EUCAST new definitions of **S, I, R** and area of technical uncertainty (**ATU**)

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On behalf of the **Belgian National Antibiogram Committee**

24/09/2021

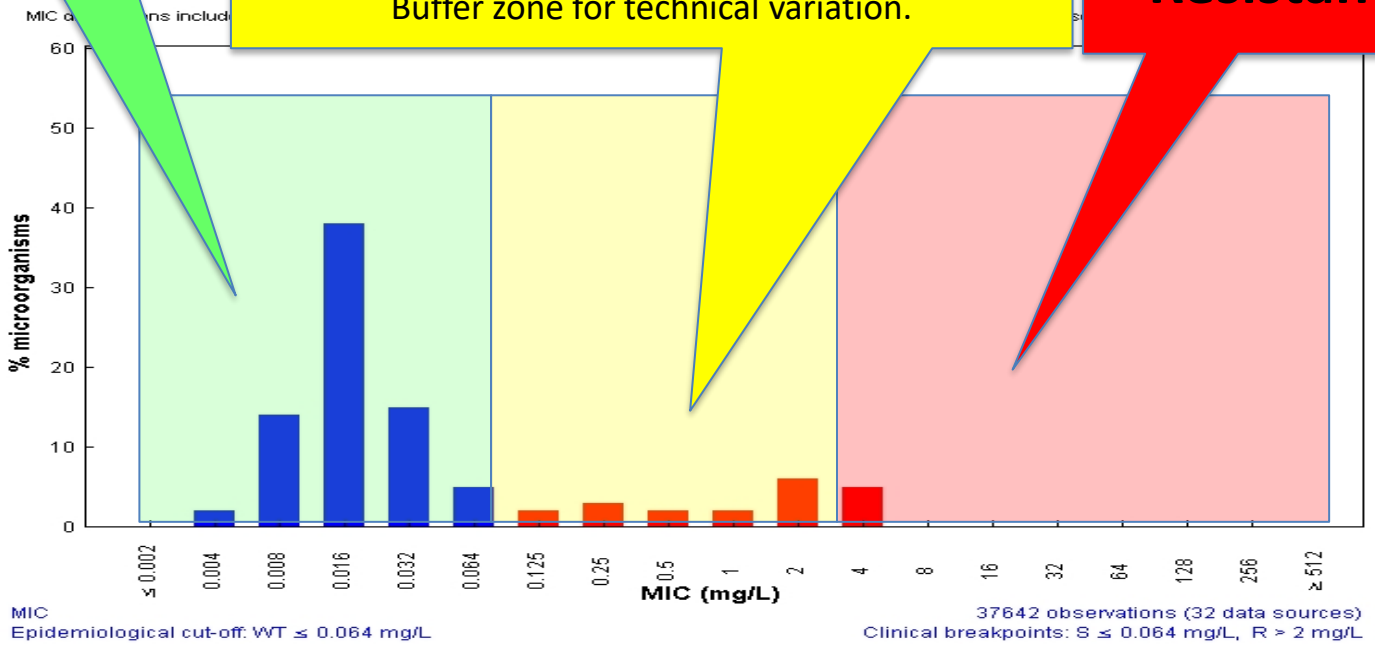
SIR – the old definitions

Susceptible

Intermediate

Uncertain therapeutic effect.
For a high dosage of drug.
Where physiologically concentrated.
Buffer zone for technical variation.

Resistant



Different meanings in one definition of ”I”

No indication at which of the meaning(s) was the individual reported ”I”.

- INTERMEDIATE results were undefined, poorly understood, distrusted
- INTERMEDIATE results were grouped together with RESISTANT results
  - By laboratories
  - By clinical colleagues
  - By surveillance programmes (R+I = ”non-susceptible”)

➔Clinicians avoided using agents reported as INTERMEDIATE.

EUCAST agreed for a need for a new definition of ”I” (definitions of S and R basically unchanged)

I – Susceptible, increased exposure

A microorganism is categorized 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.

