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INTERNATIONAL SOCIETY FOR HUMAN AND ANIMAL MYCOLOGY

MMTN
MEDICAL MYCOLOGY TRAINING NETWORK

Candida auris and rare yeasts

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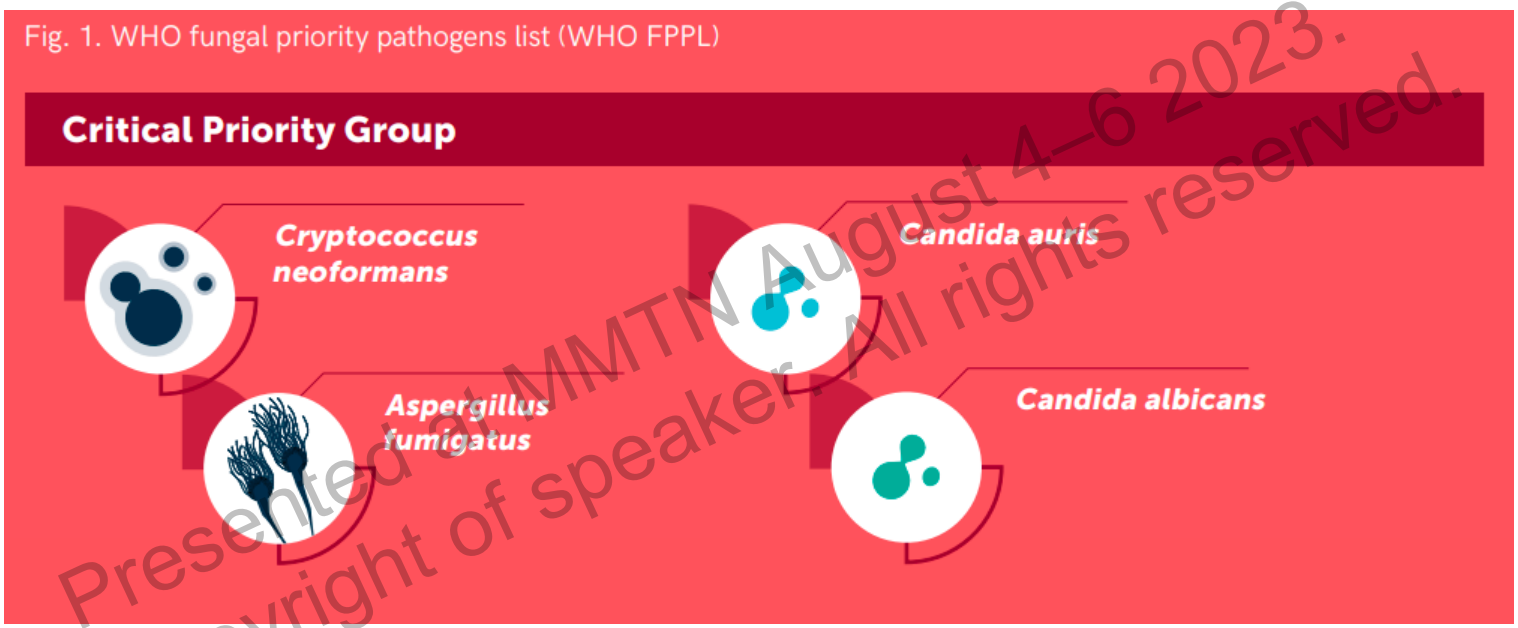
Disclosures

- In the past three years, Dr Tan has served on the advisory boards of Pfizer and MSD.

Fig. 1. WHO fungal priority pathogens list (WHO FPPL)



WHO fungal priority pathogens list to guide research, development and public health action. Geneva: World Health Organization; 2022.

Candida auris – brief summary

- First reported in Japan in 2009, but now reported in >47 countries
- Associated with difficult-to-control healthcare outbreaks – nosocomial pathogen
- Can survive on surfaces (viable though non-culturable) for at least 2 weeks
- Tends to be multi-drug resistant
- Clinically significant too – NY outbreak (echinocandin-susceptible) had 30%, 44% mortality at 30 days, 90 days
- Easy to mis-identify
- Emergence related to climate change (C. auris is thermotolerant), increasing use of antifungals, gaps in infection control, global shortage of healthcare workers & equipment

Mishra SK et al. *Lancet Microbe* 2023;4:e482

Microbiol Immunol 2009; **53**: 41–44
doi:10.1111/j.1348-0421.2008.00083.x

ORIGINAL ARTICLE

Candida auris sp. nov., a novel ascomycetous yeast isolated from the external ear canal of an inpatient in a Japanese hospital

Kazuo Satoh[1,2], Koichi Makimura[1,3], Yayoi Hasumi[1], Yayoi Nishiyama[1], Katsuhisa Uchida[1] and Hideyo Yamaguchi[1]

ABSTRACT

A single strain of a novel ascomycetous yeast species belonging to the genus *Candida* was isolated from the external ear canal of an inpatient in a Japanese hospital. Analyses of the 26S rDNA D1/D2 domain, nuclear ribosomal DNA ITS region sequences, and chemotaxonomic studies indicated that this strain represents a new species with a close phylogenetic relationship to *Candida ruelliae* and *Candida haemulonii* in the Metschnikowiaceae clade. This strain grew well at 40 °C, but showed slow and weak growth at 42 °C. The taxonomic description of *Candida auris* sp. nov. is proposed (type strain JCM15448^T = CBS10913^T = DSM21092^T).

2013-2016

2022

Number of *C. auris* clinical cases through December 31, 2022

In 2022, there were 2,377 clinical cases and 5,754 screening cases.

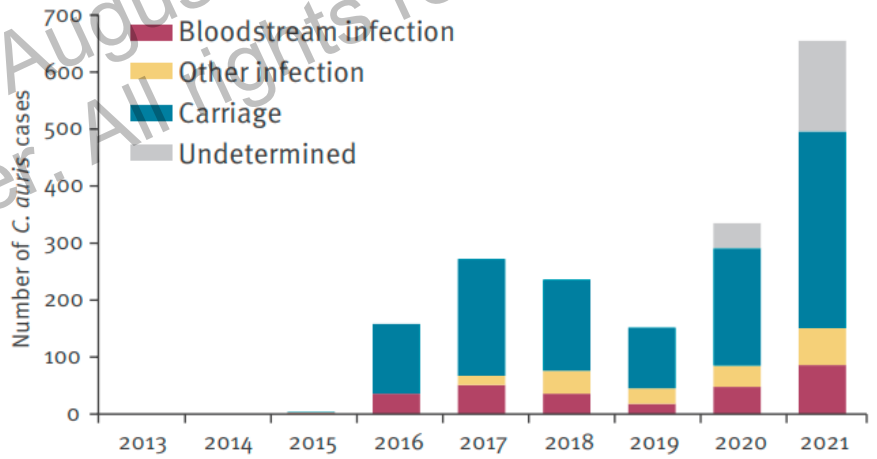
- 0 clincial cases and at least 1 screening case
- 1 to 10
- 11 to 50
- 51 to 100
- 101 to 500
- 501 to 1000
- 1001 or more

1. Candida auris | Candida auris | Fungal Diseases | CDC (last accessed 28th June 2023)

Rising threat

- Survey of EU/EEA countries, Apr 2022
- 11 countries had not detected *C. auris* until 2021
- In 4 countries, no national-level info available
- Whether imported or locally acquired – info unavailable for 97% of cases
- Cases without a clear link to hospitalization abroad → local transmission → undetected transmission

Reported cases of *Candida auris* infection or carriage, EU/EEA, 2013–2021 (n = 1,812)[a]

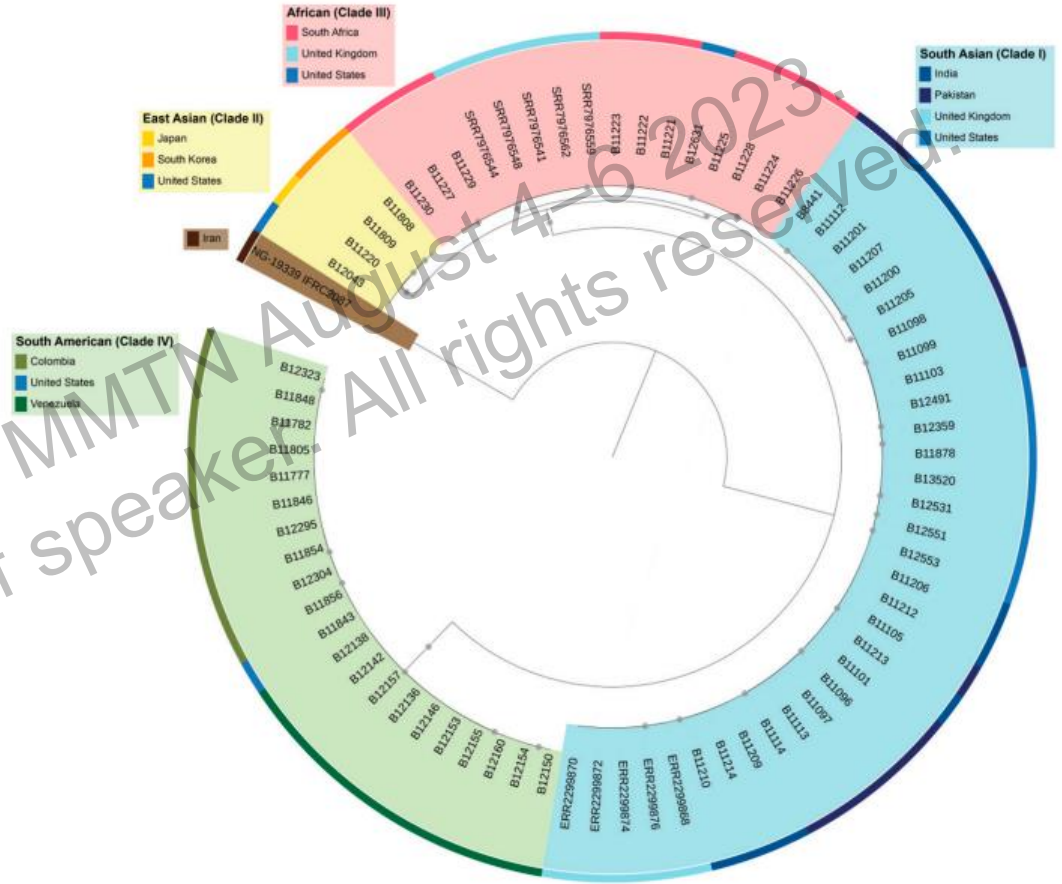


Kohlenberg A et al. *Euro Surv* 2022;27:pii=2200846

5th clade

5th clade from an Iranian girl with otomycosis. She had never travelled out of the country.

East Asian clade may have predilection for ear. Iranian clade most closely related to East Asian clade.



