Practical consequences of the new I category of EUCAST on epidemiological surveillance and on changes in dosing of antimicrobial agents: experience at one university hospital

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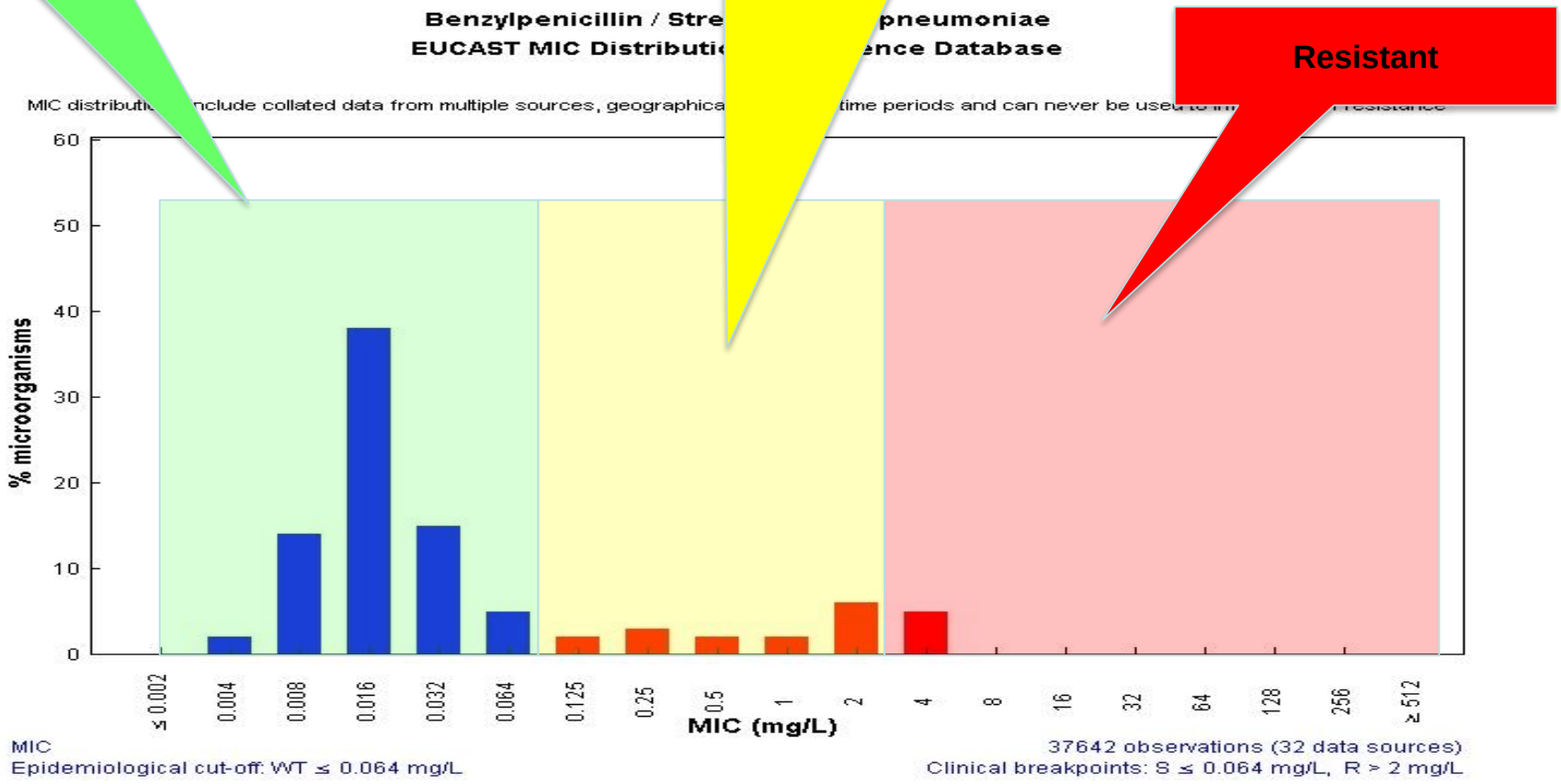
SIR – the old definitions