- **↑ Exposure (amount of drug reaching the infecting organisms)**
  - Change of the mode of administration
  - Use the pharmacokinetics features of the agent
- **↑ Dose (amount of drug given to the patient)**
  - Increase of the individual dose
  - Shortening of the interval between doses

Following 6 consultations 2015 – 2019, the new definitions were introduced 2019

EUCAST decided to:

- Keep S, I and R (>80% in poll, IT difficulties)
- Emphasize relationship between breakpoints AND antimicrobial exposure.
- Verify that breakpoints correspond to the new definitions.
- Remove ”uncertain effect” and ”uncontrolled errors” from the definition
- Task laboratories to deal with uncontrolled errors (introduction of “ATU”).

The EUCAST dosing tab

- EUCAST has listed the minimum dosing requirements for the breakpoints (S, I and R) to be valid.
- The dosing document is not a therapy guideline – it simply informs of what dosing EUCAST used in the process of determining breakpoints.
- If on a local or national level, lower doses than EUCAST dosing tab are generally used, breakpoints may not be valid → discussion
- Available at https://www.eucast.org/clinical_breakpoints/

EUCAST dosing tab

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 **For S**	1.2 g (2 MU) x 4-6 iv **For I/S**		**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.
Piperacillin	4 g x 4 iv	4 g x 4 iv by extended 3-hour infusion		High dosage for more serious infections.
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.
Ticarcillin	3 g x 4 iv	3 g x 6 iv		
Ticarcillin-clavulanic acid	(3 g ticarcillin + 0.1-0.2 g clavulanic acid) x 4 iv	(3 g ticarcillin + 0.1 g clavulanic acid) x 6 iv		
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.
Phenoxymethylpenicillin	0.5-2 g x 3-4 oral depending on species and/or infection type	None		
Oxacillin	1 g x 4 iv	1 g x 6 iv		
Cloxacillin	0.5 g x 4 oral or 1 g x 4 iv	1 g x 4 oral or 2 g x 6 iv		
Dicloxacillin	0.5-1 g x 4 oral or 1 g x 4 iv	2 g x 4 oral or 2 g x 6 iv		
Flucloxacillin	1 g x 3 oral or 2 g x 4 iv (or 1 g x 6 iv)	1 g x 4 oral or 2 g x 6 iv		
Mecillinam oral (pivmecillinam)	None	None	0.2-0.4 g x 3 oral	

The ”new I” (Susceptible, increased exposure) is related to the lower sensitivity of an organism to an agent and the need for a higher than standard exposure…

either

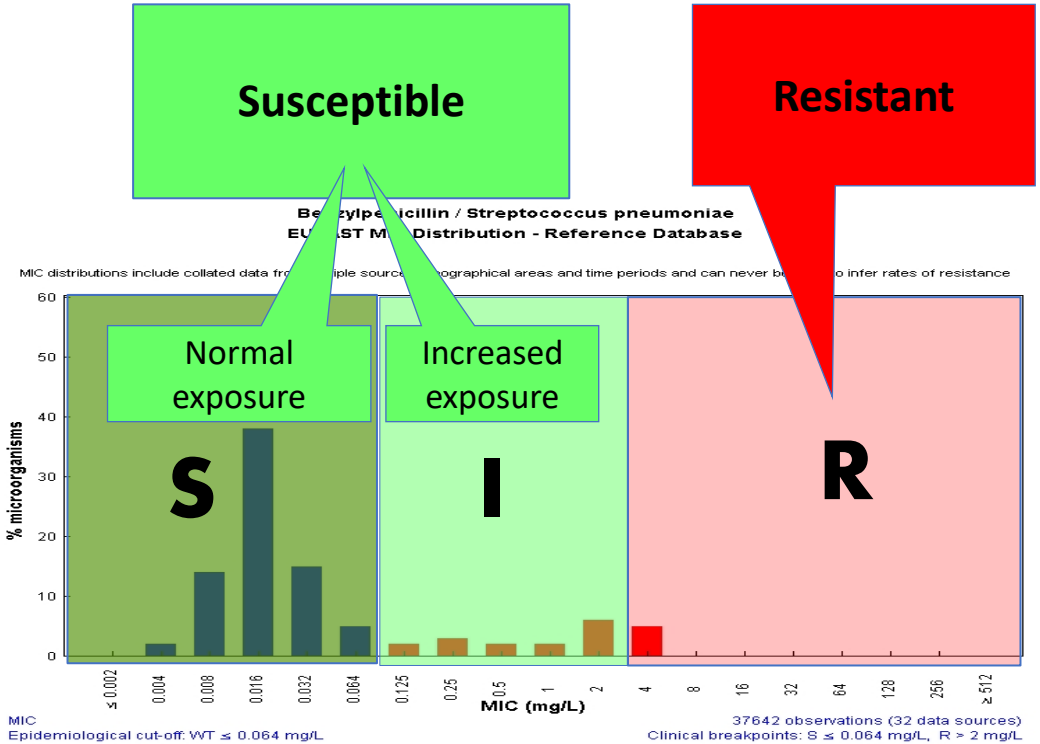
1. because **acquired low-level resistance** has reduced the sensitivity of the organism

