Complicanze micotiche in pazienti COVID ed EUCAST

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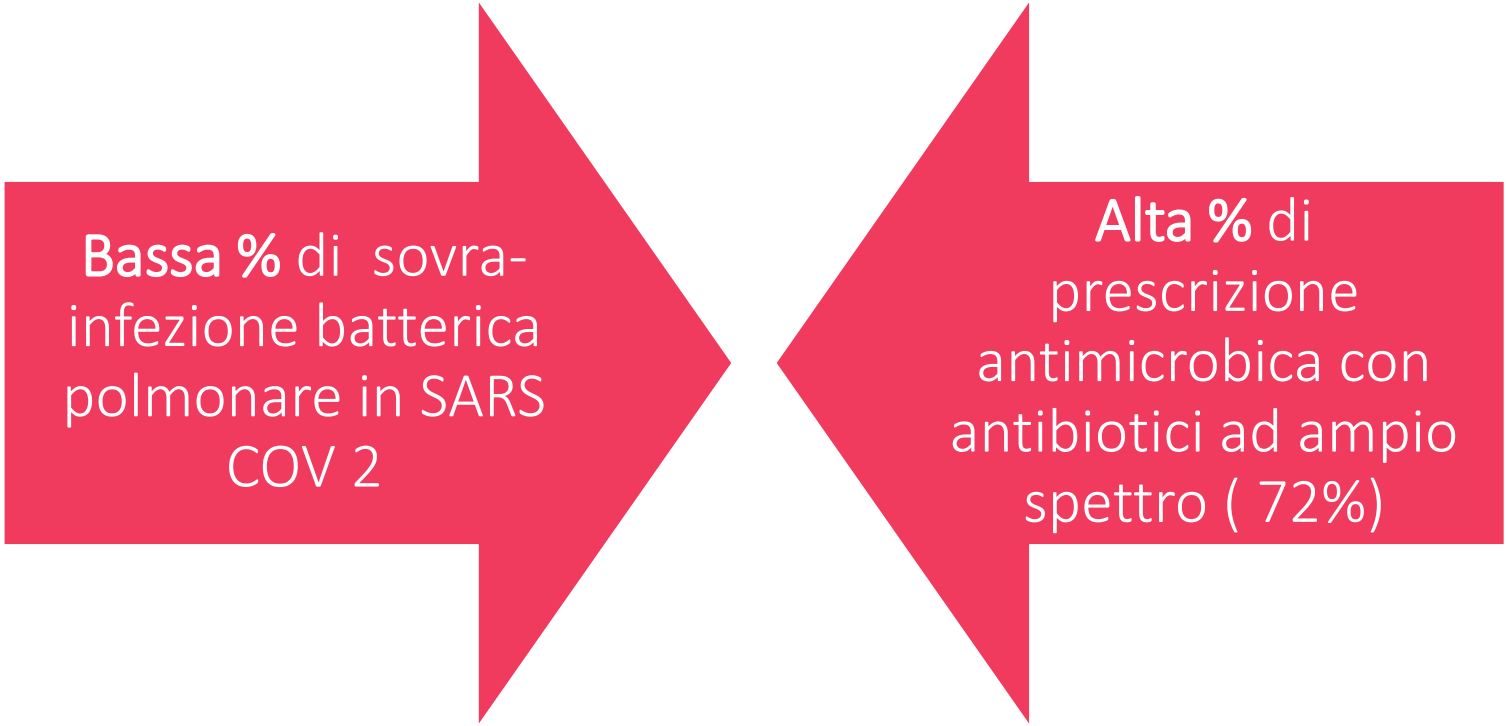
Premessa

- Una recente review relativa al ruolo della co-infezione nei pazienti con COVID-19 ha selezionato nuovi studi che riportano un 8 % di co-infezioni batteriche/fungine in generale.

- Oltre alle co-infezioni conosciute da più tempo, come ad esempio quelle da *S. pneumoniae* o *S. aureus*, recentemente è stata dimostrata l'importanza delle infezioni fungine, in particolare da *Aspergillus spp. (incidenza 5-33%)*

Per tali motivi
per aumentare la sopravvivenza dei pazienti
è essenziale mantenere

- un elevato livello di sospetto clinico
- un approccio diagnostico-terapeutico corretto e precoce


Bassa % di sovra-infezione batterica polmonare in SARS COV 2
Alta % di prescrizione antimicrobica con antibiotici ad ampio spettro (72%)

La terapia antibiotica empirica : quando?