Chow NA et al. *Emerg Infect Dis* 2019;25:1780

Candida auris – laboratory identification

- Culture – CHROMagar; Sabaroud dextrose agar supplemented with chloramphenicol & gentamicin[1]
- Identification
  - Vitek 2 or API 20C AUX may mis-identify C. auris as other species[2]
  - Biomerieux Vitek MS was approved by US FDA for C. auris identification in 2019[3]
  - MALDI[1]
  - Sequencing (18S gene)[1]
- PCR protocol available[4]

1 Welsh RM et al. J Clin Microbiol 2017;55:2996
2 Identification of Candida auris | Candida auris | Fungal Diseases | CDC accessed @2112hrs on 23052023
3 New FDA Clearance for VITEK® MS: Expanded ID for Challen (rapidmicrobiology.com) accessed @2121hrs on 23052023
4 Leach L et al. J Clin Microbiol 2017;56:e01223

Characteristics of different Candida species on chromogenic media

Culture medium	Saboraud dextrose agar	Brilliance™ Candida Agar	CHROMagar™ Candida Medium	CHROMID® Candida Medium	CHROMagar™ Candida Plus
C. auris	White to cream	Beige to pink	Pale pink	Pale pink	Blue halo
C. albicans	White to cream	Green	Green	Blue	Green
C. parapsilosis	White to cream	Beige/yellow/brown	White, pale pink or light lavender	White	White
C. glabrata complex	White to cream	Beige/yellow/brown	Dark pink to purple	White	Pink
P. kudriavzevii (*C. krusei*)	White to cream	Dry, irregular pink-brown	Light rose to pink	White	Purple
C. tropicalis	White to cream	Dark blue	Gray, blue to blue-greenish	Pink	Purple

Keighley C et al. *Curr Fungal Infect Rep* 2021;15:116

TABLE 1 Growth results for panel of *Candida* isolates[a]

Candida species (location of collection)	Growth by strain and type of medium[b]				
	SAB			YNB	
	Dextrose	Dulcitol	Mannitol	Dulcitol	Mannitol
C. auris (South Asia)	+	+	+	+	+
C. auris (Africa)	+	+	+	+	+
C. auris (South America)	+	+	+	+	+
C. auris (East Asia)	+	+	+	+	+
C. glabrata	+	−	−	−	−
C. albicans	−	−	−	−	−
C. doubushaemulonii	−	−	−	−	−
C. haemulonii	−	−	−	−	−
C. parapsilosis	−	−	−	−	−
C. tropicalis	−	NA[c]	NA	NA	NA

[a]Isolates incubated at 40°C with shaking at 250 rpm in a Sabouraud broth or yeast nitrogen base with either dextrose, dulcitol, or mannitol as the added carbon source.
[b]SAB, Sabouraud broth; YNB, yeast nitrogen base. All media contained 10% NaCl (wt/vol).
[c]NA, not available.

A hardy organism!

Welsh RM et al. *J Clin Microbiol* 2017;55:2996

From the US CDC

Identification Method	Organism *C. auris* can be misidentified as
Vitek 2 YST*	*Candida haemulonii* *Candida duobushaemulonii*
API 20C	*Rhodotorula glutinis* (characteristic red color not present) *Candida sake*
API ID 32C	*Candida intermedia* *Candida sake* *Saccharomyces kluyveri*
BD Phoenix yeast identification system	*Candida haemulonii* *Candida catenulata*
MicroScan	*Candida famata* *Candida guilliermondii*** *Candida lusitaniae*** *Candida parapsilosis***
RapID Yeast Plus	*Candida parapsilosis***

Identification of Candida auris | Candida auris | Fungal Diseases | CDC accessed @2112hrs on 23052023

Risk factors for *C. auris* candidemia

- Subset analysis of Candidemia in Indian ICUs
- 74 (5.3%) were *C. auris*
- *C. auris* candidemic pts had stayed longer in ICU (25d) vs 15d for other candidemias
- Risk factors for *C. auris* candidemia
  - Public sector hospital
  - Underlying respiratory illness
  - Vascular surgery
  - Prior antifungal

- Feb 2020 – May 2021 (Genoa hosp)
- 59% of *C. auris* candidemia pts had COVID-19
- Candidemia at median of 29d after colonization detected
- Cumulative risk of candidemia after colonization = 25% at 60d
- Multisite colonization was only independent risk factor for candidemia

Rudramurthy SM et al. *J Antimicrob Chemother* 2017;72:1794

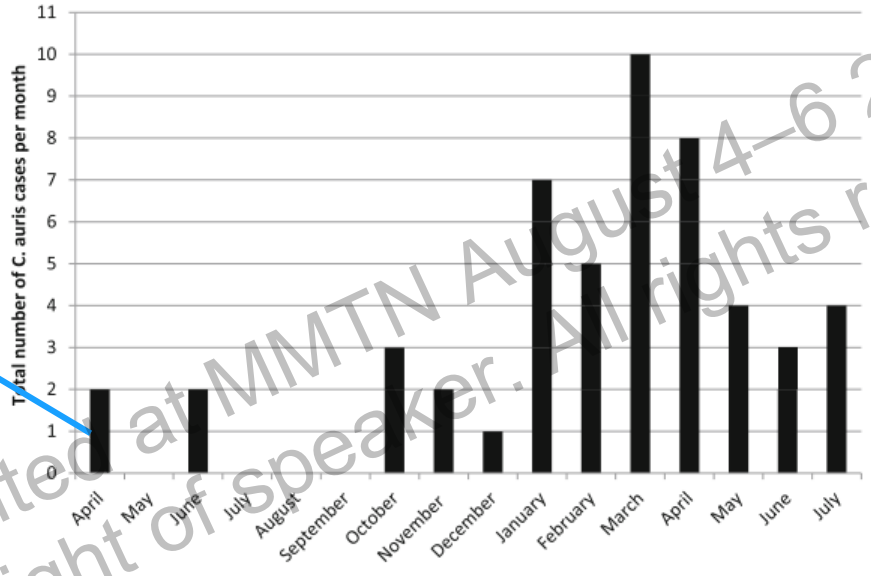
Briano F et al. Infect Dis Ther 2022;11;1149

Ecology

- Ecological niche unknown
- Propensity for transmission in healthcare settings
- Able to survive for long periods on plastic surfaces

First reported outbreak – Royal Brompton Hospital, London

First 2 cases in ICU – 1st pt grew it from sternal wound; 2nd pt in neighbouring bed (same mth) – grew it in sputum and then blood (line sepsis)



New cases of *C. auris* per month. Total number of monthly new cases of *C. auris* are listed from the 1 April 2015 to the end of July 2016

Shelenz S et al. *Antimicrob Resist Infect Control* 2016;5:35

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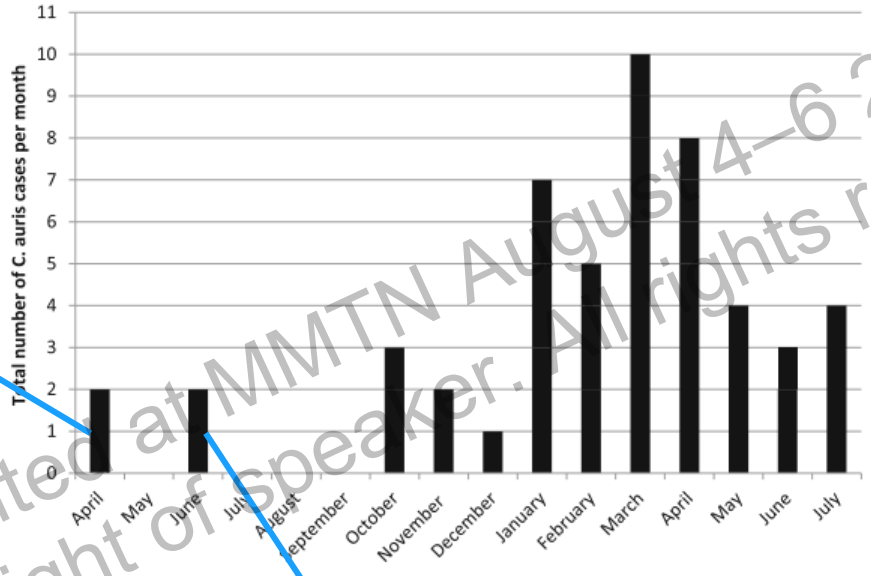

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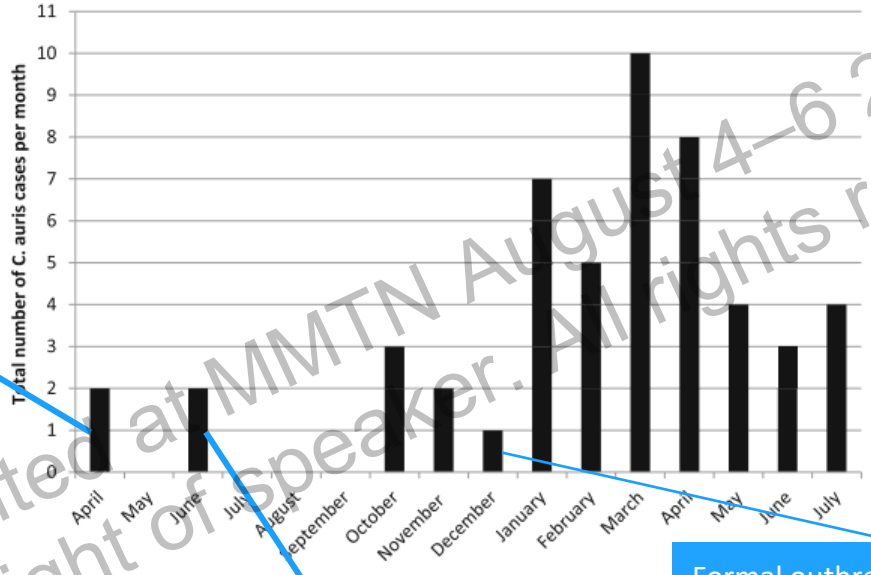

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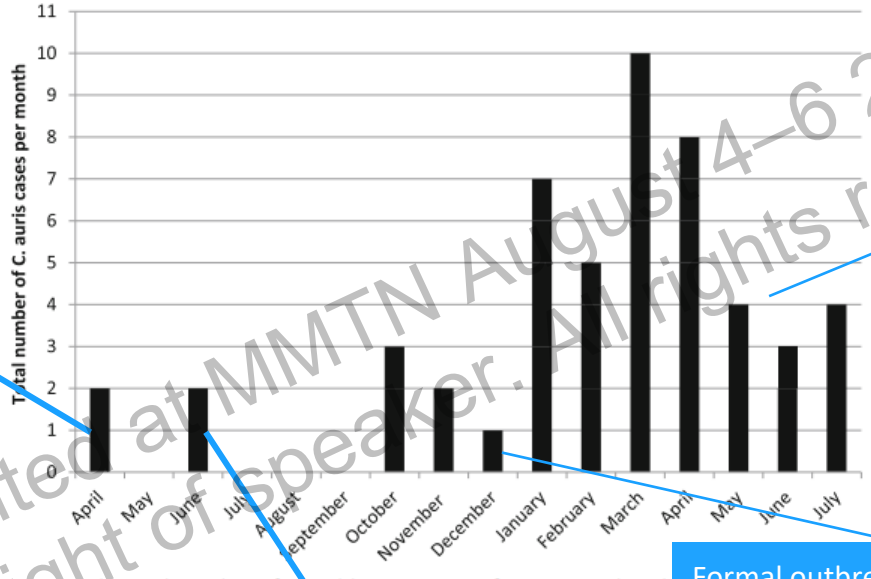

