.8	0	100	0	100
	Caspofungin	0	100	22.2	77.8	0	100	0	100	3.2	93.5	8.2	89.8	0	100
	Fluconazole*	80	n/a	100	n/a	100	n/a	100	n/a	93.5	n/a	93.9	n/a	100	n/a
	Micafungin	0	100	0	100	0	100	0	100	3.2	96.8	2	98	0	100

861 isolates from 13 centers, 2014 *Tan TY, et al. Med Mycology* 2016:54, 471

Invasive candidiasis in intensive care units in China

the China-SCAN study

			MIC (mg/L)						ECV (mg/L)	
Species	Isolates, *n* (%)	Agent	range	50%	90%	Susceptible, *n* (%)	SDD, *n* (%)	Resistant, *n* (%)	WT	non-WT
Candida albicans	156 (40.1)	fluconazole	0.06–64	1	4	134 (85.9)	7 (4.5)	15 (9.6)		
		voriconazole	0.03–0.5	0.03	0.03	145 (93.0)	11 (7.1)	0 (0.0)		
		itraconazole	0.06–4	0.06	1	6 (3.9)	125 (80.1)	25 (16.0)		
		caspofungin	0.03–0.25	0.06	0.125	156 (100.0)	0 (0.0)	0 (0.0)		
		amphotericin B	0.25–1	0.5	0.5				156 (100.0)	0 (0.0)
Candida parapsilosis	83 (21.3)	fluconazole	0.125–64	4	8	40 (48.2)	27 (32.5)	16 (19.3)		
		voriconazole	0.03–2	0.03	0.125	77 (92.8)	3 (3.6)	3 (3.6)		
		itraconazole	0.06–2	0.5	1				50 (60.2)	33 (39.8)
		caspofungin	0.03–0.5	0.25	0.25	83 (100.0)	0 (0.0)	0 (0.0)		
		amphotericin B	0.25–1	0.5	0.5				83 (100.0)	0 (0.0)
Candida tropicalis	67 (17.2)	fluconazole	0.25–64	2	4	42 (62.7)	21 (31.3)	4 (6.0)		
		voriconazole	0.03–0.5	0.03	0.25	60 (89.6)	7 (10.4)	0 (0.0)		
		itraconazole	0.03–4	0.5	2				46 (68.7)	21 (31.3)
		caspofungin	0.03–0.25	0.06	0.125	67 (100.0)	0 (0.0)	0 (0.0)		
		amphotericin B	0.25–1	0.5	1	67 (100.0)[a]		0 (0.0)[a]		
Candida glabrata	50 (12.9)	fluconazole	0.5–64	4	32	0 (0.0)	48 (96.0)	2 (4.0)		
		voriconazole	0.03–2	0.06	0.125				47 (94.0)	3 (6.0)
		itraconazole	0.5–4	1	2	0 (0.0)			48 (96.0)	2 (4.0)
		caspofungin	0.03–0.25	0.125	0.25	43 (86.0)	7 (14.0)	0 (0.0)		
		amphotericin B	0.03–1	0.5	0.5	50 (100.0)[a]		0 (0.0)[a]		
Candida haemulonii	15 (3.9)	fluconazole	1–64	16	16	—		—		
		voriconazole	0.03–4	0.25	0.5	—		—		
		itraconazole	0.5–2	1	2	—		—		
		caspofungin	0.06–0.125	0.06	0.06	—		—		
		amphotericin B	0.5–1	0.5	1	—		—		

67 ICUs

Liu W, et al. J Antimicrob Chemother 2014; 69: 162

ICU-acquired candidemia in India

Antifungal	AFST	All species ($n = 918$)	*C. tropicalis* ($n = 382$)
Amphotericin B	MIC_{50} (μg/ml)	–	0.50
	MIC_{90} (μg/ml)	–	1.00
	Resistant (%)	2.1 %	4 (1.0)
	MIC percentile (25–75)		0.25–1
Fluconazole	MIC_{50} (μg/ml)	–	0.50
	MIC_{90} (μg/ml)	–	2.00
	Resistant (%)	6.2 %	10 (2.6)
	SDD (%)	11.0 %	9 (2.4)
	MIC percentile (25–75)		0.25–1
Itraconazole	MIC_{50} (μg/ml)	–	0.06
	MIC_{90} (μg/ml)	–	0.12
	Resistant (%)	1.2 %	1 (0.3)
	SDD (%)	9.3 %	27 (7.1)
	MIC percentile (25–75)		0.03–0.12
Posaconazole	MIC_{50} (μg/ml)	–	0.03
	MIC_{90} (μg/ml)	–	0.25
	MIC percentile (25–75)		0.03–0.12
Voriconazole	MIC_{50} (μg/ml)	–	0.12
	MIC_{90} (μg/ml)	–	0.50
	Resistant (%)	5.6 %	31 (8.1)
	SDD (%)	22.9 %	128 (33.5)
	MIC percentile (25–75)		0.06–0.25
Anidulafungin	MIC_{50} (μg/ml)	–	0.03
	MIC_{90} (μg/ml)	–	0.25
	Resistant (%)	1.7 %	8 (2.1)
	Intermediate (%)	1.6 %	8 (2.1)
	MIC percentile (25–75)		0.03–0.06
Caspofungin	MIC_{50} (μg/ml)	–	0.25
	MIC_{90} (μg/ml)	–	0.50
	Resistant (%)	5.6 %	16 (4.2)
	Intermediate (%)	10.1 %	50 (13.1)
	MIC percentile (25–75)		0.12–0.25
Micafungin	MIC_{50} (μg/ml)	–	0.03
	MIC_{90} (μg/ml)	–	0.12
	Resistant (%)	1.7 %	5 (1.3)
	Intermediate (%)	2.2 %	11 (2.9)
	MIC percentile (25–75)		0.03