- NO di routine

- SI se la diagnosi è incerta , il sospetto clinico di co-infezione batterica alto

Cenni di laboratorio ed indici di flogosi in COVID-19

- Basso numero totale di linfociti e piastrine all'inizio della malattia (fattori predittivi di esito avverso)
- Livelli elevati di PCR
- Aumento ferritina
- Livello normale di PROCALCITONINA
- D-dimero significativamente elevato (casi più gravi)
- Aumento IL-4, IL-6 , IL-10, TNFα , IFN γ
- Altro

- Rapido e significativamente aumento di PCR
- Valori elevati di PROCALCITONINA

Possibile infezione secondaria, batterica ma non solo !

Micosi polmonari invasive in Coronavirus 19

Non è nota l'incidenza delle micosi polmonari invasive nei pazienti con malattia da coronavirus 2019 (COVID-19). Probabilmente bassa

…… MA BISOGNA PENSARCI!!!

La disponibilita' di nuovi metodi diagnostici e di nuove molecole antifungine ha comportato nuove possibilita di diagnosi e terapia.

Aspergillosi polmonare invasiva in COVID 19

Ipotesi saggiata e confermata in diverse occasioni ma la % esatta ad oggi non è nota

Antimicogramma

Obiettivo ambizioso :

- guidare il clinico nella scelta del protocollo terapeutico più adeguato
- dare informazioni sull'identificazione di specie
- fornire allarmi circa l'insorgenza di resistenze anomale il più precocemente possibile
- fornire dati epidemiologici utili alla gestione della terapia empirica

Eucast .....Cenni storici.

EUCAST AFST **(European Committee on Antimicrobial Susceptibility Testing) :** Organismo originatosi nel 1997 con l'iniziale intento di armonizzare i breakpoints utilizzati nei diversi Paesi europei.

Istituito da ESCMID ((European Society for Clinical Microbiology and Infectious Diseases) e dai comitati nazionali esistenti in Europa che ne finanziano l'attività insieme all'Unione Europea e ad altri Organismi sovranazionali

Tabella 1. I sei comitati nazionali per i *breakpoints* già esistenti in Europa prima dell'istituzione di EUCAST.

Comitati	Paese
BSAC (British Society for Antimicrobial Chemotherapy)	Regno Unito
CA-SFM (Comité de l'Antibiogramme de la Societé Française de Microbiologie)	Francia
CRG (Commissie Richtlijnen Gevoeligheidsbepalingen)	Olanda
DIN (Deutsches Institut fur Normung)	Germania
NWGA (Norwegian Working Group on Antimicrobials)	Norvegia
SRGA (Swedish Reference Group of Antibiotics)	Svezia

In altri Paesi, e tra questi anche l'Italia, ci si è sempre affidati fino a pochi anni fa all'americano **CLSI (Clinical and Laboratory Standards Institute)**, versione recente del **NCCLS (National Committee for Clinical Laboratory Standards)**.

Tabella 3. Principali differenze tra EUCAST e CLSI.

EUCAST	CLSI
Fondato da ESCMID, ECDC e dai comitati nazionali per i *breakpoints*	Fondato dall'industria
I comitati sono rappresentativi dei comitati nazionali e delle diverse professionalità	I comitati sono costituiti da membi che provengono dalle professioni, dall'industria, dal mondo scientifico e dalle autorità di controllo
L'industria ha un ruolo di consulenza	L'industria influenza in modo sostanziale il livello decisionale
Le decisioni dei comitati sono assunte per *consensus*	Le decisioni sono assunte tramite voto a maggioranza
EUCAST è considerato ufficialmente il comitato per i *breakpoint* dell'EMEA	FDA determina i *breakpoints*
EUCAST definisce i *breakpoints* clinici e i cut-off epidemiologici	CLSI definisce i *breakpoints* clinici
EUCAST prevede una revisione sistematica dei *breakpoints*	CLSI non prevede una revisione sistematica dei *breakpoints*
EUCAST prevede 5 *meetings* annuali	CLSI prevede 2 *meetings* annuali
Tutti i documenti sui razionali e sulle decisioni clinico-sperimentali sono disponibili *online*	I documenti sui razionali e sulle decisioni clinico-sperimentali non sono disponibili
Tutta la documentazione prodotta è disponibile e gratuita	Tutta la documentazione prodotta è a pagamento

