Muudatused EUCAST AFST dokumentides anno 2020

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ECCMID Aprill 2020 jäi ära, EUCAST AFST töötas *on-line*

EUCAST-AFST Activities
EUCAST AFST Subcommittee meeting
Prepared for ECCMID 2020

Chairman's report: Methods and QC

1. Alternative method for echinocandin versus *Aspergillus* testing
2. Dermatophyte testing EUCAST method
3. Plastic tray study- impact on MICs
4. Molecular detection of Resistance
5. QC table update

EUCAST dokument EUCAST BP ver 10.0

- **How to: Interpretation of MICs of antifungal compounds according to the revised clinical breakpoints v. 10.0 European Committee on Antimicrobial Susceptibility Testing (EUCAST)**

Maiken Cavling Arendrup[1,2,3]*, Nathalie Friberg[4], Mihai Mares[5], Gunnar Kahlmeter[6], J Meletiadis[7,8#], J Guinea[9,10#], and the Subcommittee on Antifungal Susceptibility Testing (AFST) of the ESCMID European Committee for Antimicrobial Susceptibility Testing (EUCAST)**

https://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/AFST/Clinical_breakpoints/AFST_BP_v10.0_200204_updatd_links_200924.pdf

New/Updated doc.s valid from 4-feb-2020

1. Clinical breakpoint table v 10.0
   Revised BPs, ATU explanation, new dosage table
2. Overview of antifungal ECOFFs and clinical breakpoints for yeasts and moulds v 1.0
   Including ECOFFs for species without BPs → wt versus non-wt interpretation

Rationale documents: more species included and…..

3. Amphotericin B v 2.0 (2020)
   No longer an I category (most ”I”s → ”R”s)
4. Anidulafungin vs. *Candida* v 3.0 (2020)
   C. parapsilosis BP revised (I→S)
5. Fluconazole vs. *Candida* v 3.0 (2020)
   C. glabrata BP revised (S ≤32→ ≤16 mg/l) , BP for *C. dubliniensis* established (S/R ≤2/>4 mg/l)
6. Isavuconazole vs. *Aspergillus* v 2.0 (2020)
   R revised. ATU introduced for *A. fumigatus* & *A. flavus* (2 mg/L classification depends on voriconazole MIC)
7. Itraconazole vs. *Aspergillus* v 2.0 (2020)
   R revised. ATU introduced for 4 *Aspergillus* species (2 mg/L =R but can be used in some/non-invasive infections)
8. Micafungin vs. *Candida* v 2.0 (2020)
   ATU introduced for *C. albicans* (0.03 mg/L classification depends on anidulafungin MIC). *C. parapsilosis* BP revised
9. Posaconazole v 3.0 (2020)
   BP for *C. dubliniensis* established.
   R revised and ATU introduced for *A. fumigatus* & *A. terreus* (0.25 mg/L classification depends on itraconazole MIC)
10. Voriconazole v 4.0 (2020)
    BP for *C. dubliniensis* established
    R revised and ATU introduced for *A. fumigatus* & *A. nidulans* (2 mg/L =R but can be used in some/non-invasive infections)

MC Arendrup (chair), J Guinea (secretary), J Meletiadis (data coordinator), G Kahlmeter (EUCAST SC repr.), M Mares & N Friberg (NACs)

EUCAST dokument E Def 11.0

- **How to: perform antifungal susceptibility testing of microconidia-forming dermatophytes following the new reference EUCAST method E.Def 11.0, exemplified by Trichophyton**

Maiken Cavling Arendrup, Gunnar Kahlmeter, Jesus Guinea, Joseph Meletiadis, the Subcommittee on Antifungal Susceptibility Testing (AFST) of the ESCMID European Committee for Antimicrobial Susceptibility Testing (EUCAST)

DOI: https://doi.org/10.1016/j.cmi.2020.08.042

https://www.clinicalmicrobiologyandinfection.com/article/S1198-743X(20)30526-7/fulltext?dgcid=raven_jbs_aip_emai

MIK määratud, EUCAST „kaardi“ legendi lugemine

The I category is not listed but is interpreted as the values between the S and the R breakpoints. If the S and R breakpoints are the same value there is no I category.

Agent A: No I category
Agent B: I category: 4 mg/L
Agent G: I category: 1-2 mg/L

Antifungal agent	MIC breakpoint (mg/L)		
	MIC breakpoint (mg/L)		
	S ≤	R >	ATU
Antimicrobial agent A	1[1]	1[1]	
Antimicrobial agent B	2[2]	4	
Antimicrobial agent C	IE	IE	
Antimicrobial agent D	-	-	
Antimicrobial agent E	IP	IP	
Antimicrobial agent F	NA	NA	
Antimicrobial agent G	0.5	2	
Antimicrobial agent H	0.001	1	

Notes. Numbered notes relate to general comments and/or MIC breakpoints.

1. Notes that are general comments and/or relating to MIC breakpoints.

2. New comment

~~Removed comment~~

Area of Technical Uncertainty
See specific information on how to handle technical uncertainty in antimicrobial susceptibility testing.