Susceptible

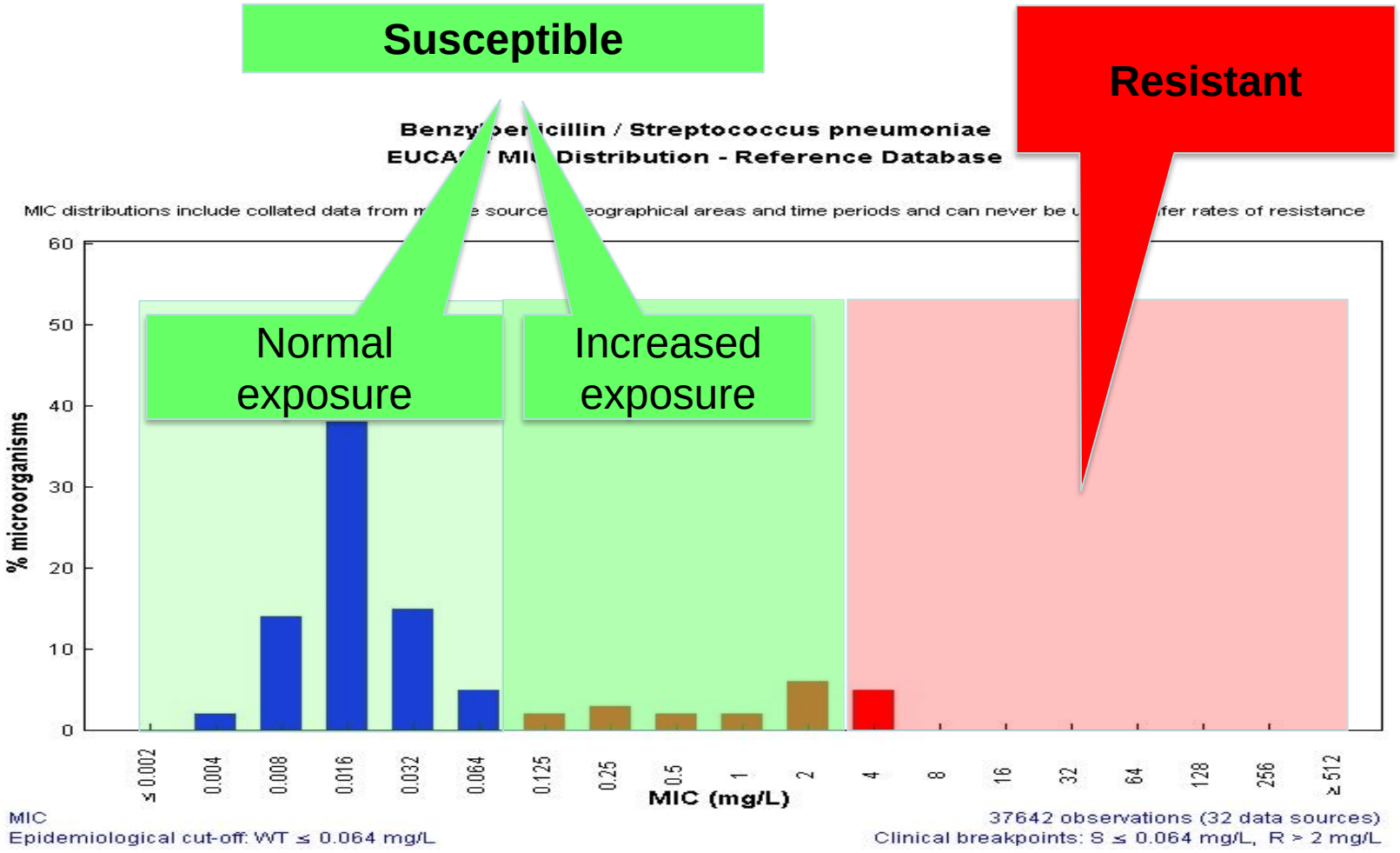
Intermediate
Uncertain effect.
Buffer zone for technical variation.
For a high dose.
Where concentrated for pharmacokinetic reasons.

