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IEQAS Annual Participants Conference 2021

Revised EUCAST guidelines- the SVUH perspective

Orla Donoghue

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Overview

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- What/who are Eucast?
- What changed in 2020?
- How did we approach the changes?
- Problems encountered?
- Challenges remaining?

Introduction

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- EUCAST: European body responsible for
  - developing and standardising AST testing methods
  - setting, reviewing and revising clinical breakpoints

Traditional definitions of S and R

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- S: a level of antimicrobial activity associated with a high likelihood of therapeutic success
- R: a level of antimicrobial activity associated with a high likelihood of therapeutic failure

Traditional definition of I

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- I: a level of antimicrobial agent activity associated with uncertain therapeutic effect
  - use in body sites where drugs are concentrated
  - or when a high dose can be used
  - also indicates a buffer zone that should prevent small, uncontrolled, technical factors from causing major discrepancies in interpretations

Consultation process 2015-2019

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- EUCAST proposed changing definition of I
- Concept of area of technical uncertainty (ATU) introduced- warning to lab staff about a technical issue that needs to be resolved before reporting
- Footnotes added to some drug/bug combinations re higher exposure

New definition of I

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- I: Susceptible, Increased Exposure
  - 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
  - Change emphasises relationship between concentration at site of infection and breakpoints

2020 changes

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- EUCAST not advising on dose but doses listed are the minimum required for breakpoint to be valid
- All breakpoints evaluated to decide why an I category existed- Dose dependent or technical uncertainty?

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- Is the result I due to being intrinsically less susceptible e.g. *Pseudomonas* and Ciprofloxacin- only I and R categories possible

OR

- Do low level resistance mechanisms exist e.g. *S. pneumoniae* and Penicillin- S, I and R categories are possible

Expert Rules and Intrinsic Resistance Tables

An MIC breakpoint of S ≤ 0.001 mg/L is an arbitrary, "off scale" breakpoint (corresponding to a zone diameter breakpoint of "S ≥ 50 mm") which categorises wild-type organisms (organisms without phenotypically detectable resistance mechanisms to the agent) as "Susceptible, increased exposure" (I). For these organism-agent combinations, never report "Susceptible, standard dosing regimen" (S).

MIC determination (broth microdilution according to ISO standard 20776-1 except for mecillinam and fosfomycin where agar dilution is used)
Medium: Mueller-Hinton broth (for cefiderocol, see http://www.eucast.org/guidance_documents/)
Inoculum: $5x10^5$ CFU/mL
Incubation: Sealed panels, air, 35±1ºC, 18±2h
Reading: Unless otherwise stated, read MICs at the lowest concentration of the agent that completely inhibits visible growth.
Quality control: *Escherichia coli* ATCC 25922. For agents not covered by this strain and for control of the inhibitor component of beta-lactam inhibitor combinations, see EUCAST QC Tables.

Disk diffusion (EUCAST standardised disk diffusion method)
Medium: Mueller-Hinton agar
Inoculum: McFarland 0.5
Incubation: Air, 35±1ºC, 18±2h
Reading: Unless otherwise stated, read zone edges as the point showing no growth viewed from the back of the plate against a dark background illuminated with reflected light.
Quality control: *Escherichia coli* ATCC 25922. For agents not covered by this strain and for control of the inhibitor component of beta-lactam inhibitor-combination disks, see EUCAST QC Tables.

*** Recent taxonomic studies have narrowed the definition of the family Enterobacteriaceae. Some previous members of this family are now included in other families within the Order *Enterobacterales*. Breakpoints in this table apply to all members of the *Enterobacterales*.**

Penicillins[1]	MIC breakpoints (mg/L)			Disk content (µg)	Zone diameter breakpoints (mm)		
	S ≤	R >	ATU		S ≥	R <	ATU
Benzylpenicillin	-	-			-	-	
Ampicillin[1]	8	8		10	14[A]	14[A]	
Ampicillin-sulbactam[1]	8[2]	8[2]		10-10	14[A]	14[A]	
Amoxicillin[1]	8	8		-	Note[B]	Note[B]	
Amoxicillin-clavulanic acid[1]	8[2]	8[2]		20-10	19[A]	19[A]	19-20
Amoxicillin-clavulanic acid (uncomplicated UTI only)	32[3]	32[3]		20-10	16[A]	16[A]	
Piperacillin	8	8		30	20	20	
Piperacillin-tazobactam	8[4]	8[4]	16	30-6	20	20	19
Ticarcillin	8	16		75	23	20	
Ticarcillin-clavulanic acid	8[3]	16[3]		75-10	23	20	
Temocillin (infections originating from the urinary tract), *E. coli*, *Klebsiella* spp. (except *K. aerogenes*) and *P. mirabilis*	0.001	16		30	50[C]	17[C]	
Phenoxymethylpenicillin	-	-			-	-	
Oxacillin	-	-			-	-	
Cloxacillin	-	-			-	-	
Dicloxacillin	-	-			-	-	
Flucloxacillin	-	-			-	-	
Mecillinam oral (pivmecillinam) (uncomplicated UTI only), *E. coli*, *Citrobacter* spp., *Klebsiella* spp., *Raoultella* spp., *Enterobacter* spp. and *P. mirabilis*	8[5]	8[5]		10	15[C]	15[C]	

Notes
Numbered notes relate to general comments and/or MIC breakpoints.
Lettered notes relate to the disk diffusion method.