Insufficient evidence that the organism or group is a good target for therapy with the agent

No breakpoints. Susceptibility testing is not recommended

Changes from previous version highlighted in yellow

In Preparation

Not Applicable

MIC breakpoints in blue are linked to MIC distributions

Antifungal agents in blue are linked to EUCAST rationale documents

An arbitrary "off scale" breakpoint which categorises wild-type organisms as "Susceptible - increased exposure"

Kokkuvõte muudatustest seente ja antifungaalsete toimeainete osas

Version 10.0, 2020-02-04	**Changes (cells containing a change, a deletion or an addition) from v. 9.0 are marked yellow.** **New or changed comments are underlined. Removed comments are shown in strikethrough font style.**
General	• Harmonization of the Breakpoints Table document to the one for Antibacterials. Format and content changed accordingly. • Columns for Area of Technical Uncertainty (ATU) added (MIC). • Comments relating to high-dose therapy have been exchanged with HE (High Exposure) superscript on the antimicrobial name. • Adoption of new breapoints for less common species taken from the respresentative type species (*C. albicans* for yeasts and *A. fumigatus* for moulds) when the ECOFF for the combination in question is below or comparable to the breakpoint for the type species. • The format for MICs below 0.125 mg/L has been changed as follows (0.125→0.125, 0.0625→0.06, 0.03125→0.03, 0.015625→0.016, 0.0078125→0.008, 0.00390625→0.004 and 0.001953125→0.002 mg/L).
Notes	• Definitions of susceptibility categories added (Note 4 in *Candida* sheet) • Interpretation of fluconazole categories in *C. glabrata* (Note 4)
Technical uncertainty	• New sheet describing EUCAST recommendations for how to handle technical uncertainty (ATU) in antimicrobial susceptibility testing.
***Candida* and *Cryptococcus* spp.**	• The *Candida* sheet has been renamed to *Candida* and *Cryptococcus* and *Cryptococcus neoformans* breakpoints have been added. • Breakpoints of amphotericin and the azoles against *C. albicans* have been adopted for *C. dubliniensis* given that these species are similar in terms of antifungal susceptibility to these agents and in terms of virulence. • The fluconazole I and R breakpoints have been revised for *C. glabrata* to encompass the revised I category and the fact that new MIC data support an ECOFF of 16 mg/L. • Breakpoints of micafungin and anidulafungin against *C. parapsilosis* have been changed given that the clinical response is not statistically different from that for other agents despite the intrinsic target gene alteration.
***Aspergillus* spp.**	• Breakpoints for Amphotericin B, isavuconazole, voriconazole, and posaconazole against *A. fumigatus* have been changed to accommodate the new definition of the I category. • Breakpoints for isavuconazole against *A. flavus*, voriconazole against *A. nidulans*, and posaconazole against *A. terreus* have been set.
Dosages	• New sheet describing the standard dosing regimen, increased exposure dosing regimen, and the dosing regimens(s) for special clinical circumstances of antifungal with EUCAST breakpoints.

EUCAST breakpoints valid from 04-02-2020
Candida sp ja *Cryptococcus sp*

Antifungal agent	MIC breakpoint (mg/L)																		Comments on the I category	Comments on the ATU
	Candida albicans			*Candida dubliniensis*		*Candida glabrata*		*Candida krusei*		*Candida parapsilosis*		*Candida tropicalis*		*Candida guilliermondii*		*Cryptococcus neoformans*		Non-species related breakpoints for *Candida*[1]			
	S ≤	R >	ATU	S ≤	R >	S ≤	R >	S ≤	R >	S ≤	R >	S ≤	R >	S ≤	R >	S ≤	R >	S ≤	R >		
Amphotericin B	1	1		1	1	1	1	1	1	1	1	1	1	IE	IE	1	1	IE	IE	No data to support an I category according to the new definitions	
Anidulafungin	0.03	0.03				0.06	0.06	0.06	0.06	4	4	0.06	0.06	IE[2]	IE[2]	-	-	IE	IE		
Caspofungin	Note[3]	Note[3]				Note[3]	Note[3]	Note[3]	Note[3]	Note[3]	Note[3]	Note[3]	Note[3]	IE[2]	IE[2]	-	-	IE	IE		
Fluconazole	2	4		2	4	0.001[4]	16	-	-	2	4	2	4	IE[2]	IE[2]	IE	IE	2	4	See dosages table for appropriate dose	
Isavuconazole	IE	IE		IE	IE	IE	IE	IE	IE	IE	IE	IE	IE	IE	IE	IE	IE	IE	IE		
Itraconazole	0.06	0.06		0.06	0.06	IE[2]	IE[2]	IE[2]	IE[2]	0.125	0.125	0.125	0.125	IE[2]	IE[2]	IE	IE	IE	IE		
Micafungin	0.016	0.016	0.03			0.03	0.03	IE[5]	IE[5]	2	2	IE[5]	IE[5]	IE[5]	IE[5]	-	-	IE	IE		If S to anidulafungin, report as S and add the following comment: "Isolates susceptible to anidulafungin with micafungin MIC of 0.03 mg/L do not harbour an *fks* mutation conferring resistance to the echinocandins". If not S to anidulafungin, report as R and refer to reference laboratory for *fks* sequencing and confirmation of MICs.
Posaconazole	0.06	0.06		0.06	0.06	IE[2]	IE[2]	IE[2]	IE[2]	0.06	0.06	0.06	0.06	IE[2]	IE[2]	IE	IE	IE	IE		
Voriconazole[6]	0.06[7]	0.25[7]		0.06[7]	0.25[7]	IE	IE	IE	IE	0.125[7]	0.25[7]	0.125[7]	0.25[7]	IE[2]	IE[2]	IE	IE	IE	IE	4 mg/kg iv twice daily	