27 Indian ICUs   Arunaloke Chakrabarti et al. Intensive Care Med (2015) 41:285

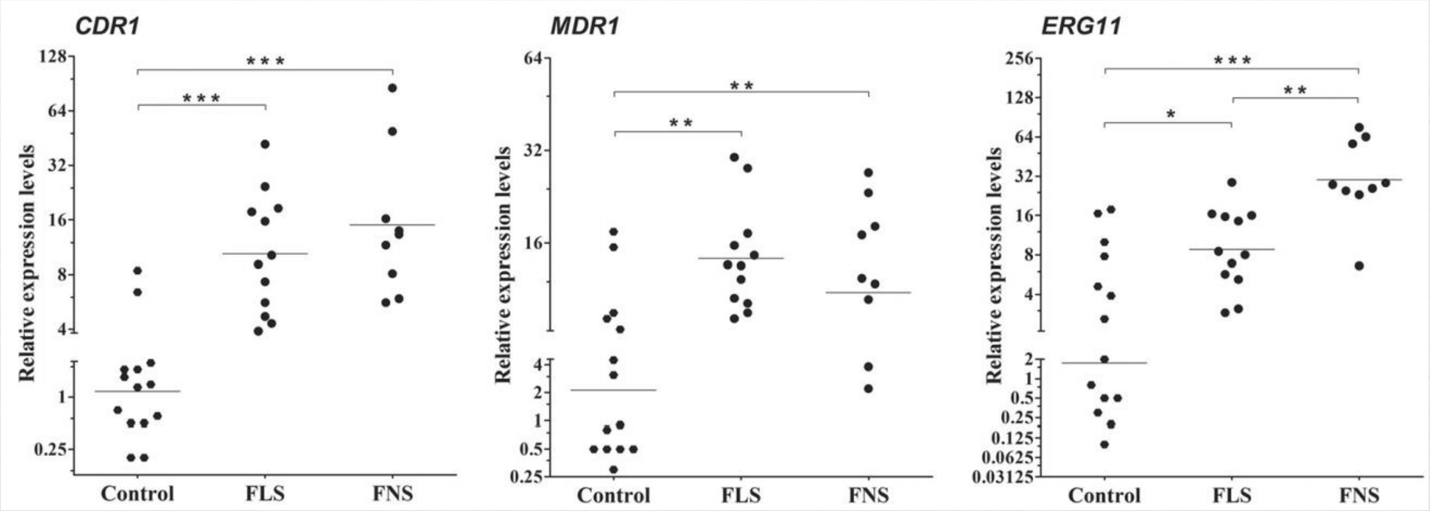
C. tropicalis

- The time-to-positivity (TTP) of blood cultures of *C. tropicalis* was significantly shorter than that of other species[1]
- Septic shock and skin emboli are common findings of candidemia[2]
- Both short TTP[3] and septic shock are associated with poor prognosis.
- A survey in Taiwan found genetically related *C. tropicalis* exhibiting reduced susceptibility to fluconazole from the human hosts and environmental samples. [4]

1. Lai et al.J Med Microbiol 2012;61:701
2. Leung et al. J Hosp Infect 2002;50:316
3. Kim et al. J Antimicrob Chemother 2013
4. Yang et al. PLoS One 2012;7:e34609.

Fluconazole-nonsusceptible/less-susceptible *C. tropicalis*

- FNS (MIC ≥4 g/ml), isolates were identified more frequently from patients with previous azole exposure (6/6 versus 3/10; *P* = 0.011) and immunosuppression (6/6 versus 3/10; *P* = 0.011).
- FNS and FLS (1-2 g/ml), bloodstream isolates were associated with azole therapeutic failure (3/4 versus 4/7) or uncleared fungemia (4/6 versus 4/10)