   - S and R, and sometimes I, are all possible.

2. because the species is intrinsically less sensitive to the agent (the wild type is reported “I”)

   - only “I” and “R” are possible

SIR – new definitions 2020



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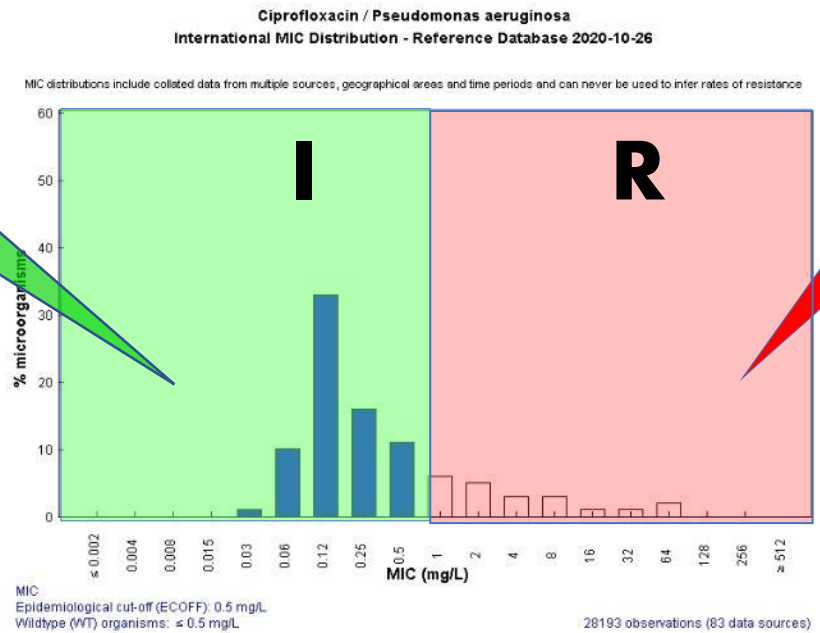
SIR – new definitions 2020

Susceptible, increased exposure

Resistant



”Arbitrary S-breakpoint” to ensure that you obtain an ”I” rather than an ”S” when testing.

S≤0.001 mg/L

S≥50 mm

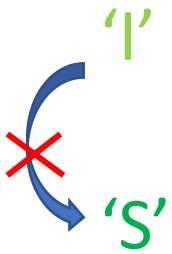
Most common organisms-agents where “Susceptible, increased exposure” (I) is the routine susceptible category.