Ravim Flukonasool

EUCAST breakpoints for Candida species valid from 04-02-2020

Antifungal agent	*Candida albicans*			*Candida dubliniensis*		*Candida glabrata*		*Candida krusei*		*Candida parapsilosis*		*Candida tropicalis*		Non-species related breakpoints[1]	
	S ≤	R >	ATU	S ≤	R >	S ≤	R >	S ≤	R >	S ≤	R >	S ≤	R >	S ≤	R >
Amphotericin B[2]	1	1		1	1	1	1	1	1	1	1	1	1	IE	IE
Anidulafungin[2,3]	0.03	0.03				0.06	0.06	0.06	0.06	4	4	0.06	0.06	IE	IE
Fluconazole[4]	2	4		2	4	0.001[5]	16	-	-	2	4	2	4	2	4
Itraconazole[2]	0.06	0.06		0.06	0.06	IE[6]	IE[6]	IE[6]	IE[6]	0.125	0.125	0.125	0.125	IE	IE
Micafungin[2,3]	0.016	0.016	0.03[7]			0.03	0.03	IE[8]	IE[8]	2	2	IE[8]	IE[5]	IE	IE
Posaconazole[2]	0.06	0.06		0.06	0.06	IE[6]	IE[6]	IE[6]	IE[6]	0.06	0.06	0.06	0.06	IE	IE
Voriconazole[9]	0.06[10]	0.25[10]		0.06[10]	0.25[10]	IE	IE	IE	IE	0.125[10]	0.25[10]	0.125[10]	0.25[10]	IE	IE

LIIGILE CANDIDA KRUSEI FLUKONASOOLI RAVIMTUNDLIKKUST EI MÄÄRA

Ravim Flukonasool

EUCAST breakpoints for Candida species valid from 04-02-2020

Non-albicans CANDIDA RAVIS SAAB SOOVITADA AINULT FLUKONASOOLI RAVIMTUNDLIKKUSE MÄÄRAMIST!?

TEISTE RAVIMITE OSAS ON ANDMED EBAPIISAVAD

Antifungal agent	*Candida albicans*			*Candida dubliniensis*		*Candida glabrata*		*Candida krusei*		*Candida parapsilosis*		*Candida tropicalis*		Non-species related breakpoints[1]	
	S ≤	R >	ATU	S ≤	R >	S ≤	R >	S ≤	R >	S ≤	R >	S ≤	R >	S ≤	R >
Amphotericin B[2]	1	1		1	1	1	1	1	1	1	1	1	1	IE	IE
Anidulafungin[2,3]	0.03	0.03				0.06	0.06	0.06	0.06	4	4	0.06	0.06	IE	IE
Fluconazole[4]	2	4		2	4	0.001[5]	16	-		2	4	2	4	2	4
Itraconazole[2]	0.06	0.06		0.06	0.06	IE[6]	IE[6]	IE[6]	IE[6]	0.125	0.125	0.125	0.125	IE	IE
Micafungin[2,3]	0.016	0.016	0.03[7]			0.03	0.03	IE[8]	IE[8]	2	2	IE[8]	IE[5]	IE	IE
Posaconazole[2]	0.06	0.06		0.06	0.06	IE[6]	IE[6]	IE[6]	IE[6]	0.06	0.06	0.06	0.06	IE	IE
Voriconazole[9]	0.06[10]	0.25[10]		0.06[10]	0.25[10]	IE	IE	IE	IE	0.125[10]	0.25[10]	0.125[10]	0.25[10]	IE	IE

- 1 No breakpoints. Susceptibility testing is not recommended.

Ravim Flukonasool

EUCAST breakpoints for Candida species valid from 04-02-2020

Antifungal agent	*Candida albicans*			*Candida dubliniensis*		*Candida glabrata*		*Candida krusei*		*Candida parapsilosis*		*Candida tropicalis*		Non-species related breakpoints[1]	
	S ≤	R >	AFC	S ≤	R >	S ≤	R >	S ≤	R >	S ≤	R >	S ≤	R >	S ≤	R >
Amphotericin B[2]	1	1		1	1	1	1	1	1	1	1	1	1	IE	IE
Anidulafungin[2,3]	0.03	0.03				0.06	0.06	0.06	0.06	4	4	0.06	0.06	IE	IE
Fluconazole[4]	2	4		2	4	0.001[5]	16	-		2	4	2	4	2	4
Itraconazole[2]	0.06	0.06		0.06	0.06	IE[6]	IE[6]	IE[6]	IE[6]	0.125	0.125	0.125	0.125	IE	IE
Micafungin[2,3]	0.016	0.016	0.03[7]			0.03	0.03	IE[8]	IE[8]	2	2	IE[8]	IE[5]	IE	IE
Posaconazole[2]	0.06	0.06		0.06	0.06	IE[6]	IE[6]	IE[6]	IE[6]	0.06	0.06	0.06	0.06	IE	IE
Voriconazole[9]	0.06[10]	0.25[10]		0.06[10]	0.25[10]	IE	IE	IE	IE	0.125[10]	0.25[10]	0.125[10]	0.25[10]	IE	IE