Resistant

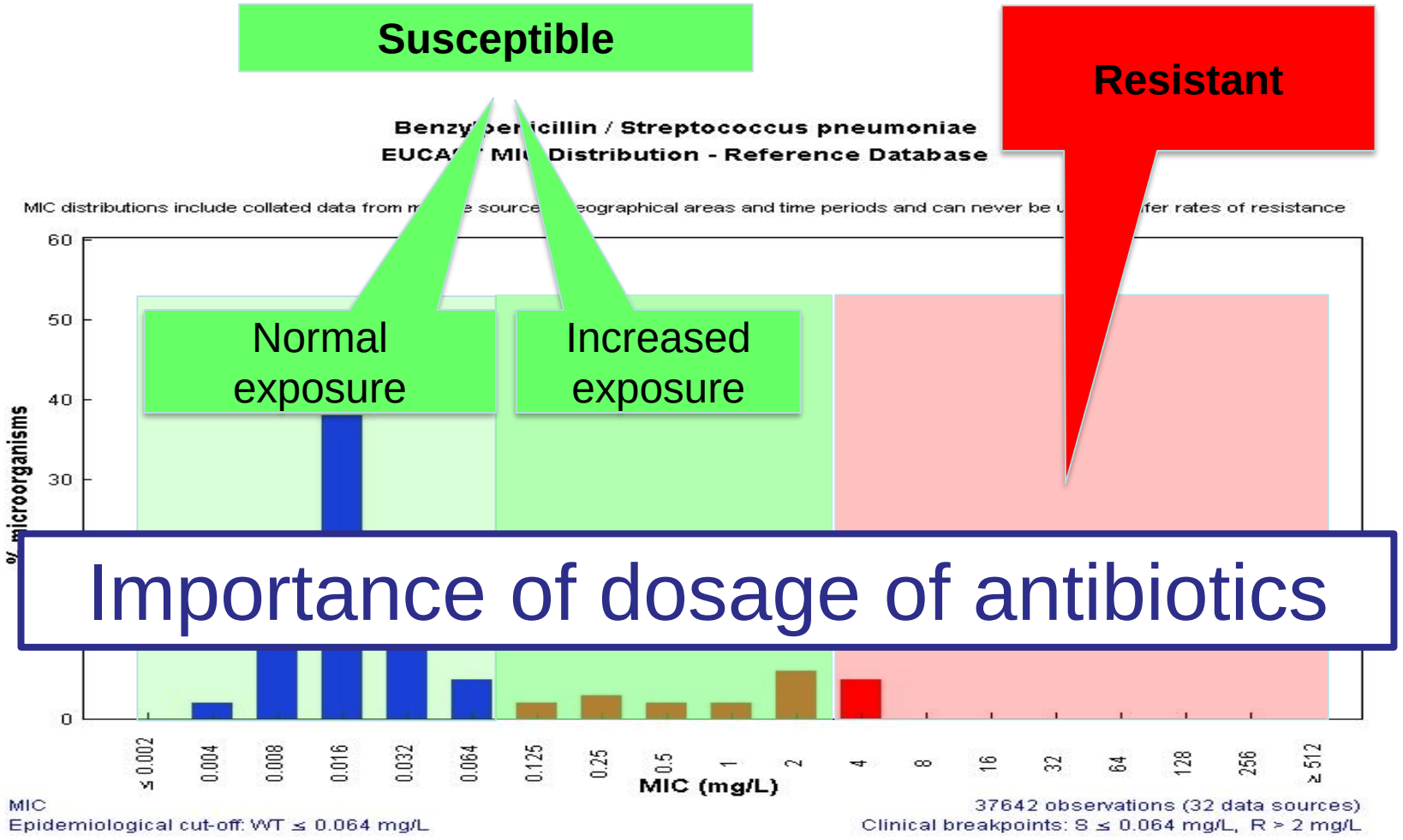
4 definitions in one definition



SIR - new definitions 2019



SIR - new definitions 2019



EUCAST breakpoints are based on dose and mode of administration as indicated in rationale documents and breakpoint table

