Meeting Title:	**CLSI Subcommittee (SC) on Antifungal Susceptibility Tests**	**Contact:**	clam@clsi.org
		Secretary	Camille Hamula, PhD, D(ABMM)
Virtual Meeting Dates/Times:	**Saturday, 20 January 2024 in Tempe, AZ, from 7:30 – 11:30 AM US Mountain Standard Time and 12:30 – 4:30 PM US Mountain Standard Time**		
Meeting Purpose:	The purpose of this meeting is to review any new breakpoint, epidemiological cutoff value, or quality control data and to discuss SC business.		
Requested Attendee(s):	SC Chairholder, Vice-chairholder, Members, Advisors, and Reviewers; Presenters; Other Interested Parties; CLSI Staff		

Attendee(s):	
Philippe J. Dufresne, PhD, RMCCM **Chairholder**	**Institut national de santé publique du Québec**
Nathan P. Wiederhold, PharmD **Vice-chairholder**	**University of Texas Health Science Center at San Antonio**
Members Present:	
Barbara Alexander, MD, MHS	Duke University Medical Center
David Andes, MD	University of Wisconsin - Madison Medical School
Andrew M. Borman, BSc, PhD	UK Health Security Agency
Tanis Dingle, PhD, D(ABMM), FCCM	Alberta Precision Laboratories - Public Health Laboratory
Hari P. Dwivedi, BVSc(DVM), MVSc, PhD	bioMérieux, Inc.
Shawn R. Lockhart, PhD, D(ABMM), F(AAM)	Centers for Disease Control and Prevention
Stephanie Mitchell, PhD, D(ABMM)	Cepheid
Chris Pillar, PhD	Microbiologics
Audrey N. Schuetz, MD, MPH, D(ABMM)	Mayo Clinic Rochester
Amir Seyedmousavi, VMD, PhD, FECMM	National Institutes of Health
Paul E. Verweij, MD, FECMM	Radboud University Medical Center
Sean X. Zhang, MD, PhD, D(ABMM)	Johns Hopkins University
Advisors Present:	
Esther Babady, PhD, D(ABMM)	Memorial Sloan Kettering Cancer Center
Shukal Bala, PhD	FDA Center for Drug Evaluation and Research
Elizabeth Berkow, PhD	Centers for Disease Control and Prevention
Cecilia Carvalhaes, MD, PhD, D(ABMM)	bioMérieux
Sharon Chen, PhD, MBBS; FRACP, FRCPA, FECMM	Centre for Infectious Diseases and Microbiology Laboratory Services, ICPMR, New South Wales Health Pathology
Anuradha Chowdhary, MD, PhD	Vallabhbhai Patel Chest Institute
Sharon K. Cullen, BS, RAC	Beckman Coulter, Inc. Microbiology Business
Ryan Demkowicz, MD	West Virginia University
Jeff Fuller, PhD, FCCM, D(ABMM)	London Health Sciences Centre
Guillermo Garcia-Effron, PhD	Universidad Nacional del Litoral - CONICET
Mahmoud Ghannoum, PhD,FIDSA,MBA	Case Western Reserve University
Natasha Griffin, PhD	FDA Center for Devices and Radiological Health
Camille Hamula, PhD, D(ABMM)	Saskatoon Health Region/University of Saskatchewan
Kimberly Hanson, MD, MHS	ARUP Laboratories
Nicole M. Holliday, BA	Affinity Biosensors
Scott Killian	Thermo Fisher Scientific
Laura Kovanda, BA, PhD	Astellas Pharma Global Development, Inc.
Julianne Kus, HONBSc, MSc, PhD, FCCM	Public Health Ontario
Sixto M. Leal, Jr., MD, PhD	University of Alabama at Birmingham
Mary Motyl, PhD, D(ABMM)	Merck & Company, Inc.
Luis Ostrosky-Zeichner, MD, FACP, FIDSA, FSHEA, CMQ	McGovern Medical School

Jeffrey Rybak, PharmD, PhD	St. Jude Children's Research Hospital
Vera Tesic, MD, MS, D(ABMM)	University of Chicago Hospital
Priyanka Uprety, MSPH, PhD, D(ABMM)	Quest Diagnostics
Thomas Walsh, MD, PhD(Hon), FIDSA, FAAM, FECMM	New York Presbyterian/Weill Cornell Medical Center
Adrian M. Zelazny, PhD, D(ABMM)	National Institutes of Health Department of Laboratory Medicine
Yanan (Nancy) Zhao, MD, PhD	University at Buffalo, School of Pharmacy and Pharmaceutical Sciences

Staff:	
Jennifer Adams, MLS(ASCP), MSHA	CLSI
Kathy Castagna, MS, MT(ASCP)CT, MB	CLSI
Emily Gomez, MS, MLS(ASCP)MB	CLSI
Christine Lam, MLS(ASCP)	CLSI

NOTE: Subcommittee Reviewers and Guest Attendees Listed at End of Summary Minutes.

AGENDA (Part 1) Saturday, 20 January 2024: 7:30 AM – 11:30 AM All times are Mountain Standard (US) time					
#	**Time**	**Length**	**Presenter**	**Description**	**Background**
1.	7:30 AM	5 min.	Ms. Lam	Zoom meeting instructions	N/A
2.	7:35 AM	5 min.	Dr. Dufresne	**Opening Remarks**	N/A
3.	7:40 AM	5 min.	Ms. Adams	**CLSI Update**	N/A
4.	7:45 AM	30 min.	Dr. Dufresne	**SC Status presentation** • Agenda review (VOTE) • Summary minutes from 2023 August meeting (VOTE) • SC Roster rotations • Process review • Status of antifungal documents	4_Presentation
5.	8:15 AM	15 min.	Dr. Zhang/Dr. Fuller Dr. Castanheira/Dr. Garcia-Effron	**M27 and M38 standards to review** • Update on the process • Document review WG creation	5_Presentation
6.	8:30 AM	15 min.	Dr. Hanson Dr. Griffin	**M44 review recommendations**	6_Presentation
7.	8:45 AM	15 min.	Dr. Dufresne	**M57S, M27M44S and M38M51S updates** • Draft documents	7_Presentation
8.	9:00 AM	10 min.	Dr. Wiederhold Dr. Andes Dr. Dufresne	**Breakpoint Working Group Update** • *Afumigatus* voriconazole BP RD document (corrected version submitted to FDA) • *Afumigatus* isavuconazole BP draft RD (submitted to FDA for review) • Rezafungin tentative BP review	8_Presentation
9.	9:10 AM	30 min.	Melinta and JMI	**Rezafungin – new data**	9_Presentation Melinta Rezafungin Presentation
10.	9:40 AM	25 min.	Dr. Wiederhold Dr. Andes	**Breakpoint WG – recommendation for rezafungin BP**	10_Presentation
11.	10:05 AM	20 min.		**Break**	N/A

AGENDA (Part 1) Saturday, 20 January 2024: 7:30 AM – 11:30 AM All times are Mountain Standard (US) time					
#	Time	Length	Presenter	**Description**	Background
12.	10:25 AM	20 min.	Dr. Dufresne Dr. Lockhart Dr. Wiederhold	**ECV Working Group Update** • **Ongoing projects** -Sporothrix -Fonsecaceae -Aspergillus • **M57S - ECV guidance annex tables** ○ Yeast taxonomy /expected susceptibility profile ○ Yeast MIC distribution table	12_Presentation
13.	10:45 AM	30 min.	Dr. Dufresne Dr. Santos	**Sporothrix ECVs**	13_Presentation
14.	11:15 AM	20 min.	Dr. Garcia-Effron	***C. lusitaniae* Amphotericin susceptibility testing**	14_Presentation
15.	11:35 AM	60 min.		**Lunch Break**	N/A

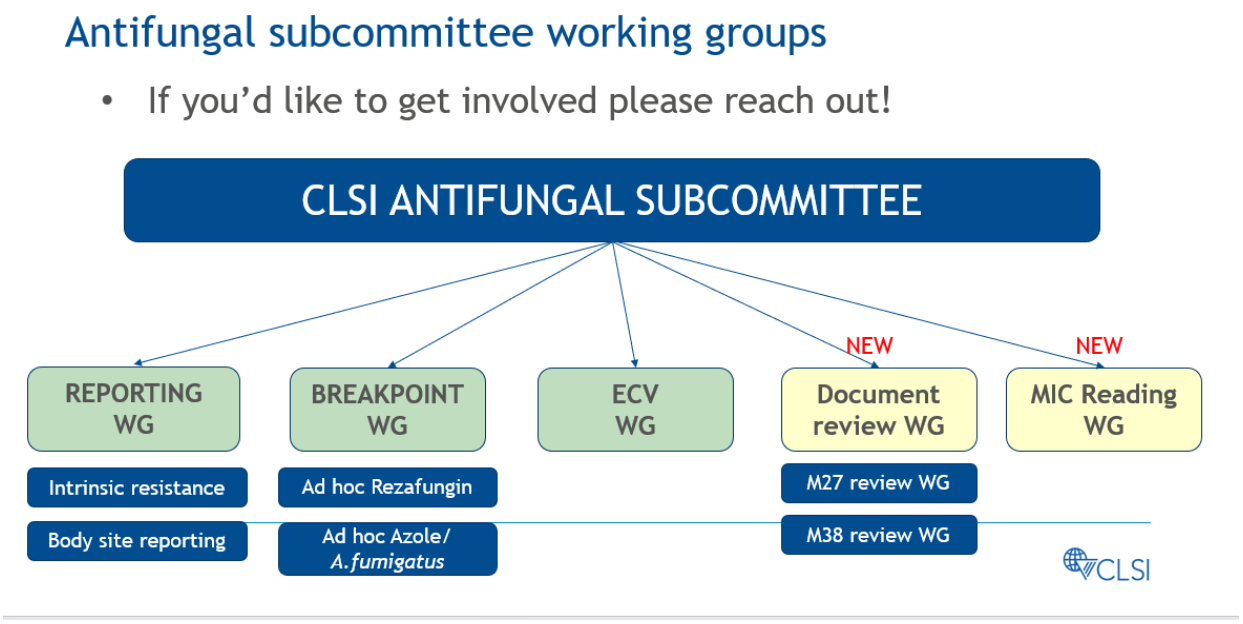
AGENDA (Part 2) Saturday, 21 January 2024: 12:30 PM – 4:30 PM All times are Mountain Standard (US) time					
#	Time	Length	Presenter	Description	Background
16.	12:30 PM	45 min.	Dr. Schuetz	**Intrinsic Resistance Working Group Updates** - EUCAST «expected resistance and susceptibility definition to replace IR»	16_Presentation
17.	1:15 PM	30 min.	Dr. Schuetz Dr. Dingle	**Discussion on «Reduced susceptibility» definition**	Included in 16_Presentation
18.	1:45 PM	20 min.		**Break**	N/A
19.	2:05 PM	30 min	Dr. Chaturvedi	**Dermatophyte susceptibility testing *T. indotineae* update**	19_Presentation
20.	2:35 PM	15 min.	Dr. Dufresne	**Other business**	TBD
21.	2:50 PM	5 min.	Dr. Dufresne	**Plans for next virtual meeting**	N/A
22.	2:55 PM PM	N/A	Dr. Dufresne	**Adjournment**	N/A

Summary of Voting Decisions

Motion Made and Seconded	Voting Results[a]	Page[b]
To perform a limited revision of M44 as presented by Dr. Hanson and Dr. Griffin was made and seconded.	12-0-0-0	7
To revise M57S, M38M51S, and M27M44S as presented by Dr. Dufresne was made and seconded.	12-0-0-0	8
To move forward to make rezafungin BPs no longer tentative, and to draft a rationale document to explain difference between FDA and CLSI, as presented by Dr. Wiederhold was made and seconded.	11-1-0-0	26
To accept proposed ECVs for *C. glabrata*, *C. albicans* and *C. tropicalis* as TRL and *C. krusei* ECV of 32 as presented by Dr. Dufresne was made and seconded.	12-0-0-0	28
To accept proposed ECVs for *Sporothrix* spp. shown on slide as presented by Dr. Dufresne was made and seconded.	12-0-0-0	33

[a] Key for voting: X-X-X-X = For-against-abstention-absent

[b] Page links can be used to go directly to the related topic presentation and voting discussions.

SUMMARY MINUTES Saturday, 20 January 2024	
#	Description
1.	**ZOOM MEETING INSTRUCTIONS (MS. LAM)** • Ms. Lam provided Zoom meeting instructions to meeting participants.
2.	**OPENING REMARKS (DR. DUFRESNE)** • Dr. Dufresne welcomed everyone to the meeting and presented some housekeeping items.
3.	**CLSI UPDATE (MS. ADAMS)** • Ms. Adams provided an update on the fiscal year 2023 publications by the 10 topic areas covered by CLSI, as well as the current projects in progress.
4.	**SUBCOMMITTEE STATUS PRESENTATION (DR. DUFRESNE)** • Vote on meeting agenda: 12-0-0-0. Motion passes. • Vote on August 2023 meeting summary minutes: 12-0-0-0. Motion passes. • Dr. Dufresne provided a summary of the subcommittee members and advisors, and outlined the rotations that took place. • Nathan Wiederhold is new Vice-Chairholder, will become Chairholder in 2 years. Gary Procop is former Chair, and is now an advisor for the subcommittee. • 12 new advisors joining us this year. • Increased voting members from 9 to 12. • Antifungal Subcommittee working group structure:  • 3 main WGs, with 2 New WGs: Document Review WG, Antifungal MIC Reading WG. Volunteers and photos needed for MIC reading guide WG. • MIC Reading WG will work with M27 and M38 revision document development committees. • Antifungal document status review: – Procedural documents (M27, M38, M44, M57, M51 archived) generally locked for 3-5 years, reviewed at 5 year mark to determine if revision is needed. – Supplements (M27M44S, M38M51S and M57S) can be updated annually. – M27, M38 currently being revised.