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Cases in general wards as well (wards to which ICU pts were discharged), despite their being in single rooms; outbreak ongoing at time of report

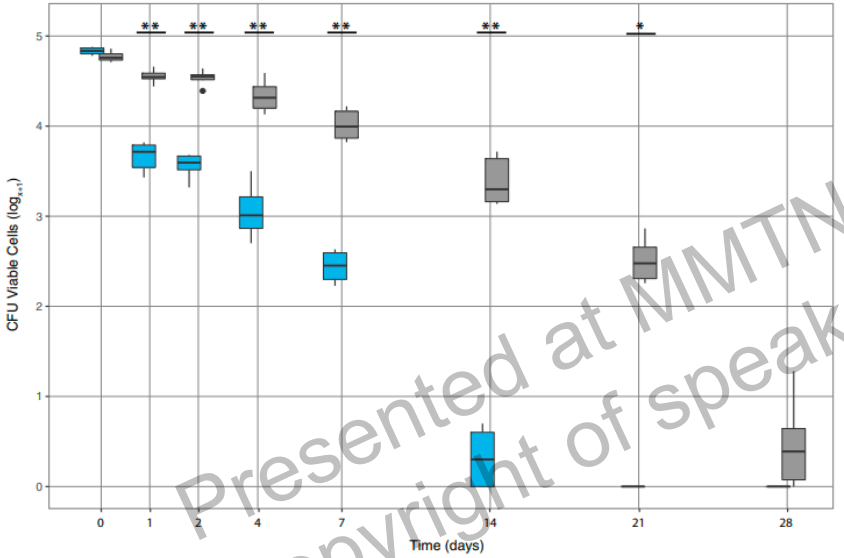
Shelenz S et al. *Antimicrob Resist Infect Control* 2016;5:35

Infection control measures at the Royal Brompton

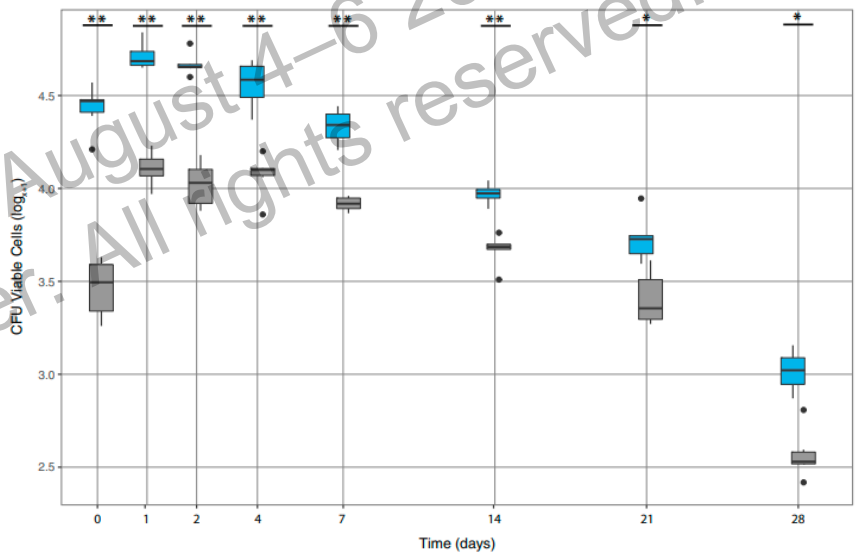
- Environmental swabbing – positive cultures from many surfaces [floor around beds, trolleys, equipment surfaces, windowsills, radiators, key pads, air sample(1)]
- Cleaning in 1,000 ppm Chlorine-based products; equipment sent for HPV
- Isolation of + pts for duration of hospitalization
- Closure of affected rooms to new pts
- Screening of contacts – discovered that minimal contact of 4hr enough to cause spread
- HCW, visitors all required to wear disposable long-sleeved gowns (as for CP-CRE)
- Screening of staff (but only 1 was +)

Shelenz S et al. *Antimicrob Resist Infect Control* 2016;5:35

C. auris survives long on plastic surfaces



Log-transformed recovery of C. auris (blue) and *C. parapsilosis* (grey) on plastic, by culture



Log-transformed recovery of *C. auris* (blue) and *C. parapsilosis* (grey) on plastic, by esterase activity*

*an assay that highlights viable cells

Welsh RM et al. *J Clin Microbiol* 2017;55:2996

Use of the esterase activity assay

- Gave insights into understanding *C. auris*
- This assay detects viable cells – as few as a single yeast or bacterium
- Viability as detected by esterase activity was higher than that detected by culture at most time points – *C. auris* enters a “viable but non-culturable” state
- Use of this assay provided a “comprehensive picture” of the fungus’ “survival and persistence” in the environment
- Note that *C. parapsilosis* also remained viable for at least 4 weeks on plastic surfaces

Welsh RM et al. *J Clin Microbiol* 2017;55:2996

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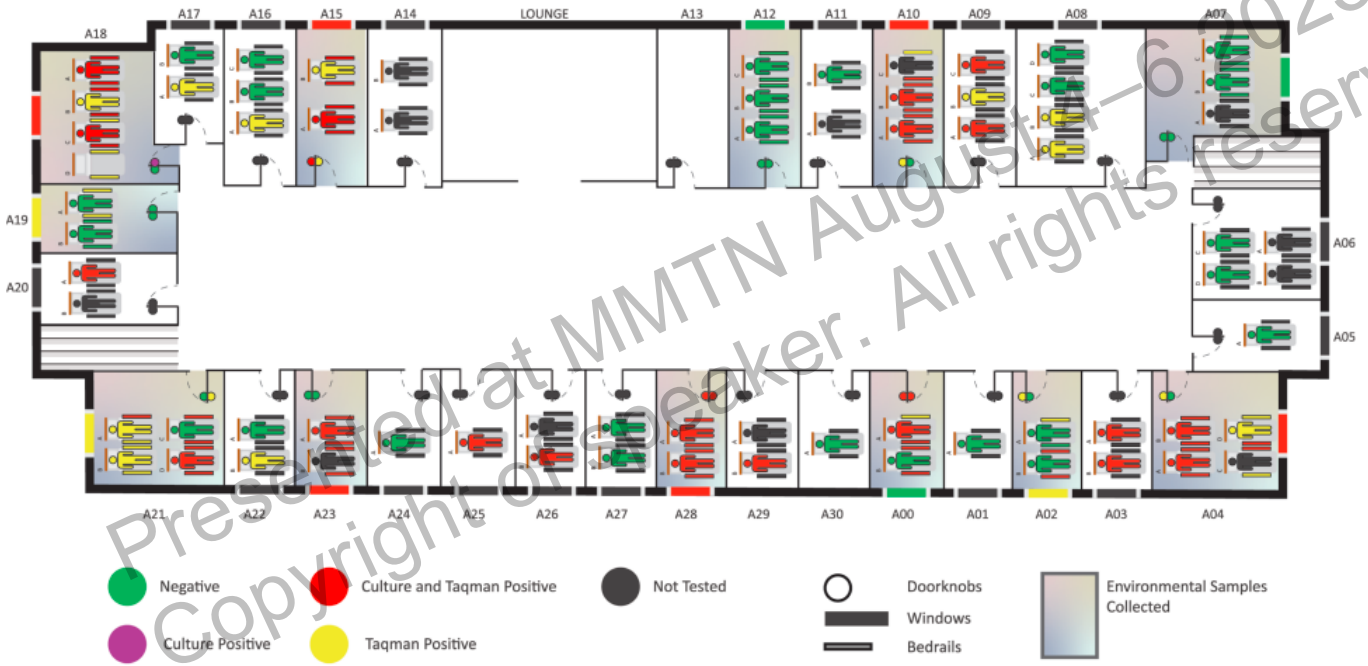
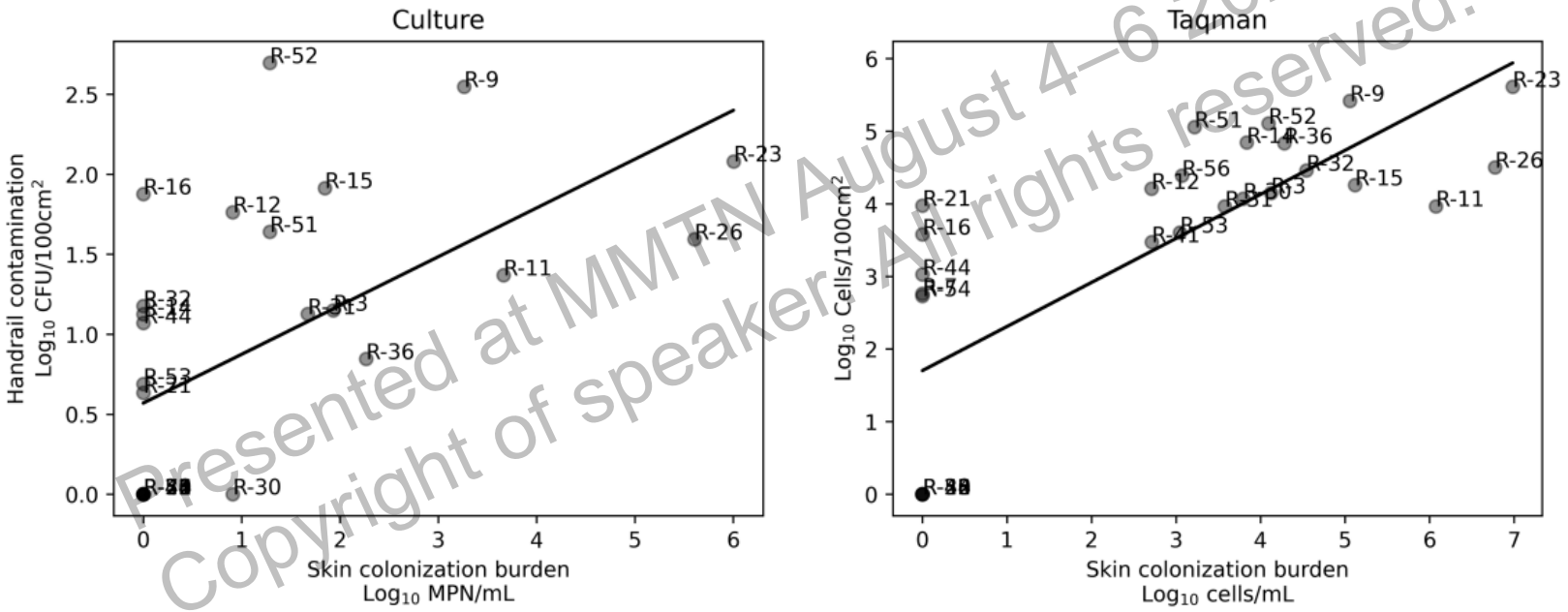
Relationship between skin & environmental colonization