Dosages **EUCAST Clinical Breakpoint Tables v. 11.0, valid from 2021-01-01**

EUCAST breakpoints are based on the following dosages (see section 8 in Rationale Documents). Alternative dosing regimens may result in equivalent exposure. The table should not be considered a guidance for dosing in clinical practice, and does not replace specific local, national, or regional dosing guidelines. However, if national practices significantly differ from those listed below, EUCAST breakpoints may not be valid. Situations where less antibiotic is given as standard or high dose should be discussed locally or regionally.

Uncomplicated UTI: acute, sporadic or recurrent lower urinary tract infections (uncomplicated cystitis) in patients with no known relevant anatomical or functional abnormalities within the urinary tract or comorbidities.

Penicillins	Standard dosage	High dosage	Uncomplicated UTI	Special situations
Benzylpenicillin	0.6 g (1 MU) x 4 iv	1.2 g (2 MU) x 4-6 iv		**Meningitis caused by *S. pneumoniae:*** For a dose of 2.4 g (4 MU) x 6 iv, isolates with MIC≤0.06 mg/L are susceptible. **Pneumonia caused by *S. pneumoniae:* breakpoints are related to dosage:** For a dose of 1.2 g (2 MU) x 4 iv, isolates with MIC ≤0.5 mg/L are susceptible. For a dose of 2.4 (4 MU) g x 4 iv or 1.2 g (2 MU) x 6 iv, isolates with MIC ≤1 mg/L are susceptible. For a dose of 2.4 g (4 MU) x 6 iv, isolates with MIC ≤2 mg/L are susceptible.
Ampicillin	2 g x 3 iv	2 g x 4 iv		**Meningitis:** 2 g x 6 iv
Ampicillin-sulbactam	(2 g ampicillin + 1 g sulbactam) x 3 iv	(2 g ampicillin + 1 g sulbactam) x 4 iv		
Amoxicillin iv	1 g x 3-4 iv	2 g x 6 iv		**Meningitis:** 2 g x 6 iv
Amoxicillin oral	0.5 g x 3 oral	0.75-1 g x 3 oral	0.5 g x 3 oral	
Amoxicillin-clavulanic acid iv	(1 g amoxicillin + 0.2 g clavulanic acid) x 3-4 iv	(2 g amoxicillin + 0.2 g clavulanic acid) x 3 iv		
Amoxicillin-clavulanic acid oral	(0.5 g amoxicillin + 0.125 g clavulanic acid) x 3 oral	0.875 g amoxicillin + 0.125 g clavulanic acid) x 3 oral	(0.5 g amoxicillin + 0.125 g clavulanic acid) x 3 oral	Amoxicillin-clavulanic acid has separate breakpoints for systemic infections and uncomplicated UTI. When amoxicillin-clavulanic acid is reported for uncomplicated UTI, the report must make clear that the susceptibility category is only valid for uncomplicated UTI.

Dosages

?

EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING

European Society of Clinical Microbiology and Infectious Diseases

- Targeted therapy
  - sometimes depending on
    - indication
      (e.g. meningitis/non-meningitis: 3th generation cephalosporins)
    - micro-organism
      (e.g. *P. aeruginosa*: meropenem)
- Empirical therapy
  - Standard dose
  - Alternative dose
    - Depending on indication

- Standard dosage
- High dosage

- Uncomplicated UTI
- Special situations

UZL doses versus EUCAST doses

SD (standard dose) and HD (high dose)

For **90%** of the antibiotics

UZL SD en HD = EUCAST doses

UZL SD = HD EUCAST

UZL SD > EUCAST SD

→ No problem to use clinical breakpoints

UZL doses versus EUCAST doses

SD (standard dose) and HD (high dose)

- UZL SD = HD EUCAST (+/- 20% of antibiotics)