Eucast principali obiettivi:

1. Raggiungere un modo uniforme di valutare i livelli dei breakpoints clinici, e con essi il livello di sensibilità ai farmaci antimicrobici.
2. Creare un network di professionisti nel campo dell'infettivologia e dell'industria del farmaco e dei diagnostici in grado di lavorare in modo univoco
3. Promuovere la diffusione di linee guida e documenti per la standardizzazione dei metodi per l'esecuzione e l'interpretazione dei test di sensibilità, lavorando d'intesa con gli organismi al di fuori dell'Europa, come ad esempio il CLSI.

IN EUROPA

EUCAST - EMEA (European Medicines Agency)

IN AMERICA

CLSI (Clinical and Laboratory Standards Institute) - FDA (Food and Drug Administration)

Vera novità di EUCAST rispetto a CLSI

Due Breakpoint clinici (sistema SIR):

- Breakpoint della sensibilità divide i ceppi sensibili (S) da quelli intermedi (I)
- Breakpoint della resistenza divide i ceppi intermedi (I) da quelli resistenti (R)

Un Cut-off epidemiologico ECOFF (Epidemiological Cut- Off) :

- divide i ceppi *wild-type* (WT) da quelli *non-wild-type* (NWT)

ATU: area di incertezza tecnica

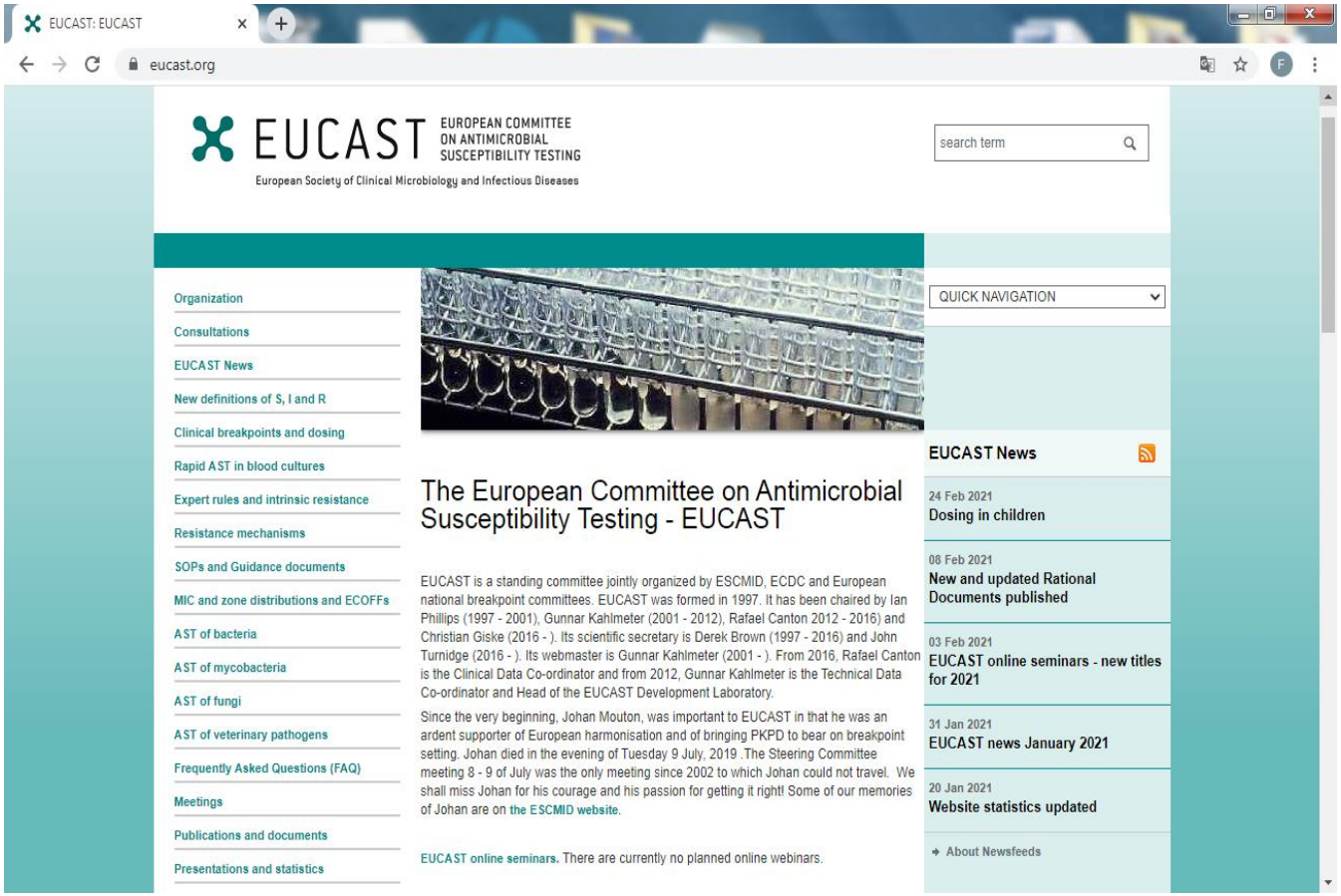
EUCAST-CLSI

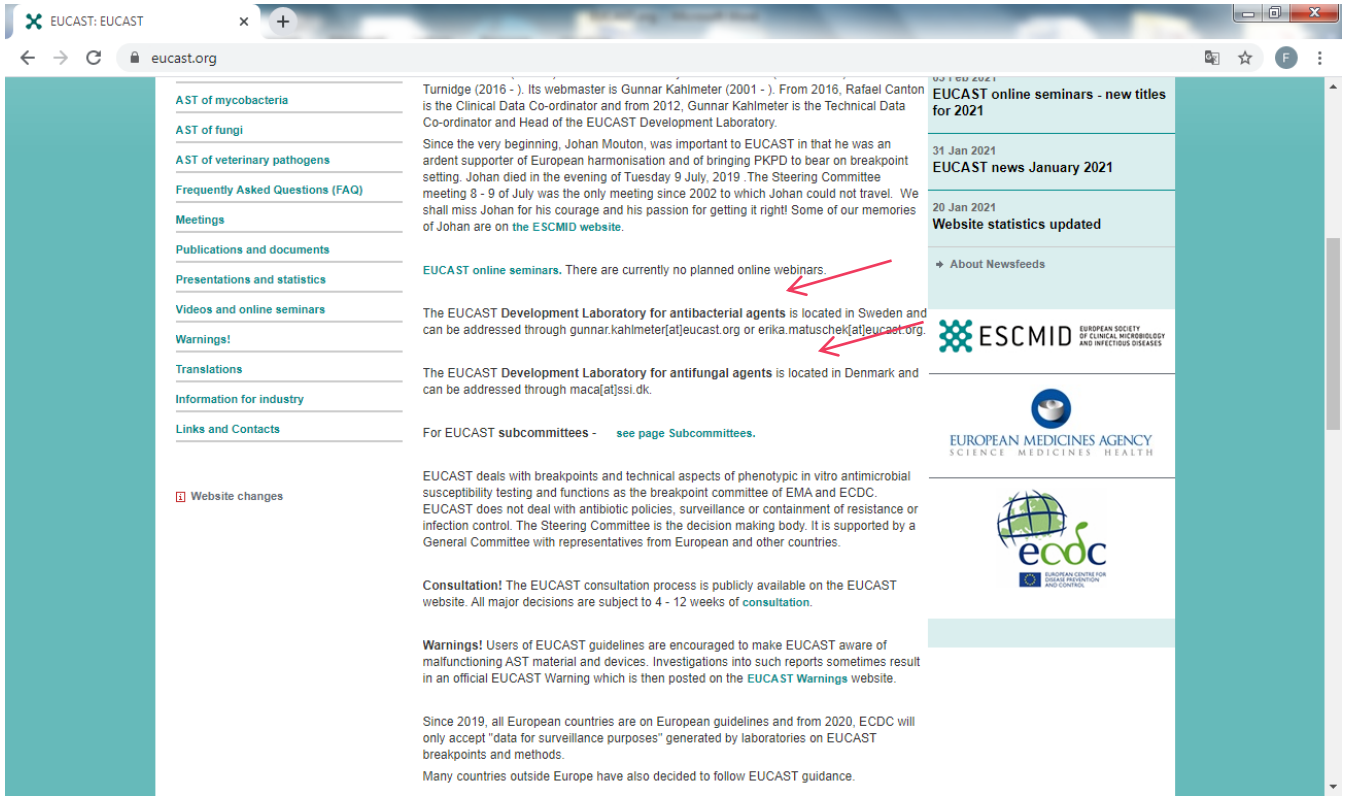
Differenze anche analitiche ed interpretative per i lieviti:

Il sottocomitato EUCAST sui test di suscettibilità antifungina ha pubblicato degli standard per determinare la suscettibilità del lievito fermentativo agli antimicrobici….

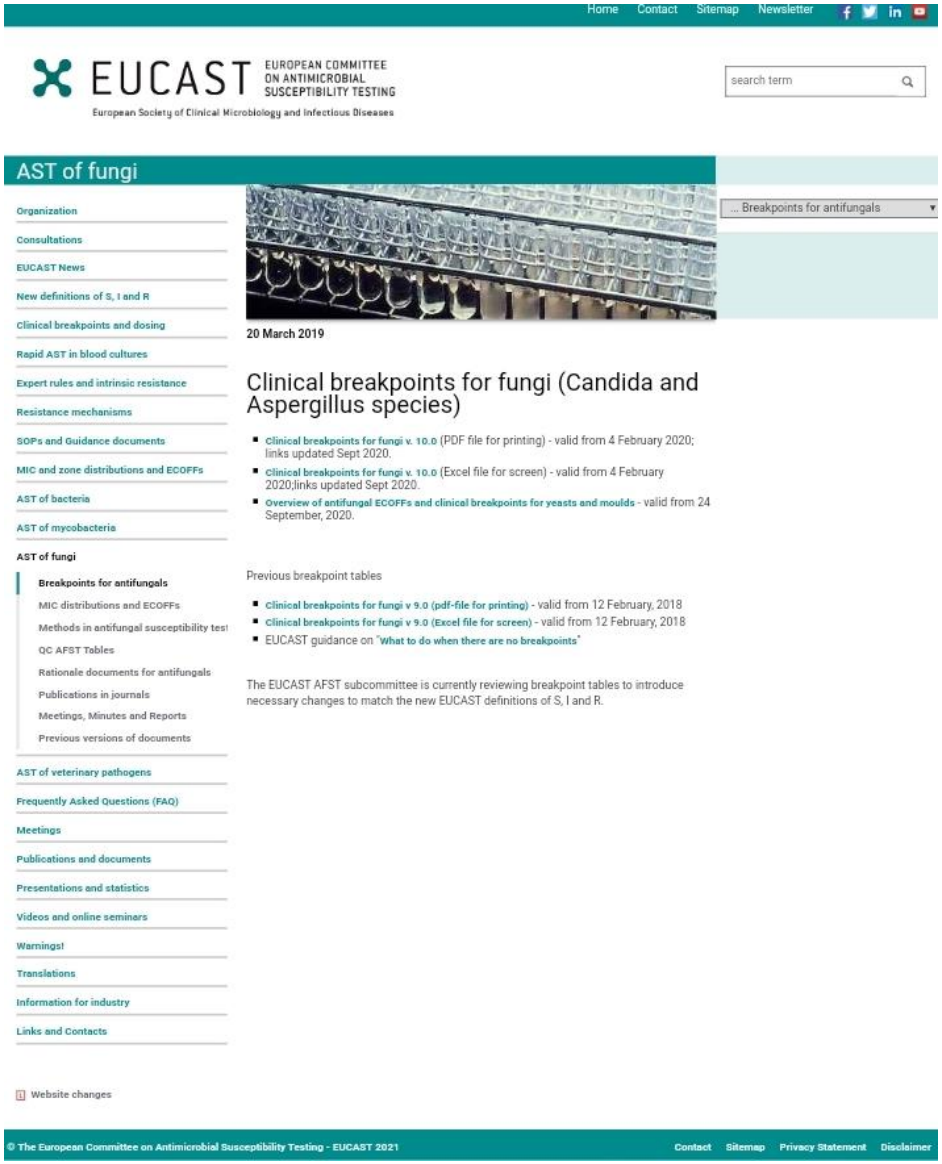
…….ma per questo chiedo lumi ai microbiologi!