C. auris found on all handrails of beds occupied by positive residents

Sexton DJ et al. *Clin Infect Dis* 2021;73:1142

+ relationship between environmental contamination & skin colonization burden



Sexton DJ et al. *Clin Infect Dis* 2021;73:1142

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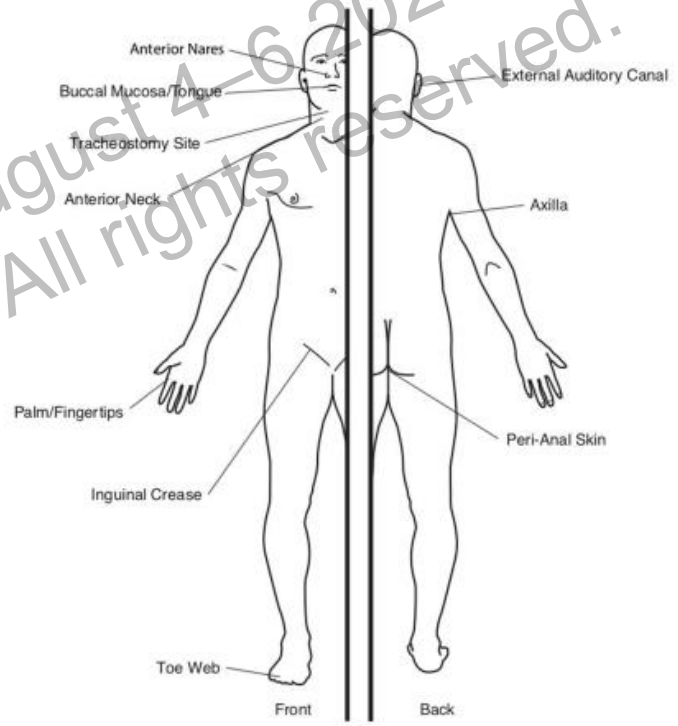
(Tentative) conclusions from one study

- Colonized patients carry hundreds of millions of *C. auris* cells per sample – colonization is usually heavy
- Colonization burdens not uniform – vary by several orders of magnitude – exact reason(s) unknown
- Colonized patients likely shed *C. auris* continually, hence contaminating the environment
  - ***Diligent and frequent disinfection is necessary, for the duration of the patient's stay***
- Will daily CHG bathing suppress colonization, and will it reduce transmission?

Sexton DJ et al. *Clin Infect Dis* 2021;73:1142

Best body sites to detect *C. auris*?

- Study swabbed 10 body sites of NH residents three times over 3-mth period



Proctor DM et al. *Nat Med* 2021;27:1401

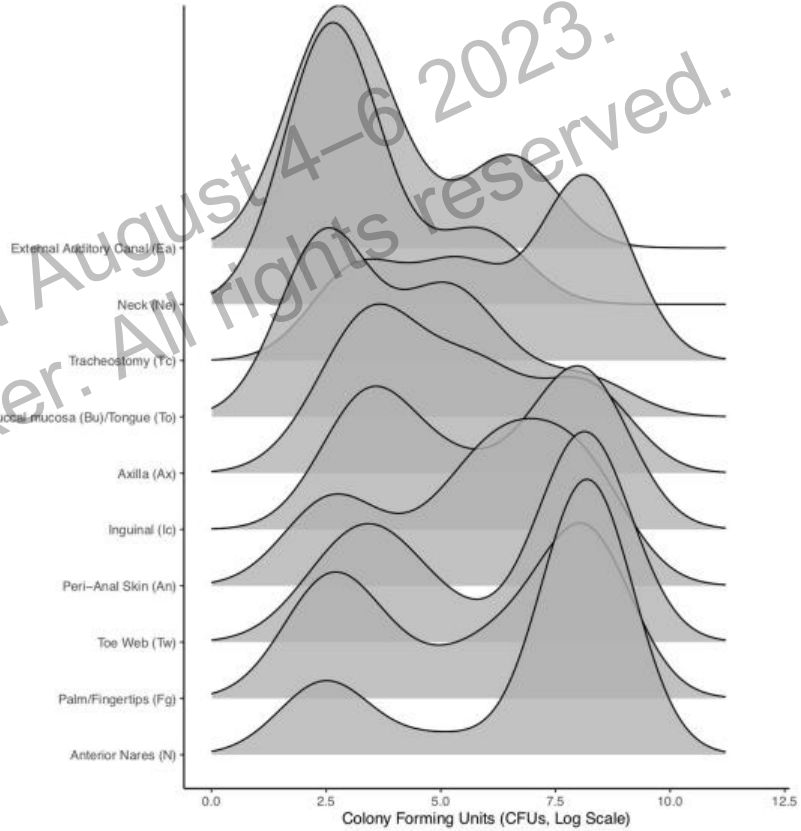
Likely bioburden of *C. auris* at different sites

Ridgeline plot

Peaks correspond to peak bioburden (CFU) for each site

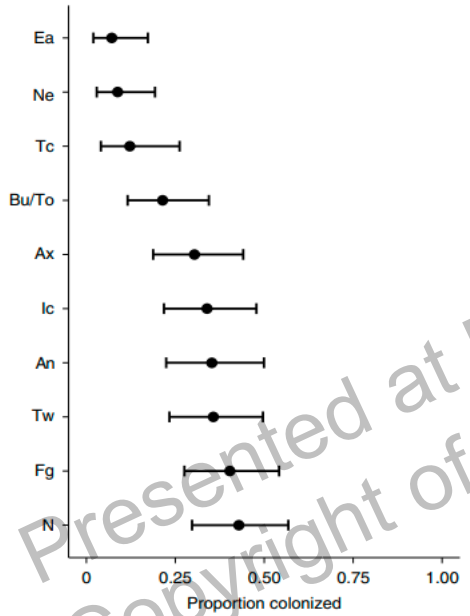
Bimodal distribution → there were subjects with low CFUs at that site and other with high bioburden at that site

Nares, inguinal crease contain high burdens; external auditory canal quite low

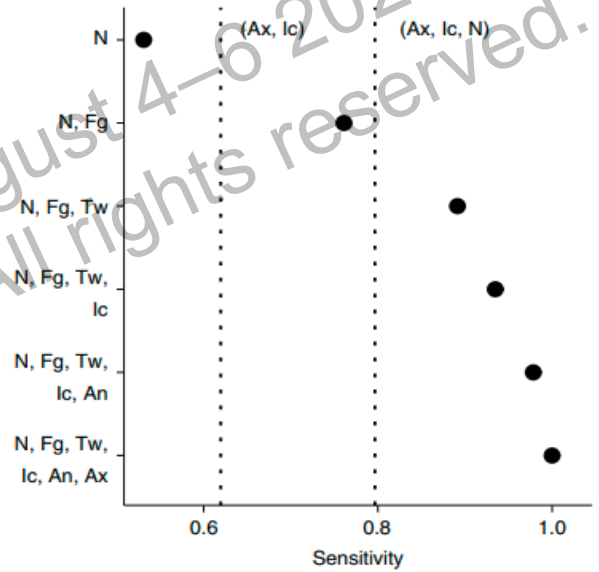


Proctor DM et al. Nat Med 2021;27:1401

Sensitivity of various sites for *C. auris*



Anterior nares most likely site to be positive, but almost 50% of carriers are negative at this site! Fingertips are next most likely site.

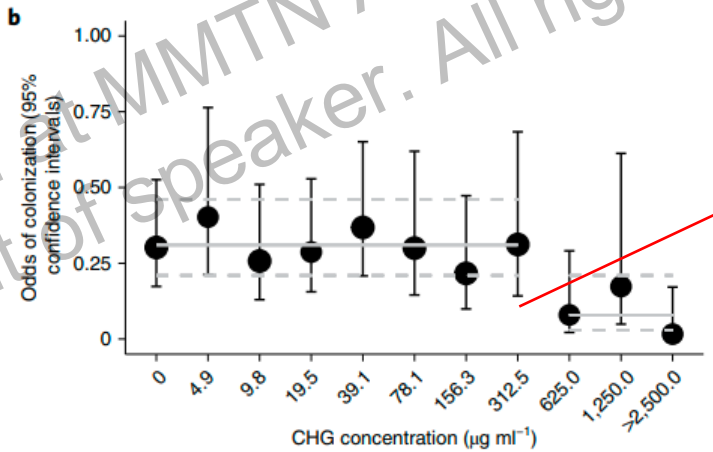


Sensitivity of nares swab 53%; add fingertips →76%, add toe webs also → 89%

Proctor DM et al. Nat Med 2021;27:1401

Role of CHG?

- In this NH, everyone bathed or was wiped with CHG.
- Modest association between odds of finding C. auris at a certain site with CHG concentration at that site



- ✓ Significant reduction in odds of *C. auris* colonization at sites with [CHG] >625μg/ml, a [ ] found only at 7.3% of sites.
- ✓ [CHG] needed to inhibit *C. auris* in vitro 16 – 32.

Proctor DM et al. *Nat Med* 2021;27:1401

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Infection control – look into every detail!

Cases in an Indian CCU

- Decontaminated CCU with 5% phenol (carbolic acid) – but after cleaning, environmental swabs still +
- Cleaner used brush/towel and after cleaning, dipped it back into the bowl of phenol
- New method: cleaner had two stainless steel bowls, one with water, one with Ecoshield (stabilized H2O2 11%v/w with silver nitrate). After wiping, brush/towel dipped into the water first. Then into Ecoshield.
- Repeat swabs negative

Biswal M et al. *J Hosp Infect* 2017;97:363

Every detail matters – lessons from PGIMER

Cases in Trauma ICU

- Despite changing to Ecoshield and giving everyone CHG baths, patient swabs remained positive
- Discovered that ECG leads and BP cuff were positive for C. auris
- Disinfection of ECG leads – spraying with alcohol – switched to ethylene oxide disinfection
- Hands of HCWs were also positive – subjected to HH training
- Training also of ICU staff

Biswal M et al. *J Hosp Infect* 2017;97:363

List P: Antimicrobial Products Registered with EPA for Claims Against Candida Auris

Registration	Active Ingredient	Product Brand Name	Company	Contact Time (minutes)	Formulation Type	Surface Types	Use sites
10324-214	Hydrogen Peroxide and Paracetic Acid	Maguard 5626	Mason Chemical Company	2	Dilutable	Hard Non-Porous (HN)	Hospital; Institutional; Residential
1677-226	Hydrogen Peroxide, Paracetic Acid and Octoanoic Acid	Virasept	Ecolab Inc.	4	Ready to Use	Hard Non-Porous (HN)	Hospital; Institutional
1677-237	Hydrogen Peroxide and Paracetic Acid	Oxycide™ Daily Disinfectant Cleaner	Ecolab Inc.	3	Dilutable	Hard Non-Porous (HN)	Hospital; Institutional
1677-262	Dodecylbenzenesulfonic Acid	Disinfectant 1 Spray	Ecolab Inc.	1	Ready to Use	Hard Non-Porous (HN)	Hospital; Institutional
1677-263	Dodecylbenzenesulfonic Acid	Disinfectant 1 Wipe	Ecolab Inc.	1.25	Ready to Use/Wipe	Hard Non-Porous (HN)	Hospital; Institution
37540-1	Sodium Hypochlorite	Micro-Kill Bleach Germicidal Bleach	Medline Industries	2	Ready to	Hard Non-Porous	Hospital;