KÕIK CANDIDA GLABRATA TÜVED MILLE MIK ON < 16 µg/ml KLASSIFITSEERUVAD KATEGOORISSE „I“

Kategooria „*Intermediate*“ uus sisu

I (Susceptible, Increased exposure) when current evidence support that there is a high likelihood of therapeutic success because exposure to the agent is increased by adjusting the dosing regimen or by its concentration at the site of infection.

Infektsionist/konsulteeriv mikrobioloog teab, millised on selle konkreetse ravimi Euroopas kasutatavad ravimdoosid ning koostöös raviarstiga annab soovitused korrigeerida ravi vastavalt labori poolt väljastatud MIK väärtuse hinnangule.

EUCAST Antifungal Clinical Breakpoint Table v. 10.0 valid from 2020-02-04

EUCAST breakpoints are based on the following adult dosages (see section 8 in Rationale Documents). Alternative dosing regimens which result in equivalent exposure are acceptable. The table should not be considered an exhaustive guidance for dosing in clinical practice, and does not replace specific local, national, or regional dosing guidelines.
Note: duration of treatment only indicated for loading doses, because the total duration of therapy is not only dependent on the type and site of infection but also on the underlying disease of the patient. Please consult clinical management guidelines for recommendations on total duration.

Azoles	Standard dose	Increased Exposure Dose	Special situations
Fluconazole	800 mg x 1 for first day followed by 400 mg x 1 iv/oral (or 6 mg/kg)	800 mg x 1 iv/oral (or 12 mg/kg)	Indicated doses are those appropriate for invasive candidiasis Mucosal infections (Mendling et al; Mycoses. 2012;55 Suppl 3:1-13): Standard doses is 100-200 mg x 1 and increased dose 800 mg x 1 (for *C. glabrata*)

Ravimdoosid

EUCAST Antifungal Clinical Breakpoint Table v. 10.0 valid from 2020-02-04

Azoles	Standard dose	Increased Exposure Dose	Special situations
Fluconazole	800 mg x 1 for first day followed by 400 mg x 1 iv/oral (or 6 mg/kg)	800 mg x 1 iv/oral (or 12 mg/kg)	Indicated doses are those appropriate for invasive candidiasis Mucosal infections (Mendling et al; Mycoses. 2012;55 Suppl 3:1-13): Standard doses is 100-200 mg x 1 and increased dose 800 mg x 1 (for *C. glabrata*)
Itraconazole	200 mg x 2 for first day followed by 100*-400** mg iv/po Target trough level***: >0.5 mg/L for prophylaxis, >1 mg/L for therapy		*Superficial infections only **Daily doses up to 200 mg x 2 may be given depending on the infection. Capsules have 30% lower bioavailability than the oral solution ***HPLC assay method and Parent compound only.
Isavuconazole	200 mg x 3 for first 2 days followed by 200 mg x 1 iv/oral		
Posaconazole	Tablets/iv: 300 mg x 2 for first day followed by 300 mg x 1 Oral suspension: 200 mg x 4 for first day or 400 mg x 2 Target trough level: >0.7 mg/L for prophylaxis and >1.25 mg/L for therapy		
Voriconazole	6 mg/kg x 2 for first day followed by 4 mg/kg x 2 iv 400 mg x 2 for first day followed by 200 mg x 2 po Target trough level: >0.5 mg/L for prophylaxis, 2-5.5 mg/L for therapy	*Candida* : The I-category only applies for the iv dosage (not the standard oral dose)	Increased exposure can be achieved by elevated dosage (note non-linear kinetics in adults) or with a proton pump inhibitor, in patients with low blood levels.
Amphotericin B formulations	**Standard dose**	**Increased Exposure Dose**	**Special situations**
Liposomal amphotericin B	3 mg/kg x 1		Increased doses up to 7 mg/kg (or even 10 mg/kg e.g. *Mucorales* CNS infections) can be used in specific situations.
Amphotericin B deoxycholate	1 mg/kg x 1		
ABLC	5 mg/kg x1		
Echinocandins	**Standard dose**	**Increased Exposure Dose**	**Special situations**
Anidulafungin	200 mg x 1 for first day followed by 100 mg x 1		
Caspofungin	70 mg x 1 for first day followed by 50* mg x 1 (weight ≤ 80 kg) 70 mg x 1 (weight > 80 kg)		
Micafungin	100 mg x 1 (weight >40 kg) 2 mg/kg x 1 in patients weighing <40 kg	200 mg x 1 (weight >40 kg) 4 mg/kg x 1 in patients weighing <40 kg	Increased dose indicated in patients not responding to standard dose Standard dose for chronic aspergillosis is Micafungin 150 mg x 1 (Chronic pulmonary aspergillosis: rationale and clinical guidelines for diagnosis and management. Eur Resp J 2016)