#	Description
	– M44 two volunteers Kim Hanson and Natasha Griffin have performed 5 year review and will present recommendations. – Overview of CLSI document review process. Timeline 14 months.
5.	**M27 AND M38 STANDARDS TO REVIEW (DR.ZHANG, DR. FULLER, DR. CASTANHEIRA, DR. GARCIA-EFFRON)** • M27 revision document development committee (DDC) Chairholders are Dr.Mariana Castanheira and Dr. Guillermo Garcia-Effron. • M38 revision DDC Chairholders are Dr. Sean Zhang and Dr. Jeff Fuller. • DDC rosters in process of being finalized, appointment letters to be sent in February 2024. • M27 review timeline: – March 2024 inaugural meeting – March-November 2024 drafting document – March-April 2025 voting period for document – April-June 2025 final revision – November 2025 expected date of publication • M38 review timeline same as M27 except launches one month later, with expected publication in December 2025
6.	**M44 REVIEW RECOMMENDATIONS (DR. HANSON, DR. GRIFFIN)** • M44Ed3 published in 2018. Disk diffusion testing of yeasts. – Disk diffusion testing-inexpensive, reproducible, easy to interpret. – MH agar with 2% glucose and 24h incubation, 48h some strains. – Low utilization in US. Most labs use Vitek or YeastOne. Only 2% use DD. – In M44, validated for the below drugs and organisms: Validated for select *Candida* spp* **Breakpoints** • Fluconazole • Voriconazole • Caspofungin • Micafungin **Quality Control** • Fluconazole • Voriconazole • Posaconazole • Caspofungin • Micafungin * *C. albicans, C. glabrata, C. tropicalis, C. krusei and C. parapsilosis* * *C. guillermondii* caspo and mica only

#	Description
	– FDA does not clear many disks (1 clearance in 15 years). Not frequently performed, but document has needed information and recommendations. No egregious errors or omissions in document. – M44 Review Options (Specific comments in background material file M44 Review Recommendation). – Document has value for the users so there is a need. – Does use of an archived document present CLIA or other regulatory challenges to labs? – Does adding clerical details addressing the clarification comments rise to the level of "revise"? – Can the document be "reaffirmed?" – Does M44 have to be revised to update breakpoints in M27M44S? – Questions are procedural, need clarification before issuing recommendations. • Discussion: – Dr. Castenheira thinks we should keep the document and not close the door since it is a standard method and is used for new drugs like rezafungin. Important for developing countries. They don't have access to VITEK or YeastOne. Nice method to use in respect to screening, nice to have something standardized to use if you have new drugs to test. Should be active, and reaffirmed. – Dr. Schuetz mentioned there is still a limited revision process in CLSI and is asking if that is still available? It is less onerous than a full revision. – CLSI: Yes this is an option. Limited revision allows a few edits to be added. Other option is that we can call the edits as consensus comments, do consensus comments and hold those comments for next revision. Also, be aware that archived documents are still available for purchase but archiving will pull the document out of the 5 year review process. – Dr. Dufresne mentions whereas it will be reviewed in 5 years if you reaffirm with limited revision. – Dr. Berkow: in under resourced countries, the standard is DD. I strongly recommend to keep the document. – Dr. Lockhart: mentioned that in Africa, gradient diffusion is more expensive than Vitek. Huge amount of interest in disk diffusion. In Asia, they are moving to Vitek 2 or gradient diffusion more. DD also used in Argentina. A motion to perform a limited revision of M44 as presented by Dr. Hanson and Dr. Griffin was made and seconded. Vote: 12 for, 0 against, 0 abstain, 0 absent (Pass).
7.	**M57S, M27M44S and M38M51S UPDATES (DR. DUFRESNE)** • CLSI AST committee would like to clarify that for antifungals DD is a standardized CLSI method but **not** a reference method like BMD (unlike bacterial committees which list it as a reference method). • Only mentioned as a reference method in foreword of M27M44S and M38M51S. • Proposal to reformulate: BMD as sole "reference method" and DD as "standardized" method? • Discussion: – Dr. Castanheira says this is a contentious topic in bacterial subcommittee, and if our document does not match bacterial documents it will confuse people. Issue is people use DD to validate other methods in their labs so is it really a reference method? Calling it a standard allows it to be used in validations. – Ms. Cullen asks if the semantics of the words impacts the desire to use it as a comparator for laboratory verification? Her understanding is that the words don't matter and it is still appropriate to use in verifications. Committee should vote to say if bacteria does it, we will do it and leave the debate to them. If they decide to go that way we should follow suit. – Dr. Lockhart completely disagrees it is NOT a good reference method and it is not a good comparator. Only 3 drugs and 4 bugs that can be used. Very limited validation possible. We don't always have to do what bacterial does. Our bugs and standards are different from theirs and that's ok. – Dr. Castanheira thinks if we write validation rules for tests and our committee has a different nomenclature, that's confusing. Maybe the language needs to be changed in other documents because in the end it doesn't matter. – Ms. Cullen says proposal is to call DD a standardized method. There may be other considerations about what is appropriate to use as a comparator. However, it does describe the reference MIC as what you

#	Description
	start with. When you use a comparative method, use your brain. However for CLSI there should be a generalized understanding of how we are using the terms. – Dr. Dufresne mentions with DD you can't get an MIC, you can't calculate Essential Agreement. – Dr. Schuetz says this is coming up for vote under methods application and interpretation working group. Suggests we wait to see what the results of their vote is and try to align if possible. These words are throughout all documents and it is important for labs to understand "reference" and "standard." – Dr. Fuller agrees as a standard setting organization we need to be clear and what is our motivation? Aligning with bacteriology is not a motivation. But we have identified a risk that the terms could be misused to verify or validate an assay. – General consensus that we list DD as a standard, and make sure the definition of reference and standard is consistent with bacterial definitions. – Barb Alexander: What is the risk to the patient? Or the laboratory? That should be our determinant to how we apply these. If we are using DD to validate a commercial product for a lab is there a risk we will get errors? We need to examine our own antifungal data to see if it is ok or not? – Dr. Castanheira says nobody is using this to validate anything antifungal. There isn't a risk anyone will use this for antifungals. Risk is more for bacterial. The bacterial subcommittee will resolve this. They will likely call it a standard. – Dr. Alexander still thinks it is confusing and needs to be crystal clear to laboratories what you can and can't use to validate. – FDA from a regulatory standpoint these semantics do not matter as we collect the appropriate data. – Dr. Castanheira proposes that we add a note to the document that DD is not appropriate for validation. Verification vs validation be careful to use terms appropriately they are different. Bacterial subcommittee has an ad hoc WG to discuss. – Dr. Dingle says she thinks we should wait to hear more about their decisions. We will need to put some language in the antifungal documents in regards to verifications. – Dr. Lockhart points out that DD of fungi is NOT the same test as DD of bacteria. – Dr. Dufresne proposes we keep an eye on what happens with bacterial, provide our feedback to Dr.Romney Humphries on the view of this WG. We do not need to vote at this point. • M57S: Antifungal ECVs: – M57S ED4 published 2022 – M57S ED5 draft – 25 ECVs to be added, 15 yeast and 10 molds – New Tables: MIC distribution tables, susceptibility profile according to yeast/family/complex – 5 yeast species ECVs to be added: *C.inconspicua, C. rugosa, C.pelliculosa, C.haemulonii, T.asahii, C.parapsilosis* – Adding olorofim. New antifungals we are missing have been added to the glossary including ibrexafungerp, manogepix, olorofim, oteseconazole. – Updated summary table 6

#	Description

Table 6. Summary of Available Epidemiological Cutoff Values and/or Breakpoints by Fungal Species

Species	Antifungal Agent										
	Amphotericin B	Anidulafungin	Caspofungin	Fluconazole	Flucytosine	Isavuconazole	Itraconazole	Micafungin	Posaconazole	Rezafungin[a]	Voriconazole
Yeasts											
Candida albicans	ECV	BP/ECV	BP	BP/ECV	-	-	-	BP/ECV	ECV	BP/ECV	BP/ECV
Candida auris	-	ECV	ECV	-	TR-L	-	-	ECV	-	BP/ECV	-
Candida dubliniensis	ECV	ECV	-	ECV	TR-L	-	ECV	ECV	ECV	BP/ECV	-
Candida duobushaemulonii	TR-H	ECV	ECV	ECV	TR-L	ECV	ECV	ECV	ECV	-	ECV
Candida glabrata[b]	ECV	BP/ECV	BP	BP/ECV	-	-	ECV	BP/ECV	ECV	BP/ECV	ECV
Candida guilliermondii[b]	ECV	BP/ECV	BP/ECV	ECV	TR-L	-	ECV	BP/ECV	ECV	-	-
Candida haemulonii	-	ECV	-	ECV	-	-	ECV	-	ECV	-	ECV
Candida inconspicua	ECV			ECV			ECV				ECV
Candida kefyr[b]	ECV	ECV	-	ECV	TR-L	-	ECV	ECV	ECV	-	-
Candida krusei[b]	ECV	BP/ECV	BP	IR	-	-	ECV	BP/ECV	ECV	BP/ECV	BP/ECV
Candida lusitaniae[b]	ECV	ECV	ECV	ECV	TR-L	-	ECV	ECV	ECV	-	-
Candida metapsilosis	ECV	ECV	ECV	ECV	TR-L	-	ECV	ECV	ECV	-	ECV
Candida orthopsilosis	ECV	ECV	ECV	ECV	TR-L	-	ECV	ECV	ECV	-	-
Candida parapsilosis	ECV	BP/ECV	BP/ECV	BP/ECV	TR-L	TR-L	ECV	BP/ECV	ECV	BP/ECV	BP/ECV
Candida pararugosa[b]	-	-	-	ECV	-	-	-	-	-	-	-
Candida pelliculosa[b]	ECV	ECV	-	ECV	TR-L	-	ECV	ECV	ECV	-	ECV
Candida rugosa[b]	ECV	ECV	ECV	ECV	-	-	ECV	ECV	ECV	-	ECV
Candida tropicalis	ECV	BP/ECV	BP	BP/ECV	-	-	ECV	BP/ECV	ECV	BP/ECV	BP/ECV
Cryptococcus gattii (VGI)	ECV	IR	IR	ECV	ECV	-	ECV	IR	-	-	ECV

ECVs we voted last year. That would be added. If you look at the summary table in red, those would be the additions we put in.

Table 6. (Continued)

Species	Antifungal Agent											
	Amphotericin B	Anidulafungin	Caspofungin	Fluconazole	Flucytosine	Isavuconazole	Itraconazole	Micafungin	Olorofim	Posaconazole	Rezafungin[a]	Voriconazole
Yeasts (Continued)												
Cryptococcus deuterogattii (VGII)	ECV	IR	IR	ECV	ECV	-	ECV	IR		-	-	ECV
Cryptococcus neoformans (VNI)	ECV	IR	IR	ECV	ECV	-	ECV	IR		ECV	-	ECV
Rhodotorula mucilaginosa	ECV	IR[c]	IR[c]	IR[d]	TR-L	-	ECV	IR[c]		ECV	-	ECV
Saccharomyces cerevisiae	ECV	ECV	ECV	ECV	TR-L	-	ECV	ECV		ECV	-	ECV
Trichosporon asahii	ECV	IR[c]	IR[c]	ECV	-	-	ECV	IR[c]		ECV	-	ECV
Molds												
Aspergillus flavus	ECV	-	ECV	IR	-[e]	ECV	ECV	-		ECV	-	ECV
Aspergillus fumigatus	ECV	-	ECV	IR	-[e]	ECV	ECV	-		-	-	BP/ECV
Aspergillus niger	ECV	-	ECV	IR	-[e]	ECV	ECV	-		ECV	-	ECV
Aspergillus terreus	ECV[f]	-	ECV	IR	-[e]	ECV	ECV	-		ECV	-	ECV
Aspergillus versicolor	ECV	-	-	IR	-[e]	-	-	-		-	-	-
Lomentopora prolificans	IR		TR-H	IR	IR	IR	TR-H	TR-H	ECV	TR-H		TR-H
Scedoporium apiospermum	ECV		TR-H	TR-H	IR	TR-H	TR-H	ECV	ECV	ECV		ECV
Scedosporium aurantiacum	TR-H		TR-H	TR-H	IR	TR-H	TR-H					
Scedoporium boydii	IR			TR-H	IR	ECV	TR-H		ECV	ECV		ECV
Scedosporium ellipsoideum	TR-H			TR-H	IR	TR-H	TR-H					

Doing this quite a bit, we're also adding over film. As a anti fungal in in in table.

#	Description

- M38M51S Ed 3 Mould BP and QC Update:
  - Waiting for publication of new *A.fumigatus* isavuconazole BP.
  - New footnotes for isavuconazole and voriconazole interpretation.
  - New IR designations for *Scedosporium* and *Lomentospora*.
- M27M44S ED 4. Yeast BP and QC. Published August 2022.
  - Minor changes
  - BMD as sole reference method, IR definition and comments, rezafungin BK update, ibrexafungerp new agent in Table 2.
- All supplements are ready for update. M57S and M38SM51S are higher priority. Supplements can be updated annually but most reserve a spot in the line up. Priority in queue decided by CLSI.
- 3-6 month delay at the moment.
- Need a vote to move these 3 supplements forward.

A motion to revise M57S, M38M51S, and M27M44S as presented by Dr. Dufresne was made and seconded. Vote: 12 for, 0 against, 0 abstain, 0 absent (Pass).

- Discussion:
  - Dr. Alexander: why does CLSI take so long to publish supplements? Disturbed by potential delay as it impacts patient care. What can we do to make sure this happens as quickly as possible?
  - CLSI will take these comments back.
  - Dr. Alexander understands it is a resource and manpower issue, whole point of supplements is to only focus on key stuff and get it out quickly rather than entire document revision. CLSI needs to figure it out.
  - Dr. Dufresne also says we need to finish our documents as quick as possible to reserve a spot in the line as we compete with bacterial AST group that also has a number of documents to revise and publish.

