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Subcommittee on Antifungal Susceptibility Tests
Web Conference Agenda

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Meeting Title:	Antifungal Subcommittee Web conference	**Contact:**	mhackenbrack@clsi.org
Meeting Date:	Thursday, 4 June 2015	**Secretary**	P. Dufresne
Start Time:	4:00 PM Eastern (US) time	**End Time:**	6:00 PM
Meeting Purpose:	To review, vote on, and finalize antifungal ECVs		
Requested Attendee(s):	Chairholder, Vice-chairholder, Members, Advisors, and Reviewers of the Antifungal Subcommittee		
Actual Attendee(s):	B. Alexander, M. Castanheira, S.Cullen, A. Espinel-Ingroff, A. Fothergill, L. Kovanda, S.Lockhart, J. Meis, D.Perlin, N. Wengenack, L. Berkley, P. Dufresne, C. Knapp, M. Motyl, G. Procop, M. Traczewski, K. VanHorn, N. Weiderhold, J. Fuller, W. Gregory, B. Goldstein, H. Gupta, P. Hogan, K. Suvarna, M. Hackenbrack		

AGENDA

Item	Time	Presenter	Description
1.	4:00 PM	Dr. Alexander	Opening remarks Review goals for Web conference
2.	4:05 PM	Dr. Alexander	January meeting summary minutes – Vote to approve
3.	4:10 PM	Dr. Alexander	Review and discuss outcomes of ECV Working group data review • Analysis of raw data for *Candida* and amphotericin B, itraconazole, and flucytosine • Re-analysis of raw data for *Aspergillus* and posaconazole • *A. nidulans* issues
4.	4:30 PM	Dr. Alexander	Vote on ECVs from re-analyzed data
5.	4:40 PM	Dr. Alexander	Review and confirm approved ECVs
6.	4:50 PM	Dr. Ghannoum Dr. Lockhart	M57 Status update • ECV data criteria revision • Request for new data
7.	5:05 PM	Dr. Lockhart	Overview ECV database, data collection, and data submission

AGENDA

Item	Time	Presenter	Description
8.	5:15 PM	Dr. Alexander	Overview of new ECV standing working group charter
9.	5:30 PM	Working groups	Overview/discussion on document revisions (M27, M27/M44, M38, M38/M51)
10.	5:45 PM	Dr. Perlin	Update on Caspofungin Working Group
11.	5:55 PM	Dr. Alexander	Plans for next meeting: Is another Web conference needed? Next face-to-face meeting: Saturday, 9 January 2016 at the Mission Palms in Tempe, Arizona
12.	6:00 PM	Dr. Alexander	Adjourn

SUMMARY MINUTES

Item	Description
1.	Dr. Alexander opened the Web conference at 4:05 PM Eastern (US) time by thanking the participants for joining the call. • She reminded the participants to identify themselves and state any new disclosures when commenting. • It was noted that 9 voting members were in attendance. Therefore, the following voting rule applied: 9-0, 8-1, 7-2, or 6-3 will constitute a "pass" vote.
2.	The January 2015 meeting summary minutes were reviewed. • A motion to approve the minutes was made and seconded. • The January 2015 meeting summary was approved (9-0).
3.	The participants reviewed and discussed the outcomes of Epidemiological Cut off Values (ECV) Working group (WG) data review. • It was noted that the ECV data was acceptable if it included data from at least 3 laboratories, less than 50% of the data was generated by one laboratory, and if there were at least 100 isolates from each laboratory. • Dr. Alexander compiled the ECVs voted on during past Antifungal meetings and the ECV WG reviewed the primary data associated with those values during a recent Web conference. • It was noted during the ECV Web conference that there were some discrepancies with a few of the drug/organism combinations. The primary data was reviewed and re-analyzed by the ECV WG. • Amphotericin and *Candida* spp. – The primary data was reviewed and the data was re-analyzed with weighting and unweighting by Dr. Turnidge. – The ECV WG was satisfied with the final 97.5% statistical ECVs (see below). • Itraconazole and *Candida* spp. – For *C. albicans* and *C. parapsilosis*, the modes were spread across a wide range and several laboratories were truncated at lower end. – It is not possible to use the data from remaining (non-truncated laboratories) as this would artificially raise ECV. – It was agreed that more data is needed for these species. • Flucytosine and *Candida* spp. – The majority of laboratories had truncated data for all species resulting in only 2 to 3 laboratories