www.eucast.org




EUCAST: EUCAST
eucast.org
AST of mycobacteria
AST of fungi
AST of veterinary pathogens
Frequently Asked Questions (FAQ)
Meetings
Publications and documents
Presentations and statistics
Videos and online seminars
Warnings!
Translations
Information for industry
Links and Contacts
Website changes
Turnidge (2016 -). Its webmaster is Gunnar Kahlmeter (2001 -). From 2016, Rafael Canton is the Clinical Data Co-ordinator and from 2012, Gunnar Kahlmeter is the Technical Data Co-ordinator and Head of the EUCAST Development Laboratory.
Since the very beginning, Johan Mouton, was important to EUCAST in that he was an ardent supporter of European harmonisation and of bringing PKPD to bear on breakpoint setting. Johan died in the evening of Tuesday 9 July, 2019 .The Steering Committee meeting 8 - 9 of July was the only meeting since 2002 to which Johan could not travel. We shall miss Johan for his courage and his passion for getting it right! Some of our memories of Johan are on the ESCMID website.
EUCAST online seminars. There are currently no planned online webinars.
The EUCAST Development Laboratory for antibacterial agents is located in Sweden and can be addressed through gunnar.kahlmeter[at]eucast.org or erika.matuschek[at]eucast.org.
The EUCAST Development Laboratory for antifungal agents is located in Denmark and can be addressed through maca[at]ssi.dk.
For EUCAST subcommittees - see page Subcommittees.
EUCAST deals with breakpoints and technical aspects of phenotypic in vitro antimicrobial susceptibility testing and functions as the breakpoint committee of EMA and ECDC. EUCAST does not deal with antibiotic policies, surveillance or containment of resistance or infection control. The Steering Committee is the decision making body. It is supported by a General Committee with representatives from European and other countries.
Consultation! The EUCAST consultation process is publicly available on the EUCAST website. All major decisions are subject to 4 - 12 weeks of consultation.
Warnings! Users of EUCAST guidelines are encouraged to make EUCAST aware of malfunctioning AST material and devices. Investigations into such reports sometimes result in an official EUCAST Warning which is then posted on the EUCAST Warnings website.
Since 2019, all European countries are on European guidelines and from 2020, ECDC will only accept "data for surveillance purposes" generated by laboratories on EUCAST breakpoints and methods.
Many countries outside Europe have also decided to follow EUCAST guidance.
EUCAST online seminars - new titles for 2021
31 Jan 2021
EUCAST news January 2021
20 Jan 2021
Website statistics updated
About Newsfeeds
ESCMID
EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH
ecdc

European Committee on Antimicrobial Susceptibility Testing
Breakpoint tables for interpretation of MICs for antifungal agents
Version 10.0, valid from 2020-02-04



EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING
European Society of Clinical Microbiology and Infectious Diseases

European Committee on Antimicrobial Susceptibility Testing

Breakpoint tables for interpretation of MICs for antifungal agents

Version 10.0, valid from 2020-02-04

This document should be cited as: "The European Committee on Antimicrobial Susceptibility Testing. Breakpoint tables for interpretation of MICs for antifungal agents, version 10.0, 2020. http://www.eucast.org/astoffungi/clinicalbreakpointsforantifungals/.

European Committee on Antimicrobial Susceptibility Testing

Breakpoint tables for interpretation of MICs for antifungal agents

Version 10.0, valid from 2020-02-04

Notes

1. The EUCAST tables of clinical breakpoints for antifungal agents contain clinical MIC breakpoints determined over the period **2007-2019**. The EUCAST breakpoint table version **10.0** includes corrected typographical errors, clarifications, breakpoints for new agents and/or organisms, and revised MIC breakpoints. Changes are best seen on screen or on a colour printout since cells containing a change are yellow.