8. **BREAKPOINT WORKING GROUP UPDATE (DR. WIEDERHOLD, DR. ANDES, DR. DUFRESNE)**

- Reviews data for new BP determination, rationale document when needed. Seek data to bring existing antifungals to BP step.
- Azole breakpoints vs *A.fumigatus:*
  - Voriconazole RD, FDA review expected January to March 2024 (published 2020, rationale document complete and submitted to FDA April 2023).
  - Isavuconazole RD in draft.
    - BP voted on in January 2023, rational document drafted, FDA review expected Mar-June 2024.
  - Posaconazole
    - Data presented by Merck in November 2022.
    - BP not yet established.
    - Concerns with intra-lab MIC variability for posaconazole, review of pre-clinical PK/PD pending, declined to make rationale document for Posaconazole at November 2022 meeting.
    - Review of preclinical PK/PD data, studies underway.
  - Tentative BKs for Rezafungin in Spring 2021. FDA set BKs last year, there were differences between CLSI and FDA.

Species	CLSI BP – Susceptible (Tentative)	FDA BP - Susceptible
C. albicans	≤0.25	≤0.12
C. auris	≤0.5	---
C. dubliniensis	≤0.12	---
C. glabrata	≤0.5	≤0.12
C. krusei	≤0.25	---
C. parapsilosis	≤2	≤2
C. tropicalis	≤0.25	≤0.12

- 1-dilution difference for *C.albicans* and *C.tropicalis*, 2 dilution difference for *C.glabrata and C.parapsilosis*.
- Neither CLSI or FDA set BP for resistance, only for susceptible.
- WG Action Plan:

ACTION ITEM	TIMELINE
VORICONAZOLE BP (rationale document only)	
Discussed revisions to voriconazole RD at AFSC meeting (revised based on FDA feedback)	August 2023 (completed)
Resubmit revised version to FDA (final submission to the docket)	January-March 2024
ISAVUCONAZOLE BP (rationale document only)	
Discussed revised isavuconazole RD at AFSC meeting (new comments added based on discussion at January meeting)	August 2023 (completed)
Initial submision to FDA (pre-IND file preliminary draft)	March-June 2024
POSACONAZOLE BP	
Interlaboratory variability study	Summer-Fall 2024
Begin to review published pre-clinical PK/PD	Winter-Spring 2024
REZAFUNGIN BP	
Meet with Melinta Therapeutics & discussed BPs	Fall 2023
Present and propose BP at annual meeting	January 2024
Prepare RD & submit to FDA	Fall 2024?

So this has been our action plan. As previously mentioned, the Volcano is all a breakpoint has been set.

- Two RDs prepared and awaiting feedback from FDA.
- One RD document ready to be prepared by WG for Rezafungin.
- FDA will not revisit their BPs in the near future unless new data available. Should CLSI AFST Subcommittee pause RD submission for FDA feedback for Rezafungin?
- Goal was to publish RD within 6 months of BP publication (delay now at 18 to 24 months).
- FDA submitted to a pre-IND process for preliminary high level review only, they have not officially submitted BP for recognition. FDA can consider the BPs we submitted without a RD unless they request one.
- Discussion:
  - Dr. Schuetz asks if we pause, will we not get the FDA feedback?
  - Dr. Wiederhold says that the 6 month timeline seems unreasonable given limited resources.
  - Dr. Castanheira from JMI asks that FDA usually recognizes breakpoints by CLSI so what is the hold up? FDA says they have quarterly meetings but they don't want to hold up any CLSI projects.
  - Dr. Wiederhold says that the initial comments were received in July 2023 but has to be resubmitted to FDA.
  - Ms. Castagna external affairs CLSI says neither document has gone to the FDA docket only the very first one. So the RDs have not been submitted yet, only for preliminary high level review not an official submission. However the FDA can consider recognizing the BPs without a RD unless they specifically request one. Both voriconazole and isavuconazole RDs are under review. Voriconazole at final review stage and isavuconazole at initial review.
  - Dr. Schuetz states the RDs are used a lot by pharmacists, physicians, would hate to hold these up. Has CLSI given a timeline? If FDA can't look at them, how long will it take for CLSI to be able to send them out?
  - Dr. Dufresne: For voriconazole RD it took 3 months, so March to June would be realistic. It's also due to CLSI required prep time and also limited resources at FDA. It is becoming harder and harder to meet 6 month timelines.
  - Dr. Alexander says there are 2 purposes for RDs. One is for FDA to set BPs and the other is to get information to users. She thinks we need to publish these RDs in the literature and not delay further.
  - Rezafungin FDA data has been posted online.
  - Less work to get a RD out for readership than for FDA.
  - Dr. Griffin FDA: Potential for CLSI to publish BPs and then reengage with FDA for further discussion? FDA could reengage with BPs if enough interest generated. Is it possible the BPs may change? How will this affect the users?

SUMMARY MINUTES Saturday, 20 January 2024	
#	**Description**
	– Ms. Castagna says that right now the submission to FDA and publication process are one so that when the documents make it to doctors they are in line with FDA. Separating the documents may lead to discrepancies and more need to update the documents in future. – Dr. Dufresne suggests perhaps a tentative RD review? – CLSI says resource wise for both FDA and CLSI is a challenge. Once it is published, the laboratories have it. Keep that in mind. CLSI work is all done. CLSI needs to format so FDA can use it. – Dr. Dufresne says as a user would rather have the RD sooner than later even if it needs a revision after speaking to FDA. Of course, we need to synchronize timing with the FDA. What is the answer to the RD question for Reza? Are we going to delay? Yes we are going to pause. – Dr. Alexander: If the fundamental problem is having BPs out there without a RD in the hands of users, this already happens so what? – Dr. Wiederhold: We will continue with preparing the RD, but may pause once complete. We need to recognize that the 6 months is not feasible.

9. **REZAFUNGIN – NEW DATA (MELINTA AND JMI)**

- Introduction and rezafungin overview.
- 2nd generation echinocandin FDA approved March 2023.
- Patients 18 years or older with no alternative options for invasive Candidiasis/candidemia treatment.
- Resistant *Candida* spp., those for whom azole step-down therapy is not an option, daily IV echinocandin therapy not an option, those who need to be discharged from hospital or with adherence issues.
- Long acting PK profile, front-loaded plasma drug exposure (400 mg loading dose, 200 mg weekly after), broad spectrum antifungal activity (*Candida, Aspergillus, Pneumocystis*), once weekly dosing. Ideal for renally impaired patients.
- Today will present data on MIC distributions and ECVs, PD/PK studies showing probability of target attainment in population, clinical outcomes data.
- Preliminary data on shorter time to negative blood culture.

Rezafungin: Proposal to CLSI

PROPOSAL: Melinta Therapeutics requests that the Anti-Fungal Subcommittee adopt the tentative breakpoints as final breakpoints (as listed in CLSI Supplement M27M44S, 3rd ed., "Performance Standards for Antifungal Susceptibility Testing of Yeasts", 2022).

Candida Species	Tentative CLSI Susceptible Breakpoint	Current FDA Susceptible Breakpoint
C. albicans	≤0.25	≤0.12
C. glabrata	≤0.5	≤0.12
C. tropicalis	≤0.25	≤0.12
C. krusei	≤0.25	Not recognized
C. parapsilosis	≤2	≤2
C. auris	≤0.5	Not recognized
C. dubliniensis	≤0.12	Not recognized

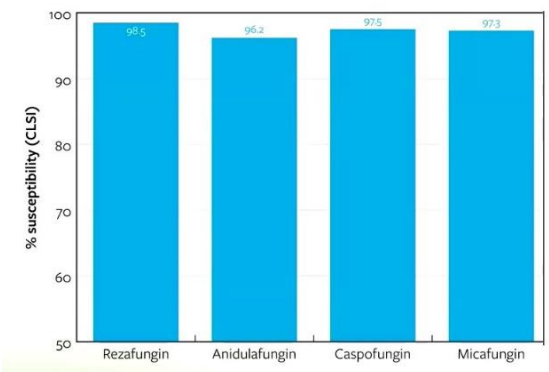
- Proposal to CLSI subcommittee: approve the BPs as listed in tentative/provisional in CLSI document M27M44S 3rd edition including *C.auris*.
- Dr. Castenheira *in vitro* activity and ECVs JMI laboratory data on *Candida* spp.
- Preliminary BPs and ECVs were approved by this committee in 2021
- Global surveillance of invasive fungal infections 2014-2022 of main *Candida* spp. and 2 *Aspergillus* spp. (fumigatus and Flavi)
- MIC distribution of different species. Proposed BP in green boxes below:

Global surveillance of invasive fungal infections (2014-2022)

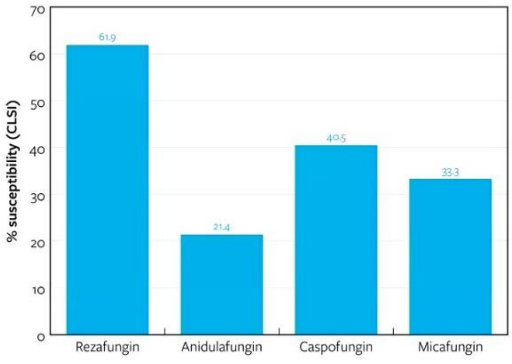
Organism (no. of isolates tested)	No. of isolates at the rezafungin MIC/MEC (µg/mL)											MIC$_{50}$/ MEC$_{50}$	MIC$_{90}$/ MEC$_{90}$
	≤0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	>4		
Candida albicans (2,603)	265	806	1034	434	57	4	2	1				0.03	0.06
Candida glabrata (1,156)	4	40	520	459	93	12	5	9	13	1		0.06	0.12
Candida parapsilosis (979)	1	1	2	1	3	25	201	478	263	1	3	1	2
Candida tropicalis (598)	47	160	242	120	23	4		1	1			0.03	0.06
Candida krusei (190)	1	53	102	25	9							0.03	0.06
Candida dubliniensis (194)	5	10	74	74	28	1	2					0.06	0.12
Cryptococcus neoformans var. *grubii* (192)							1				191	>2	>2
Aspergillus fumigatus (680)	188	310	156	25	1							0.015	0.03
Aspergillus flavus species complex (121)	56	48	14	3								0.015	0.03

- MIC data for rezafungin shows it is very similar to other echinocandins, particularly micafungin, just that rezafungin is longer lasting in patient blood.
- *FKS* mutations are clinically important but vary in prevalence. Several studies show that the presence of *FKS* mutations in *Candida* species results in elevated MICs and clinical failure.
- Alexander et al. 2013. CID 56(12): 1724.
  - Resistance to echinocandins associated with *FKS1* and *FKS2*.
  - 293 episodes of bloodstream infection, 313 isolates: 25 (7.9%) harbored *FKS* mutations.
  - 80% (8/10) patients infected with *FKS* mutants demonstrating intermediate or resistant MICs to echinocandins failed treatment after subsequent echinocandin treatment.
- Shields R et al. AAC 2013; 57(8): 3528
  - 8% (10/120) sterile site *C.glabrata* isolates harbored *FKS1* or *FKS2* mutations.
  - 14 day echinocandin treatment success rate of 67% (44/66) failure more likely with *FKS* mutant or echinocandin resistant isolates. Failure rate among patients with prior echinocandin exposure and infection with resistant isolate was 91% (10/11).
- Echinocandin NWT *C.glabrata*.
  - Rezafungin behaves a bit differently than other echinocandins (ECHs). Carvalhaes et al. ID week 2023 data. Proportion of NWT *C.glabrata* fairly low in Asia and Latin America, higher in North America (29/488 total). More ECH-NWT *C.glabrata* in general in Europe and NA. Overall proportion of NWT is 4% (42 isolates).
  - Rezafungin and WT *C. glabrata* similar to other echinocandins.
  - Rezafungin works much better against ECH resistant *Candida glabrata* strains (with and without *FKS*). 62% susceptibility of rezafungin compared to 21.4-40.5% for other echinocandins.

Rezafungin and comparators activity against 1,045 *C. glabrata* isolates



Rezafungin and comparators activity against 42 ECH-NWT *C. glabrata* isolates



- Data with and without *FKS* mutations. 26% of tested NWT strains have *FKS* mutation. For these *FKS* mutant strains, rezafungin MICs were similar between the echinocandins against isolates with *FKS* mutations.
- Echinocandin NWT *Candida* spp. (n=73)

Organism	No. of isolates at MIC (µg/mL; no. of isolates with *FKS* HS mutation)										MIC_{50}/MIC_{90} (no. of isolates)		
Echinocandin	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	≥8	all	*FKS*	non-*FKS*
C. albicans											(10)	(5)	(5)
Rezafungin		2 (1)	3 (1)	2	1 (1)		2 (2)				0.06/1	0.25/1	0.06/0.12
Anidulafungin	2 (1)	2 (1)	2	2 (1)			2 (2)				0.06/1	0.12/1	0.06/0.12
Caspofungin	1	1 (1)	4 (1)	1			2 (2)		1 (1)		0.06/1	1/4	0.06/0.12
Micafungin			7 (2)				2 (2)	1 (1)			0.06/1	1/2	0.06/0.06
C. glabrata											(44)	(30)	(14)
Rezafungin		2	5 (3)	9 (5)	8 (3)	6 (6)	8 (8)	6 (5)			0.25/2	0.5/2	0.12/0.25
Anidulafungin			4 (1)	7 (3)	11 (5)	3 (3)	10 (10)	7 (7)	2 (1)		0.25/2	1/2	0.12/0.25
Caspofungin		2 (1)	15 (6)	6 (3)	5 (5)	5 (5)	7 (7)	1 (1)	2 (1)	1 (1)	0.12/1	0.25/1	0.06/0.12
Micafungin		1 (1)	19 (7)	6 (5)	5 (5)	4 (4)	7 (7)	1 (1)	1		0.12/1	0.25/1	0.06/0.12
C. tropicalis											(17)	(6)	(11)
Rezafungin		1	5	2	3	1 (1)	2 (2)	3 (3)			0.25/2	1/2	0.06/0.25
Anidulafungin		2	4	2	3	2 (2)	2 (2)	2 (2)			0.25/2	1/2	0.06/0.25
Caspofungin	1	3	4	2	1			1 (1)	4 (4)	1 (1)	0.12/4	4/>8	0.06/0.12
Micafungin		1	1	9			3 (3)	3 (3)			0.12/2	1/2	0.12/0.12

Antifungal agent	MIC_{50} (µg/mL)	MIC_{90} (µg/mL)
Rezafungin	0.25	2
Anidulafungin	0.5	4
Caspofungin	0.25	4
Micafungin	0.12	1

- *Candida auris* global prevalence is increasing. JMI labs has collected 78 isolates, 33 collected in 2022. Huge increase since 2018.
- Rezafungin performs against *C.auris* very similar to other echinocandins.
- *In vitro* activity of rezafungin and comparators against *C.auris*.