- *Enterobacterales*:
  - Cefazoline
  - Cefuroxime
  - Temocillin
- *Pseudomonas*:
  - Piperacillin-tazobactam
  - Ceftazidime
  - Cefepime
  - Aztreonam
  - Ciprofloxacin
- *Acinetobacter*:
  - Cipro/levofloxacin
- *Stenotrophomonas*:
  - Cotrimoxazole
- *Staphylococcus*:
  - Cipro/levofloxacin
- *Streptococcus* gr. A,B,C,G:
  - Levofloxacin
- *S. pneumoniae*:
  - Levofloxacin
- *H. influenzae*:
  - Amoxicillin oral
  - Amox-clav oral
  - Cefuroxime oral
- *M. catarrhalis*:
  - Cefuroxime oral
- *Campylobacter*:
  - Ciprofloxacin

Potential impact of no S category…

- **AB stewardship:** shift of choice?
  - Ex: *Pseudomonas aeruginosa*
    - IV drugs (hospital setting)
    - Discourage low dose (i.e. oral cipro)

    → Encourage more ID/CM discussion



EUCAST breakpoints for *Pseudomonas* spp.	MIC (mg/L)		Disk charge (µg)	Zone diam (mm)	
	S ≤	R >		S ≥	R <
Piperacillin-tazobactam	0.001	16	30-6	50	18
Ceftazidime	0.001	8	10	50	17
Cefepime	0.001	8	30	50	21
Aztreonam	0.001	16	30	50	18
Ciprofloxacin	0.001	0.5	5	50	26
Meropenem	2	8	10	24	18
Ceftazidime-avibactam	8	8	10-4	17	17
Ceftolozane-tazobactam	4	4	30-10	23	23
Cefiderocol	2	2	30	22	22

- **AMR surveillance:**
  - Data report must clearly separate R from S/I (no more « non-susceptible » of I/R)

  → Monitor impact on (local/national) surveillance data

Laboratory technical variation and uncertain results

- Old definition of "**I**" includes uncertainty and/or technical variation → removed
- Situations where laboratories must take specific action to avoid reporting uncertain results:
  - Breakpoints **split** within a S/R **population**
  - **Poor reproducibility** of results is predictable
  - **Poor correlation** of results between methods

Area of Technical Uncertainty (ATU)

- EUCAST has improved the ability to detect areas where the technical uncertainty affects the predictive value of AST.

- In 2019 the term ”ATU” was introduced in AST as a warning to alert the laboratory to the uncertainty of the result.

- The warning affects the laboratory, not the clinician, and the laboratory needs to implement a strategy
  - To ascertain the correctness

