

# Suggestions on how to manage the implementation of new I breakpoints and the ATU in the laboratory system

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# How to apply in AST systems?

- New EUCAST “I” breakpoints
- ATU

Focus on automated systems

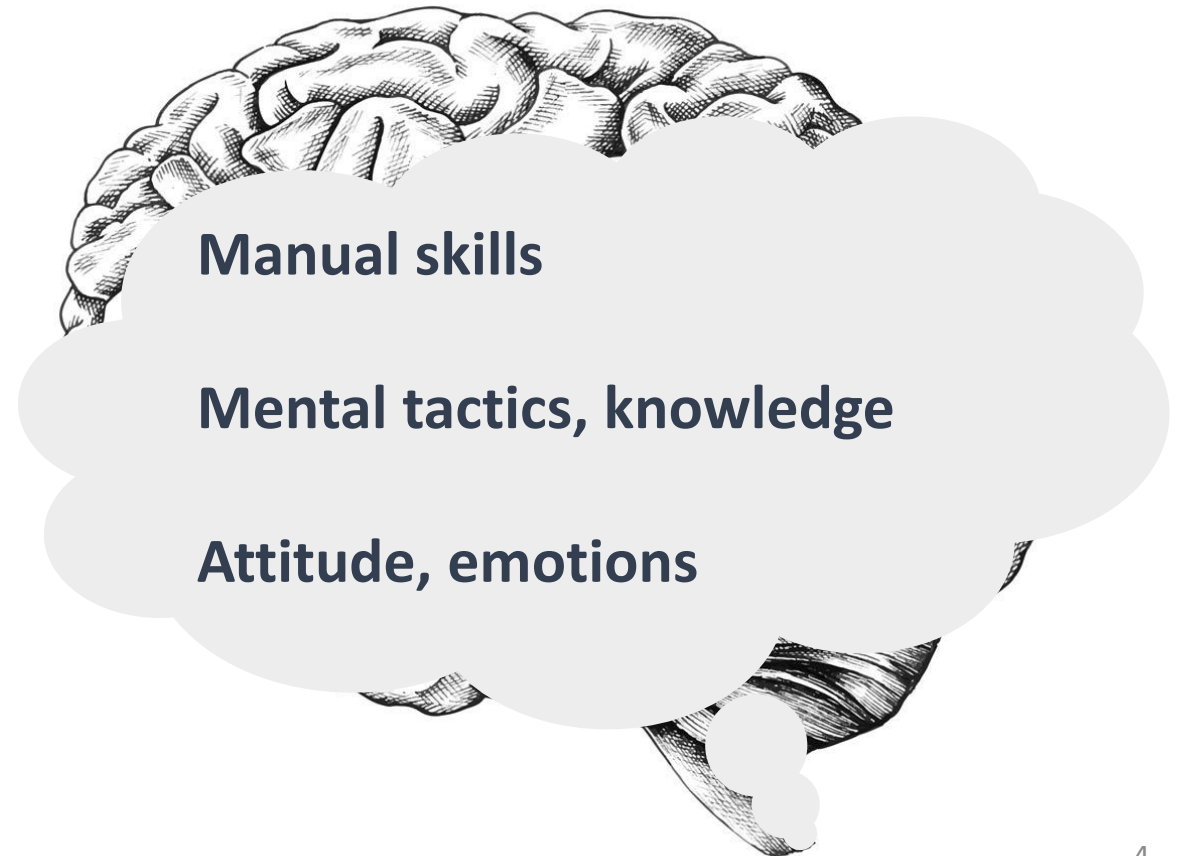
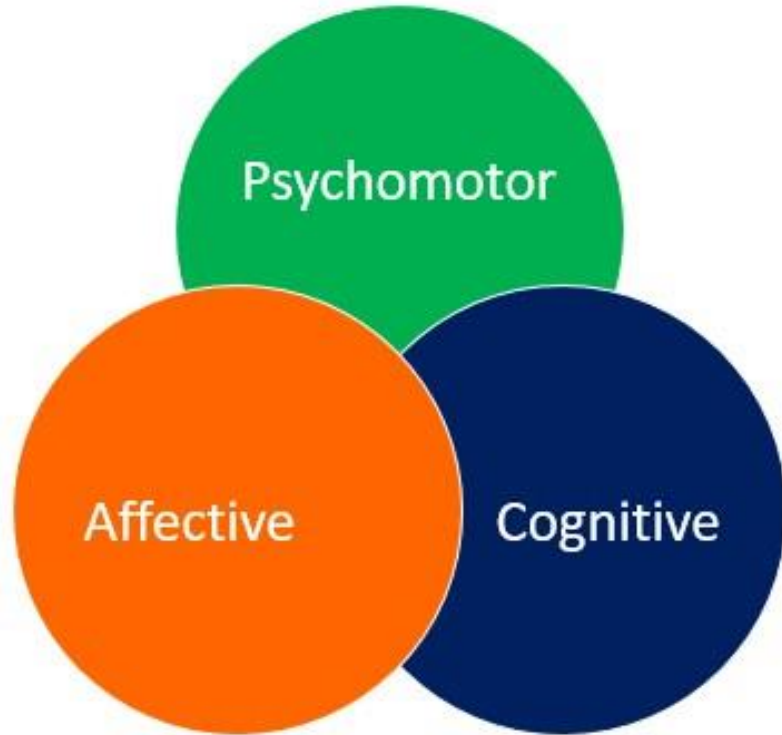
- Phoenix Becton Dickinson
- VITEK bioMérieux