Choi MJ, et al. Antimicrob. Agents Chemother 2016 60: 3653

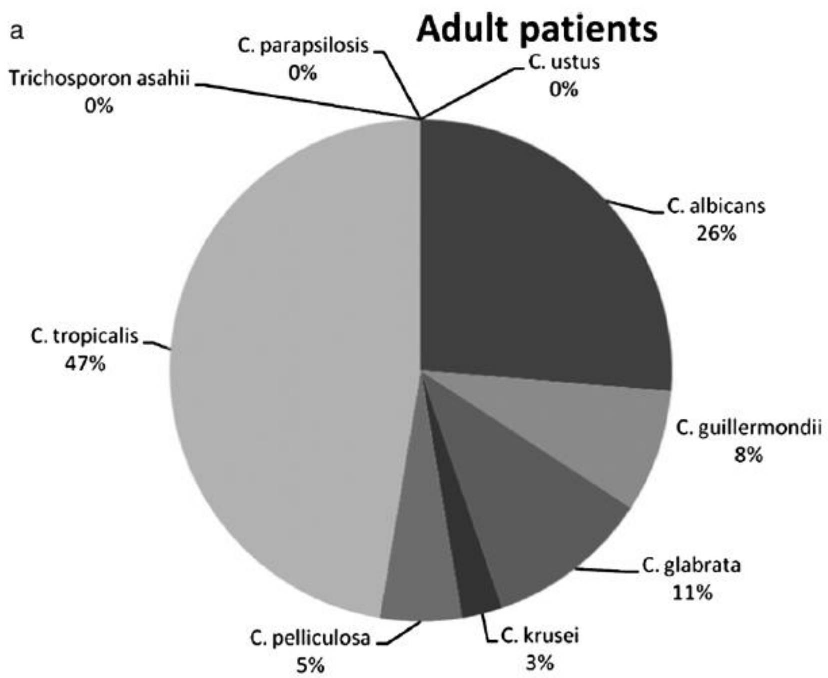
C. pelliculosa

- *C. pelliculosa*, also known as *Pichia anomala* or *Hansenula anomala*, is mainly found in plants, fruits and oil.
- Ten out of 14 episodes in this cohort were reported from a single hospital, clustered in the ICUs. Tan et al. Clin Microbiol Infect 2015;21:946
- In the preceding year, this hospital identified a monoclonal outbreak of *C. pelliculosa.*

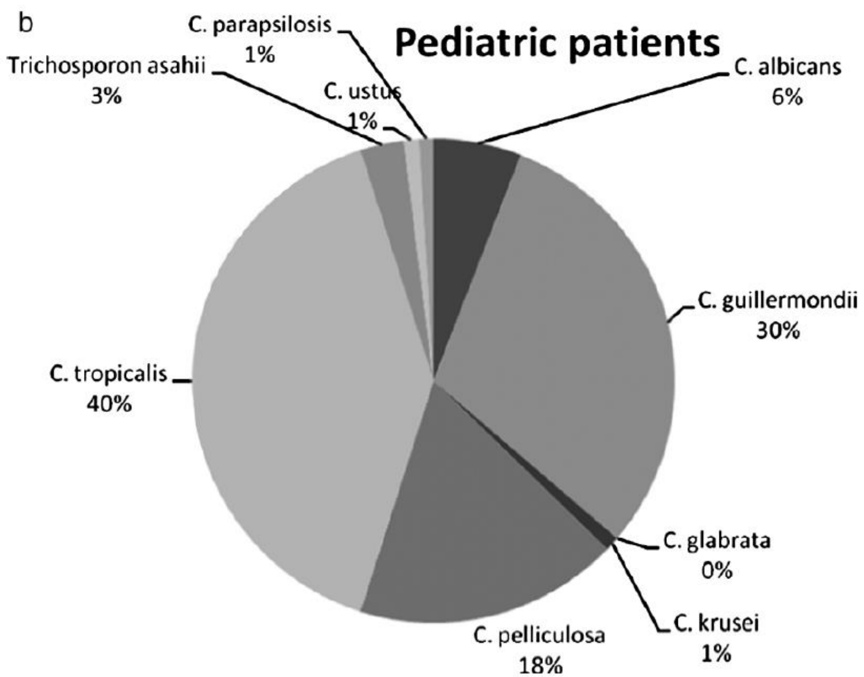
J Microbiol Immunol Infect 2013;46:456

4-month prospective study in a tertiary care center, India, Sept-Dec 2007

N=38



N=102



Chakrabarti et al. Scand J Infect Dis 2009;41:275-84

Pichia anomala (C. pelliculosa) outbreak in paediatric wards during 1996-1997.

Emerging opportunistic yeast infections

- *Candida krusei* [1]
- *Candida guilliermondii* [2]
- *Candida rugosa* [3]
- *Candida lusitaniae*[4]
- *Candida dubliniensis*[5]
- *Candida pelliculosa* [6]
- *Candida kefyr* [6,7]
- *Candida nivariensis* [8]
- *Candida norvegensis*
- *Cryptococcus humicolus*
- *Cryptococcus uniguttulatus*
- *Geotrichum capitatum* [9]
- *Hansenula*
- *Saccharomyces cerevisiae*

1. Intrinsic resistance to fluconazole, susceptible to voriconazole
2. Potential for decreased susceptibility to polyenes, azoles, flucytosine, and the echinocandins
3. Cross resistance to fluconazole and voriconazole
4. Can develop secondary resistance to amphotericin B
5. Can develop stable fluconazole resistance, especially in patients with HIV/AIDS
6. Outbreak
7. Dairy products
8. Gardens or potted plants
9. Presence of blastoconidia with hyphae differentiates *Trichosporon* from *Geotrichum,* predominantly in Italy.