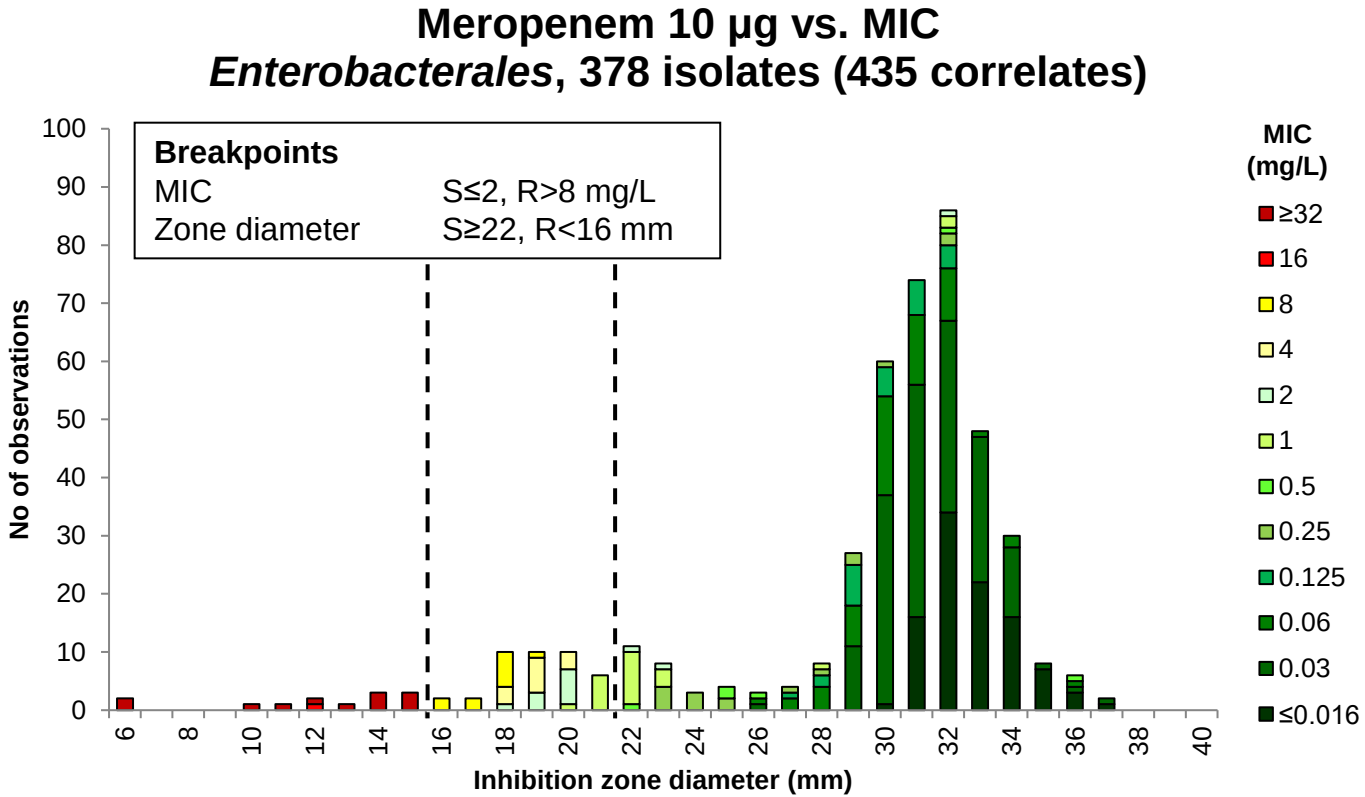
  OR
  - To report the uncertainty of the result

Most susceptibility testing (AST) is unproblematic

- ...if your testing materials (antimicrobials, media) and measuring devices (inoculum, automate) are reliable
  - Correct storage
  - QC-monitored

  ➔...if your method is robust and reproducible
- …if the expression of resistance mechanisms is stable

Meropenem and *Enterobacterales* – one of many examples where an ATU is not needed.