# Off-scale breakpoints:

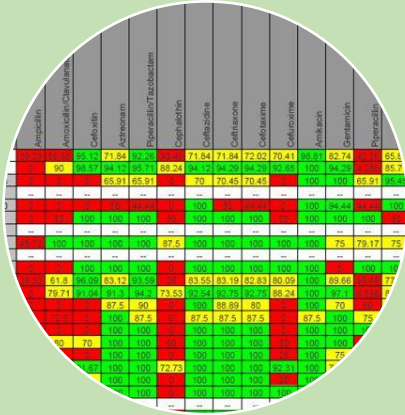
From two levels of resistance to two levels of susceptible?

- Implementation in AST system
- Implementation in LIS
- Implementation for clinical use

# Learning takes place in three domains...



# Acting on different levels



AST  
device



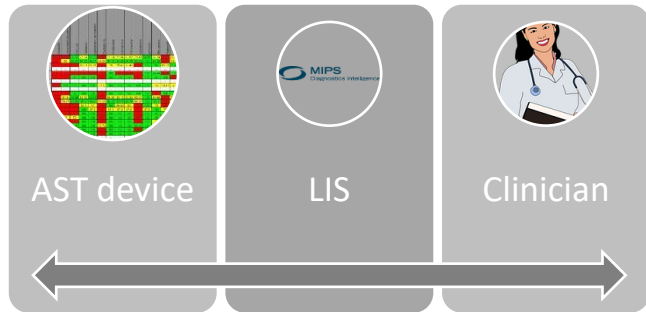
LIS



Clinician



# Acting on different levels



- Drug
  - Type
  - IV/PO
- 
- Bug
- Infection site
  - urine
  - other

- FQ/penicillins/temocillin/...
  - IV
- *Pseudomonas aeruginosa*
- Urine

# EUCAST advice for off-scale breakpoints:

For these situations laboratories should consider adding a note about the need for high exposure, particularly with...

- *Pseudomonas* and piperacillin-tazobactam, ceftazidime, cefepime, imipenem, aztreonam, fluroquinolones, aminoglycosides.
- *Enterobacterales* and aminopenicillins (with or without inhibitor) and cefuroxime.

**But how to implement?**

# INTRODUCTION IN VITEK AES



EUCAST breakpoints table V11 (2021)  
available at <http://www.eucast.org>



EUCAST

EUROPEAN COMMITTEE  
ON ANTIMICROBIAL  
SUSCEPTIBILITY TESTING

European Society of Clinical Microbiology and Infectious Diseases

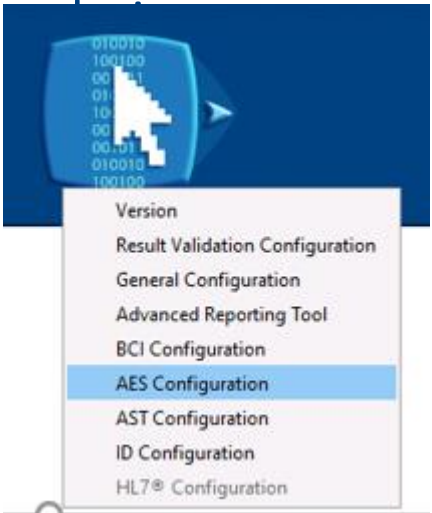
Cephalosporins <sup>1</sup>	MIC breakpoints (mg/L)		
	S ≤	R >	ATU
Cefuroxime iv, <i>E. coli</i> , <i>Klebsiella</i> spp. (except <i>K. aerogenes</i> ), <i>Raoultella</i> spp. and <i>P. mirabilis</i>	0.001	8	