Antibiotic	EUCAST SD	UZL SD	IGGI SD
Amoxicillin PO	500 mg q8h	1g q8h	500 mg q6-8h
Amoxicillin-clavulanic acid po 875 mg	500 mg q8h	875 mg q8h	500-875 q8h
Cefuroxime iv	750 mg q8h	1500 mg q8h	1500 mg q8h
Cefotaxime iv	1 g q8h	2 g q8h	2 g q8h
Ceftazidime iv	1 g q8h	2 g q8h	2 g q8h
Cefepime iv	1 g q8h	2 g q8h	2 g q8h
Clarithromycin iv=po	250 mg q12h	500 mg q12h	500 mg q12h
Metronidazole po=iv	400 mg q8h	500 mg q8h	500 mg q8h
Erythromycin po=iv	500 mg q8-12h	1g q6h	500 mg q6h
Fosfomycin iv	4g q8h	8g q8h	-
Imipenem iv	500 mg q6h	1g q6h	-

Only one dosage in UZL dosing table = HD EUCAST

For S and I reported micro-organisms → same (high) dose

UZL doses versus EUCAST doses

SD (standard dose) and HD (high dose)

For **90%** of the antibiotics

UZL SD en HD = EUCAST doses

UZL SD = HD EUCAST

UZL SD > EUCAST SD

→ No problem to use clinical breakpoints

For **other** antibiotics

UZL SD or HD < EUCAST doses

→ check of differences

UZL doses versus EUCAST doses

- UZL doses < EUCAST doses

Antibiotic	EUCAST SD	UZL SD	EUCAST HD	UZL HD
amikacin iv	25-30 mg/kg q24h	**15 mg/kg q24h** (non-septic) 25 mg/kg q24h (septic)	-	-
tobramycin iv	7 mg/kg q24h	**5 mg/kg q24h**	-	-
flucloxacillin po	1g q8h	**500 mg q6h**	1g q6h	-
piperacillin-tazobactam iv	4g q6h	4g q6h	4g q6h by extended 3-hour infusion	-
temocillin iv	2g q12h	2g q12h	2g q8h	-

→ Discussion in antibiotic management team

Change piperacillin-tazobactam breakpoints and dosage

The European Committee on Antimicrobial Susceptibility Testing. Breakpoint tables for interpretation of MICs and zone diameters. Version 11.0, 2021. http://www.eucast.org.

Penicillins	Standard dose	High dose	Uncomplicated UTI	Special situations
Piperacillin-tazobactam	(4 g piperacillin + 0.5 g tazobactam) x 3 iv	(4 g piperacillin + 0.5 g tazobactam) x 4 iv		~~*Pseudomonas* spp.: High dose only~~

2021

Piperacillin-tazobactam	(4 g piperacillin + 0.5 g tazobactam) x 4 iv or x 3 by extended 4-hour infusion	(4 g piperacillin + 0.5 g tazobactam) x 4 iv by extended 3-hour infusion		A lower dosage of (4 g piperacillin + 0.5 g tazobactam) x 3 iv is adequate for some infections such as complicated UTI, intraabdominal infections and diabetic foot infections, but not for infections caused by isolates resistant to third-generation cephalosporins.

Enterobacterales | **Pseudomonas species**

Penicillins[1]	MIC breakpoints (mg/L)			Disk content (µg)	Zone diameter breakpoints (mm)			MIC breakpoints (mg/L)			Disk content (µg)	Zone diameter breakpoints (mm)		
	S ≤	R >	ATU		S ≥	R <	ATU	S ≤	R >	ATU		S ≥	R <	ATU
Piperacillin-tazobactam	8[4]	16[4]	16	30-6	20	17	17-19	16[1]	16[1]		30-6	18	18	18-19
	2021								2021					
Piperacillin-tazobactam	8[4]	8[4]	16	30-6	20	20	19	0.001[1]	16[1]		30-6	50	18	18-19

UZL dose piperacillin-tazobactam: 4*4g
For Enterobacterales: no change
For *Pseudomonas aeruginosa:* continuous infusion of 16 g

Temocillin

	Standard dosage	High dosage
Temocillin	2 g x 2 iv	2 g x 3 iv

The 2 g x 2 iv dose has been used in the treatment of uncomplicated UTI caused by bacteria with beta-lactam resistance mechanisms.