Miceli et al. Lancet Infect Dis 2011;11:142

Candida haemulonii and Closely Related Species, Korea

- A yeast species that often exhibits antifungal resistance (AmB, azole), rarely causes human infection
- Recovered from 8 patients with fungemia and 15 patients with chronic otitis media in 5 hospitals in Korea during 2004–2006.
- Species identification
  - Vitek 2 YST yeast card system: identified as *C. haemulonii*
  - API 20C system: identified as *Kodamaea ohmeri* and *Rhodotorula glutinis*
- Drug resistance were associated with therapeutic failure
- All susceptible to caspofungin and micafungin

Kim et al. Clin Infect Dis 2009;48: e57

One size not fit all

Activity of antifungal drugs against emerging yeasts

	Azoles		Polyenes	Echinocandins
	Fluconazole	Voriconazole	Amphotericin formulations	Caspofungin
Candida species				
Candida glabrata	Susceptible (dose dependent) to resistant	Susceptible (dose dependent) to resistant	Susceptible to intermediate susceptibility	Susceptible*
Candida tropicalis	Susceptible	Susceptible	Susceptible	Susceptible*
Candida parapsilosis	Susceptible	Susceptible	Susceptible	Susceptible to resistant*
Candida krusei	Resistant	Susceptible (dose dependent) to resistant	Susceptible to intermediate susceptibility	Susceptible
Candida kefyr	Susceptible	Susceptible	Susceptible	Susceptible
Candida lusitaniae	Susceptible	Susceptible	Susceptible to resistant	Susceptible*
Candida dubliniensis	Susceptible to resistant	Susceptible	Susceptible	Susceptible
Candida rugosa	Very low activity	Low activity	Susceptible	Susceptible
Candida guilliermondii	Low activity	Susceptible	Susceptible	Susceptible
Trichosporon species				
Trichosporon asahii	Low activity	Susceptible	Resistant	Resistant
Trichosporon beigelii (cutaneum)	Low activity	Low activity	Resistant	Resistant
Rhodotorula species	Very low activity	Variable susceptibility/ very low activity	Susceptible	Resistant
Non-*neoformans* cryptococcus species				
Overall	Low activity	Susceptible	Susceptible	NA
Cryptococcus laurentii	Very low activity	NA	Susceptible*	Resistant
Other uncommon yeasts				
Geotrichum species	Variable susceptibility	Susceptible	Susceptible	NA
Hansenula anomala	Fluconazole: low activity; itraconazole: very low activity	Susceptible	Susceptible	Susceptible
Malassezia species	Fluconazole: low activity; itraconazole: susceptible	Susceptible	Variable susceptibility	NA
Saccharomyces species	Low activity/variable susceptibility	Susceptible	Susceptible	NA

Resistant was defined as less than 40% of isolates tested reported as active. Susceptible was defined as more than 90% of isolates tested reported as active. Low activity was defined as 60–89% of isolates tested reported as active. Very low activity was defined as 40–59% of isolates tested reported as active. NA=data not available. *Susceptible but resistance reported after exposure (ie, breakthrough infections).

Lancet Infect Dis 2011;11: 142

Comparative In vitro Activities of Various Antifungal Drugs against *Candida* and *Cryptococcus* Singapore General Hospital, 2004-2006

Fungal isolates	No.	POS		FLU		VOR		AMB		CAS	
		MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}
All *Candida* sp.	100	0.064	1.5	0.38	16	0.032	0.38	0.38	0.75	0.094	0.25
C. albicans	24	0.032	0.064	0.125	0.19	0.006	0.008	0.094	0.125	0.032	0.125
C. tropicalis	28	0.094	0.125	0.38	0.75	0.047	0.094	0.5	1	0.094	0.19
C. glabrata	27	1	2	16	48	0.25	0.5	0.5	0.75	0.094	0.19
C. parapsilosis	12	0.023	0.047	0.38	0.75	0.012	0.023	0.125	0.5	0.25	1
C. dubliniensis	7	0.012	0.023	0.094	0.25	0.004	0.006	0.012	0.032	0.125	0.125
C. krusei	1	0.25	0.25	24	24	0.19	0.19	0.5	0.5	0.25	0.25
C. famata	1	0.006	0.006	0.094	0.094	0.003	0.003	0.016	0.016	0.19	0.19
Cryptococcus sp.	10	0.125	0.38	8	32	0.023	0.094	0.25	0.25	>32	>32
C. neoformans	8	0.125	0.38	4	32	0.016	0.094	0.25	0.38	>32	>32
C. gattii	2	0.19	0.5	8	32	0.064	0.125	0.25	0.25	>32	>32