Cefuroxime oral (uncomplicated UTI only), <i>E. coli</i> , <i>Klebsiella</i> spp. (except <i>K. aerogenes</i> ), <i>Raoultella</i> spp. and <i>P. mirabilis</i>	8	8
---	---	---

Cephalosporins	Standard dosage	High dosage	Uncomplicated UTI
Cefuroxime iv	0.75 g x 3 iv	1.5 g x 3 iv	
Cefuroxime oral	0.25 g x 2 oral	0.5 g x 2 oral	0.25 g x 2 oral



# AES CONFIGURATION - BREAKPOINTS



AES Configuration

Available Parameter Sets

- Custom
  - Copy of EUCAST+EUCAST-based
    - MIC Interpretation
      - Breakpoints**
      - Forcing rules
    - Therapeutic Interpretation
      - Interpretations
      - Deduction rules
      - Disabled Phenotypes
      - Graphic
- Pre-defined
  - CLSI
    - CLSI+Natural Resistance
  - MIC Interpretation
    - Breakpoints
    - Forcing rules
  - Therapeutic Interpretation
    - Interpretations
    - Deduction rules
    - Disabled Phenotypes
    - Graphic
- EUCAST+EUCAST-based
  - MIC Interpretation
    - Breakpoints
    - Forcing rules
  - Therapeutic Interpretation
    - Interpretations
    - Deduction rules
    - Disabled Phenotypes
    - Graphic
- EUCAST+Phenotypic
  - Global CLSI-based+CLSI
  - Global CLSI-based+Natural Resistance
  - Global CLSI-based+Phenotypic
  - Global European-based+EUCAST-based

MIC Interpretation Guideline

Name: Copy of EUCAST 2017

Based On: EUCAST 2017

Knowledge Base Version: 09.02 - Aug 5, 2021 11:49:57 AM

Parameter Set Status: Inactive

Breakpoints

Type of AST Card: All

Sort By: Antibiotic, Organism, Infection Site

Organism/Antibiotic/Version	Infection Site	S	SDD	I	R	IE/(-)	Source	Comment
AST-ST01, AST-ST02 (cro0 In)		<= 0.5		1 - 2	> 2		EUCAST	
Streptococcus viridans group except S.pne...								
Streptococcal Susceptibility								
AST-ST01, AST-ST02 (cro0 In)		<= 0.5			> 0.5		EUCAST	
Cefuroxime								
Acinetobacter								
Gram Negative Susceptibility								
AST-EXN5, AST-EXN8, AST-GN04, ...		(-)	(-)	(-)	(-)	(-)	EUCAST	
Enterococcus								
Gram Positive Susceptibility								
AST-BE04, AST-BE06 (comb0 In)		(-)	(-)	(-)	(-)	(-)	EUCAST	
Escherichia coli								
Gram Negative Susceptibility								
AST-EXN5, AST-EXN8, AST-GN04, ...	Other			<= 8	> 8		EUCAST	EU2021 IV
AST-EXN5, AST-EXN8, AST-GN04, ...	Urine	<= 8			> 8		EUCAST	EU2021 oral
Gram Negative Susceptibility								
AST-EXN5, AST-EXN8, AST-GN04, ...		<= 8			> 8		EUCAST	
Proteus mirabilis								
Gram Negative Susceptibility								
AST-EXN5, AST-EXN8, AST-GN04, ...		<= 8			> 8		EUCAST	
Pseudomonas								

Organism/Antibiotic/Version	Infection Site	S	SDD	I	R	IE/(-)	Source	Comment
Escherichia coli								
Gram Negative Susceptibility								
AST-EXN5, AST-EXN8, AST-GN04, AST-N020, AST-N315, AST-NT...	Other			<= 8	> 8		EUCAST	EU2021 IV
AST-EXN5, AST-EXN8, AST-GN04, AST-N020, AST-N315, AST-NT...	Urine	<= 8			> 8		EUCAST	EU2021 oral