Criterium for ‘susceptible, increased exposure’ fullfilled with doses of 2*2g as long as infection is confined to the urinary tract. For all other infections (originating from but not confined to the urinary tract) the dose of 3*2g corresponds to the breakpoint.

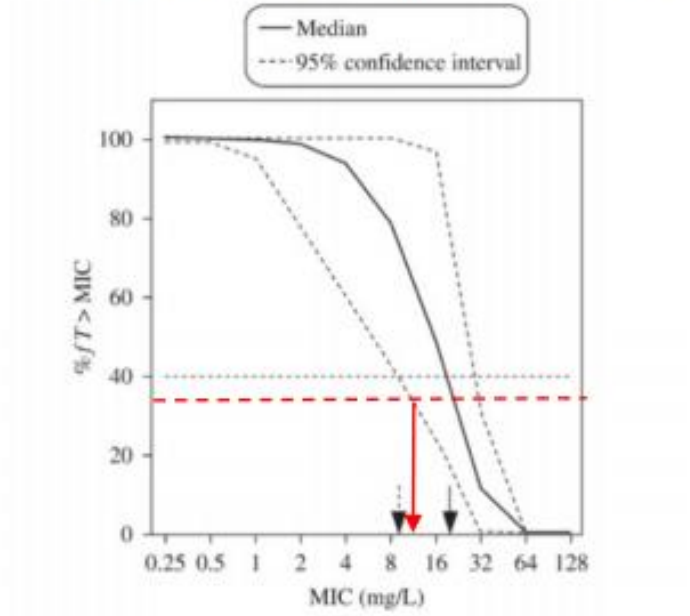
	MIC breakpoints (mg/L)			Disk content (µg)	Zone diameter breakpoints (mm)		
	S ≤	R >	ATU		S ≥	R <	ATU
Temocillin (infections originating from the urinary tract), *E. coli, Klebsiella* spp. (except *K. aerogenes*) and *P. mirabilis*	0.001	16		30	50[C]	17[C]	

The European Committee on Antimicrobial Susceptibility Testing. Breakpoint tables for interpretation of MICs and zone diameters. Version 11.0, 2021. http://www.eucast.org.

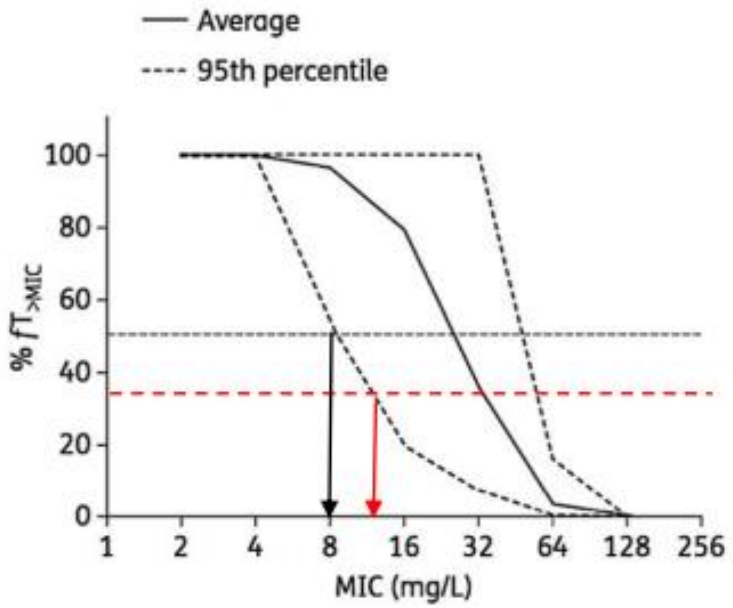
Temocillin

6. Monte Carlo simulations and Pk/Pd breakpoints

Temocillin 2g x 2 (De Jongh et al., JAC 2016)