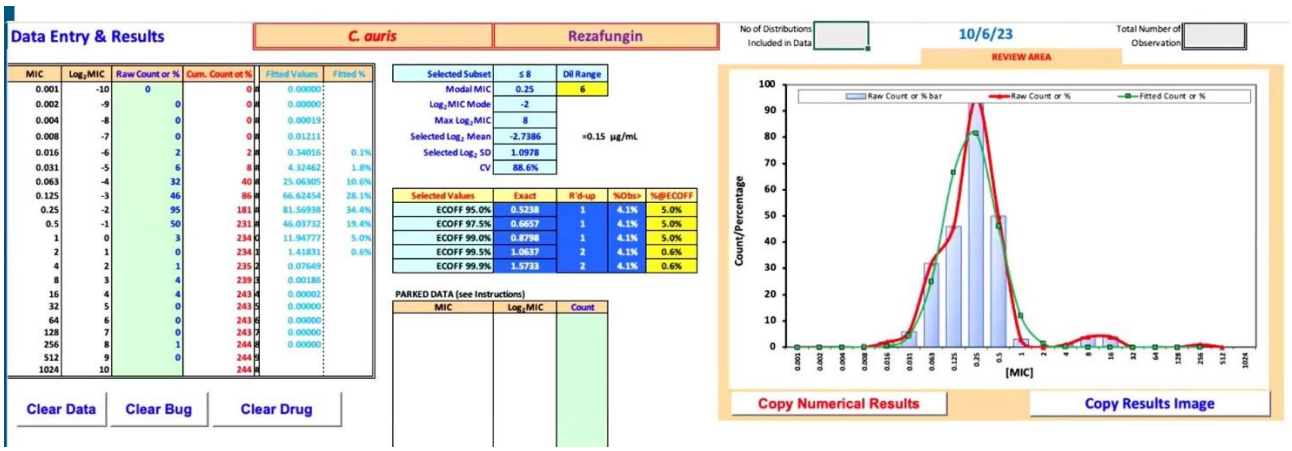
Antifungal agent	MIC_{50} (mg/L)	MIC_{90} (mg/L)	Range (mg/L)	%Susceptible[a]	%Resistant[a]
Rezafungin	0.25	0.5	0.03 to >4	96.2	
Anidulafungin	0.25	0.5	0.06 to 4		1.3
Caspofungin	0.12	0.25	0.015 to >4		1.3
Micafungin	0.12	0.25	0.06 to 4		1.3
Fluconazole	64	>128	2 to >128		82.1
Amphotericin B	1	2	0.5 to 4		17.9

[a] Resistance breakpoints for anidulafungin, caspofungin, micafungin, fluconazole and amphotericin B are published at https://www.cdc.gov/fungal/candida-auris/c-auris-antifungal.html. Rezafungin susceptible only breakpoints are provisional breakpoints approved by the CLSI Antifungal Susceptibility Testing Subcommittee (January 2022).

- If you divide the *Candida auris* isolates by clade, you can see a slight difference between rezafungin and other candidates with switching clades. Had limited isolates for Clades III and II.

Antifungal agent	Clade I: South Asia (40 isolates)[a,b]					Clade IV: South America (30 isolates)[a,b]					Clade III: South Africa (7 isolates)[a,b,c]				Clade II: East Asia (1 isolate)[a,b]	
	MIC_{50}	MIC_{90}	Range	%S	%R	MIC_{50}	MIC_{90}	Range	%S	%R	MIC_{50}	Range	%S	%R	MIC value	Interpretation
Rezafungin	0.25	0.5	0.06 to 0.5	100.0		0.25	0.5	0.03 to >4	96.7		0.5	0.12 to 1	71.4		0.008	Susceptible
Anidulafungin	0.25	0.5	0.06 to 1		0.0	0.25	0.5	0.06 to 4		3.3	0.5	0.25 to 1		0.0	0.25	Not resistant
Caspofungin	0.12	0.25	0.03 to 0.5		0.0	0.06	0.12	0.015 to >4		3.3	0.06	0.06 to 0.12		0.0	0.03	Not resistant
Micafungin	0.12	0.25	0.06 to 0.5		0.0	0.12	0.25	0.06 to 4		3.3	0.12	0.12 to 0.25		0.0	0.06	Not resistant
Fluconazole	128	>128	4 to >128		97.5	64	128	2 to >128		56.7	>128	128 to >128		100.0	64	Resistant
Amphotericin B	1	2	1 to 2		30.0	1	1	0.5 to 4		6.7	0.5	0.5 to 1		0.0	1	Not resistant

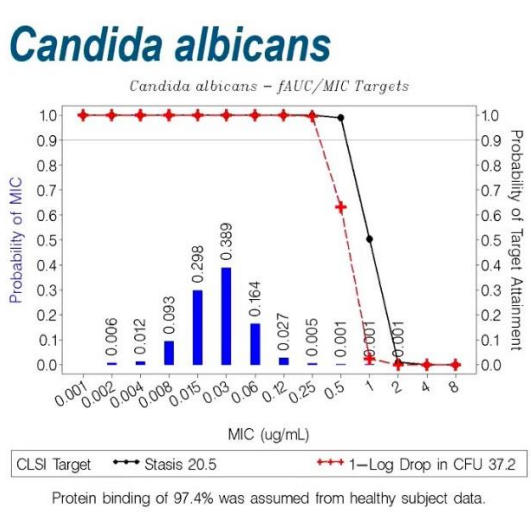
- Rezafungin ECV *C.auris*. Total of 4 labs, not all consistent. Differences in how the labs distribute the isolates. JMI is Lab 1. So some inconsistency with the data but still went ahead and made an ECV.
- ECV is 1.0 for both 97.5% and 99% ECOFF, with modal MIC of 0.25 for *C.auris* (red below):

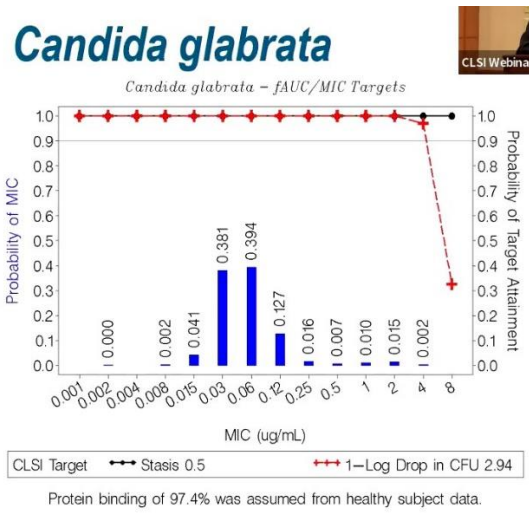


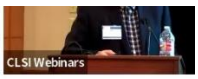
- Summary of rezafungin ECVs:

Agent	Species	No. of Distributions	No. of Isolates	Modal MIC	ECV 97.5% (only in range distributions)	ECV 99%
Rezafungin	*C. albicans*	9	1620	0.03	0.06	0.12
Rezafungin	*C. glabrata*	9	742	0.06	0.12 (0.25)	0.25
Rezafungin	*C. tropicalis*	9	406	0.03	0.12	0.12
Rezafungin	*C. krusei*	9	295	0.03	0.12	0.12
Rezafungin	*C. parapsilosis*	10	707	1	4	4
Rezafungin	*C. dubliniensis*	7	140	0.06	0.12	0.12
Rezafungin	*C. auris*	4	244	0.25	1	1
Rezafungin	*A. fumigatus*	7	401	0.015	0.03 (0.06)	0.03
Anidulafungin	*C. albicans*	7	1475	0.015	0.06	0.06
Anidulafungin	*C. glabrata*	9	822	0.06	0.25	0.25
Anidulafungin	*C. tropicalis*	8	387	0.03	0.06	0.12
Anidulafungin	*C. krusei*	8	280	0.03	0.12	0.12
Anidulafungin	*C. parapsilosis*	8	678	2	4	8
Anidulafungin	*C. dubliniensis*	6	138	0.03	0.12	0.12
Anidulafungin	*A. fumigatus*	6	356	0.008	0.03	0.03

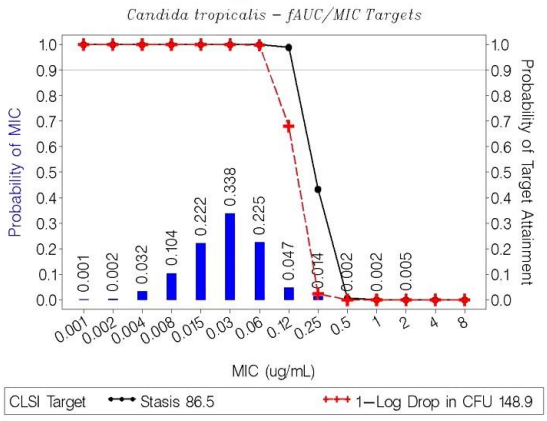
- No data published on *C.auris* and anidulafungin.
- Mark Redell, Melinta: PK/PD data for rezafungin:
  - Percent probabilities of achieving nonclinical PK/PD targets applied to 6 *Candida* spp., no data for *C. krusei*.
  - MIC distributions from 10 studies, 5 from JMI studies.
  - Estimated PK/PD target attainment for stasis and 1-log drop in CFU using fAUC values following the 400 mg loading dose and CLSI methodology to calculate MIC over the *Candida* MIC distribution for each species. PTAs based on protein binding in normal healthy humans: 97.4%.
  - Stasis endpoint is darker line.
  - Red line is the organism specific rezafungin data.
  - For *C.albicans, C.glabrata, C.tropicalis,* the target attainment was well to the left of the stasis line.





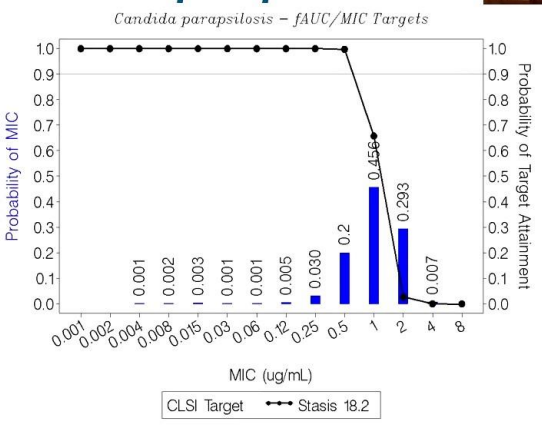


Candida tropicalis



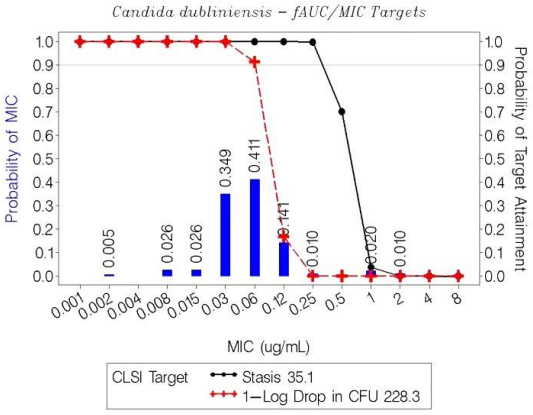
Protein binding of 97.4% was assumed from healthy subject data.

Candida parapsilosis



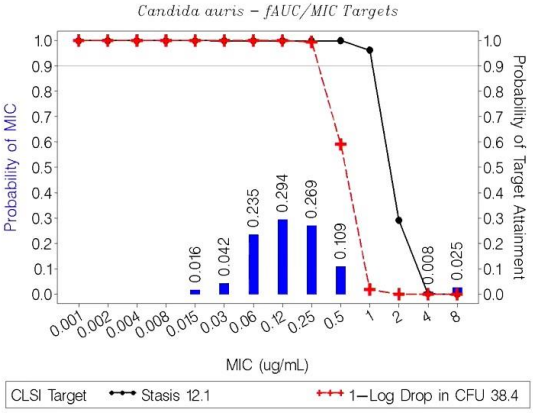
Protein binding of 97.4% was assumed from healthy subject data.