List P: Antimicrobial Products Registered with EPA for Claims Against Candida Auris | US EPAList P: Antimicrobial Products Registered with EPA for Claims Against Candida Auris | US EPA accessed @2115hrs on 13052023

Registration	Active Ingredient	Product Brand Name	Company	Contact Time (minutes)	Formulation Type	Surface Types	Use sites
1677-262	Dodecylbenzenesulfonic Acid	Spray	Ecolab Inc.	1	Ready to Use	(HN)	Institutional
1677-263	Dodecylbenzenesulfonic Acid	Disinfectant 1 Wipe	Ecolab Inc.	1.25	Ready to Use/Wipe	Hard Non-Porous (HN)	Hospital; Institutional
37549-1	Sodium Hypochlorite	Micro-Kill Bleach Germicidal Bleach Wipes	Medline Industries Inc.	2	Ready to Use/Wipe	Hard Non-Porous (HN)	Hospital; Institutional; Residential
37549-2	Sodium Hypochlorite	Micro-Kill Bleach Solution	Medline Industries, LP	2	Ready to Use	Hard Nonporous (HN)	Hospital; Institutional; Residential
46781-12	Isopropyl Alcohol and Quaternary Ammonium	Cavicide 1	Metrex Research	1	Ready to Use	Hard Non-Porous (HN)	Hospital; Institutional; Residential
46781-13	Isopropyl Alcohol and Quaternary Ammonium	CaviWipes 1	Metrex Research	1	Ready to Use/Wipe	Hard Non-Porous (HN)	Hospital; Institutional; Residential
46781-14	Sodium Hypochlorite	CaviWipes Bleach	Metrex Research	3	Ready to Use/Wipe	Hard Non-Porous (HN)	Hospital; Institutional; Residential

Which anti-fungal to use for treatment?

- Reference std – set by CLSI, EUCAST[1]
- Neither has set breakpoints for *C. auris*[1]
- CDC recommends susceptibility testing for all *C. auris* isolates[2]
- Breakpoints based on those of related Candida species[2]
- Azoles sometimes exhibit trailing growth[1]
- Correlation between breakpoints and clinical outcomes not known[2]

Fluconazole	≥32	Modal minimum inhibitory concentration (MIC) to fluconazole among isolates tested at CDC was ≥256; isolates with MICs ≥32 were shown to have a resistance mutation in the *Erg11* gene, making them unlikely to respond to fluconazole.
Voriconazole and other second generation triazoles	N/A	Consider using fluconazole susceptibility as a surrogate for second generation triazole susceptibility assessment. However, isolates that are resistant to fluconazole may respond to other triazoles occasionally. The decision to treat with another triazole will need to be made on case-by-case basis.

1. Keighley C et al. Curr Fungal Infect Rep 2021;15:116
2. https://www.cdc.gov/fungal/candida-auris/c-auris-antifungal.html accessed @2147hrs on 28072023

More on *C. auris* susceptibility testing

Amphotericin B	≥2	Recent pharmacokinetic/pharmacodynamic analysis of *C. auris* in a mouse model of infection indicates that under standard dosing, the breakpoint for amphotericin B should be 1 or 1.5, similar to what has been determined for other *Candida* species. Therefore, **isolates with an MIC of ≥2** should now be considered resistant. **If using Etest for amphotericin B and an MIC of 1.5 is determined, that value should be rounded up to 2.**

Higher amB MIC tends to be noted with Vitek 2 than E-test[1]

Tables a "general guide"[2]

High MIC "should not necessarily preclude its use, especially if the use of other antifungal drugs for the patient has been ineffective".[2]

1. Keighley C et al. Curr Fungal Infect Rep 2021;15:116
2. https://www.cdc.gov/fungal/candida-auris/c-auris-antifungal.html accessed @2147hrs on 28072023

Echinocandins?

Anidulafungin	≥ 4	Tentative breakpoints are based on the modal distribution of echinocandin MICs of approximately 100 isolates from diverse geographic locations.
Caspofungin	≥ 2	
Micafungin	≥ 4	

https://www.cdc.gov/fungal/candida-auris/c-auris-antifungal.html accessed @2147hrs on 28072023

Trichosporon

- Not so rare in nature or in human health/disease
- Widely distributed in nature
  - Soil, decomposing wood, lakes, scarab beetles, bat droppings, pigeon
- Can cause superficial infections, an allergic form of pneumonitis, or invasive infection
- Commonly said to be 2nd or 3rd (behind *Candida*) in yeast bloodstream infections
- Most common underlying conditions: hematologic malignancies, cancer, neutropenia, presence of central catheters
- 12 species #; *T. asahii* has 15 identified genotypes*

Colombo AL et al. *Clin Microbiol Rev* 2011;24:682
#Sprute R et al. *J Antimicrob Chemother* 2022;77:1779
*Francisco EC et al. *Antimicrob Agents Chemother* 2021;65;e01104

TABLE 2. Human trichosporonosis: sources of infection, main associated conditions, and etiological agents

Infection category	Main type(s) of infection	Major agent(s)	Main associated conditions
Invasive	Fungemia, urinary tract infections, peritonitis, endocarditis, others[a]	*T. asahii*, *T. mucoides*, *T. asteroides*	Cancer, vascular and urinary catheters, organ transplantation, broad-spectrum antibiotic therapy
Allergic pneumonia	Summer-type hypersensitivity pneumonitis	*T. cutaneum*[b]	Hot and humid weather, environmental contamination
Superficial	White piedra	*T. inkin*, *T. cutaneum*, *T. ovoides*, *T. loubieri*	Young age and female sex, long hair, humidity, poor hygiene, headband use

Colombo AL et al. *Clin Microbiol Rev* 2011;24:682

Also part of normal flora

- ✓ Cultured stools of healthy Japanese volunteers
- ✓ IGS 1 (intergenic spacer 1) region of rRNA gene amplified
- ✓ *T. asahii* IGS1 was detected in 43 of 72 participants

Trichosporon asahii genotypes detected in human feces

Species	Gut	Skin (%)[6]	Clinical specimens (%)[3]	Environmental (%)[9]
T. asahii genotype 1	36 (83.7%)	78.8	86.7	5.6
T. asahii genotype 2		3.5	3.3	
T. asahii genotype 3	6 (14.0%)	2.9		83.3
T. asahii genotype 4	1 (2.3%)	6.5	6.7	2.8
T. asahii genotype 5		2.4	3.3	8.3
T. asahii genotype 6		5.3		
T. asahii genotype 7		0.6		
T. asahii genotype 8				
T. asahii genotype 9				
T. asahii genotype 10				
T. asahii genotype 11				
T. asahii genotype 12				
Trichosporon faecale	2			
Trichosporon asteroides	1			
Trichosporon ovoides	1			

Cho O et al. *Int J Infect Dis* 2015;39:87

The MD Anderson series

- 1998 – 2002
- 17 patients [10 fungemia (3 line-related), 3 lung, 3 soft tissue]
- “Lung”- isolated from sputum of ETT PLUS positive blood culture
- 65% had leukemia, 65% were neutropenic (2 – 42d before diagnosis), 53% had received steroids
- 53% dead by D30
- (None treated with voriconazole – note study period)

Kontoyiannis DP et al. *Scand J Infect Dis* 2004;36:564

43 patients growing Trichosporon from NTUH - lessons

Table 2. Discordant identification of 11 *Trichosporon* isolates other than *T. asahii* from 11 patients by the API 32C system and by sequencing analysis.

	Sequencing analysis			API 32C				
Pattern	Species	IGS1 region[a]	Maximal identity, % (matches/full-length bp)	Species	Profile	Identity, %	*t* value	No. of isolates
1	*T. dermatis*	EU559339	98 (484/489)	*T. mucoides*	7777777377	97.0	1.0	3
2	*T. dermatis*	EU559339	99 (480/481)	*T. mucoides*	7777777277	70.7	0.81	2
3	*T. montevideense*	AB066432	99 (717/719)	*Cryptococcus curvatus*	…	…	…	1
4	*T. montevideense*	AB066432	99 (717/719)	*T. inkin*	7153654335	97.1	0.52	1
5	*T. asteroides*	EU938059	99 (587/588)	*T. asahii* or *T. inkin*	7355640225	NA	NA	1
6	*T. cutaneum*	FJ153586	100 (331/331)	*Cryptococcus laurentii*	5577777375	99.7	0.97	1
7	*T. faecale*	FJ153607	99 (602/603)	*T. inkin*	7357640335	99.2	0.63	1
8	*T. ovoides*	EU934805	92 (575/622)	*T. inkin*, *T. asahii*, or *C. curvatus*	7373645337	NA	NA	1

NTUH lessons susceptibility testing

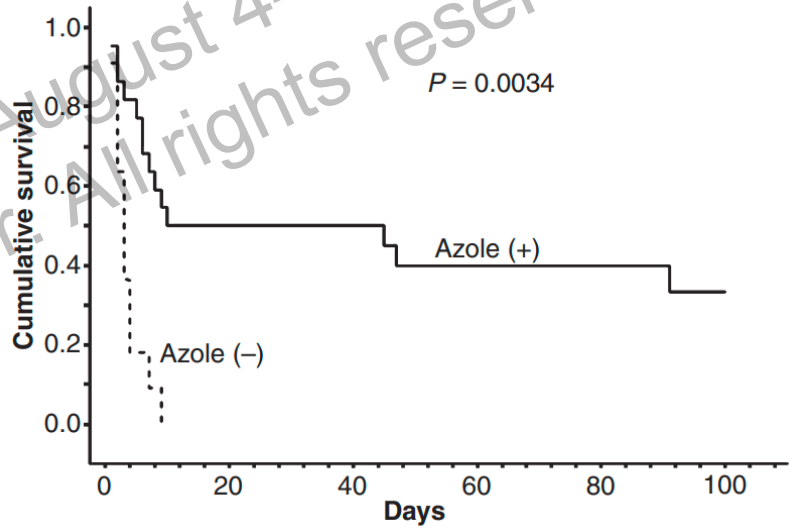
One of the earliest large studies to show importance of azoles (especially voriconazole) for treatment of Trichosporon infections

Drug, time point	Range of MIC	MIC_{50}	MIC_{90}
Fluconazole			
24 h	0.5 to 64	4	8
48 h	0.5 to 64	4	8
Voriconazole			
24 h	0.015 to 0.5	0.03	0.12
48 h	0.015 to 0.5	0.03	0.12
Itraconazole			
24 h	0.03 to 0.5	0.12	0.25
48 h	0.03 to 0.5	0.12	0.25
Posaconazole			
24 h	0.015 to 0.5	0.12	0.25
48 h	0.03 to 0.5	0.12	0.25
Amphotericin B			
24 h	0.06 to 2	0.5	1
48 h	0.12 to 8	1	2
Caspofungin			
24 h	0.25 to >16	16	>16
48 h	0.5 to >16	>16	>16
Anidulafungin			
24 h	16 to >16	>16	>16
48 h	>16[a]	>16	>16
Micafungin			
24 h	16 to >16	>16	>16
48 h	16 to >16	>16	>16
Flucytosine			
24 h	0.5 to 64	4	8
48 h	0.5 to 64	4	8