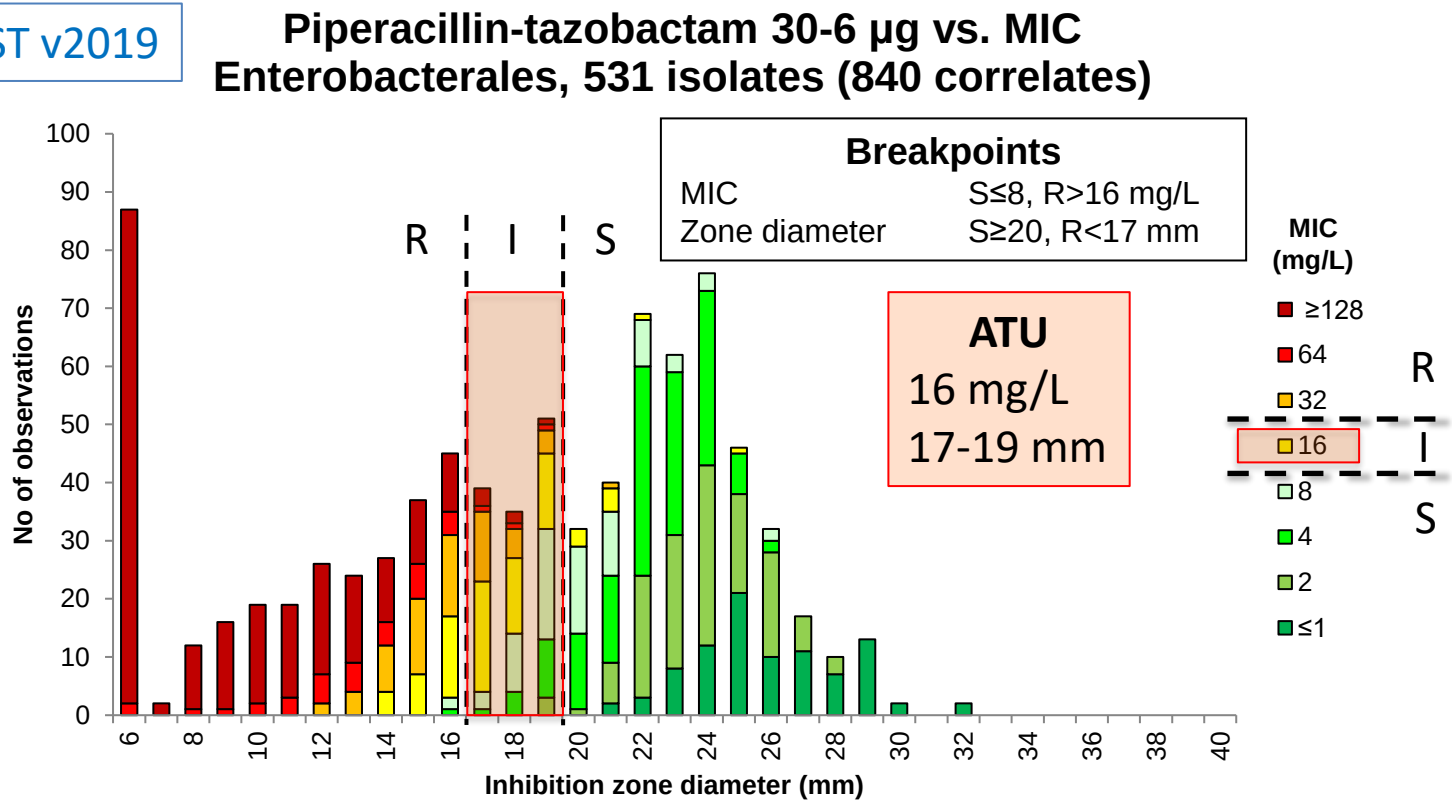
Sometimes an ATU is helpful

- **Difficult-to-control variation in the <u>method</u>**
  - Piperacillin-tazobactam in *Enterobacterales* and *Pseudomonas*

- **Difficult-to-control variation in the <u>interpretation</u>**
  - Breakpoint splits wild type (mostly avoided by EUCAST)
    - colistin in *P. aeruginosa*
  - Breakpoint splits an important resistant population
    - ceftaroline in MRSA
    - ciprofloxacin in *E. coli*