Candida dubliensis



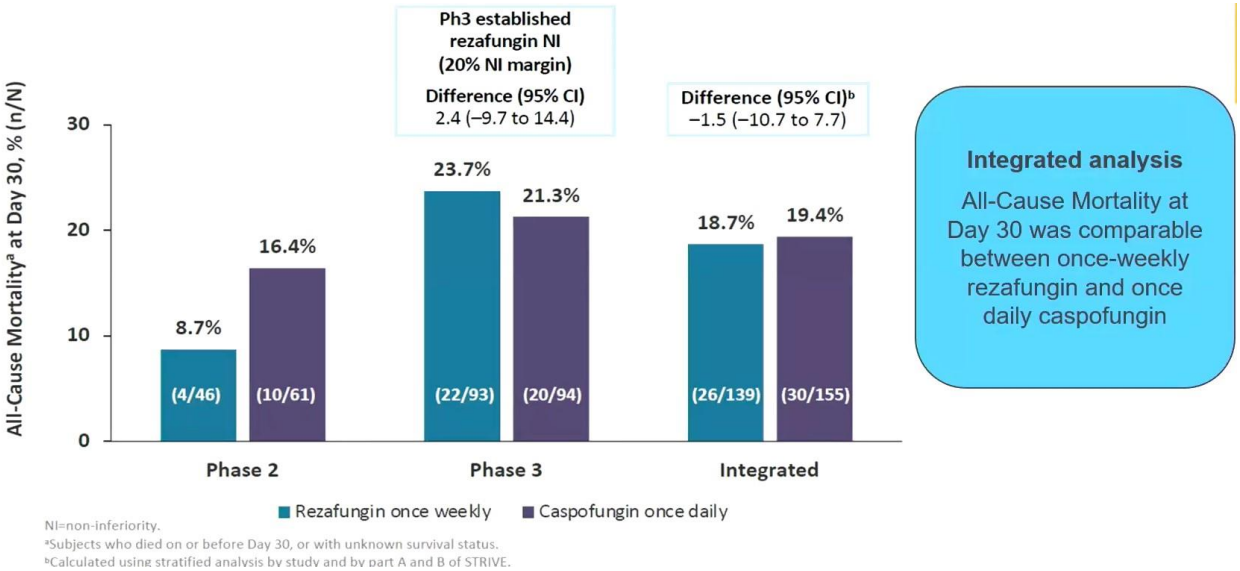
Protein binding of 97.4% was assumed from healthy subject data.

Candida auris



Protein binding of 97.4% was assumed from healthy subject data.

- Rezafungin Pooled Data Analysis (STRIVE and ReSTORE trials combined).
- STRIVE phase 2 study. Looking at 400mg as a load and also weekly.
- Part B2 we looked at 200 mg load and 200mg weekly.
- ReSTORE study. Phase 3 treatment trial. Stepdown to oral fluconazole in 2/3 patients, patients had minimum 2 doses of rezafungin. Compared to caspofungin.
- Species distribution for studies: 43% *C.albicans*, 25% *C.glabrata*, 17% *C.tropicalis*, 14% *C.parapsilosis*. Similar to JMI study data.



NI=non-inferiority.
[a]Subjects who died on or before Day 30, or with unknown survival status.
[b]Calculated using stratified analysis by study and by part A and B of STRIVE.

- Conclusion: rezafungin is non-inferior to caspofungin for treatment of candidemia/invasive candidiasis.
- High probability of target attainment, MIC distributions match.
- Melinta therapeutics requests CLSI to adopt the tentative BPs as final BPs in M27M44S 3rd edition.

- Additional data to support the *Candida glabrata* breakpoint of 0.5 from Melinta therapeutics:
  - Disparate MICs between CLSI tentative BP and FDA BP is a 2 dilution difference (0.5 vs 0.12).
  - Pooled data Clinical outcomes by Pathogen MIC (presented by Dr. McCurdy).
  - *Candida glabrata:*

Organism	Outcome	Subjects with favorable outcome (n1)/Total subjects (n) at indicated baseline MIC (µg/mL) (%; n1/n)								
		≤0.008	0.016	0.03	0.06	0.12	0.25	0.5	1	2
C. glabrata	30-Day all-cause mortality			9/10 (90.0)	14/17 (82.4)	8/10 (80.0)		1/1 (100.0)		
	5-day mycological response			8/10 (80.0)	16/17 (94.1)	5/10 (50.0)		0/1 (0.0)		
	14-day mycological response			9/10 (90.0)	15/17 (88.2)	7/10 (70.0)		1/1 (100.0)		

All-cause mortality at Day 30 outcomes= success (subject was alive at Day 30) or failure (subject died on or before Day 30 or had unknown survival status).
Mycological response=eradication (which included presumed eradication) or failure (which included indeterminate and presumed persistence).

C. tropicalis

Organism	Outcome	Subjects with favorable outcome (n1)/Total subjects (n) at indicated baseline MIC (µg/mL) (%; n1/n)								
		≤0.008	0.016	0.03	0.06	0.12	0.25	0.5	1	2
C. tropicalis	30-Day all-cause mortality		3/3 (100)	9/11 (81.8)	8/10 (80.0)	2/3 (66.7)				
	5-day mycological response		3/3 (100)	9/11 (81.8)	7/10 (70.0)	3/3 (100)				
	14-day mycological response		3/3 (100)	8/11 (72.7)	6/10 (60.0)	3/3 (100)				

C. parapsilosis - higher MIC values observed

Organism	Outcome	Subjects with favorable outcome (n1)/Total subjects (n) at indicated baseline MIC (µg/mL) (%; n1/n)								
		≤0.008	0.016	0.03	0.06	0.12	0.25	0.5	1	2
C. parapsilosis	30-Day all-cause mortality							1/1 (100)	7/8 (87.5)	4/4 (100)
	5-day mycological response							0/1 (0.0)	7/8 (87.5)	4/4 (100)
	14-day mycological response							1/1 (100)	6/8 (75.0)	4/4 (100)

Candida krusei

Organism	Outcome	Subjects with favorable outcome (n1)/Total subjects (n) at indicated baseline MIC (µg/mL) (%; n1/n)								
		≤0.008	0.016	0.03	0.06	0.12	0.25	0.5	1	2
C. krusei	30-Day all-cause mortality			1/2 (50.0)	3/3 (100)					
	5-day mycological response			1/2 (50.0)	1/3 (33.3)					
	14-day mycological response			1/2 (50.0)	1/3 (33.3)					

***Candida dubliniensis*-not a lot of isolates**

Organism	Outcome	Subjects with favorable outcome (n1)/Total subjects (n) at indicated baseline MIC (µg/mL) (%; n1/n)								
		≤0.008	0.016	0.03	0.06	0.12	0.25	0.5	1	2
C. dubliniensis	30-Day all-cause mortality		1/1 (100)				1/1 (100)			
	5-day mycological response		1/1 (100)				1/1 (100)			
	14-day mycological response		1/1 (100)				1/1 (100)			

Summary of BPs, ECV, data from pooled studies

Organism	CLSI S	FDA S	ECV	MIC Range Sentry Surveillance	Prevalence of higher MIC values (MVP Surveillance)*	MIC_{90} (surveillance)	MIC Range Clinical Trial (overall; pooled)	Highest MIC with outcome (pooled); 14 day mycological response (n;%)	PTA (from PTA graphs) stasis	PTA (from PTA graphs) 1-log kill
C. albicans	≤0.25	≤0.12	0.06	≤0.008-1	<0.1%	0.06	0.004-0.12	0.12 (7/8; 87.5)	≤0.5 (>90%)	≤0.25 (>90%)
C. glabrata	≤0.5	≤0.12	0.12	≤0.008-4	≥1 (23/1156; 2.0%)	0.12	0.016-0.5	0.5 (1/1; 100)	≤4 (>90%)	≤4 (>90%)
C. tropicalis	≤0.25	≤0.12	0.12	≤0.008-2	<0.1%	0.06	0.016-0.12	0.12 (3/3; 100)	≤0.12 (>90%)	≤0.06 (>90%)
C. parapsilosis	≤2	≤2	4	≤0.008->4	<0.1%	2	0.5-2	2 (4/4; 100)	≤0.5 (>90%)	no data
C. krusei	≤0.25		0.12	≤0.008-0.12	<0.1%	0.06	0.03-0.06	0.06 (1/3; 33.3)	not done	not done
C. dubliensis	≤0.12		0.12	0.008-0.5	<0.1%	0.12	0.03-0.25	0.25 (1/1; 100)	≤0.25(>90%)	≤0.06 (>90%)
C. auris	≤0.5		1	0.03 to >4	≥1 (1/9; 11.1%)	0.5	(no isolates)	(no isolates)	≤1.0 (>90%)	≤0.25 (>90%)

- In conclusion, clinical trial data demonstrates that rezafungin is non-inferior to caspofungin for treatment of invasive candidiasis/candidemia. High probability of target attainment achieved for most species using the stasis target, clinical trial MIC distributions matched surveillance data.
- No relationship between clinical outcome and MIC in the pooled analysis of STRIVE and ReSTORE studies.
- Proposal: Melinta therapeutics requests that the antifungal subcommittee adopt the tentative breakpoints as final breakpoints (as listed in M27M44S 3rd edition).

Candida Species	Tentative CLSI Susceptible Breakpoint	Current FDA Susceptible Breakpoint
C. albicans	≤0.25	≤0.12
C. glabrata	≤0.5	≤0.12
C. tropicalis	≤0.25	≤0.12
C. krusei	≤0.25	Not recognized
C. parapsilosis	≤2	≤2
C. auris	≤0.5	Not recognized
C. dubliniensis	≤0.12	Not recognized

#	Description
	Discussion: • Difference between clinical outcomes data and preclinical animal data for *C. parapsilosis* may be due to an artifact of the animal models since it is hard to establish a *C. parapsilosis* infection in mice. • Question about *Candida auris* data for Dr. Castanheira. Where are the isolates coming from? Can you share the geography? And are these published mutations in the targets? Third, you had a lab with 96 isolates can you share the geography of this lab? Dr. Castanheira says the *C.auris* comes from all over, some are from New York. Majority are from US and Panama. There were 9 countries. Did not see any new *FKS* mutations. One had an *FKS* mutation that was previously described, one with elevated rezafungin MIC and not any *FKS* mutations and susceptible to other echinocandins. • Chat question: Can other echinocandins serve as surrogate markers for rezafungin susceptibility? Dr. Castanheira and Dr. Redell say it is based on the breakpoints we decide but they are going to look at this since the drugs are very similar. • *Candida auris* breakpoints are not in the clinical trials, will be reviewed in next presentation. • Dr. Dingle *C.tropicalis* our BP is 0.25, Melinta data is 0.12 for stasis. Is our BP too high? • Dr. Redell does not have an answer they just want to go ahead with the tentative BPs. • Dr. Wiederhold: One of the things that will be in the next presentation. • Dr. Dufresne says lets move to Dr. Wiederhold's presentation because it will show what the WG is proposing. • Dr. Schuetz: summary of what is new in the presentation: MIC distributions for *Candida auris,* PKPD data was updated and 2 patients in the early access program that were presented to the FDA. That is all that is new? Can you review the early access patient slide. Patient 1 had *C.glabrata*, NS to Micafungin, switched to AmB and 5FC for 6 weeks, then 200 mg weekly rezafungin for 3 years without recurrence. Patient 2, gunshot wound *C.glabrata* R to echinos and S to vori, started on voriconazole, switched to AMB, then *C.glabrata* rezafungin MIC of 1 with *FKS* mutation, 2 weekly doses of rezafungin and was considered cured. Publication in Lancet ID of target attainment rates since last time.

10 **BREAKPOINT WG – RECOMMENDATION FOR REZAFUNGIN BP (DR. WIEDERHOLD, DR. ANDES)**

- Nathan Wiederhold on behalf of BP WG: Rezafungin breakpoints vs. *Candida* spp.
- Unique drug due to slow clearance, long half life, very high AUC (under 800 to over 1000 ug x h/mL over 7 day period). Takes advantage of AUC:MIC ratio.
- Some reduced *C.parapsilosis* activity.
- Rezafungin PK/PD vs *Candida* spp. including *C.auris* (Lepak et al. 2018 and 2019 antimicrobial agents and chemotherapy). Yellow highlighted cells are PK/PD targets used in studies presented by Dr. Redell.
- Roepcke et al. 2023 Antimicrobial Agents and Chemotherapy 67. For *C.albicans*, stasis can be achieved at MIC of ≤ 0.5 µg/mL with a 1 log CFU drop at < 0.25 µg/mL. For *C.glabrata*, stasis and 1 log CFU drop both at MIC of ≤ 4 µg/mL. For *Candida parapsilosis* stasis achieved ≤ 0.5 µg/mL and cidal activity not achieved. *C.auris* stasis achieved at MIC of 1 µg/mL or less, 1 log CFU drop at < 0.25 µg/mL. For *C.tropicalis*, stasis achieved at ≤ 0.12 µg/mL with 1 log CFU drop at ≤ 0.06 µg/mL and for *C.dubliniensis* stasis achieved at ≤ 0.25 µg/mL and 1 log CFU drop at ≤ 0.06 µg/mL.
- FDA set rezafungin BPs lower for 4 species. One dilution difference except for *C.glabrata* which is a 2 dilution difference from CLSI.
- *Candida glabrata* outcomes by MIC. PK/PD data at 4. CLSI BP a few dilutions below this. WG felt we did not need to lower the breakpoint for Rezafungin against *C.glabrata*. Some overlap between *FKS* mutations and *FKS* WT, can't separate them with BP. Doesn't just apply to rezafungin, but also ECHs as well (anidula, mica, caspo). It's an echinocandin issue. Our CLSI BPs don't fully capture *FKS* mutations for all echinocandins.
- Same for *C.albicans*. MIC is at 90% target attainment, no need to lower this BP.
- *C.tropicalis*: we might have set the BP one dilution too high in 2021, all echinocandins are 0.25. However, if we lower it will not match other echinocandins and this organism. Since rezafungin has a very big AUC/MIC and we are achieving a big Cmax we didn't feel there was compelling data to lower the BP as we don't want Rezafungin BP to be lower than other drugs in the class. Open for discussion.
- *C.parapsilosis:* Kept the BP at 2 µg/mL, also recommended by FDA.
- *C.krusei* no FDA BP set, PK/PD not determined by FDA. We said to keep it 0.25 µg/mL as for other echinocandins and this species.
- *C. dubliniensis*: BP sent 0.12 µg/mL, one dilution lower than most *Candida* spp. 1 log kill 0.06, stasis at 0.25 so from a PK/PD standpoint we are splitting the difference. Also the same as the published ECV.
- *Candida auris* is based on PK/PD results. Published by Lakota et al. AAC 2017; 61. Stasis seen at MIC of 1 µg/mL, 1-log reduction at 0.25 µg/mL, we split the difference and set the BP at 0.5 µg/mL.
- Shape of concentration response curve is important (AUC and Cmax elevated in first 24h and long half life).
- Proposal from WG: Keep rezafungin BPs keep the same as tentative BPs. RD document prep is next step, to explain why CLSI and FDA BPs differ. No BP set for resistance yet by CLSI or FDA.
- Proposed rezafungin breakpoints:

Species	CLSI Breakpoint (Susceptible)	FDA Breakpoint (Susceptible)	Dilution Difference
C. albicans	≤ 0.25	≤ 0.12	1
C. auris	≤ 0.5	---	---
C. dubliniensis	≤ 0.12	---	---
C. glabrata	≤ 0.5	≤ 0.12	2
C. krusei	≤ 0.25	---	---
C. parapsilosis	≤ 2	≤ 2	0
C. tropicalis	≤ 0.25	≤ 0.12	1

#	Description

- *FKS* Mutations among echinocandin non WT *C. glabrata* isolates stratified by rezafungin MIC.