Ruan S-Y et al. *Clin Infect Dis* 2009;49:e11

A fearsome infection in the neutropenic

- 33 *Trichosporon fungemias* – 82% underlying acute leukemia, 85% neutropenic
- 91% were anti-fungal breakthroughs (18 of these 30 were on micafungin)
- 25/33 (76%) died, 22 of 25 died within 10 days
- Risk factors for survival: recovery from neutropenia, absence of hyperglycemia, azole-inclusive therapy



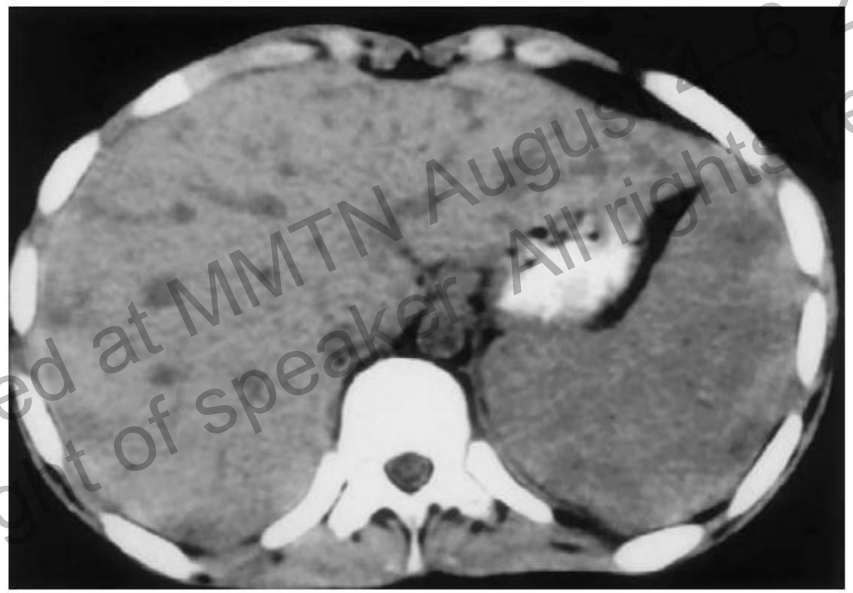
Suzuki K et al. *Euro J Haematol* 2009;84:441

Chronic disseminated trichosporonosis

- 13 yo girl, acute leukemia
- D3 neutropenia – high fever – persisted despite vancomycin, ceftazidime, amikacin
- Blood cultures – *T. asahii*
- Despite continuation of amB → skin nodules →septic shock (APACHE 25)
- Switched to ABLC – improved but became febrile 4 wk later, with abdo pain, hepatomegaly
- CT – next pg
- Switched to itraconazole. Pt stabilized when syrup was used (and levels improved)

Meyer MH et al. *Clin Infect Dis* 2002;35:e22

French report – chronic disseminated trichosporonosis



Meyer MH et al. *Clin Infect Dis* 2002;35:e22

Interesting fact – cross-reactivity with cryptococcal antigen assay

- *T. beigelii* phylogenetically related to *Cryptococcus neoformans*.
- Produces an antigen that shares antigenic determinants with the capsular polysaccharide glucoronoxylomannan (GXM) of *C. neoformans*
- Experiment: *T. begeilii* supernatant tested for CrAg

Lyman CA et al. *J Clin Microbiol* 1995;33:126

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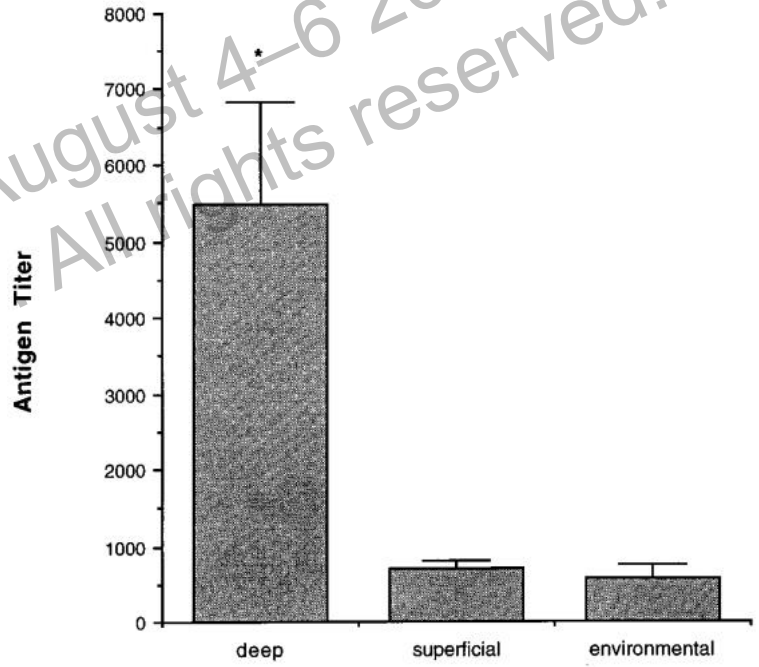
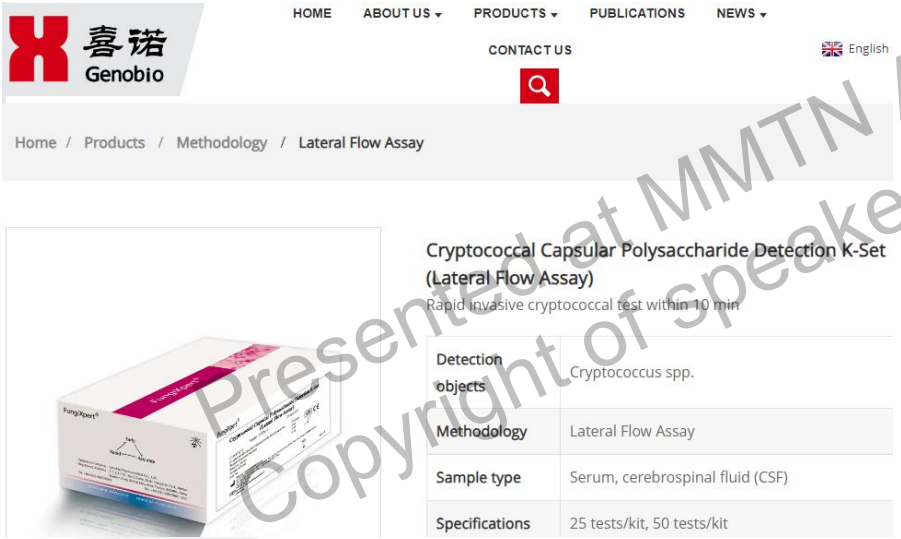


Lyman CA et al. *J Clin Microbiol* 1995;33:126

Does cross-reactivity happen with the LFA?



Liu Y et al. *Med Mycol* 2022;60:myac020

T. asahii suspension produced + CrAg by LFA (both kits)

Tested fungi	Strain number	CrAg LFA result (CFU/ml)	
		K-set	IMMY
Cryptococcus neoformans	2 002 281 141	2×10^1	4×10^1
Rhodotorula mucilaginosa	1 811 291 311	-	-
	1 812 091 171	-	-
	1 812 151 237	-	-
	1 812 021 164	-	-
Geotrichum candidum	1 811 251 155	-	-
	2 009 092 046	-	-
Exophiala dermatitidis	1 810 102 037	-	-
	2 008 102 024	-	-
Trichosporon asahii	1 903 221 157	3.1×10^2	6.3×10^2
	1 907 181 261	3.1×10^2	6.3×10^2
Aureobasidium pullulans	1 902 071 112	-	-
	2 006 091 186	-	-
	2 101 072 067	-	-
Sporothrix schenckii complex	2 005 132 019	-	-
	2 004 292 039	-	-
Acremonium	1 903 132 048	-	-
Alternaria alternata	2 012 312 072	-	-
Trichophyton tonsurans	1 810 171 245	-	-
Trichophyton mentagrophytes complex	2 008 272 025	-	-
Mucor racemosus	1 905 082 039	-	-
Fusarium oxysporum	1 903 251 241	-	-
Fusarium solani	1 912 041 304	-	-
Candida albicans	ATCC90028	-	-
Candida parapsilosis	ATCC22019	-	-
Candida krusei	ATCC6258	-	-
Candida tropicalis	CAP2013 F-1	-	-
Aspergillus fumigatus	2015CAP F-04	-	-
Tested bacterium			
Capnocytophaga sputigena	2 012 233 021	-	-

1:320 (FungiXpert)

1:160 (IMMY)

Liu Y et al. *Med Mycol* 2022;60:myac020

Checking out the CrAg by LFA

- Crypto-Ag LA, Fumouze, France
- Stored serum/csf from pts proven to have cryptococcosis, as well as proven infection with *Histoplasma capsulatum, Aspergillus fumigatus, Trichopsoron asahii, Pneumocystis jirovecii, Candida albicans, Rhodotorula*
- All tested using the LFA above
- Only 2 false –positives – both from the two pts with *T. asahii* infection

Rivet-Danon D et al. *J Hosp Infect* 2015;70:499

ESCMID/ECMM guidance - trichosporon

- amB tends to have high MICs – amB not recommended
- Trichosporon are resistant to flucytosine, echinocandins
- Triazoles assoc with good response in reports, especially voriconazole
- Voriconazole is the preferred agent
- Remove vascular catheters

Arendrup MC et al. *Clin Microbiol Infect* 2014;20(Suppl 3): 76

MMTN
MEDICAL MYCOLOGY
TRAINING NETWORK

QC

- Culture blood, fluids
- Identify to species level (MALDI-TOF ok)
- Image CNS if trichosporonosis confirmed
- (S) testing recommended, though no data linking (S) with clinical outcomes
- Useful for epidemiology, establishing ECVs
- Voriconazole is drug of choice
- Remove source (eg, CVC)

(a)

EQUAL *Trichosporon* Score 2022

Diagnosis	Imaging incl. CNS to document the extent of disease	2
	ID and/or mycological reference laboratory consultation	3
	Direct microscopy including Gram stain of clinical samples	3
	Culture from blood, other sterile fluid, or tissue + urease test	3
	Identification to species level by PCR (IGS1 sequencing)	3
	Identification to species level by MALDI-TOF MS	2
	Antifungal susceptibility testing	2
	Organ involvement	
	Histopathology of affected tissue using fungal stains	3
Treatment	Immediate treatment initiation	2
	Consider source control, e.g., catheter removal	2
	1st line treatment	
	Triazole monotherapy: Voriconazole, posaconazole in BT-IFI on voriconazole*	3
	Echinocandin monotherapy	-1
	Therapeutic drug monitoring, if azole treatment	1
	2-week treatment if fungemia only, ≥4 weeks if organ involvement	2
	Organ involvement	
	Surgical debridement of infected body sites, if applicable	2
	2nd line treatment (if uncontrolled disease)	
	Concomitant therapy with triazole and polyene	1
Follow-up	Blood cultures until negative on 3 consecutive days	3
	Organ involvement	
	Imaging of infected body sites: Weekly in acute disease, monthly in chronic disease	2