Temocillin 2g x 3 (Laterre et al., JAC 2016)



https://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Rationale_documents/Temocillin_rationale_document_v1.0_20200327.pdf

2 g × 3 will ensure successful outcomes in all patients with infections originating in the urinary tract

Giske C et al. JAC 2021 https://doi.org/10.1093/jac/dkab081

Temocillin

MIC distributions for Temocillin, 2021-09-23

Antimicrobial: Temocillin (Method: MIC)

	0.002	0.004	0.008	0.016	0.03	0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	512	Distributions	Observations	(T)ECOFF
Burkholderia cepacia complex	0	0	0	0	0	0	0	0	0	3	12	27	37	31	17	3	6	1	0	2	137	-
Citrobacter freundii	0	0	0	0	0	0	0	0	0	9	51	24	25	2	0	0	0	0	0	2	111	-
Enterobacter cloacae	0	0	0	0	0	0	0	0	2	10	126	81	48	50	15	1	0	0	0	4	333	-
Escherichia coli	0	0	0	0	0	0	2	1	18	156	532	1502	1812	862	357	146	142	79	31	35	5640	16
Escherichia coli ATCC 25922	0	0	0	0	0	0	0	0	0	0	0	17	92	85	15	1	0	0	0	1	210	-
Escherichia coli ATCC 35218	0	0	0	0	0	0	0	0	0	0	45	131	33	1	0	0	0	0	0	1	210	-
Haemophilus influenzae	0	0	0	0	0	0	0	52	134	14	0	0	0	0	0	0	0	0	0	3	200	(1)
Klebsiella aerogenes	0	0	0	0	0	0	0	0	0	0	10	37	79	84	44	3	0	0	0	4	257	(32)
Klebsiella oxytoca	0	0	0	0	0	0	0	0	0	7	14	21	6	1	0	0	0	0	0	2	49	-
Klebsiella pneumoniae	0	0	0	0	0	0	0	0	3	61	193	117	52	27	22	35	23	71	1	7	605	8
Morganella morganii	0	0	0	0	0	0	0	1	4	28	70	55	11	0	0	0	0	1	0	5	170	8
Neisseria gonorrhoeae	0	0	6	24	28	34	62	72	96	238	296	52	2	0	0	0	0	0	0	6	910	-
Proteus mirabilis	0	0	0	0	0	0	0	1	9	118	136	48	2	2	0	0	0	0	0	7	316	4
Proteus vulgaris	0	0	0	0	0	0	0	0	8	78	19	1	0	0	0	0	0	0	0	3	106	(2)
Serratia marcescens	0	0	0	0	0	0	0	0	0	0	0	10	99	147	57	9	6	4	0	4	332	(64)
	0.002	0.004	0.008	0.016	0.03	0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	512	Distributions	Observations	(T)ECOFF
Yersinia enterocolitica	0	0	0	0	0	0	0	0	0	2	5	8	0	0	0	0	0	0	0	1	15	-

EUCAST MIC distributions https://mic.eucast.org/

The breakpoints susceptible ≤0.001 mg/L and resistant >16 mg/L avoid dividing the WT of relevant organisms and increase the chance of reproducible susceptibility results. The variability in MIC-testing and disk diffusion is such that breakpoints of 4 or 8 mg/L will not yield reproducible AST results because of natural and mostly random variation within the wild type. Therefore, a breakpoint of S<=8 mg/L is not a possible solution, whereas a breakpoint of 16 mg/L will ensure a more robust distinction between susceptible and resistant isolates and a better reproducibility in categorization.

https://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Consultation/2019/Responses_to_General_Consultation_on_Temocilin_20191202_final.pdf