Rezafungin MIC value in mg/L (no. of isolates)	FKS Mutation	MIC range in mg/L		
		Anidulafungin	Caspofungin	Micafungin
0.25 (55)	WT (44) FKS1 HS1 S639P (2), L630Q (1), F625S (1) FKS2 HS1 S663P (2), F659Y (2), F659 deletion (2), R665G (1)	0.06 to 0.5	0.03 to 0.5	0.015 to 0.25
0.5 (21)	WT (7) FKS1 HS1 S639P (2), D632E (1), F625S (1) FKS2 HS1 S663P/F (6/1), F659Y (1), Y657 deletion + F658Y (2)	0.06 to 0.5	0.03 to 0.5	0.015 to 0.25
1 (31)	WT (9) FKS1 HS1 S639P (3) FKS2 HS1 S663P (14), F659Y (1), F659Y deletion (2), Y657 deletion + F658Y (2)	0.06 to 4	0.03 to >4	0.03 to 2
2 (19)	WT (9) FKS1 HS1 S639P (1) FKS2 HS1 S663P (8) FKS1 HS1 S639P + FKS2 HS1 S663P (1)	2 to 4	1 to >8	0.5 to 4
4 (3)	WT (2) FKS1 HS1 S639P + FKS2 HS1 S663P (1)	4	>4	4

Coming from, to Dr. Vndy. Thank you, Thank you. Thank you, again.

- Discussion:
- Dr. Lockhart biggest difference with rezafungin is PK/PD. But according to Dr. Andes, we actually may have dosing wrong on other echinocandins, in his experience if he changes his dosing he can get some clinical response if he changes dosing on other echinocandins to *FKS* mutants. So we may want to rethink how we dose and the other BPs in future, but biggest reason rezafungin overcomes the *FKS* mutants is due to PK/PD and front-loading.
- Dr. Wiederhold agrees that as more data becomes available, ECV working group will have to look at it especially for *C. auris* and *C. glabrata*.
- Dr. Schuetz: why are we using the term tentative in this case? We don't always use this term. Did we have some concerns about some species we wanted to watch in particular?
- Dr. Castanheira responds that we need clinical BPs to move forward to FDA. No discussion at time but it was because the clinical trial data was not complete. BPs are always tentative 1 year from when they are published, in this case we have overextended how long it was called tentative.
- Dr. Babady asks if there is any recommendation for labs to test for *FKS* mutations?
- Dr.Wiederhold says no.

A motion to move forward to make rezafungin BPs no longer tentative, and to draft a rationale document to explain difference between FDA and CLSI, as presented by Dr. Wiederhold was made and seconded. Vote: 11 for, 1 against, 0 abstain, 0 absent (Pass).

- Dr. Dingle does not support 0.25 µg/mL for *C. tropicalis* when data is good and suggests 0.12 µg/mL.

11	**BREAK**

12 **ECV WORKING GROUP UPDATE (DR. DUFRESNE, DR. LOCKHART, DR. WIEDERHOLD)**

- Main goals: collect and analyze CLSI MIC/MEC information for ECV determination, publish in M57S and peer-review journals.
- Membership active since 2017, Dr. Lockhart and Dr. Dufresne co-chairs.
- Ongoing projects and requests for MICs.

A manuscript is planned for each + *C. parapsilosis* complex
Need to get those ECV papers published in 2024.

- Round 7 *Fonsecaea pedrosi* ECVs
  - CDC initiative, no ECV on this, only a few studies looking at MICs so far. Dr. Dallas Smith/Dr. Lockhart
  - Few studies of MIC distribution, no ECV/ECOFF published.
  - Dr. Dallas Smith recruited 7 labs to participate, labs in US, Brazil, Canada, Netherlands. First meeting June 2023. 8 follow-up meetings. MIC data to be submitted by February 2024, ECV analysis calculated by June 2024. Data will be shared with CLSI AFSC at next meeting.

- Cryptic *Aspergillus* project. Round 5.
  - Focus on *A.Fumigati* and *A.Nigri* sections first.
  - ID by BenA and CaM sequencing. Support from Thermo.
  - Still missing some isolates (totals on right). In blue are isolates only, no MIC yet.

		LSPQ isolates with MIC	PHE (A. Borman)	UTHSA (N. Wiederhold)	CDC (S. Lockhart)	JHH (S. Zhang)	JMI	Jacques Meis	NIH (A. Seyedmousavi)	LSPQ isolate to test if needed	PHO isolates to test if needed	TOTAL
	Section Fumigati											
1	*A. fumigatus (sensu stricto)*	300	52		222	110	233	819	275		16	2027
2	*A. lentulus*	6	2	35			10	10	15	6	4	88
3	*A. hiratsukae*	10	9	21			1		2	38	6	87
4	*A. undagawae*	3	5	9			1		4	11		33
5	*A. viridinutans*	1								0		1
6	*A. thermomutatus*	10	3	9			2		5	20	8	57

	Section Nigri											
1	*A. niger*	30	5				1		18	7	3	64
2	*A. tubingensis*	18		215			1		8	5	7	254
3	*A. brasiliensis*	1								0		1
4	*A. luchuensis (syn. A. acidus)*	1								0	1	2
5	*A. welwitschiae*	3		148						0	9	160
6	*A. brunneoviolaceus*	0									1	1

  - Need to contact more labs-few published reports.
  - Ferry Hagen and Joe Houbraken at Westerdijk Institute to test isolates this spring.
  - Target completion end of 2024.

- *A.fumigatus* posaconazole
  - Unable to set ECV or BP due to interlab variation issues.
  - Panel of 25 *A.fumigatus* assembled by Dr.Wiederhold and Dr. Lockhart, distribution by CDC AR-BANK end of spring 2024.
  - Interested labs please contact ECV or BP WG.
  - Will target the half dozen labs with interlab variation.

ARISOLATEBANK

AR Bank #	Organism	Resistance Mechanisms
0731	*Aspergillus fumigatus*	L98H, TR34
0732	*Aspergillus fumigatus*	F495I, L98H, S297T, TR34
0733	*Aspergillus fumigatus*	L98H, TR34
0734	*Aspergillus fumigatus*	L98H, TR34
0735	*Aspergillus fumigatus*	F495I, L98H, S297T, TR34
0736	*Aspergillus fumigatus*	
0737	*Aspergillus fumigatus*	
0738	*Aspergillus fumigatus*	
0739	*Aspergillus fumigatus*	
0740	*Aspergillus fumigatus*	

New isolates from FTL San Antonio to be added

Species	Isolate No.	PSC MIC	VRC MIS	ISC MIC	Cyp51A
A. fumigatus	DI15-93	0.5	0.25	1	M220V
A. fumigatus	DI15-95	1	4	4	WT
A. fumigatus	DI15-97	0.25	2	2	WT
A. fumigatus	DI15-96	0.5	>16	>16	TR46/Y121F/T289A
A. fumigatus	DI15-99	1	0.06	0.125	G54R
A. fumigatus	DI15-106	0.5	>16	>16	TR46/Y121F/T289A
A. fumigatus	DI15-111	>16	0.06	0.06	G54W
A. fumigatus	DI15-110	1	4	4	WT
A. fumigatus	DI15-112	1	0.125	0.125	G54R
A. fumigatus	DI15-118	2	1	1	M220K
A. fumigatus	DI20-98	>16	2	2	G54R
A. fumigatus	DI20-103	0.5	>16	>16	TR46/Y121F/T289A/N512I
A. fumigatus	DI20-106	0.5	>16	>16	TR46/Y121F/T289A
A. fumigatus	DI20-124	0.25	4	4	G448S
A. fumigatus	DI20-134	0.5	>16	>16	TR46/Y121F/T289A

- MIC distribution and susceptibility according to group tables
  - New M57 annex MIC distribution tables underway, listed by antifungals (ampho, azole, echino)
  - Aim is to include yeast distributions in next edition and mold distributions if possible
  - Very dense tables may be a challenge to print in our supplement
  - Must decide if rank by mode, genetic group, or alphabetically.
  - Yeast susceptibility profile according to group

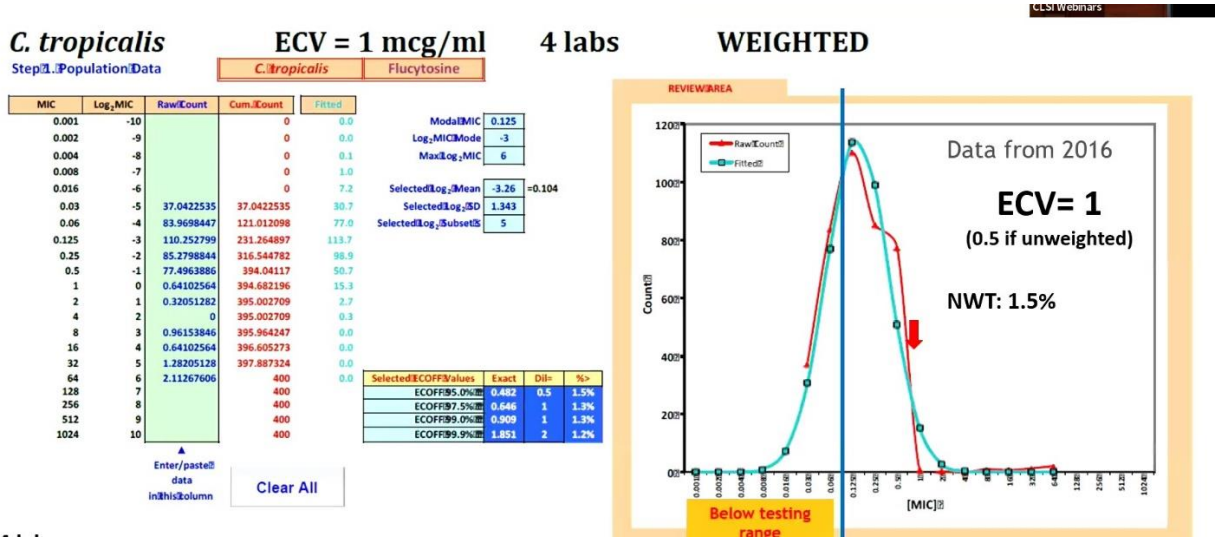
- Focus on main yeast groups:
  - *C. albicans-C. tropicalis-C. parasilosis* (Lodderomyces)
  - *C. guilliermondii* group (Meyerozyma)
  - *C. glabrata* group (Saccharomycetaceae)
  - *C. haemulonii* group (Metschikowiaceaea)
  - *C. krusei* group (Pichiaceae)

Expected susceptibility		
Azole S	Amb B S	Echino S
Azole R	Amb B S	Echino S
Azole R	Amb B S	Echino S
Azole R	Amb B S	Echino S
Azole R	Amb B S	Echino S

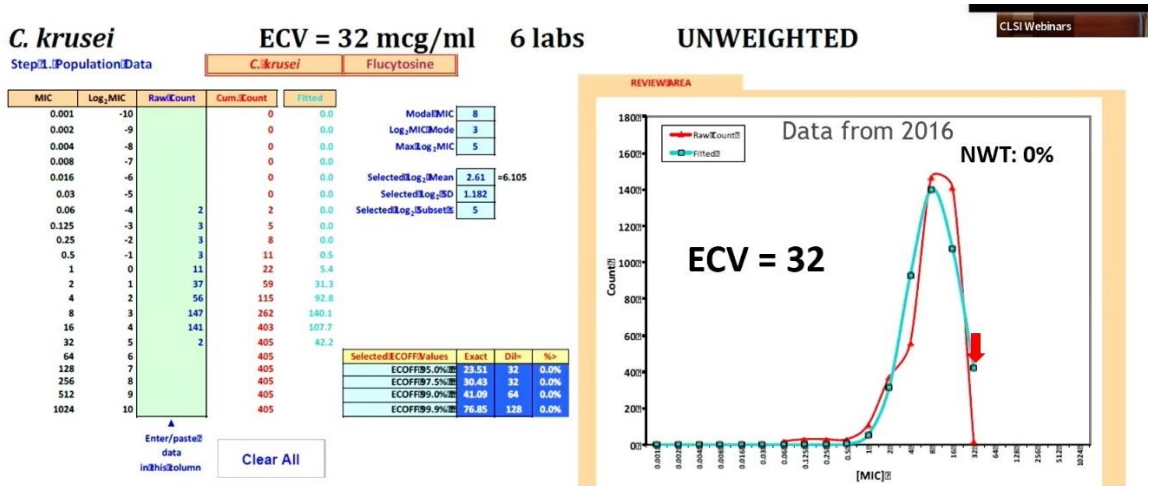
  - Yeast susceptibility profile work, focus on major yeast groups and look something like on the right just to flag the users.
  - Will circulate draft tables for comment and feedback once draft is complete. Publish companion manuscript?