Ravim Amfoteritiin B

EUCAST breakpoints for Candida species valid from 04-02-2020

Märkused

2 No data to support an I category for amphotericin B according to the new definition of I

No evidence exist that dose escalation is a valid option for isolates in the former Intermediate category. The PK/PD relationship of different amphotericin B formulations is not well understood and the link between serum concentrations of different formulations with the efficacy is not well defined

MIK väärtus ATU-vahemikus - punane hoiatusmärk laboris

ATU (Area of Technical Uncertainty) to warn the laboratory staff that the value is in an area where there are interpretative difficulties. The reason is that a breakpoint is in a place where reproducible interpretation cannot be achieved.

The ATU is not related to uncertainties in the testing procedures although the natural unavoidable variation in testing will influence the actions that may need to be taken.

The ATU assumes that the susceptibility test is correctly performed and that the value obtained is correct in itself.

MIK väärtus ATU-vahemikus

Antifungal agent	MIC breakpoint (mg/L)																Comments on the I category	Comments on the ATU
	A. flavus			*A. fumigatus*			*A. nidulans*			*A. niger*		*A. terreus*			Non-species related breakpoints[1]			
	S ≤	R >	ATU	S ≤	R >	ATU	S ≤	R >	ATU	S ≤	R >	S ≤	R >	ATU	S ≤	R >		
Amphotericin B	-	-		1	1		-	-		1	1	-	-		IE	IE	No data to support an "I" category according to the new definition of "I"	
Anidulafungin	IE	IE		IE	IE		IE	IE		IE	IE	IE	IE		IE	IE		
Caspofungin	IE	IE		IE	IE		IE	IE		IE	IE	IE	IE		IE	IE		
Fluconazole	-	-		-	-		-	-		-	-	-	-		-	-		
Isavuconazole	1	2	2	1	2	2	0.25	0.25		IE[2]	IE[2]	1	1		IE	IE	Isavuconazole MIC = 2 mg/L should not be interpreted as I but only followed up as an ATU	If voriconazole wild-type (*A. flavus*: voriconazole MIC ≤2 mg/L; *A. fumigatus*: voriconazole MIC ≤1 mg/L) report as isavuconazole S and add the following comment: The MIC of 2 mg/L is one dilution above the S breakpoint but within the wild-type isavuconazole MIC range due to a stringent breakpoint susceptibility breakpoint. See rationale documents for more information. If voriconazole non wild-type report as isavuconazole R and refer to reference laboratory for *CYP51A* sequencing and confirmation of MICs[3]."
Itraconazole[4]	1	1	2	1	1	2	1	1	2	IE[2,5]	IE[2,5]	1	1	2	IE[5]	IE[5]		Report as R with the following comment: "In some clinical situations (non-invasive infections forms) traconazole can be used provided sufficient exposure is ensured".
Itraconazole	IE	IE		IE	IE		IE	IE		IE	IE	IE	IE		IE	IE		
Posaconazole[4]	IE[2]	IE[2]		0.125	0.25	0.25	IE[2]	IE[2]		IE[2]	IE[2]	0.125	0.25	0.25	IE	IE	Posaconazole MIC = 0.25 mg/L should not be interpreted as I but only as ATU	If S to itraconazole report as S and add the following comment: "The MIC is 0.25 mg/L and thus one dilution above the S breakpoint due to overlapping wt and non-wt populations". If not S to itraconazole report as R and refer to reference laboratory for *CYP51A* sequencing and confirmation of MICs.
Voriconazole[4]	IE[2]	IE[2]		1	1	2	1	1	2	IE[2]	IE[2]	IE[2]	IE[2]		IE	IE		Report as R with the following comment: "In some clinical situations (non-invasive infections forms) voriconazole can be used provided sufficient exposure is ensured".

MIK väärtus ATU-vahemikus - hoiatusmärk laboris

- Seentel MIK väärtus ATU-vahemikus – peamiselt hallitusseente ravimtundlikkusega seotud teema

- ATU väärtus vajab laboris kõrgendatud tähelepanu –

NB! Mõttekoht enne vastuse väljastamist

- Raviarst ootab laborist selget tulemust –

ei väljasta kategooriat „ATU“

Mõtlesin…välja mõtlesin
Mida labor teeb ATU tulemusega?