Etest, MIC in µg/mL

Tan AL et al. Ann Acad Med Singapore 2008;37:841

Antifungal Susceptibility of 216 cryptococcal clinical isolates in Taiwan, 1997–2010

Antifungal agent	Genotype	No. of isolates	Minimum inhibitory concentration (μg/mL)					% (No.) above ECV	
			Range	Geometric Mean	MIC_{50}	MIC_{90}	ECV	This study	Global studies[a]
Amphotericin B									
	VNI	203	0.03–1	0.48	0.5	0.5	0.5	3.4% (7)	2.8%
	VNII	4	0.13–1	0.42	0.5	1	NA[a]		
	VGI	3	0.25–0.25	0.25	0.25	0.25	0.5	0%	0.8%
	VGII	6	0.06–1	0.31	0.5	1	1	0%	0.8%
Flucytosine									
	VNI	203	0.13–32	1.14	1	2	8	0.5% (1)	3.4%
	VNII	4	0.13–2	0.30	0.19	2	NA[a]		
	VGI	3	0.5–1	0.63	0.5	1	4	0%	4.3%
	VGII	6	1–2	1.59	2	2	16	0%	2.9%
Fluconazole									
	VNI	203	0.03–16	2.35	4	8	8	0.5% (1)	2.9%
	VNII	4	0.13–8	0.84	0.75	8	NA[a]		
	VGI	3	1–4	2	2	4	8	0%	1.2%
	VGII	6	0.13–16	5.04	8	16	32	0%	6.9%
Voriconazole									
	VNI	203	0.03–0.25	0.06	0.06	0.13	0.25	0%	2.4%
	VNII	4	0.03–0.13	0.05	0.05	0.13	NA[a]		
	VGI	3	0.03–0.06	0.04	0.03	0.06	0.5	0%	0%
	VGII	6	0.13–0.25	0.20	0.25	0.25	0.25	0%	4.1%

Tseng et al. Plos One 2013;8(4): e61921.

Is antifungal resistance in *Aspergillus* and other molds a problem in Asia?

Comparative In vitro Activities of Various Antifungal Drugs against Moulds

Fungal isolates	No.	POS		ITR		VOR		AMB		CAS	
		MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}
All moulds	50	0.047	>32	0.19	>32	0.094	4	0.25	3	0.016	>32
Aspergillus sp.	34	0.023	0.125	0.094	0.25	0.064	0.19	0.125	2	0.008	0.047
A. fumigatus	12	0.032	0.047	0.094	0.19	0.094	0.125	0.19	0.25	0.003	0.047
A. niger	12	0.012	0.032	0.064	0.19	0.032	0.064	0.125	0.19	0.012	0.064
A. flavus	7	0.094	0.19	0.19	0.25	0.125	0.19	2	4	0.008	0.023
A. clavatus/A. nidulans	3	0.016	1	0.25	0.38	0.094	0.25	0.032	0.38	0.016	0.032
Fusarium solani	10	>32	>32	>32	>32	2	4	3	4	>32	>32
Others	6	0.38	>32	1	>32	6	64	0.25	>32	>32	>32

Etest, MIC in µg/mL

Tan AL et al. Ann Acad Med Singapore 2008;37:841

Invasive infections caused by moulds other than *Aspergillus*

- A tertiary care hospital in Taiwan, 2000-2008
- 103 patients with cultures positive for non-Aspergillus moulds
- The overall mortality rate was 40.7%, and was highest in cases zygomycosis.

Characteristic	*Fusarium*	*Paecilomyces*	*Zygomycetes*	*Scedosporium*
Number (%) of patients	12 (44.4)	7 (25.9)	5 (18.5)	3 (11.1)
Age, median (range)	39.5 (0–79)	60 (9–82)	37 (23–81)	65.4 (48–78)
Male	6 (50)	4 (57)	3 (60)	3 (75)
Diagnosis				
Acute leukaemia	5	2	4	0
Lymphoma	1	0	0	0
MDS	1	0	0	0
Solid tumour	1	1	0	1
AIDS	0	2	0	0
Diabetes mellitus	0	2	0	0
HSCT	0	0	1	0
Solid organ transplant	1	0	1	1
Immunological risk factors				
Steroid use	6	1	1	2
Neutropenia < 500/μL	4	2	2	0
Lymphopenia < 1500/μL	7	2	2	0

Hsiue HC et al. Clin Microbiol Infect. 2010;16:1204

Cutaneous T cell lymphoma with acute leukemic change

Disseminated fusariosis

Liu et al. Med Mycol. 2011;49:872

Recommendations for treatment of *Fusarium* infection in immunocompromised patients

Population	Intention	SoR	QoE	Comment
Immunocompromised patients	First-line treatment			
	Voriconazole	A	IIt,r	Therapeutic drug monitoring required Response rate was associated with underlying condition and infection site
	Liposomal amphotericin B	B	IIt,r	Fungi may be resistant to amphotericin B
	Amphotericin B lipid complex	C	III	Limited case reports
	Amphotericin B deoxycholate	D	IIt,u	Fungi often resistant to amphotericin B Breakthrough infections may occur Excessive toxicity
	Any echinocandin	D	III	Intrinsically resistant
	Any combination therapy	C	III	Limited reports Combination not better than voriconazole alone
	Salvage treatment			
	Posaconazole	A	II	Overall success rate 50% Breakthrough infections Therapeutic drug monitoring required
	Voriconazole	A	III	Substantial efficacy Therapeutic drug monitoring required

QoE, quality of evidence; SoR, strength of recommendation.