Temocillin

Higher dose (3*2g) of temocillin: impact on cost

antibiotic	dose	price per day
Negaban 2g (30,59 euro/vial)	3*2g	91,77 euro
Meropenem Fresenius 1g (11 euro/vial)	3*1g	33 euro
Piperacilline-tazobactam Fresenius 4g/0.5g (9.21 euro/vial)	4*4g	36,84 euro
Zavicefta 2g/0.5 g (105,58 euro/vial)	3*2g	316,74 euro

https://ondpanon.riziv.fgov.be/SSPWebApplicationPublic/nl/Public/ProductSearch

Impact of 'I' interpretation of all wild type isolates → risk of more carbapenem use

No final decision yet at UZ Leuven

Practical consequences

- Dosage antibiotics
- Reporting of susceptibility testing results
- Epidemiological surveillance of resistance

No S category - only I and R category

Enterobacterales
cefuroxime
temocillin
***Pseudomonas* species**
piperacillin-tazobactam
ceftazidime
cefepime
ciprofloxacine/levofloxacine
Stenotrophomonas maltophilia
trimethoprim-sulfamethoxazole

Staphylococcus species
ciprofloxacin/levofloxacin
Streptococcus pneumoniae
levofloxacin
Haemophilus influenzae
amoxicilline oral
amoxicilline-clavulanic acid oral

→ Discussion in antibiotic management team

- Comment on the lab report for (some of) these antibiotics
- Pro-active control of choice of antibiotic therapy for some of these drug-bug combinations

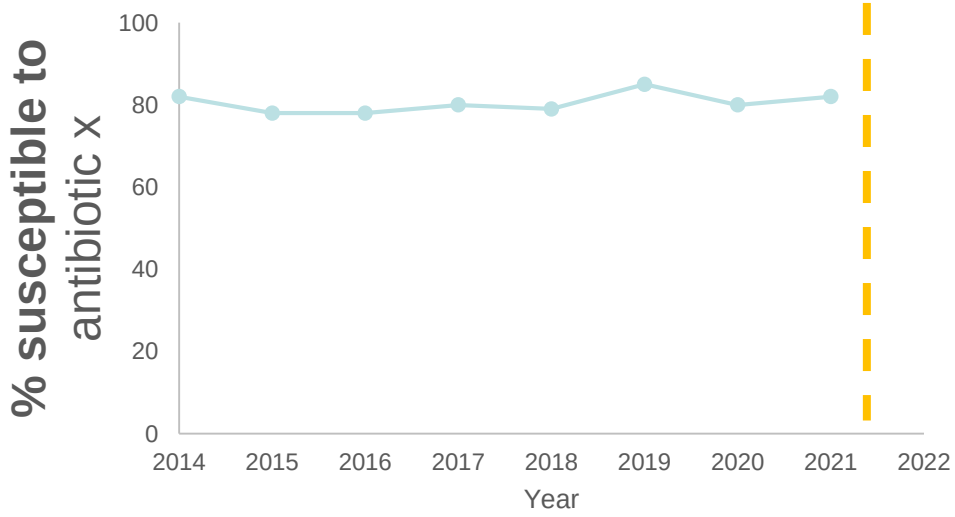
Practical consequences

- Dosage antibiotics
- Reporting of susceptibility testing results
- Epidemiological surveillance of resistance

Epidemiological surveillance of resistance

Susceptible

%S → % S and I



Impact of new definition mainly expected on bug-drug combinations with significant proportion of I categorised bacteria:

levofloxacin – Enterobacterales

meropenem - *Pseudomonas aeruginosa*

Consequences of new definition of I

- Dosage
  - Majority of antibiotics doses are according to EUCAST doses
  - For the ones with different dose
    - Mainly higher dose than EUCAST → no problem for use of clinical breakpoints
    - Some noticeable differences: piperacillin-tazobactam and temocillin
- Effect on surveillance of resistance (‘I’ together with ‘R’→ ‘I’ taken together with ‘S’)
- Important role for hospital antibiotic management team
- Multidisciplinary approach is needed
  - Preparation of the switch
  - Education of clinicians
  - Reporting of results
  - Proactive adjustment of antibiotic choice and dose once implementation of new guideline is done

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- Marnix Mylemans (ASO clinical biology UZ Leuven)
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  - Infectiologists
  - Clinical pharmacists
  - Microbiologists