- Resistentsuse määramiseks alternatiivse meetodil – genotüpiseerimise – kasutamine (kui tegu kindla infektsioonitekitajaga ja alternatiivsete ravimite osas valik olematu)

Candida sp FKS mutatsiooni määramine, *Aspergillus* sp cyp51 geeni mutatsioonide määramine

- MIK väärtuse ümardamine allapoole R…S, I…S

Juhul kui MIK väärtus ühe kategooria võrra erinev (piiripealne), kindlasti lisada raviarstile kommentaar - *a la* ravimit võib kasutada, on alust arvata, et kliiniliselt tundlik – ECOFF!, vaatamata MIK tulemusele, mis klassifitseerub ATU, mitte S, I v R (tüvi säilitada ja määrata uuesti alternatiivsel meetodi)

- MIK väärtuse ümardamine ülespoole S…I, I…R, S…R

Kasutatakse juhul kui valida on alternatiivseid ravimeid (sama raportiga väljastatakse MIK väärtused ning tüvi säilitatakse täiendavaks testimiseks - genotüpiseerimiseks)

Mida labor teeb ATU tulemusega?

ATU-alas MIK väärtused võib ka labori vastusesse panna juhul kui

- Keerukate haigusjuhtude osas labor konsulteerib raviarstiga
- Soovitada võimalusel kasutada sellele ravimile alternatiivset ja lisada laborivastusele vastav kommentaar
- Liigitades ATU tulemus siiski *breakpoint*' alla lisatakse kommentaar ebaselge kategoriseerimise osas.

Soovitus: selge R töötab hästi juhul kui ravialternatiiv on olemas

Kuidas sellised kommentaarid ja lisandused labori arvutisüsteemile söödavaks muuta, on omaette mõttekoht

Kokkuvõtteks BP ja kategoriseerimisest

S is for **S**usceptible, and for **S**imilar response as in other patients on **S**tandard dose. **I** is for susceptible **I**ncreased exposure, and for **I**ntelligence needed as **I**ncreased dosage is **I**mportant, and **R** is for **R**esistance, and for **R**isk because change of therapy is **R**equired.

By MC Arendrup

Projekt „*Aspergillus spp* susceptibility to antifungals in Estonia“

1. september 2019 - 31. august 2020

Projektis osalejad: Eesti Mükoloogia Uuringutekeskus, ITKH, PERH, TÜK ja SYNLAB

Projekti finantseeriti Pfizer Luxembourg SARL Estonia grantist nr 53590099

Eesmärk

- Uurida Eestis liigi *Aspergillus fumigatus* ravimtundlikkust triasoolide suhtes
- Määrata vähemalt 100 *Aspergillus fumigatus* kliinilise tüve ravimtundlikkus 3 asooli - itrakonasooli, vorikonasooli ja posakonasooli suhtes

Meetodid

Agarlahjendus & skriiningtest VIPCheck (Mediapodukten AB, Holland)

Metoodika valik *Aspergillus sp* ravimtundlikkuse määarmiseks

- Ullmann, AJ et al. 2018. Diagnosis and managment of Aspergillus diseases: executive summary of 2017 ESCMID-ECCM-ERS guidelines. Clinical Microbiology and Infection 24:e1-e38.
- Guinea, J et al. 2019. How to: EUCAST recommendations on the screening procedure E.Def 10.1 for the detection of azole resistance in Aspergillus fumigatus isolates using four-well azole-containing agar plates. Clin Microbiol Infect 25 (6), 681-687.
- Buil JB et al. AGAR-BASED SCREENING FOR AZOLE RESISTANCE IN ASPERGILLUS FUMIGATUS USING VIPcheck™: A SINGLE CENTRE EVALUATION. Antimicrobial Agents and Chemotherapy 2017.