- ECV Gaps to fill for common *Candida* spp.
  - Yellow Table 6: we should have data for these combinations as they are very common.
  - Found data for flucystosine and 4 species: *C.albicans, C. glabrata, C.krusei, C.tropicalis*
  - Unpublished data from 2016 available. *C.krusei* and *C.tropicalis*. Truncated low for *C.albicans* and *C. glabrata*. Recommended testing range in M27 is 0.12 to 64 ug/ml. when MIC distributions fall below we list as truncated.
  - *C.albicans* flucytosine if we keep it in testing range, everything is truncated.
  - *C. glabrata* same story truncated low MIC distribution.
  - *C. tropicalis* flucystosine 4 labs, 488 isolates weighted to 400. In 2016 data ECV = 1, 0.5 if unweighted.

- NWT 1.5% data from 2016. Do we put it as 1, or as truncated low? If we keep it to the testing range it splits the distribution in two. Since range is mostly below 0.12. Dr. Dufresne favors putting it as truncated low.

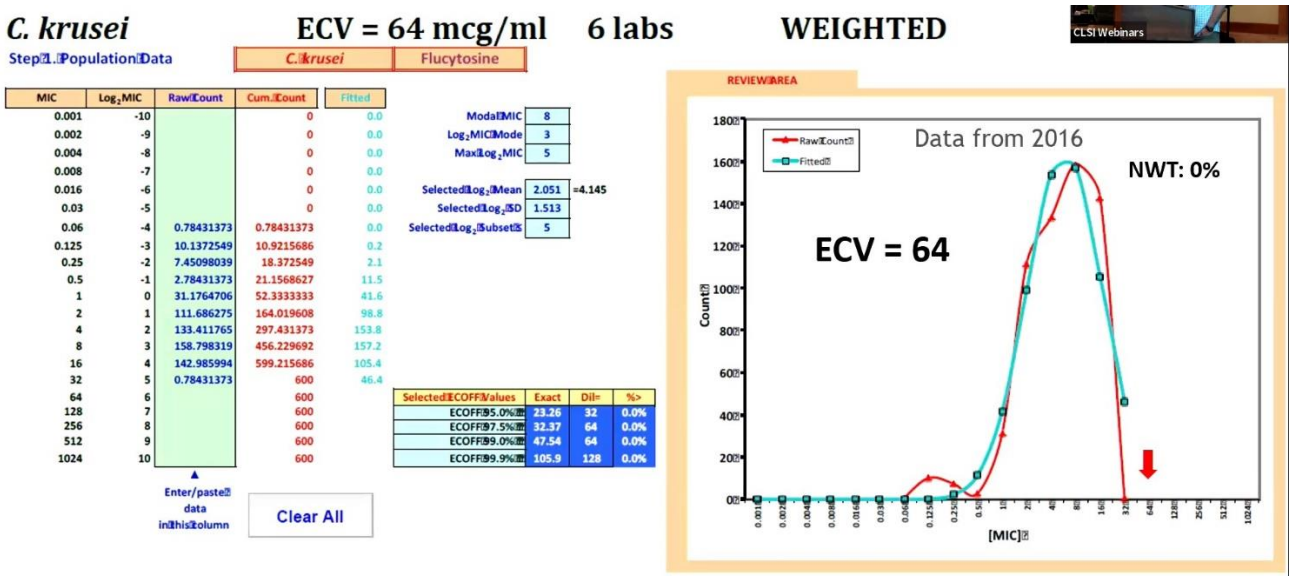


- *C. krusei* flucytosine ECV=32, NWT 0%
- All MICs are above testing range



6 labs (of 7) - One lab bi-modal (low MIC peak)
405 isolates

- 1 lab removed since it was bimodal, data weighted



ECV for vote

Species	Antifungal	MICs (labs)	Proposed ECV (µg/mL)
C. albicans	Flucytosine	3668 (10)	TR-L
C. glabrata	Flucytosine	2191 (10)	TR-L
C. tropicalis	Flucytosine	827 (10)	TR-L or 1
C. krusei	Flucytosine	299 (6)*	32

TR-L Truncated low
* Weighted

- Discussion:
- ECV needs at least 3 labs, minimum 100 isolates, no lab can contribute more than 50% of isolates.
- Dr. Zhang: why is 5FC ECV for *C.krusei* so high?
- Dr. Dufresne: is not sure, he sees it consistently. However, flucystosine not used with *C.krusei* so impact is minimal. A lot of historical work on this, precursor of EUCAST, distrubutions were similar. Were there any known mutants in the isolates you have included? Dr. Dufresne says that would be good to have but we don't have that data. %NWT in the graphs could be potential mutants. Fair number of isolates with high MICs.
- Dr. Alexander asks if TRL gives enough information or does there need to be an asterisk to define the lower testing limit?
- Dr. Dufresne says it is defined in the M57S table but references another document. So the person has to go back and look. Also if all our data is TRL why don't we recommend a different testing range? Dr. Dufresne says because the achievable concentration is much higher than this, expected to be susceptible over 99% of the time.
- Dr. Fuller: how many 0.06 or 0.12 labs were off-scale? This was one of the reasons in the first round we departed from 5FC. If you have a resistant isolate MIC will be pretty high, over 16 or over 32. For flucystosine most *Candida* spp. already truncated low.

#	Description
	• Dr. Alexander remembers there was a lot of data for flucytosine, we tried to set breakpoints and had to call them back. Dr. Alexander remembers there are only 2 testing ranges to choose from in the M27 document. Does not recall if there was ever a vote from the committee about which range to use, may have just been a practical decision. • Dr. Wiederhold: TRL probably does not help us with *Candida* but is often used in cryptococcal meningitis in combination therapy. Most of the *Cryptococcus* isolates are higher in the MIC range of 2-4, so if we lower the range we are testing it will no longer be useful for *Cryptococcus* which is the main indication. • Dr. Dufresne thinks the range is fine, why bother lowering it if there is no known resistance and everything is susceptible? • Dr. Castanheira proposes possibly including an explanation about the testing range in the supplement. • Dr. Wiederhold agrees. • Dr. Hanson mentions with *C. krusei* with ECV of 32 (high) may not be clinically useful. Some may consider using flucytosine in urine, but what concentrations will be achievable? • Dr. Dufresne agrees concentration may not be attained and likely not be useful. Needs to put a footnote that the ECV is high. • Dr. Griffin: Why not calculate ECVs? You could. It seems inconsistent with the summary table so far. Shouldn't TRL be for cases where you can't calculate the ECV? • Dr. Dufresne said it is a lot of work with no real gain, no clinical utility, need 10 labs, everything will be susceptible. • Dr. Dingle: Can you can calculate ECV for data that is skewed? • Dr. Dufresne says no, you can't but if you extend the testing range you could but there is no incentive to do that at the moment as flucytosine is not used much for *Candida* infection. A motion to accept proposed ECVs for *C. glabrata, C. albicans* and *C. tropicalis* as TRL and *C. krusei* ECV of 32 as presented by Dr. Dufresne was made and seconded. Vote: 12 for, 0 against, 0 abstain, 0 absent (Pass).

#	Description
13	**SPOROTHRIX ECVS (DR. DUFRESNE, DR. SANTOS)**

ECV for vote

Species	Antifungal	MICs (labs)	Proposed ECV
S. *brasiliensis*	Amphotericin	81 (4)	4 (tentative)*
S. *brasiliensis*	Itraconazole	252 (5)	8
S. *brasiliensis*	Posaconazole	223 (3)	4
S. *brasiliensis*	Terbinafine	270 (4)	0.12
S. *schenckii* ss	Amphotericin	119 (7)	8
S. *schenckii* ss	Itraconazole	131 (7)	16
S. *schenckii* ss	Posaconazole	117 (6)	8
S. *globosa*	Amphotericin	100 (6)	8**

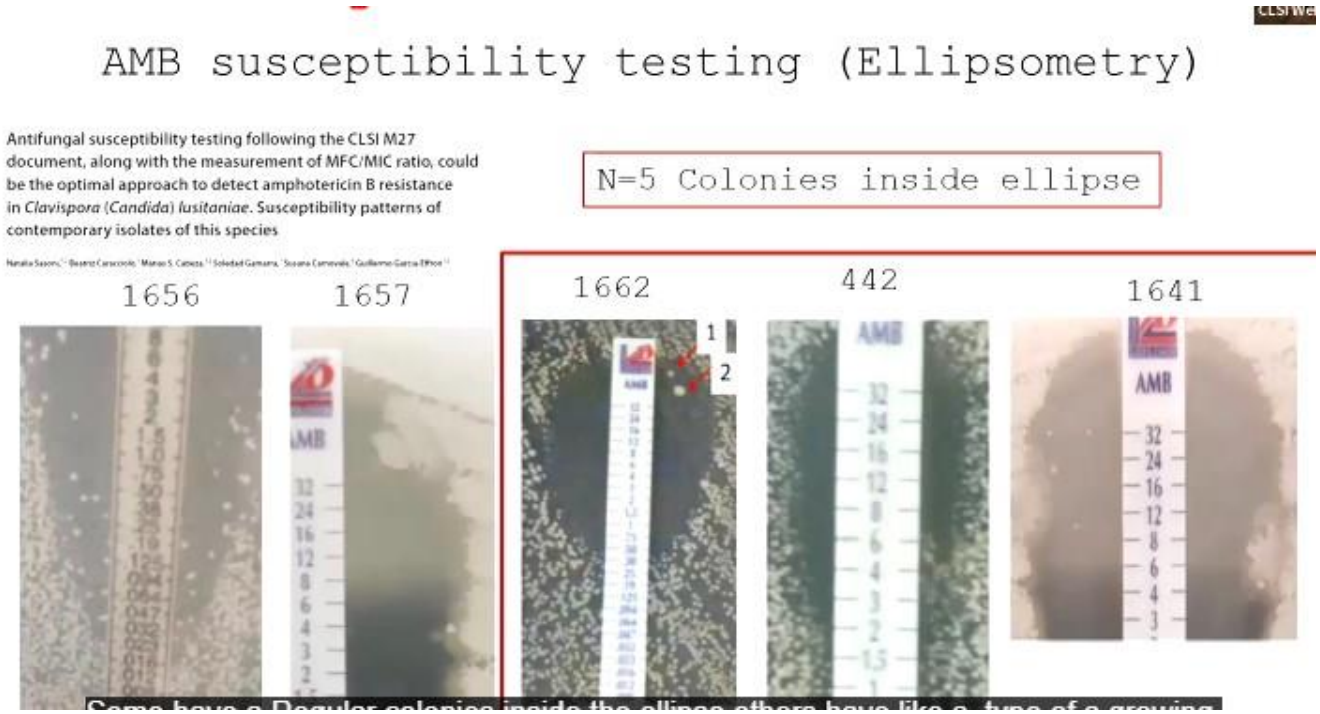
+ all 3 species Truncated High (TRH) for Fluconazole

* Insufficient number of isolates not for M57S publication. **If low MIC peak of 1 lab ignored.

A motion to accept proposed ECVs for *Sporothrix* spp. shown on slide as presented by Dr. Dufresne was made and seconded. Vote: 12 for, 0 against, 0 abstain, 0 absent (Pass).

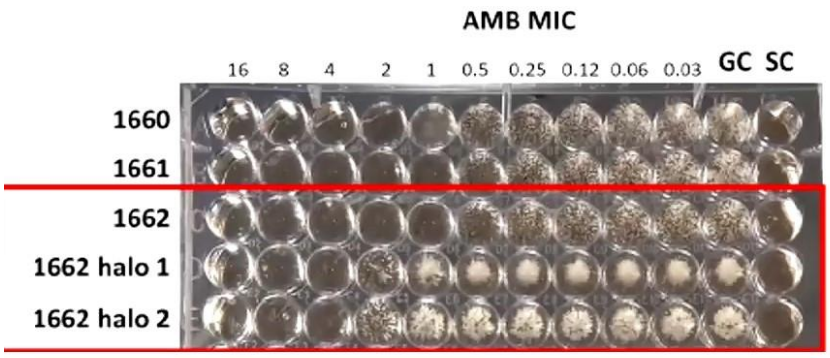
14 **C. *LUSITANIAE* AMPHOTERICIN SUSCEPTIBILITY TESTING (DR. GARCIA-EFFRON)**

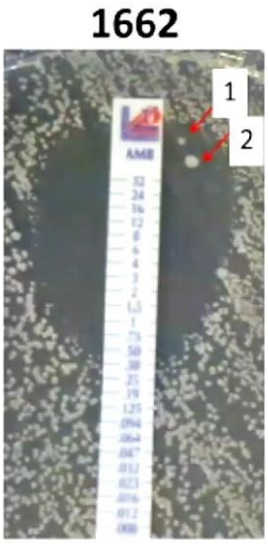
- 7.5% of all fungemias are caused by rare yeasts.
- Cause of fungemia, AST for AMB is important. Younger patients. Similar risk factors to *C.albicans*. More common in cancer patients, moderate neutropenia patients and those with corticosteroid use.
- Problems with AMB AST. Microdiultion. Most (97.5%) MIC values are packed between 0.12 and 1 ug/ml.
- Are we able to detect AMB resistance using CLSI microdilution methods?
- Gradient diffusion better than BMD to separate S and R for AMB and *C.lusitaniae*. Published more than 20 years ago in *Journal of Clinical Microbiology* 2001 by Peyron et al. "Improved detection of amphotericin B-Resistant Isolates of *Candida lusitaniae* by E test."
- Objectives: demonstrate feasibility of CLSI reference method to determine phenotype of *C.lusitaniae*. published in AAC.
- Tested strains from patient samples, characterized genetically. Total of 48 isolates from South America.
- AMB E test: 43 with clear ellipse, other strains had colonies inside ellipse (5).