Sprute R et al. *J Antimicrob Chemother* 2022;77:1779

S. cerevisiae, S. boulardii

- Most “emblematic of yeasts” (winemaking, brewing, probiotic use)
- Found in plants, fruit, soil
- May be (occasionally) a digestive tract commensal
- Commonly used in probiotics, especially for treatment of diarrhea
- *S. boulardii* – not a valid taxon – best considered a subtype/variety of *S. cerevisiae*
- Many different “synonyms” of *S. cerevisiae* have been found – all different when subjected to WGS

Pontes A et al. *Microorganisms* 2020;8:903

S. cerevisiae fungemia investigations in India

TABLE 1 Salient clinical features of the patients with fungaemia due to *Saccharomyces cerevisiae*

Sr. No.	Demography	Underlying disease	Probiotic	Risk factors	Blood culture	Treatment	Outcome
1.	Neonate/M Chennai	Preterm (27 week) Birth weight (825 gm)	*S. boulardii* (as a hospital protocol for preterm neonates, twice daily via nasogastric tubes)	Umbilical CVC. Elemental diet, Total parenteral nutrition, Piperacillin - Tazobactam, fluconazole	*S. cerevisiae* (NCCPF 920006)	ABDC (0.7 mg/kg/day) Micafungin (2 mg/kg/day) CVC re-sited	Fungus cleared by 72 h, but died due to cardiac cause
2.	Neonate/M Chennai	Preterm (31 week) Birth weight (1.5 kg)	*S. boulardii* (as a hospital protocol for premature neonates, twice daily via nasogastric tubes)	Neonatal sepsis (day 14), elemental diet, meropenem, vancomycin	*S. cerevisiae* (NCCPF 920007)	Micafungin (2 mg/kg/day) × 14 day	Recovered
3.	75/M Kolkata	Respiratory failure, multiple episodes of bacterial sepsis and one episode of *Candida. tropicalis* candidaemia	*S. boulardii* (to prevent Antibiotic associated diarrhoea)	Intubation, meropenem, colistin, teicoplanin, caspofungin	*S. cerevisiae* (NCCPF 920004)	Caspofungin for 2 days. Discharged with oral voriconazole	Discharged
4.	37/M Kolkata	Polytrauma (sub-dural and sub-arachnoid haemorrhage withGCS-4), Diabetic, multiple episodes of infection with drug resistant bacteria, diarrhoea.	*S. boulardii* (due to diarrhoea)	Intubation, colistin, meropenem, vancomycin, metronidazole, rifabutin (after chest infection)	*S. cerevisiae* (NCCPF 920009)	Voriconazole for 2 days, then, caspofungin × 2 week	Recovered
5.	25/F Kolkata	32-week pregnancy, acute pancreatitis, acute kidney injury, LUCS performed	*S. boulardii* (to prevent antibiotic associated diarrhoea)	Haemodialysis, TPN, ceftriaxone for 2 days, replaced with meropenam, metronidazole, fluconazole for *Candida*	*S. cerevisiae* (NCCPF 920012)	Micafungin (100 mg) for 2 days, patient afebrile within 3 days, discharged with fluconazole 400 mg bd	Recovered
6.	66/F Kolkata	Cerebral stroke, prolonged hospitalization, multiple episodes of sepsis	*S. boulardii* (due to diarrhoea)	Prolonged hospitalization multiple antibiotics	*S. cerevisiae* (NCCPF 920005)	Treatment history not known	Not known
7.	32/M Kolkata	Superior vena cava syndrome due to mediastinal mass, fever, respiratory distress	No history of probiotics, referred from another hospital after 12 h' stay	Multiple antibiotics	*S. cerevisiae* (NCCPF 920010)	Caspofungin	Recovered

CVC, central venous catheterization; ABDC, amphotericin B deoxycholate; MDR, multidrug resistant; GCS, Glasgow coma scale; UTI, urinary tract infections; LUCS, lower uterine segment caesarean section.

Roy U et al *Mycoses* 2017;60;375

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Roy U et al *Mycoses* 2017;60;375

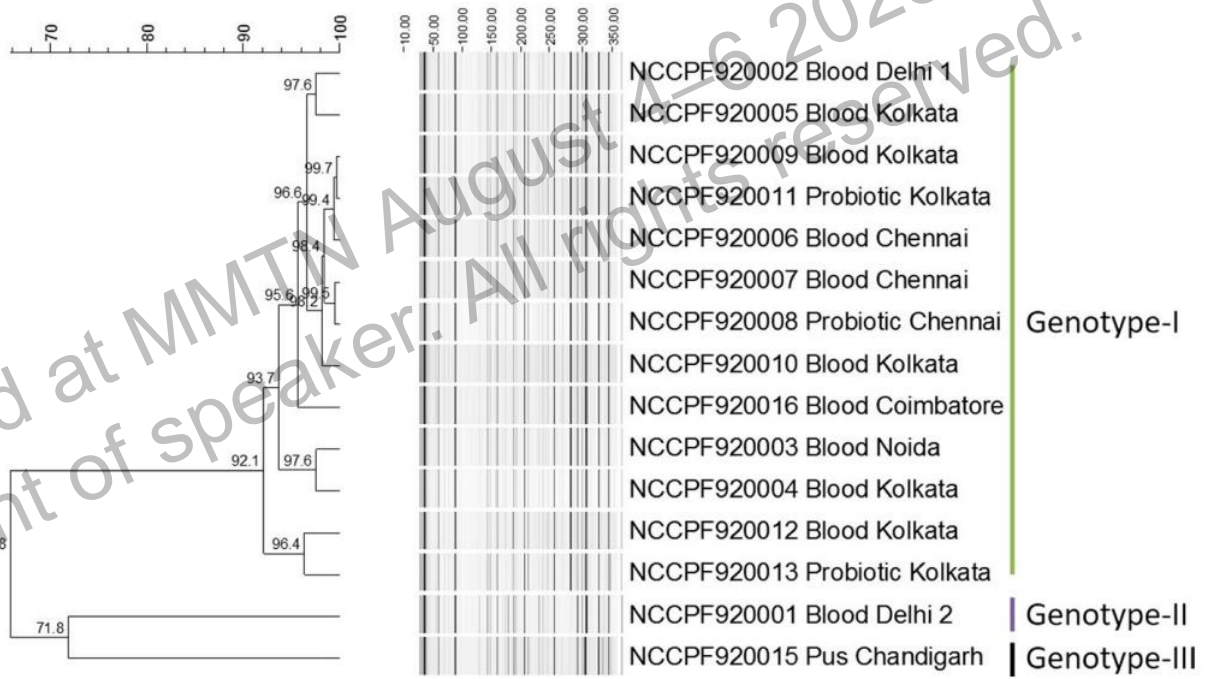
S. cerevisiae fungemia – investigations in 2 Indian hospitals

- Discovery of *S. cerevisiae* fungemia led to investigations
- All patients were on probiotics
- 2 preterm infants – part of protocol in NICU
- 5 adults – given to manage/prevent diarrhea
- Probiotic sachets obtained for testing

Roy U et al *Mycoses* 2017;60;375

Linkage between blood and probiotic isolates (India)

Isolate from patient and probiotic consumed by that patient (n=3) had high bootstrap values 99.7%, 99.5%, 96.4%.



Roy U et al *Mycoses* 2017;60;375

Saccharomyces cerevisiae infections and probiotic intake

- 5 Finnish hospitals (Jan 2009 – Dec 2018)
- Case control study: 46 *S. cerevisiae* fungemia compared with blood-culture-positive controls from same ward
- 59% of *S. cerevisiae* fungemia pts had underlying disease of digestive tract
- Use of *S. cerevisiae* var boulardii probiotic
  - 20/46 (43%) in *S. cerevisiae* fungemia group, vs 4/76 (5%) in control group (OR 14, 95CI 4 -44)

Ranniko J et al. *Emerg Infect Dis* 2021;27:2103

Incidence rate

- Hospital that routinely administers *S. boulardii* probiotic to prevent hospital-onset C. difficile
- Database mining – Pharmacy database evidence of probiotic having been served, vs Microbiology lab database of *S. boulardii* isolation from blood
- 16,404 of 46,729 pts (35%) administered *S. boulardii*
- 18 developed *S. boulardii* fungemia
- 0.11% of all patients administered *S. boulardii* probiotic
- 1.7 cases of *S. boulardii* fungemia per 10,000 patient-days, among pts administered *S. boulardii*

Wombwell E et al. *Mycoses* 2021;64:1521

MMTN
MEDICAL MYCOLOGY TRAINING NETWORK

Is it a CVC problem?

- Of the 18 fungemic pts, 14 had a central line
- Incidence of *S. boulardii* fungemia was 0.26/1,000 central line days
- Limited to ICU pts, incidence of *S. boulardii* fungemia was 0.47/1,000 ICU patient-days

- In comparison with NHSN data (2011 – 2017)
- CLABSI rate from NHSN = 0.78/1,000 central line days (ICHE 2020;41:313)
- Candida/other yeast CLABSI from NHSN = 0.41/1,000 central line days in adult ICUs

Wombwell E et al. *Mycoses* 2021;64:1521

S. cerevisiae incidence in hematological patients

- Study looked for fungal colonization systemically from patients admitted to Hematology unit (throat, urine, stool, perineal cultures)
- All patients received nystatin, TMP/SMX
- Empiric amB for fever not responding to antibiotics after 72-96hrs
- Fluconazole for superficial yeast infections
- No mention of probiotics
    - On admission 1% of all screening fungal isolates were *S. cerevisiae*
    - On follow-up, 18% of all fungal screening isolates were *S. cerevisiae* ($p<0.001$)

Salonen JH et al. *J Hosp Infect* 2000;45;293

Susceptibility may depend on azole exposure

- 20 hematological malignancy patients accounted for all the *S. cerevisiae* screening isolates in the ward
- 10 of these patients had received an azole prior to being culture-positive for *S. cerevisiae*
- Azole MIC however uniformly high among all the isolates - did nosocomial transmission account for the rest?

Table VI In-vitro *susceptibility of 160* Saccharomyces cerevisiae *isolates to three antifungal agents*

Antifungal agent	MIC (μg/mL)*		
	Range	50%	90%
Amphotericin B	0.25–4	0.5	1
Fluconazole	1–128	64	128
Itraconazole	0.25–16	8	16

*50% and 90%, MIC at which 50 and 90% of the isolates tested were inhibited.