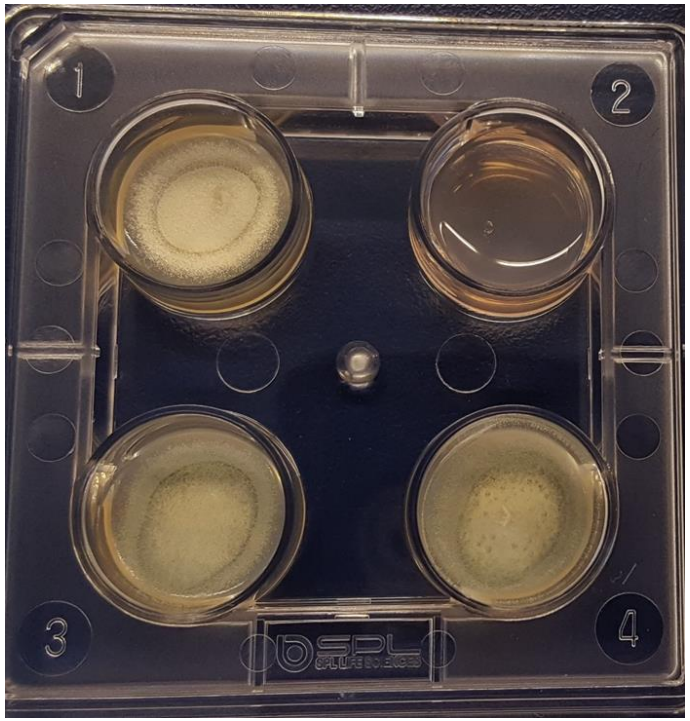
DOI: 10.1128/AAC.01250-17

Skriiningtest - VIP Check

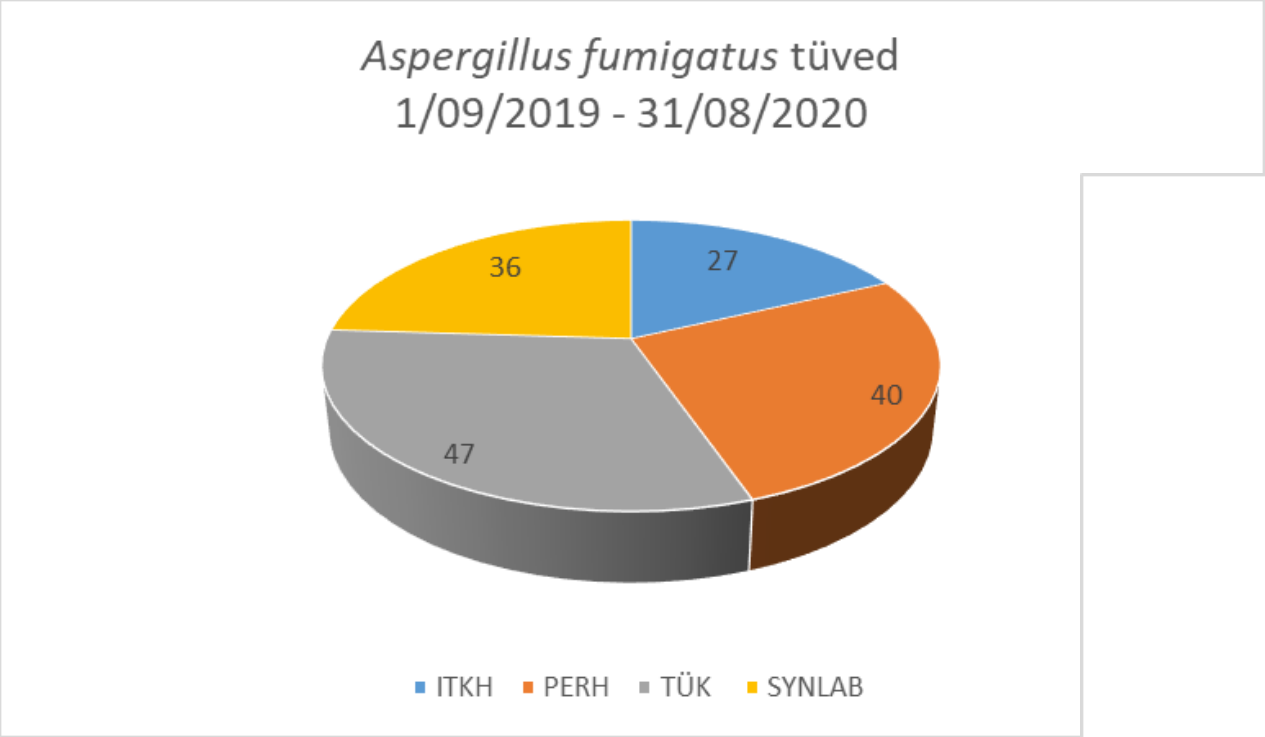
VIP Testi kontroll resistentsete tüvedega