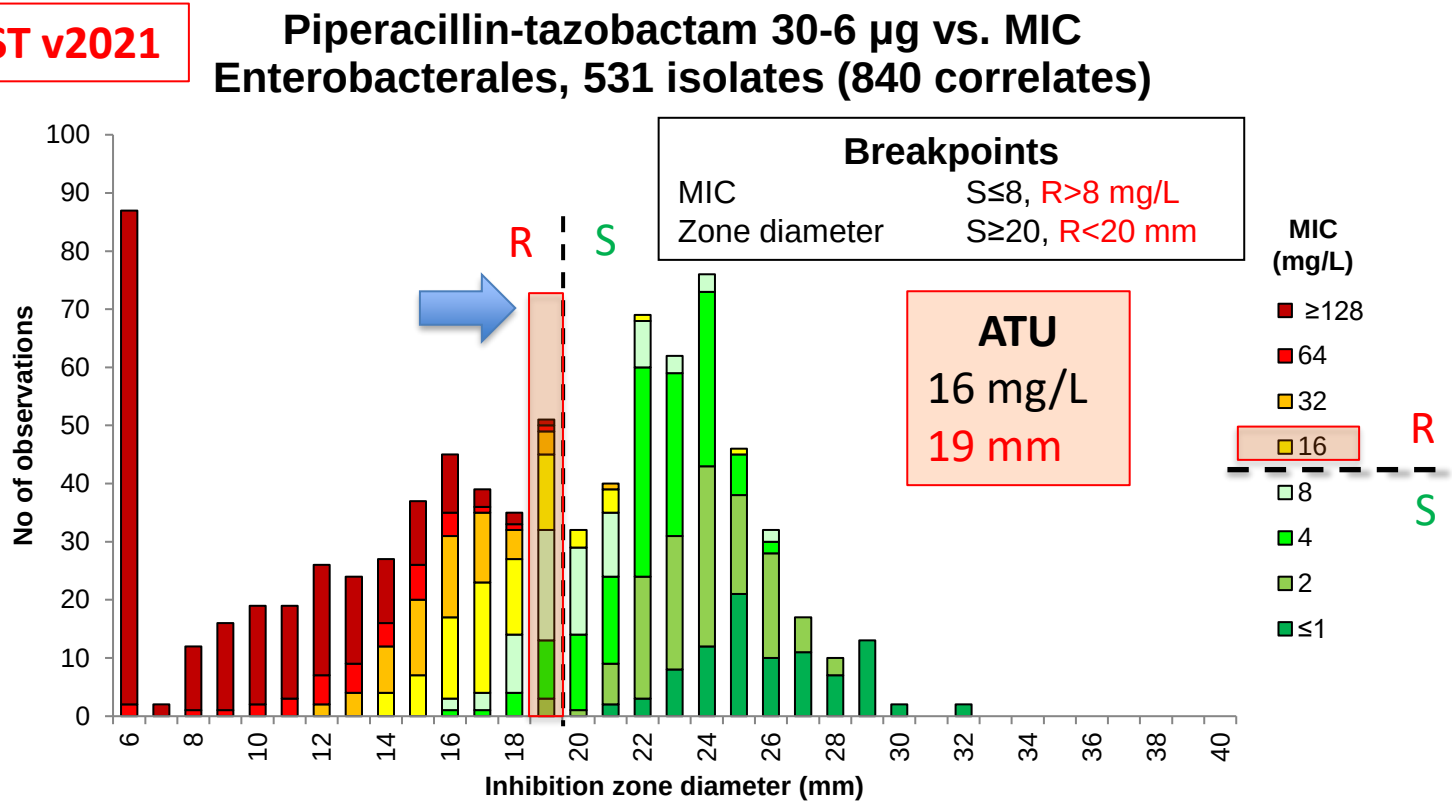
Piperacillin-tazobactam vs. *Enterobacterales*

EUCAST v2019



Piperacillin-tazobactam vs. *Enterobacterales*

EUCAST v2021



Area of Technical Uncertainty (ATU) =Warning for laboratory !

- ATU does **NOT** interfere with S/I/R interpretation.
- ATU is **NOT** a susceptibility category.
- ATU is **NOT** to replace poor methodological skills.
- ATU is defined by a single MIC-value or a short range of zone diameter values.

Limited number of ATUs

- *Enterobacterales*
  - amoxicillin-clavulanic acid (systemic)
  - piperacillin-tazobactam
  - ciprofloxacin
- *P. aeruginosa*
  - piperacillin-tazobactam
  - cefiderocol
  - colistin (MIC)
- *S. aureus*
  - ceftaroline, ceftobiprole
- *S. epidermidis*
  - cefoxitin screen (MRSE) on some media
- *H. influenzae*
  - beta-lactams (PBP3-mutations)