Clin Microbiol Infect 2014;20(Suppl. 3):27–46

Get ready for voting…

Go to webpage: **pollev.com/mmtn**

Voting question on the next slide

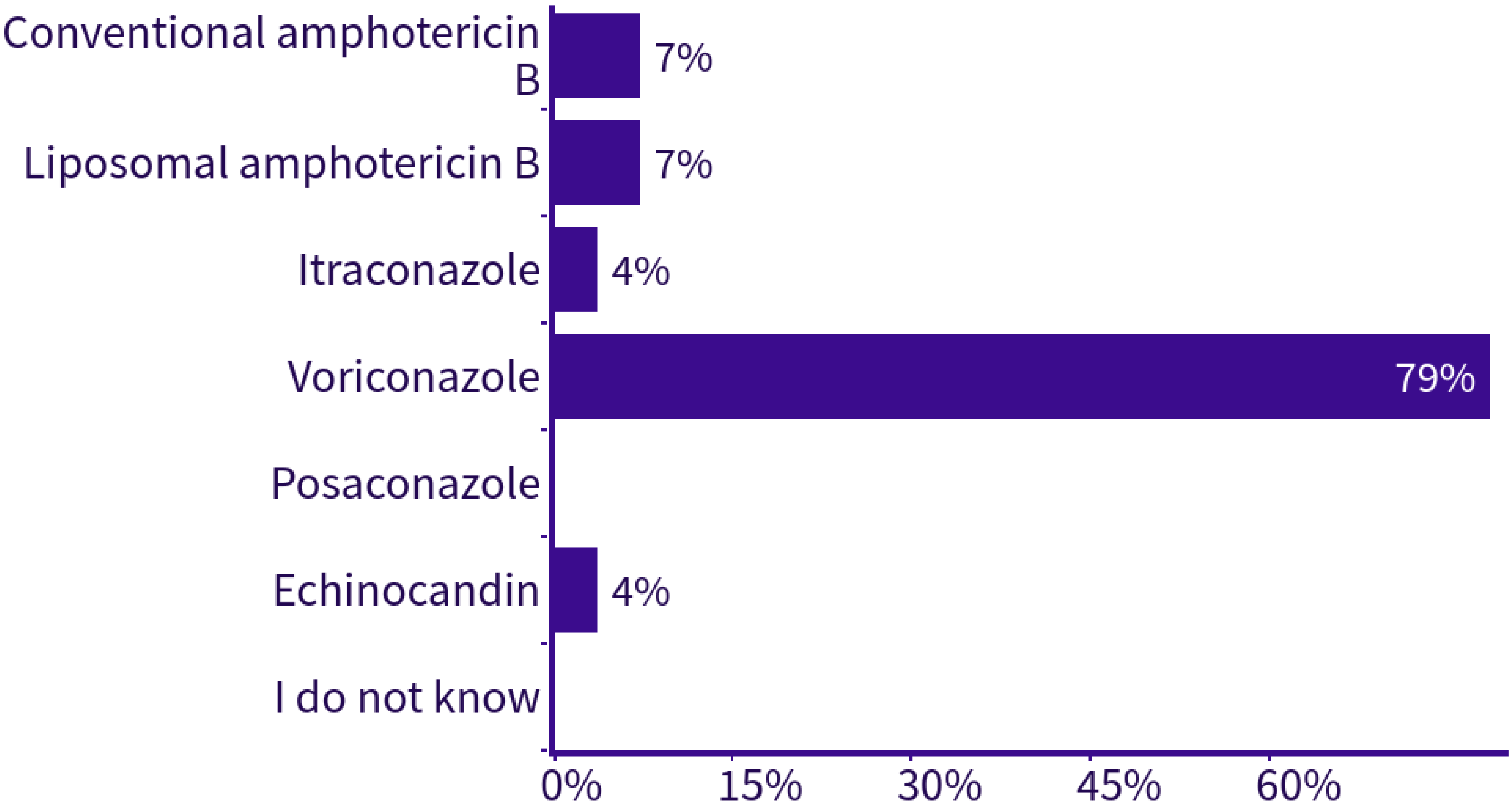
Wifi network: MMTN2016
Password: 2016mmtn

Q. Which is your most commonly used antifungal agent for invasive aspergillosis?

A. Conventional amphotericin B
B. Liposomal amphotericin B
C. Itraconazole
D. Voriconazole
E. Posaconazole
F. Echinocandin
G. I do not know

Which is your most commonly used antifungal agent for invasive aspergillosis?