contributing data for *C. albicans*, *C. glabrata*, and *C. parapsilosis* and with one laboratory contributing > 50% of data. *C. tropicalis* and *C. krusei* weighted analyses (4 laboratories contributing for each) resulted in ECVs one dilution higher than unweighted.
  - Overall, the WG is not comfortable with the data and requests additional data collection and analysis.
- Anidulafungin and micafungin and *Candida* spp.
  - The data was reviewed and re-analyzed and determined to be acceptable for ECVs from the 97.5% statistical analysis
- *Aspergillus nidulans* ECV issues
  - There is a tri-modal distribution for many of the drugs tested suggesting the data may be from more than one species or sub-species with different MIC distributions.
  - More data is needed with all drugs and the isolates should be submitted with a molecular identification.
- Itraconazole and *Aspergillus* spp.
  - Data are acceptable and 97.5% ECVs are correct (excluding *A. nidulans*).
- Posaconazole and *Aspergillus* spp.
  - One laboratory provided >50% of the data. Analysis by Dr. Turnidge with weighted and unweighted data did not change the ECVs when all 4 laboratories were included. The ECV excluding the laboratory with >50% of the data would lower the ECV by one dilution. The WG was not comfortable with this outcome.
  - For *A. fumigatus*, the data presented by Dr. Meis at the January 2015 meeting suggested that the ECV selected at 0.5 may be too high because those with mutations had ECVs at 0.5. The WG was not comfortable retaining the ECV of 0.5. The WG will request additional data and will include Dr. Meis's data (he has agreed to provide his data with and without mutations) and all data will be re-analyzed. Dr. Dufresene has also provided additional data that will be included.
- Voriconazole, Isavuconazole, Caspofungin, and Amphotericin B and *Aspergillus* spp.
  - Data for all combinations are acceptable and 97.5% ECVs are correct (excluding *A. nidulans*).
- More data for *A. nidulans* with all drugs and *A. fumigatus* with posaconazole will be requested.
  - Dr. Espinel-Ingroff will work on collecting additional data.
  - Additional data will also be requested from the subcommittee participants.
- Voriconazole and *Candida* spp.
  - Dr. Alexander noted that in her review of the ECV data, there are no ECVs for voriconazole and *Candida* spp. She stated that ECVs for voriconazole are needed especially for *C. glabrata* as there are no breakpoints. She indicated that it would be helpful to have them available quickly so that they can be included in M57-S.
  - Dr. Espinel-Ingroff stated that there are ECVs available for voriconazole and posaconazole. She will provide the raw data and analysis for the ECV WG to review. The Subcommittee will vote on the ECVs electronically (see NOTE). Dr. Espinel-Ingroff noted that a decision has to be made whether to use weighted or unweighted analysis.
  - If the analysis shows different ECVs for weighted and unweighted data, a conference call will be scheduled to vote, rather than an electronic vote. This topic will also be discussed for action going forward at the January 2016 subcommittee meeting.
  - Dr. Espinel-Ingroff, Dr. Lockart, and Dr. Turnidge will review the data

NOTE: An electronic vote consists of the following:
- An open period of debate with a specific closing date.
- Once the debate period ends and all concerns have been addressed, a specific voting period will

	commence (usually 10 – 20 days). • No additional comment may be submitted after the voting period begins.
4 -5.	Vote on final 97.5% statistical ECVs for all reviewed organism drug combinations. • A motion was made and seconded to approve the final 97.5% statistical ECVs proposed by the ECV WG as listed in the table below. These values will be included in M57-S. • The motion and the ECVs were approved (9-0).
6.	Dr. Lockhart provided an update on the status of M57 and M57-S. • He indicated that the draft is almost completed and should be ready to prepare for vote soon. The document and supplement are expected to publish in February 2016. • A request for data has been added to the Foreword. Information on where to send the data will be included. Dr. Lockhart will provide a standard submission form to be available on the Antifungal Subcommittee page on the CLSI website. • Information on weighting data when a single laboratory provides > 50% of the data and instructions for weighting will be drafted by Dr. Turnidge. This should be completed before M57 publishes. Dr. Turnidge will train others to analyze data using ECOFF finder. • It was suggested that the request for data will request that the isolates being submitted should be identified using molecular methods or MALDI-TOF MS.
7.	Dr. Lockhart provided an overview of the ECV database. • The ECV WG will have a standing request for MIC data. Criteria will follow that outlined in M57. • A standard form will be available on the website with instructions on where to send the data. The form will allow the information to be added to ECOFF finder for analysis. – It was suggested that data that is submitted come from isolates that have had their identification confirmed by molecular methods to ensure that the identification is correct. It was suggested that this may exclude a lot of data that could be useful. – It was suggested that MALDI-TOF MS is very accurate and should produce acceptable identification. Those identifications that are questionable using MALDI-TOF MS may need to be confirmed with molecular methods. • All data will be reviewed by the ECV WG periodically to determine if it is acceptable. The WG will correspond with the submitter if the data is unacceptable and request additional data. • Approved data will be submitted to the Antifungal Subcommittee for review and vote.
8.	Dr. Alexander reviewed the proposed ECV WG charter. The ECV WG will be a standing WG with membership limits. • The ECV WG will manage all the raw data for ECVs and will be responsible for updates to M57. Other responsibilities are outlined in the charter (as posted in the meeting background in Workspace). • A call for volunteers will be distributed to the Antifungal Subcommittee. Any interested in participating should send their nomination request to Ms. Hackenbrack. • The new membership will be named at the January 2016 meeting. The standing ECV WG will begin working as soon as M57 publishes.
9.	An update of the documents in revision (M27, M27/M44, M38, M38/M51) was provided. • The goal is to have all drafts completed and ready to submit for vote as soon as M57 publishes. • The working groups have met and there are a few revisions left. Formatting has been changed and the drafts have been harmonized between all antifungal documents and with the Antimicrobial susceptibility testing documents.The goal is for these documents to be easier to use at the bench. • Language to be added to Table 1 in M27/M44 will be in regards to issues with caspofungin testing with *Candida* spp. • Dr. Alexander noted that for *C. glabrata* there is no zone interpretive criteria for anidulafungin, micafungin, or voriconazole.