2. Numbered footnotes relating to MIC breakpoints are listed in a column on the right of the spreadsheet or below the table.

3. Antifungal agents names in blue link to EUCAST rationale documents. MIC breakpoints in blue link to EUCAST MIC distributions.

4. The document is released as a protected Excel® file suitable for viewing on screen and as an Acrobat® pdf file for printing. To utilise all functions in the Excel® file, use Microsoft™ original programs only. The Excel® file enables users to alter the list of agents to suit the local range of agents tested locally. The content of single cells cannot be changed. Hide lines by right-clicking on the line number and choosing "hide". Hide columns by right-clicking on the column letter and choosing "hide". If you wish to add the intermediate columns for MICs right-click on the column letter and choose "insert". The intermediate values are inferred from the "S" and "R" breakpoints when not specified in the table.

5. EUCAST breakpoints are used to categorise results into three susceptibility categories:
S - Susceptible, standard dosing regimen: A microorganism is categorised as *Susceptible, standard dosing regimen,* when there is a high likelihood of therapeutic success using a standard dosing regimen of the agent.
I - Susceptible, increased exposure: A microorganism is categorised as *Susceptible, increased exposure** when 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.
R - Resistant: A microorganism is categorised as *Resistant* when there is a high likelihood of therapeutic failure even when there is increased exposure.
*Exposure is a function of how the mode of administration, dose, dosing interval, infusion time, as well as distribution and excretion of the antimicrobial agent will influence the infecting organism at the site of infection.

6. For some organism-agent combinations, results may be in an area where the interpretation is uncertain. EUCAST has designated this an Area of Technical Uncertainty (ATU). It corresponds to an MIC value where the categorisation is doubtful. See separate page (Technical uncertainty) for more information on ATU and how to deal with results in the ATU.

7. In order to simplify the EUCAST tables, the I category is not listed. It is readily interpreted as the values between the S and the R breakpoint. For example, for MIC breakpoints listed as S ≤ 1 mg/L and R > 8 mg/L, the I category is 2-8 (technically >1-8) mg/L.

Notes

8. By international convention MIC dilution series are based on twofold dilutions up and down from 1 mg/L. At dilutions below 0.25 mg/L, this leads to concentrations with multiple decimal places. To avoid having to use these in tables and documents, EUCAST has decided to use the following format (in bold): 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.

"-" indicates that susceptibility testing is not recommended as the species is a poor target for therapy with the drug. Isolates may be reported as R without prior testing.
"IE" indicates that there is insufficient evidence that the species in question is a good target for therapy with the drug. An MIC with a comment but without an accompanying S, I or R categorisation may be reported.
NA = Not Applicable
IP = In Preparation

Guidance on reading EUCAST Antifungal Breakpoint Tables

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

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

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

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~~

In Preparation

MIC breakpoints in blue are linked to MIC distributions

Not Applicable

Antifungal agents in blue are linked to EUCAST rationale documents

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

European Committee on Antimicrobial Susceptibility Testing

Breakpoint tables for interpretation of MICs for antifungal agents

Version 10.0, valid from 2020-02-04

How to handle technical uncertainty in antimicrobial susceptibility testing

All measurements are affected by random variation and some by systematic variation. Systematic variation should be avoided and random variation reduced as much as possible. Antimicrobial susceptibility testing (AST), irrespective of method, is no exception.

EUCAST strives to minimise variation by providing standardised methods for MIC determination and disk diffusion and by avoiding setting breakpoints which seriously affect the reproducibility of the test. Variation in AST can be further reduced by setting more stringent standards for manufacturers of AST material (growth medium and antifungals) and criteria for quality control of manufacturing processes and laboratory practices.

It is tempting to think that generating an MIC value will solve all problems. However, MIC measurements also have variation and a single value is not automatically correct. Even when using the reference method, MICs vary between days and technicians. Under the best of circumstances, an MIC of 1.0 should be considered as a value between 0.5 and 2.0 mg/L. Not infrequently, there are problems with commercial testing systems including broth microdilution tests, gradient tests and semi-automated AST devices.