EUCAST ATU	MIC breakpoints (mg/L)			Disk content (µg)	Zone diameter breakpoints (mm)		
	S ≤	R >	ATU		S ≥	R <	ATU
Enterobacterales							
Amoxicillin-clavulanic acid[1]	8[3]	8[3]		20-10	19[A]	19[A]	19-20
Piperacillin-tazobactam	8[4]	8[4]	16	30-6	20	20	19
Ceftolozane-tazobactam[6]	2[7]	2[7]		30-10	22	22	19-21
Cefiderocol	2[3]	2[3]		30	22	22	18-22
Ciprofloxacin	0.25	0.5	0.5	5	25	22	22-24
Pseudomonas spp.							
Piperacillin-tazobactam	0.001[1]	16[1]		30-6	50	18	18-19
Cefiderocol, *P. aeruginosa*	2[1]	2[1]		30	22	22	14-22
Colistin[1]	2	2	4		Note[A]	Note[A]	
Staphylococcus spp.							
Cefoxitin (screen), *S. epidermidis*	Note[4]	Note[4]		30	25[A,B]	25[A,B]	25-27
Ceftaroline, *S. aureus*	1[6]	1[6]	1	5	20[D]	20[D]	19-20
Ceftobiprole, *S. aureus*	2[8]	2[8]	2	5	17[F]	17[F]	16-17
Haemophilus influenzae							
Piperacillin-tazobactam	0.25[6]	0.25[6]		30-6	27[A,B]	27[A,B]	24-27[B,C]
Cefuroxime iv	1	2	2[3]	30	27[A,B]	25[A,B]	25-27[B,C]
Cefuroxime oral	0.001	1		30	50[A,B]	27[A,B]	25-27[B,C]
Cefotaxime[4]	0.125	0.125		5	27[A,B]	27[A,B]	25-27[B,C]
Ceftriaxone[4]	0.125	0.125		30	32[A,B]	32[A,B]	31-33[B,C]
Cefepime	0.25	0.25		30	28[A,B]	28[A,B]	28-33[B,C]
Ceftolozane-tazobactam[2]	0.5	0.5		30-10	23[A,B]	23[A,B]	22-23[B,C]

How to implement ATU in laboratory?

- Have a **lab internal ATU warning** system:
  - A list of ATUs at the lab bench
  - Electronic alert in semi-automated device output
- **Define condition-action** (organisms, agent) "IF - THEN“:
  - *Pseudomonas* - colistin: IF MIC-values = 4 mg/L, THEN warning
  - *E. coli* – piperacillin/tazobactam: IF zone 19 mm, THEN warning

Try to solve the problem only IF…

- in serious infections (a positive blood culture)
- limited alternative treatments available
- frequently recurrent
- easy to solve

Results in ATU - alternative actions!

- Repeat the test only if obvious identifiable reason for failure (wrong disk, wrong plate, expired materials…).
- **Confirm** using an alternative test (MIC, PCR, PBP2a...) (and compare to the original test).
- **Report as tested** (±comment).
- **Mask as unreported** (±comment).
- **Downgrade** results to R (if no time to investigate).
- **Discuss and explain** - contact the clinical colleague.

Summary from NAC position

- **The NAC endorses the EUCAST recommendations:**
  - Continue to use the “I” letter for raw result
  - Translate into the new definition of “I” (susceptible, increased exposure)
- **The NAC urges the antimicrobial stewardship group (GGA/ABG):**
  - To ensure that the daily posology of antibiotics used locally match with the dosages recommended by EUCAST (and modify accordingly)
  - To inform infectious disease physicians and all antimicrobial prescribers on the major changes resulting from these new breakpoints

➢ The national implementation of the new EUCAST interpretative breakpoints set at **January 2022** at the latest

Thank you !

Actions by NAC for the transition

- Communication through multiple channels including Sciensano External Quality control Assessment (EQA) reports, SBIMC-BVIKM and BAPCOC.

- Organization of a NAC webinar by BAPCOC intended to target the stakeholders (microbiologists both from clinical and private laboratories, infectious disease physicians, clinical pharmacists, antimicrobial stewardship committees, general practitioners …)

- Contacts with manufacturers of AST device and materials and of laboratory information systems aiming to a more uniform “Belgian” approach to comply with EUCAST changes.

- Partnership with EUCAST, by sharing EUCAST webinars explaining the changes/novelties and providing practical hints for the implementation of local solutions on the NAC website (https://www.bvikm.org/national-antimicrobial-committee-nl or https://www.bvikm.org/national-antimicrobial-committee-fr)