1. Aminopenicillin breakpoints in *Enterobacterales* are based on intravenous administration. For oral administration the breakpoints are relevant for urinary tract infections only. Breakpoints for other infections are under review.
2. For susceptibility testing purposes, the concentration of sulbactam is fixed at 4 mg/L.
3. For susceptibility testing purposes, the concentration of clavulanic acid is fixed at 2 mg/L.
4. For susceptibility testing purposes, the concentration of tazobactam is fixed at 4 mg/L.
~~**5/C. Breakpoints still under consideration.**~~
5. Agar dilution is the reference method for mecillinam MIC determination.

A. Ignore growth that may appear as a thin inner zone on some batches of Mueller-Hinton agars.
B. Susceptibility inferred from ampicillin.
C. Ignore isolated colonies within the inhibition zone.

Implementing 2020 breakpoints

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- Lab: Compile a list of drug/bug combinations affected
- Assess if it is simple breakpoint change or a removal of S category
- Does the change apply to MIC or zone size?
- Review Vitek cards- are the new breakpoints detected by current cards?

Table showing EUCAST 2020 and 2021 changes to Enterobacterales affecting SVUH

Species	Drug	Change	MIC (mg/L)	Disc (mm)	Notes
Enterobacterales	Temocillin	New breakpoint- No S category	<=0.001 S >16 R		
	Cefuroxime IV	No S category			
	Fosphomycin oral	New breakpoint	<=8 S >8 R (IV: 32)		**FOSIV** code created
	Pipercillin-tazobactam	Breakpoint changed	<=8 S >8 R (was >16)	>=20 S <20R	
	Amikacin	Breakpoint changed & comment	<=8 S >8 R (was >16)	>=18 S <18R (was >=18 <15 R)	
	Gentamicin	Breakpoint changed & comment	<=2 S >2 R (was >4)	>=17 S <17 R (was >=17 <14 R)	
	Tobramycin	Breakpoint changed & comment	<=2 S >2 R (was >4)	>=16 S <16 R (was >=17 <14 R)	
	Trimethoprim	Breakpoint changed	<=4 S >4R (was <=2 >4)	>=15 S <15 R (was >=18 <15 R)	
	Augmentin	ATU		19-20 (R/S)	Report <20 as R
	Ciprofloxacin	ATU	0.5 (I)	22-24 (I)	Perform disc to confirm I if MIC=0.5 on Vitek

Review dosages

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- Consultant Microbiologists: Compile list of dosages recommended by EUCAST and compare with current
- Are many of these drug / bug combinations routinely reported?

Table showing suggested dosages for commonly used antibiotics in SVUH

Organism(s)	**Antibiotic**	**Dose suggested** (as per EUCAST "Dosages" table in the clinical breakpoints document)	**Other antibiotics** for which "Susceptible, increased exposure" applies for this organism, but generally not used	**Notes**
Enterobacterales	Cefuroxime	1.5 g 8^{o}	Cefazolin, imipenem	
	Imipenem*	1 g 6^{o} (over 30 min)		**Morganella morganii*, *Proteus* spp. and *Providencia* spp.
Pseudomonas spp.	Piperacillin-tazobactam	4.5 g 6^{o}	Piperacillin ticarcillin, ticarcillin-clavulanic acid, cefepime imipenem	
	Ceftazidime	2 g 8^{o}or 1 g 4 ^{o}		
	Imipenem	1 g 6^{o} (over 30 min)		
	Aztreonam	2 g 6^{o}		
	Ciprofloxacin	400 mg 8^{o}		
	Levofloxacin	500 mg 12^{o}		
Stenotrophomonas maltophilia	trimethoprim-sulfamethoxazole	1440mg 12^{o}		

Implementation

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- Amend Vitek breakpoints- awaiting validation from Biomerieux
  - New fosphomycin oral breakpoints not possible with current card
- Educate lab staff on new zone sizes esp. that S >50 essentially means always I
- Remove gentamicin from Pseudomonas ring/ remove breakpoints from Vitek

How to communicate the new definition?

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- Keep S,I,R in APEX- introduce new comment to be added if releasing I result
- "I= Susceptible IF there is increased exposure to the antimicrobial agent by adjusting the dosing regimen"

123456 DUMMY, ANNE F 01/01/1901 MICRO

Pathology Reports MICROBIOLOGY

STUDY: *I* 30/09/2021 13:56 WS

66017 50160

Specimen Number : MW011545D 30/09/2021 13:56 WOUND SWAB

CULTURE Resulted

Pseudomonas aeruginosa isolated

Amikacin s Ceftazidime i

Ciprofloxacin i Meropenem s

General Wound

LTG Comments :

Antimicrobial susceptibility results interpretation:
S= susceptible, R= resistant.
I= susceptible IF there is increased exposure to the
antimicrobial agent by adjusting the dosing regimen.

Feedback from users

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- Few queries from in house staff- many unaware of change and/or may be avoiding use if I (as per previous definition?)
- Many calls from GP's re *Pseudomonas* in particular
- Less *Haemophilus* seen than usual due to pandemic

Outstanding issues?

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- Healthlink- APEX sends an interpretation with results, I still defined as Intermediate
- Addition of comment re I not automatic- prone to human error
- Fosphomycin disc testing until Vitek card can be reformulated?

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- Gentamicin/ *Pseudomonas*: although no standalone breakpoint it can still be used in combination. Report as a comment?
- Greater education of both in house and GP's on what the new definition means and appropriate dosages?

Conclusions

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- At first look changes appeared daunting
- Broken down not all changes affected us
- Medical team already used to adding comments when releasing sensitivities- were receptive to extra comment
- What surprises will 2022 breakpoints bring?!

Resources

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- www.eucast.org:

  new definitions of S, I and R tab:
  - 3 page guide for clinical colleagues
  - explanatory video
  - previous online seminars

Thanks for listening!

Any questions?