Although AST in principle is straightforward for most agents and species, there are problematic areas. It is important to warn laboratories about these and the uncertainty of susceptibility categorisation. Analysis of EUCAST data that have been generated over the years has identified such situations, called **Areas of Technical Uncertainty (ATU)**. The ATUs are **warnings to laboratory staff** that there is an uncertainty that needs to be addressed before reporting AST results to clinical colleagues. The ATU is not to be conveyed to clinical colleagues except under special circumstances and only as part of a discussion about therapeutic alternatives in difficult cases.

Below are alternatives for how the ATUs can be dealt with by the laboratory. Which of these actions are chosen will depend on the situation. The type of sample (f.x. blood culture vs. mucosal culture), the number of alternative agents available, the severity of the disease, whether or not a consultation with clinical colleagues is feasible, will influence the action taken.

- **Repeat the test**

  This is only relevant if there is reason to suspect a technical error in the primary AST.

- **Use an alternative test (perform a genotypic test)**

  This may be relevant if the susceptibility report leaves only few therapeutic alternatives or if the result is deemed of importance. If the organism is multi-resistant, it is advisable to perform a genotypic characterization of the resistance mechanism to obtain more information (examples: *FKS* gene sequencing in *Candida* and *CYP51A* gene sequencing in *A. fumigatus*).

- **Downgrade the susceptibility category**

  If there are other therapeutic alternatives in the AST report, it is permissible to downgrade the result (from S to I, or from I to R or from S to R). However, a comment should be included and the isolate saved for further testing.

- **Upgrade the susceptibility category**

  If there are substantial evidence that the isolate will be clinically susceptible (for example in isolates with a one-step MIC elevation above the susceptibility breakpoint AND absence of FKS mutations in a *Candida* isolate with susceptible phenotype to alternative candins, or an *A. fumigatus* isolate with an MIC of 0.25 mg/L for posaconazole but susceptible to itraconazole) it is permissible to upgrade the result (from R to S, or from I to S). However, a comment should be included and the isolate saved for further testing. Such a comment could be: "based upon clinical experience the isolate will be clinically susceptible to drug x despite the one-step elevated MIC".

- **Include the uncertainty as part of the report**

  It is common practice in many other laboratory settings to include information on the uncertainty of the reported result. This can be dealt with in several alternative ways:

  * For serious situations, take the opportunity to contact the clinical colleagues to explain and discuss the results.

* Categorise the result according to the breakpoints but include information about the technical difficulties and/or the uncertainty of the interpretation. In many instances, a straight "R" is less ambiguous than other alternatives, especially when there are alternative agents.

The Area of Technical Uncertainty will typically be listed as a defined MIC value. ATUs will only be listed when obviously needed. The absence of an ATU (MIC) means that there is no immediate need for a warning. The ATUs introduced in 2019 (v. 10.0) will be evaluated and ATUs may be added as more information develops.

Link to the guidance material available on the EUCAST website.

Candida and *Cryptococcus* spp.

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

MIC method (EUCAST standardised broth microdilution method)
Medium: RPMI1640-2% glucose, MOPS buffer
Inoculum: Final $0.5x10^5$ – $2.5x10^5$ cfu/mL
Incubation: 18-24h
Reading: Spectrophotometric, complete (>90%) inhibition for amphotericin B but 50% growth inhibition for other compounds
Quality control: *C. parapsilosis* ATCC 22019 or *C. krusei* ATCC 6258

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	

Aspergillus spp.

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

MIC method (EUCAST standardised broth microdilution method)
Medium: RPMI1640-2% glucose, MOPS as buffer
Inoculum: Final 1x10(5) – 2.5x10(5) cfu/mL
Incubation: 48h
Reading: Visual, complete inhibition for amphotericin B and azoles (MIC), aberrant growth endpoint for echinocandins (MEC).
Quality control: *A. fumigatus* ATCC 204305, *A. flavus* ATCC 204304, *A. fumigatus* F 6919, *A. flavus* CM 1813, *C. parapsilosis* ATCC 22019 (read after 18-24 h) or *C. krusei* ATCC 6258 (read after 18-24 h).

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".
Micafungin	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".

Dosages

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*)
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)

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