- Compare to BMD following CLSI M27 methods. Susceptible strains are similar. However, we cannot pick up resistance with BMD. BMD does not pick up resistance.

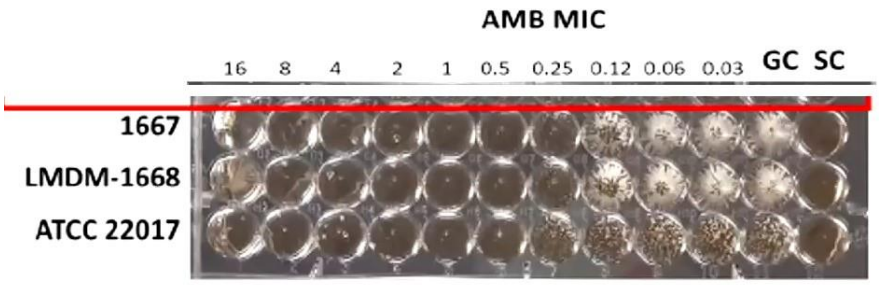
	MIC	E-test
1662 blood	1.00	>32?
1662-1/2	4.00	4.00

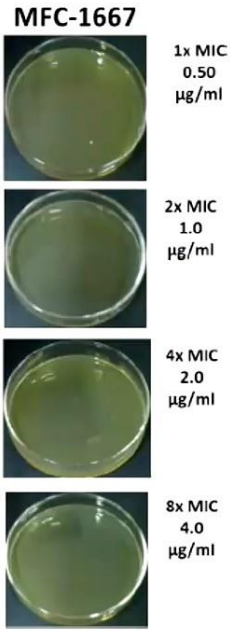




- Isolated colonies inside halo, repeat with CLSI method and the inner colonies are much higher MIC values.
- Maybe the small colonies are invisible to us when we use liquid media? Decided to perform MIC by agar dilution by inoculating the content of the titer wells. On the right are plates with various MICs from the media plate, can't see any colonies on the agar plates for susceptible strains but do see them for resistant strains as high as 8X the MIC.

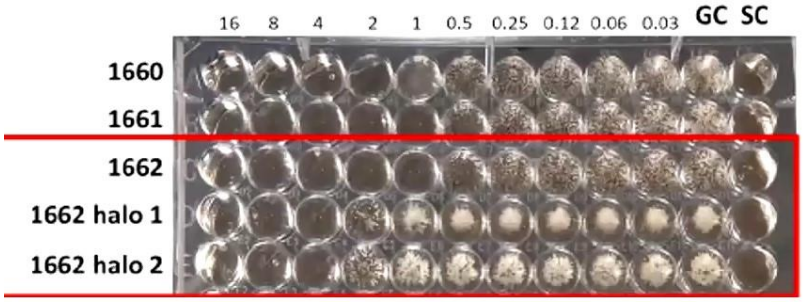
	MIC	E-test	MFC
1667	0.50	0.50	0.50

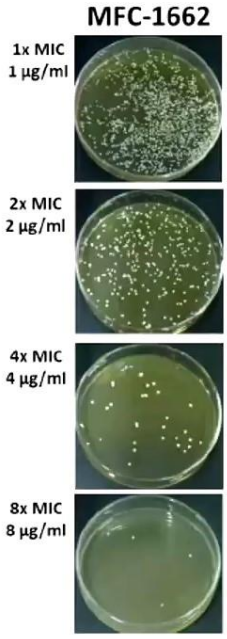




#	Description

	MIC	E-test	MFC
1662 blood	1.00	>32?	8.00
1662-1/2	4.00	4.00	8.00





- In conclusion:
  - Colonies inside ellipse MFC/MIC ≥ 4
  - No colonies inside ellipse MFC/MIC < 4
  - *C.lusitaniae* show narrow range of AMB MIC values with BMD and all tested strains are WT by CLSI method.
  - AMB clinically resistant strains show colonies inside ellipse via gradient diffusion method.
  - Colonies inside the ellipse have higher MIC and MFC values (1 to 4 fold higher MIC).
  - AMB resistant strains MFC/MIC ratio ≥ 4 (higher than expected for fungicidal agent).
  - CLSI microdilution method can identify AMB-resistant *C. lusitaniae* strains using the MFC/MIC ratio.
  - If you inoculate your BMD wells to a plate you can spot the resistance. This is what labs are often missing.
- Discussion:
- Dr. Schuetz mentions that something larger may be going on with AMB. Also see this with *C.auris*. Should test other species.
- Dr. Castanheira thinks as a group we need to address this. BMD is not ideal for AMB and we are propagating this info for years.

15	**LUNCH BREAK**

SUMMARY MINUTES Saturday, 20 January 2024	
#	**Description**
16	**INTRINSIC RESISTANCE WORKING GROUP UPDATES (DR. SCHUETZ)** • ECVs for many of these combos that fit reduced susceptibility criteria are going to be high. • *L.prolificans* and voriconazole may be a candidate for reduced susceptibility. Offscale truncated high, mid point MIC is high, very limited *in vitro* antifungal activity. • Also *Candida rugosa* and anidulafungin. • If something is IR, do we want labs to report this way instead of R? • How do we report reduced susceptibility? Footnotes? • Discussion with other areas of CLSI, bacterial and veterinary. • **Discussion** • How to explain this to vets? Difference between IR and reduced susceptibility and resistance? Need to be clear how we want clinicians to treat these. List of IR assessments and votes to date. • Future IR assessments
17	**DISCUSSION ON "REDUCED SUSCEPTIBILITY" DEFINITION (DR. SCHUETZ, DR. DINGLE)** • This discussion included in IR WG Updates above.
18	**BREAK**

SUMMARY MINUTES Saturday, 20 January 2024	
#	Description
19	**DERMATOPHYTE SUSCEPTIBILITY TESTING *T. INDOTINEAE* UPDATE (DR. CHATURVEDI)** • Emergence of Drug Resistant Dermatophytes. • Dermatophyte infection, Tinea/Ringworm. • Highly contagious infection of the skin. • *Trichophyton, Microsporum, Epidermophyton*. • *T. indotineae* new species within *T.methagrophytes/interdigitale* species complex. • Spread considerably since first found in Australia in 2007. India is now the hotspot, first in 2016. Isolates found in Canada. • Emergence of drug resistant *T. indotineae,* inappropriate use of over the counter antifungals, topical steroids, antifungal drugs, other factors. • First reported in New York City in US MMWR 72: 536-537. • Found in Canada in 2022. Terbinafine resistant isolates. • Molecular ID needed to confirm ID. • In NY, 9/11 isolates came from patients who had personal travel history or contacts in Bangladesh. • Clonal populations for 2 clusters, husband and wife 2 SNPs apart but others are not clonal. • Terbinafine is a member of the allylamine class of antifungals. • NO BPs right now, only ECV. • Thermofisher commercial plate for all drugs except terbinafine and griseofulvin, Wadsworth center makes these plates. • NY isolates ECV against terbinifine 0.0039 to 128 ug/ml, any value above 0.2 µg/mL is considered resistant. The NY isolates were highly resistant. Got griseofulvin, ECV 64. Most NY isolates were R to *T. indotineae,* also echinocandins work well. • *T. mentagropyte*/interdigitale species complex is growing - need careful analysis. • Provisional ID for *T. indotineae* is to screen for urease, *T. indotineae* is urease negative, whereas other members of the *T. mentagrophytes/interdigitale* complex are positive. Terbinafine screening medium MALDI-TOF with Bruker looks promising for ID also using Snakeskin dialysis tubing to prevent growth from going into agar. • Dr. Zhang question are they all urease negative? Dr. Chaturvedi has only tested the isolates she has, does *T. indotineae* cross react with other MALDI isolates in the library? One cross reaction with a *T. tonsurans* has been noticed.
20	**OTHER BUSINESS (DR. DUFRESNE)** • Ms.Cullen: input requested about QC. • Quality Improvement Ideas. • Reviewed fungal documents for QA and QC. Potential improvement we can do is include QC strain characteristics, Troubleshooting guide, Suggestions for confirming AST. • Interest in pursuing any or all of these? • Table 5A-2 and Appendix C in M100 as example of strain characteristics. • M100 Appendix A has examples for confirming AST. • QC more straightforward for yeasts than for molds.
21	**PLANS FOR NEXT VIRTUAL MEETING (DR. DUFRESNE)** The next meeting will be virtual and will be held in September 2024.

SUMMARY MINUTES Saturday, 20 January 2024	
#	**Description**
22	**ADJOURNMENT (DR. DUFRESNE)** Dr. Dufresne thanked everyone for attending the meeting and adjourned the meeting at 4:30 PM.

ACTION ITEMS			
#	**Description**	**Responsible**	**Status**
1.	Perform limited revision of M44.	Dr. Hanson Dr. Griffin	To start
2	Launch revision of M57S, M27M44S and M38M51S supplements.	Dr. Dufresne Ms. Lam Dr. Wiederhold	Create WGs and Edaptive drafts
3.	Add new proposed ECVs for *C. krusei* and TRL designation for *C. glabrata, C. albicans, C. tropicalis* to M57S current draft.	ECV WG	To start
4.	Launch M27 document development committee.	Dr. Castanheira Dr. Garcia-Effron Ms. Lam	To start
5.	Launch M38 document development committee.	Dr. Fuller Dr. Zhang Ms. Lam	To start
6.	Launch MIC Reading WG	Dr. Dufresne	To start
7.	Resubmit revised version of *A.fumigatus* VRC RD document.	BPWG	In progress
8.	Initial submission of *A.fumigatus* isavuconazole BP RD to FDA.	BPWG	In progress
9.	Perform the interlab variation study for voriconazole.	BPWG	In progress
10.	Prepare RD document for rezafungin BP (explain why it differs from FDA).	BPWG	To begin late 2024.
11.	Make rezafungin BP as no longer tentative and add to new edition of M27M44S.	BP WG and M27M44S WG	In progress
12.	Collect new MIC data and reanalyze *Sporothrix* ECVs.	ECV WG	In progress.
13.	Collect MIC data and analyze *Fonsecaea* ECVs.	Dr. Dallas Smith ECV WG	In progress
14.	Draft manuscript for *Scedoporium/Lomentospora,* rare *Candida* yeast.	ECV WG	In progree
15.	Collect MIC data for *Aspergillus* and associated cryptic species.	ECV WG	In progress
16.	Initiate discussion on IR definition and "reduced susceptibility" definition.	IR WG	In progress
17.	Complete draft and submit manuscript on IR of yeast and moulds.	IR WG	In progress

Respectfully submitted,
Christine M. Lam, MT(ASCP)
Camille Hamula, PhD, D(ABMM)

SC Reviewers and Guest Attendees

Dawit Abera	Alice Gray
Marwah Abdulrahman	Christopher Haddock
Stella Antonara	Stephen Hawser
Sophie Arbefeville	Esther Hernandez
Ken Babcock	Elide Herrera
Donald Bade	Rita Hoffard
Amrita Bharat	Andre Hsiung
April Bobenchik	Michael Huband
Malcolm Boswell	Dmitri Iarikov
Catherine-Audrey Boutin	Julie Ann Justo
Maryann Brandt	Ellen Kersh
John Breton	Haziq Khalid
Carrine Brown	Scott Killian
Andrew Bryan	Anna Klavins
Alexandra Bryson	Laura Koeth
Rebecca A. Burwell	Amanda Kulwicki
Shelley Campeau	Sangwon Lee
Gerald Capraro	Beth Leung
Darcie Carpenter	James Lewis
Mariana Castanheira	Xian-Zhi Li
Nydia Castillo-Martinez	Rachael Liesman
Courtney Chandler	Luiz Lisboa
Sudha Chaturvedi	Hannah Livesay
Vishnu Chaturvedi	Jeff Locke
Sebastian Cifuentes	Cristian Lozano
Sharon Cullen	Nubia Macedo
Zhixia Danielsen	Kelli Maddock
Kausik Datta	Isabella Martin
Keith DeDonder	Sandra McCurdy
Ryan Demkowicz	Sharon Min
Kaddijatou Drammeh	Susan Mindel
Rebekah Dumm	Ruel Mirasol
Gberindyer Fidelis	Anisha Misra
Marcelo Galas	Masako Mizusawa
Barb Gancarz	Brian Mochon
Rahul Garg	Nicholas Moore
Cherilyn Garner	Yesenia Morales
Samantha Giffen	Ian Morrissey
Laurel Glaser	Timothy Mudenda
Heather Glasgow	Leocrisia Mwanamoonga
Beth Goldstein	Nolonwabo Nontongana
Kerian Grande Roche	Michael North

Susan O'Rourke	Jennifer Slaughter
Evans Otima	Jennifer Smart
Sophonie Oyeniran	Chandresh Solanki
Elizabeth Palavecino	Dylan Staats
Sherle Panen	Judith Steenbergen
Logan Patterson	Lili Tao
Cau Dinh Pham	John Tedesco
Peter Piliero	Tewodros Tesfa
Sachidevi Puttaswamy	Susan Thomson
Karl Anthony Ramos	Valentine Usongo
Valerie Ravenna	Paula Snippes Vagnone
Mark Redell	Tam Van
Zachary Ruhe	Wayne Wang
Cynthia Schneider	Rebecca Weingarten
Ashley Selby	Susan Weir
Ribhi Shawar	Nancy Wengenack
Rosemary She	Eric Wenzler
Kileen Shier	Cheung Yee
Simone Shurland	Sharon Duba Zimba