Poll is full and no longer accepting responses



Total Results: 28

Q. Does antifungal resistance compromise the use of current antifungal agent for invasive aspergillosis in your hospital?

A. Yes, common (10% or more)

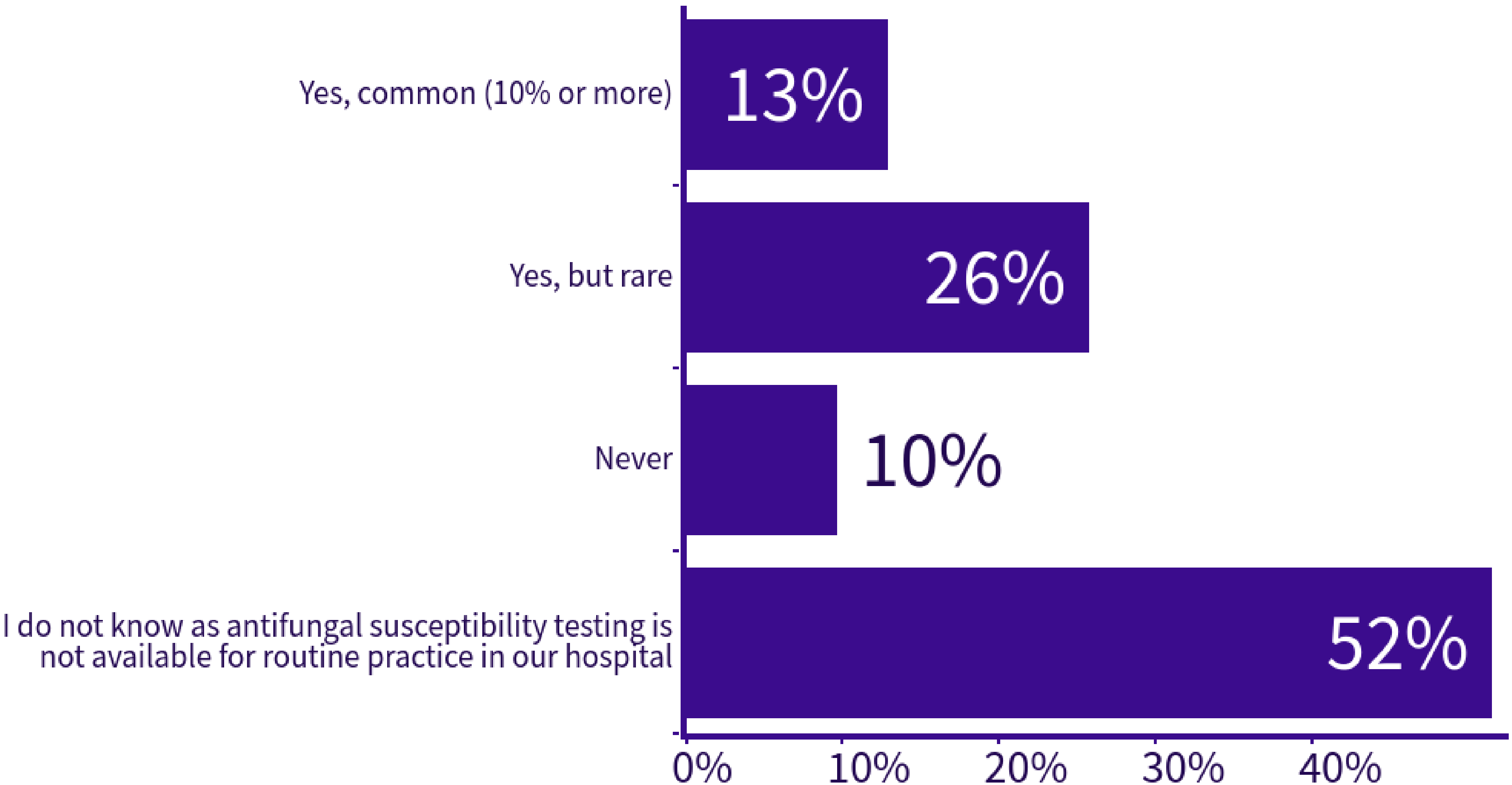
B. Yes, but rare

C. Never

D. I do not know as antifungal susceptibility testing is not available for routine practice in our hospital

Does antifungal resistance compromise the use of current antifungal agent for invasive aspergillosis in your hospital?