	– In the 2013 meeting minutes, it was noted that mutations were not taken into consideration when data was collected and that additional data was needed. Although this was an action item, no additional data was collected. – A paper was published with Dr. Arendrup and Dr. Perlin as authors that discussed *FKS* mutations. – **Action item**: The paper will be reviewed and the data reevaluated. Raw data for this paper will be requested from Dr. Arendrup. – For this new edition of M27/M44-S, no zone diameters will be available for *C. glabrata* and the echinocandins. • The other drafts are well into revision.
10.	Dr. Perlin provided an update from the caspofungin WG. • Dr. Perlin reported that the caspofungin WG held a conference call on Monday, 1 June. • The issues of discrepancies with caspofungin testing are related to specific aspects of the method. – Problems with coating of plastic. – Different QC strains may be needed. – Different groups may not be applying the testing and interpretation in a standardized way. • Issues with the drug or how it is being prepared may still be in play. • Dr. Perlin proposed that those strains that test resistant with caspofungin should be confirmed as resistant by testing anidulafungin or micafungin. This would provide interim guidance for laboratories. – Ms. Traczewski questioned whether a survey regarding methodology (eg, weighing stock solution, etc) with caspofungin testing to see if there is consistency in methodology had been distributed. She indicated that the reason for the resistant results still needs to be discovered. – Dr. Perlin indicated that this survey has been informally done and Dr. Weiderhold reported that switching from treated to untreated plastic when testing echinocandins has resulted in a decrease in caspofungin resistance in his laboratory and that for those that do test resistant to caspofungin,echinocandin resistance is confirmed by testing micafungin. It was noted that the issue seems to be related to the way the drug reacts and not with how the test is performed. – Ms. Cullen suggested revising language currently in M100 regarding testing surrogates or reflex testing to address caspofungin testing. "Oxacillin MIC interpretive criteria may overcall resistance for some CoNS, because some non–*S. epidermidis* strains for which the oxacillin MICs are 0.5 to 2 µg/mL lack mecA. For serious infections with CoNS other than *S. epidermidis*, testing for mecA or for PBP 2a or with cefoxitin disk diffusion may be appropriate for strains for which the oxacillin MICs are 0.5 to 2 µg/mL. MIC tests should be performed to determine the susceptibility of all isolates of staphylococci to vancomycin. The disk test does not differentiate vancomycin-susceptible isolates of *S. aureus* from vancomycin-intermediate isolates, nor does the test differentiate among vancomycin-susceptible, intermediate, and resistant isolates of CoNS, all of which will give similar size zones of inhibition." **Or** "Isolates of pneumococci with oxacillin zone sizes of ≥ 20 mm are susceptible (MIC ≤ 0.06 µg/mL) to penicillin. Penicillin and cefotaxime, ceftriaxone, or meropenem MICs should be determined for those isolates with oxacillin zone diameters of ≤ 19 mm, because zones of ≤ 19 mm occur with penicillin-resistant, intermediate, or certain susceptible strains. For isolates with oxacillin zones ≤ 19 mm, do not report penicillin as resistant without performing a penicillin MIC test." – Dr. Alexander will draft a comment regarding caspofungin surrogate and reflex testing and send it for review to Ms. Cullen. The comment will be included in M27 and M27/M44-S. It was noted that sequencing can also be performed to identify mutations and thus, echinocandin resistance. • Further studies to investigate the issue need funding to perform. Dr. Motyl indicated that the manufacturer would consider providing funding if a proposal for testing is submitted.