Salonen JH et al. *J Hosp Infect* 2000;45;293

Risk factor analyses in the literature

- ✓ RV of 92 cases up to 2005
- ✓ Blood most frequent site
- ✓ Main risk factors – CVCs, prior antibiotic therapy
- ✓ Clinically resembles invasive candidiasis
- ✓ Low susceptibility to amB, but 62% recovered with amB, fluconazole, catheter removal

Enache-Angoulvant A et al. Clin Infect Dis 2005;41:1559

Case series (3) and review (14) 1990 (Cleveland Clinic)
Main risk factors:

- ✓ Severe immunosuppression
- ✓ Prior antibiotics
- ✓ Prolonged hospitalization
- ✓ Prosthetic heart valves

Aucott JN et al. Rev Infect Dis 1990;12;406

Case series 2005 (Hospital Universitario Gregario Manon)

Intake of probiotics only risk factor

Munoz P et al. Clin Infect Dis 2005;40:1652

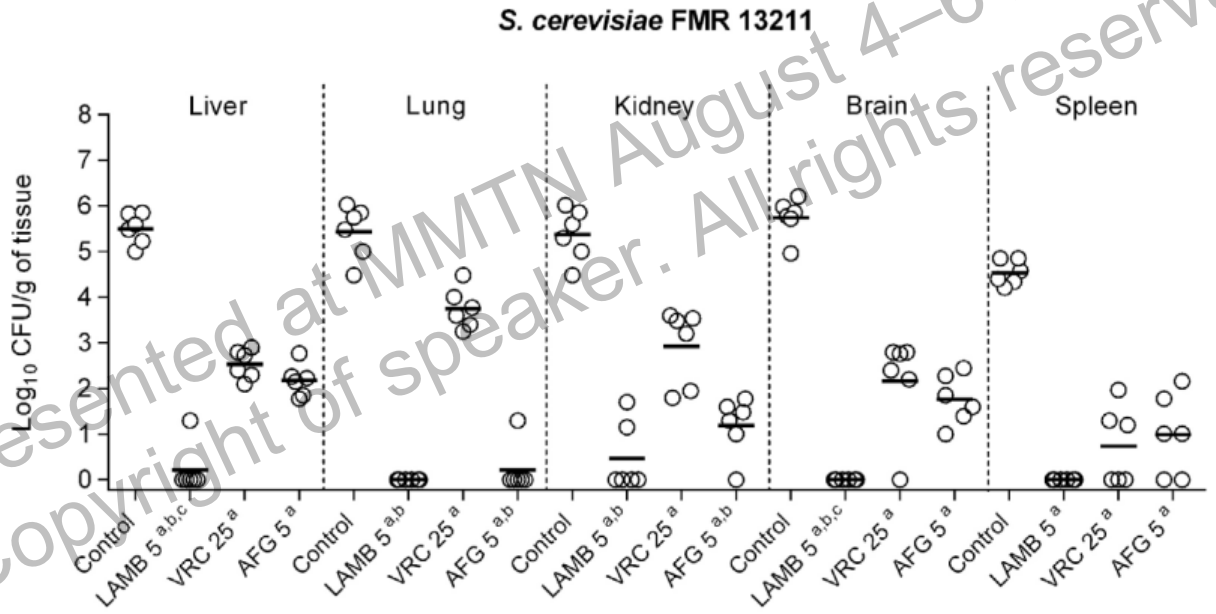
Susceptibility testing of *S. cerevisiae*

Antifungal agent	MIC (μg/ml)		
	FMR 13211	FMR 13212	FMR 13213
Amphotericin B	0.25	0.25	0.5
Itraconazole	1	1	0.5
Fluconazole	≥32	≥32	≥32
Posaconazole	0.5	0.5	0.25
Voriconazole	0.25	0.12	0.25
Anidulafungin	0.12	0.12	0.25
Caspofungin	0.25	0.25	0.25
Micafungin	0.25	0.25	0.25
5-Fluorocytosine	≤0.03	≤0.03	≤0.03

MIC: minimal inhibitory concentration.

Perez-Cantero A et al. *Rev Iber Micol* 2019;36:37

LamB appears best at lowering fungal burden in tissue (murine model)



Perez-Cantero A et al. *Rev Iber Micol* 2019;36:37

ESCMID/ECMM treatment recommendations - Saccharomyces

- Most experience with amphotericin B, fluconazole
- Case reports exist for successful use of echinocandins
  - (Author's anecdotal experience one unsuccessful case)
- Amphotericin + 5-FC has been used
- Stop *S. boulardii* probiotics, remove lines

Arendrup MC et al. *Clin Microbiol Infect* 2014;20(Suppl 3): 76

Amphotericin commonly used, outcomes favorable

Infection type, patient, reference	Age, sex	Site of isolation or associated condition		Concomitantly isolated organisms	Underlying condition	Predisposing factor			Treatment	IVC removal	Outcome
		First isolate	Additional isolates			NeutP	IVC	ATB			
Disseminated											
1 [23]	54 years, F	Blood	Urine	Diphtheroids	Valvular prosthesis	No	Yes	Yes	AmB	Yes	Favorable
2 [24]	38 years, M	Blood	…	None	IVDA, valvular prosthesis	No	NS	Yes	AmB	NS, VR	Favorable
3 [25]	68 years, M	Bone marrow[c]	Urine	None	Ingestion of brewer's yeast	Yes	NS	No	None	NS	Favorable
4 [26]	59 years, M	Blood	Esophagus	None	Severe burns	Yes	Yes	Yes	AmB	Yes	Favorable
5 [27]	61 years, M	Blood	CVC	None	Renal failure, hemodialysis, abdominal surgery	No	Yes	Yes	MCZ, 5-FC	Yes	Death
6 [28]	37 years, F	Blood	Chorioretinitis	None	AIDS, IVDA, peritoneal dialysis	NS	NS	Yes	AmB	NS	Favorable
7 [29]	26 years, M	Blood	…	NS	AML	No	Yes	NS	NS	Yes	Favorable
8 [29]	81 years, F	Blood	…	NS	AML	Yes	NS	NS	AmB	NS	Favorable
9 [30]	25 years, F	Blood	…	None	Trauma, abdominal surgery	No	Yes	Yes	AmB	Yes	Favorable
10 [31]	39 years, M	Lung[c]	Spleen,[c] digestive tract	*Pneumocystis carinii, Mycobacterium avium-intracellulare*	AIDS	No	No	No	None	No	Death
11 [32]	6 weeks, NS	Blood	CVC, urine	*Candida albicans*	Abdominal surgery	No	Yes	Yes	None	Yes	Favorable
12 [32]	71 years, M	Blood	Throat	*Kluyveromyces marxianus, Geotrichum capitatum*	Aplastic anemia	Yes	Yes	Yes	AmB, 5-FC	NS	Death
13 [33]	62 years, F	Blood	Liver abscess, biliary fluid	*Candida parapsilosis* from liver and biliary fluid	Pancreas neoplasia, digestive surgery	NS	NS	Yes	AmB	NS	Death
14 [33]	65 years, F	Blood	Heart,[c] pericardium,[c] lung,[c] serosa of colon[c]	*Aspergillus* species from heart and pericardium	Hemopathy (idiopathic pancytopenia)	Yes	NS	Yes	None	NS	Death
15 [34]	71 years, M	Blood	…	None	Epidermoid cancer, chemotherapy	No	NS	Yes	AmB, 5-FC[a]	NS	Death
16 [35]	70 years, F	Blood	…	None	Hemopathy (EBRA)	Yes	NS	Yes	None	NS	Death
17 [22]	8 weeks, F	Blood	…	*Enterobacter cloacae*	Respiratory failure, ECMO	NS	NS	Yes	None	NS	Favorable
18 [36]	48 years, F	Blood	…	None	Allogenic BMT for CML	No	Yes	NS	FLU	Yes	Favorable
19 [37]	NS, NS	Endocarditis[c]	Blood	NS	Prosthetic valve	NS	Yes	Yes	AmB	NS	Favorable
20 [38]	32 years, F	Blood	…	None	Right breast abscess, septic shock	NS	NS	NS	NS	NS	Favorable
21 [38]	16 years, M	Blood	…	None	Convulsion seizure	NS	NS	NS	NS	NS	Favorable
22 [39]	NS, NS	Blood	…	NS	Chronic alcoholism, root canal treatment	NS	NS	Yes	NS	NS	Favorable
23 [40]	NS, NS	Blood	…	NS	AIDS	NS	NS	NS	NS	NS	Death
24 [41]	34 years, M	Blood	…	None	Relapsed ALL	Yes	NS	Yes	AmB, 5-FC[a]	NS	Favorable
25 [42]	NS, NS	Blood	…	NS	BMT	NS	Yes	NS	NS	NS	NS
26 [43]	10 years, F	Blood	Lung,[c] mitral valve[c]	None	Cystic fibrosis, intestinal obstruction, ileostomy	NS	Yes	Yes	AmB	Yes	Death
27 [43]	10 weeks, NS	Blood	…	*Klebsiella pneumoniae*	Premature birth, CRD, corticosteroid therapy, gastrostomy	No	Yes	Yes	AmB	Yes	Favorable
28 [43]	7 years, M	Blood	…	*K. pneumoniae, E. cloacae*	Gastroschisis, intestinal resection, T	Yes	NS	No	AmB	Yes	Favorable

Some of these "unfavorable" outcomes occurred in pts with AIDS, ca oesophagus, aplastic anemia – was failure of treatment a drug failure?

Enache-Angoulvant A et al. *Clin Infect Dis* 2005;41:1559

An infection control problem?

JOURNAL OF CLINICAL MICROBIOLOGY, Nov. 2003, p. 5340–5343
0095-1137/03/$08.00+0 DOI: 10.1128/JCM.41.11.5340–5343.2003

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Outbreak of *Saccharomyces cerevisiae* Subtype *boulardii* Fungemia in Patients Neighboring Those Treated with a Probiotic Preparation of the Organism

Eur J Clin Microbiol Infect Dis (2000) 19:16–20

Article

Possible Role of Catheters in *Saccharomyces boulardii* Fungemia

An experiment

- Sampling of air, surrounding surfaces, before, during and after the opening of a packet of freeze-dried S. boulardii (used in their hospital for diarrhea)

Hennequin C et al. *Eur J Clin Microbiol Infect Dis* 2000;19:61

An experiment

- Sampling of air, surrounding surfaces, before, during and after the opening of a packet of freeze-dried S. boulardii (used in their hospital for diarrhea)

Table 2 Results of environmental sampling in relation to the opening of a 500 mg packet of freeze-dried *Saccharomyces boulardii*

Time of sampling (relative to the opening of a packet)	No. of cfu
Air	per 500 l impacted
1 h before	0
During the opening	25
30 min after	2
1 h after	0
2 h after	0
6 h after	0
24 h after	0
Arm of the simulated patient	per ±25 cm²
Before opening	0
30 min after	10
Surface table	per ±25 cm²
Before opening	0
2 h after	7
Hands of the operator[a]	per hand-washing
Before opening	0
Before hand-washing	confluent colonies
After hand-washing	57

*Nurse performing this experiment did not wear gloves

Hennequin C et al. *Eur J Clin Microbiol Infect Dis* 2000;19:61

MMTN MEDICAL MYCOLOGY TRAINING NETWORK

If preparing *S. boulardii* …

- Should not be prepared in patient's room
- Operator must wear gloves

Hennequin C et al. *Eur J Clin Microbiol Infect Dis* 2000;19:61

Thank you