Poll is full and no longer accepting responses



Total Results: 31

Mutations in the cyp51A gene and MICs of azole antifungals in 6 *A. fumigatus* isolates isolated from a patient with lung aspergilloma

			MIC (mg/L)	
Itraconazole	Isolate	Mutation in *cyp51A*	itraconazole	voriconazole
No	AF1	–	0.25	0.25
Yes 6M	AF2	M220I	>16	1
No 2M	AF3	–	0.5	0.5
Yes	AF4	G54R	>16	0.5
Yes	AF5	G54R	>16	0.5
Yes	AF6	G54R	>16	0.5

Chen et al. JAC 2005;55:31

Recovery of TR34/L98H and TR46/Y121F/T289A Resistance Mechanisms in *Aspergillus fumigatus*

TR_{34}/L98H

Country	First Case	Type of Isolate	Year of Publication [Reference]
Netherlands	1998	C + E	2008 [13]
Italy	1998	C + E	2015 [23]
Turkey	2000	C	2015 [26]
Spain	2003	C	2013 [12, 28]
Australia	2004	C	2015 [29]
Iran	2005	C + E	2013 [12, 30]
Belgium	2006	C + E	2012 [12, 27]
Denmark	2007	C + E	2010/2011 [12, 33]
China	2008–2009	C	2011 [30, 34]
India	2008	C + E	2012 [12, 30]
United Kingdom	2009–2011	C + E	2009 [12, 36]
France	2010	C + E	2012 [12]
United States	2010	C	2015 [25]
Germany	2012	C + E	2012 [12, 15]
Taiwan	2011	C	2015 [37]
Kuwait	2013	C + E	2015 [30, 38]
Poland	2006–2014	C	2015 [39]
Colombia	2015	E	2015 [35]

TR_{46}/Y121F/T289A

Country	First Case	Type of Isolate	Year of Publication [Reference]
United States	2008	C	2015 [25]
Netherlands	2009	C + E	2013 [24]
Belgium	2012	C + E	2012 [12, 27]
Germany	2012	C + E	2015 [12, 15]
India	2012	E	2014 [30]
France	2013	C + E	2015 [31]
Tanzania	2013	E	2014 [32]
Denmark	2014	C	2015 [33]
Spain	2014	C	2015 [28]
Colombia	2015	E	2015 [35]

Abbreviations: C, clinical; E, environmental.

[a] Due to space restriction, we were not able to include all individual publications. We have cited reviews, which included reports from individual countries over the years.

Verweij PE et al. CID 2016;62:362

Azole-resistant *Aspergillus fumigatus* isolates carrying TR_{34}/L98H mutations, Taiwan

The prevalence rates of azole resistance

- global 3–6%
- Taiwan 6.5%

Patient, sex/age(y)	Isolate	Sample type	Underlying diseases	Minimum inhibitory concentrations, mg/L					
				ITZ	VCZ	POS	AMB	TBZ	PEN
Azole-resistant isolate, n=3			two azole-naïve patients						
1, M/59	A31	BAL	Lung cancer	>16 (>16[b])	4 (4[b])	1 (0.5[b])	0.5	32	>32
2, F/66	B44	sputum	chronic hepatitis C, cirrhosis of liver, diabetes without control and adrenal insufficiency	>16 (>16[b])	2 (1[b])	1 (0.5[b])	0.5	16	>32
	B51	sputum		>16 (>16[b])	2 (1[b])	1 (0.5[b])	0.5	16	>32
Azole-susceptible isolates, n=35				0.06/0.12 [0.03-0.25] b,c	0.25/0.5 [0.12-1] b,c	0.03/0.06 [0.015-0.06] b,c	-	1/2 [0.5-4][c]	2/2 [0.5-4][c]

Wu CJ et al. Mycoses, 2015;58: 544

Environmental Multiple-Triazole-Resistant *A. fumigatus* Strains Carrying the TR34/L98H Mutations in the cyp51A Gene in India

- A total of 44 (7%) *A. fumigatus* isolates from 24 environmental samples were triazole resistant.
- Cross-resistance to voriconazole, posaconazole, itraconazole and to six triazole fungicides used extensively in agriculture.
- In contrast to the genetic uniformity of azole-resistant strains the azole-susceptible isolates from patients and environments in India were genetically very diverse.
- All Indian environmental and clinical azole resistant isolates shared the same multilocus microsatellite genotype

Chowdhary A, et al. PLoS ONE 2012;7: e52871.

The possible mechanisms or sources of antifungal resistant fungal pathogens

1. De novo occurrence of mutation in causality pathogens following the use of antifungal agents
2. Selection of drug resistant fungal pathogens following the use of antifungal agents
3. Cross transmission of antifungal resistant fungal pathogens from other patients or environment in the healthcare settings
4. Acquisition of antifungal resistant fungal pathogens from the agricultural environment

Limitation of current published data

- **Definition**
  - Clinical breakpoints
- **Detection**
  - Identification to species levels
  - In vitro susceptibility testing in routine laboratories
- **Publication**

Conclusions

- Antifungal resistance has emerged and spread in Asia.
- Antifungal susceptibility vary by fungal pathogens and by region/country/hospital
- Population surveillance data to guide local practice (empirical therapy)
- Detection of fungal pathogen and identification to species level to guide definitive therapy
- Evaluate in vitro susceptibility of individual isolate for selected fungi and/or patients