11.	Next meeting: 9 January 2016 at Mission Palms in Tempe, Arizona.
12.	There was no business to discuss. Dr. Alexander expressed her gratitude to the participants and adjourned the meeting at 5:20 PM Eastern (US) time.

Antifungal Agent	Species	Final Approved 97.5% Statistical ECV (µg/mL)	Comments
Amphotericin	*C. albicans*	2	Weighted and unweighted analyses with the same ECVs.
	C. glabrata	2	
	C. parapsilosis	2	
	C. tropicalis	2	
	C. krusei	2	
Itraconazole	*C. glabrata*	4	More data is needed to set ECVs for *C. albicans* and *C. parapsilosis*.
	C. tropicalis	0.5	
	C. krusei	1	
	C. lusitaniae	1	
Anidulafungin	*C. albicans*	0.12	Data are acceptable and 97.5% ECVs are correct and approved.
	C. glabrata	0.25	
	C. parapsilosis	8	
	C. tropicalis	0.12	
	C. krusei	0.25	
	C. lusitaniae	1	
	C. guilliermondii	8	
	C. dubliniensis	0.12	
Micafungin	*C. albicans*	0.03	Data are acceptable and 97.5% ECVs are correct and approved.
	C. glabrata	0.03	
	C. parapsilosis	4	
	C. tropicalis	0.06	
	C. krusei	0.25	
	C. lusitaniae	0.5	
	C. guilliermondii	2	
	C. dubliniensis	0.12	
Itraconazole	*A. fumigatus*	1	Data are acceptable and 97.5% ECVs are correct and approved (excluding *A. nidulans*).
	A. flavus	1	
	A. terreus	2	
	A. niger	4	
Posaconazole	*A. flavus*	0.5	Data are acceptable and 97.5% ECVs are correct and approved for all species (except *A. fumigatus* and *A. nidulans*).
	A. terreus	1	
	A. niger	2	
Voriconazole	*A. fumigatus*	1	Data are acceptable and 97.5% ECVs are correct and approved (excluding *A. nidulans*).
	A. flavus	2	

	A. terreus	2	
	A. niger	2	
Isavuconazole	*A. fumigatus*	1	Data are acceptable and 97.5% ECVs are correct and approved (excluding *A. nidulans*).
	A. flavus	1	
	A. terreus	1	
	A. niger	4	
Caspofungin	*A. fumigatus*	0.5	Data are acceptable and 97.5% ECVs are correct and approved (excluding *A. nidulans*).
	A. flavus	0.5	
	A. terreus	0.12	
	A. niger	0.25	
Amphotericin B	*A. fumigatus*	2	Data are acceptable and 97.5% ECVs are correct and approved (excluding *A. nidulans*).
	A. flavus	4	
	A. terreus	4	
	A. niger	2	
	A. versicolor	2	

ACTION ITEMS

No.	Description	Responsibility	Due Date
1.	Collect additional data for *A. nidulans* with all drugs	Dr. Espinel-Ingroff	12/1/2015
2.	Reanalzye posaconazole data for *A. fumigatus* (including data from Dr. Meis)	Dr. Turnidge	7/15/2015
3.	Review raw data for ECVs for *Candida* and voriconazole and posaconazole and perform analysis if needed.	Dr. Espinel-Ingroff Dr. Turnidge Dr. Lockhart	7/1/2015
4.	Electronic vote on ECVs for *Candida* and voriconazole and posaconazole.	SC members	7/2015
5.	Create a standardized submission form for ECV data.	Dr. Lockhart	9/1/2015
6.	Train Subcommittee representatives to perform ECOFF finder analysis	Dr. Turnidge	1/1/2016
7.	Distribute a call for volunteers for the standing ECV working group	Ms. Hackenbrack	7/1/2015
8.	Select chairholder, vice-chairholder, secretary, and members of the ECV working group	Dr. Alexander	10/1/2015
9.	Request and review data for zone interpretive criteria for anidulafungin, micafungin, and voriconazole with *C. glabrata* from Dr. Arendrup.	Dr. Perlin	12/1/2015 (for presentation at the January 2016 meeting)
10.	Draft a comment regarding caspofungin surrogate and reflex testing for review by subcommittee and inclusion in M27 and M38 and the supplements.	Dr. Alexander Ms. Cullen	In progress