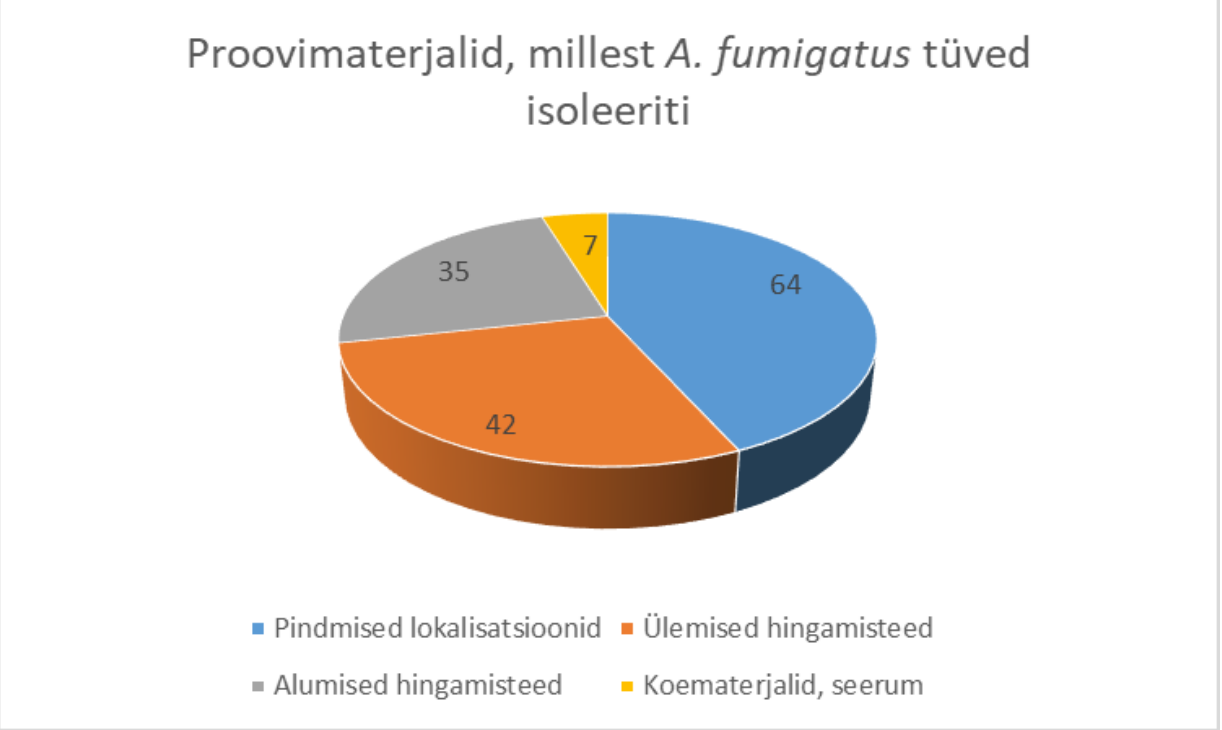
SSI 4524

SSI 5586



Aspergillus fumigatus tüved kliinilistest materjalidest





- 93 tüve meespatsientidelt vanuses 5-82 a
- 57 tüve naispatsientidelt vanuses 10-86 a

Tundlikkuse määramise tulemused

- Lõplikult testiti 149 *Aspergillus fumigatus* tüve (üks tüvi osutus *Penicillium* spp)
- Kõikile *A fumigatus* tüvedele nn temperatuuritest (kasv + 37°C) liigi kinnitamiseks
- 6 tüve osutusid esmasel skriiningul asoolidele resistentseks
- On teostatud kordustestimine
- 2 tüvel on määratud itrakonasooli, vorikonasooli ja posakonasooli MIK Radbouraud kliinikus, Hollandis – osutusid asoolidele tundlikuks
- 4 tüvest 3 resistentsed posakonasoolile ja 1 itrakonasoolile

Need tüved ootavad veel MIK määramist ja/või cyp51 geeni sekveneerimist

Enamik tüvesid on tundlikud

Olukord on hetkel kaardistatud

Edasine tegutsemine

- Peame jätkama aeg-ajalt skriining-projektidega - kui tihti???
- Uurida on vaja mitte ainult kliinilisi tüvesid, vaid ka põllumajandussaadustelt, õhust isoleeritud *Aspergillus* sp ravimtundlikkust
- Lähimad maad kus resistentsust on leitud, on Poola ja Rootsi
- Tegevus vajaks koordineerimist (ELMY, riiklikku?)

Dermatofüütide ravimtundlikkuse andmed on lisatud ECOFF väärtuste tabelisse

- European Committee on Antimicrobial Susceptibility Testing Overview of antifungal ECOFFs and clinical breakpoints for yeasts, moulds and dermatophytes using the EUCAST E.Def 7.3, E.Def 9.3 and E.Def 11.0 procedures Version 2.0, valid from 2020-09-24
- https://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/AFST/Clinical_breakpoints/EUCAST_BP_ECOFF_v2.0_20-09-24.pdf

Dermatofüütide ravimtundlikkuse määramine

Euroopas on resistentseid tüved liikvel (Saunte, D. 2019)

- Leitud Soomes
- Leitud Eestis

https://www.onygenales.org/

https://www.youtube.com/watch?v=NSliysWGaZ4&feature=youtu.be

Uus liik *Trichophyton indotineae*

Trichophyton indotineae sp. nov.: A New Highly Terbinafine-Resistant Anthropophilic Dermatophyte Species

doi.org/10.1007/s11046-020-00455-8

Peaksime suunama oma tähelepanu siia - kliiniliselt oluline!

Table 4. Summary table of current EUCAST ECOFFs for Candida species, S. cerevisiae and Cryptococcus

Table 5. Summary table of current EUCAST ECOFFs (WT ≤; mg/L, in blue) and susceptibility breakpoints (S ≤; mg/L, in black) for Aspergillus and Fusarium species.

Until, species specific clinical breakpoints are established for the rarer species, a pragmatic advice is to prefer an antifungal agent for which the ECOFF does not exceed that for the most common species in that genus. The rationale behind this advice is that the most common species within a genus is in general the most virulent one and hence, what is appropriate to treat this organism is likely also appropriate for infections caused by other species with similar susceptibility pattern in vitro from that same genus. For C. lusitaniae for example the tentative amphotericin B ECOFF is equal to that for C. albicans whereas the fluconazole ECOFF is 32 times higher suggesting that amphotericin B should be preferred.

Kokkuvõtteks

- Vaadake üle oma seente ravimtundlikkuse rutiinmeetod – korrelatsioon EUCAST metoodikaga ja BP interpreteerimine
- On võimalik saata *Aspergillus fumigatus* tüvesid Tallinnasse SYNLAB laborisse ravimtundlikkuse määramiseks – skriiningtest VIPcheck

Maksumus 31,65 EUR ja kood 66531x3

- Kas keegi tahab tegeleda dermatofüütide ravimtundlikkuse testimisega?

SYNLAB püüab *Trichophyton* sp genotüpiseerimise poole, kuid COVID-19 on meie plaane seganud