# BIOART RULES



Advanced Reporting Tool Configuration

Rules

- Custom
  - (2) staph kana
  - (3) VRE
  - (5) pseudo 2
  - (6) staph
  - (7) CRE
  - (8) mmm
  - (9) pseudo colistine
  - (10) esbl
  - (11) test comment
  - (13) shc
  - (14) TEST COMMENT 2
  - (15) sha
  - (16) ACISPP AMOX/CA AMP SUPPRESS
  - (17) Amp PL + Cron sak
  - (18) SAM PL + Cron sak
  - (19) TGC PL + Cron sak
  - (20) Copy of rule 5038 + Cron sak
  - (21) Copy of 5000 AM PL + Cron sak
  - (22) Copy of rule 5002 SAM PL +
  - (23) MRSA issue 1
  - (24) MRSA rule
  - (25) adasdasdasda
  - (26) ATU Cipro 0.5 - Enterobacteriaceae
  - (27) Off scale Cefuroxime
- Local
- Predefined
  - Product Limitation
    - Global European-based
    - Global CLSI-based
    - CLSI
    - VET:CASFM-based
    - VET:CLSI-based
    - EUCAST
  - Indications for Use

Rule: 27 Name: Off scale Cefuroxime Status: Enabled

Type: Custom

Conditions

**IF**

If these conditions are met:

Organism is Enterobacteriaceae
And Antibiotic is Cefuroxime, MIC <= 8, Antibiotic Type: Tested

Other 'conditions' available.

Actions

**Then**

Then take these actions:

Stop for review
And Add comment: Add comment: Free text, for example: Off scale breakpoint, Cefuroxime S <=0.001
And Suppress from reporting Cefuroxime

1. Not validate automatically this result

2. Internal comment: Free text add to result (or External comment to LIS)

3. Suppress for reporting

Other 'actions' available.

Not active

Active

Glob

# RESULT SCREEN



VITEK 2 Systems Web

https://localhost/vitek/viewer/#/isolate?id=126432

Isolate Detail

1 of 1

**To be reviewed** 1.

Accession ID: t38

Organism Origin: Technologist

Organism: Esch.coli

AES Findings: Consistent

Phenotypes Selected for Review: None Detected

Card Comments:

Advanced Reporting Tool Comments:  
Internal Comments:  
Add comment: Free text, for example:  
Off scale breakpoint,  
Cefuroxime S <=0.001

2.

Advanced Reporting Tool Comments:  
Internal Comments:  
Add comment: Free text, for example:  
Off scale breakpoint,  
Cefuroxime S <=0.001

3.

AST-N020

Antibiotic	MIC	INT	Antibiotic	MIC	INT	Antibiotic	MIC	INT
<input type="checkbox"/> Ampicillin	8	S	<input type="checkbox"/> Cefuroxime Axetil	4	S	<input type="checkbox"/> Gentamicin	≤1	S
<input type="checkbox"/> Amoxicillin/ Clavulanic Acid	4	S	<input type="checkbox"/> Ceftazidime	≤1	S	<input type="checkbox"/> Tobramycin	≤1	S
<input type="checkbox"/> Piperacillin	≤4	S	<input type="checkbox"/> Cefepime	≤1	S	<input type="checkbox"/> Ciprofloxacin	≤0.25	S
<input type="checkbox"/> Piperacillin/ Tazobactam	≤4	S	<input type="checkbox"/> Meropenem	≤0.25	S	<input type="checkbox"/> Norfloxacin	2	R
<input type="checkbox"/> Cefalotin			<input type="checkbox"/> Amikacin	≤2	S	<input type="checkbox"/> Ofloxacin	1	I
<input checked="" type="checkbox"/> Cefuroxime						<input type="checkbox"/> Nitrofurantoin	≤16	S
Urine	4	S				<input type="checkbox"/> Trimethoprim/ Sulfamethoxazole	≤20	S
Other	4	I						

BETA-LACTAMS, CEPHALOSPORINS 3

Patient Name:

Analysis Status:

Analysis Messages:

McFarland:

Setup Tech: Laboratory Supervisor (LabSuper)

Organism Quantity:

BP Infection Site: 4.

Bench: Urine

Supplemental Tests:

Contraindicating Tests:

Glob

# HOW TO SEND TO LIS?



- Possibility 1:

A screenshot of a software interface showing a dropdown menu labeled "BP Infection Site:". The menu is open, and the number "4." is selected and highlighted in red.

Define a 'Breakpoint Infection Site', when loading the VITEK card,

Only 1 breakpoint will be taken in account.

So only one MIC and Interpretation will be sent to LIS

A screenshot of a list of infection sites. The list includes: Meningitis, Oral, Other, Pneumonia, Urine, Genital - Veterinary, and Mastitis - Veterinary. The list is scrollable, and a dropdown arrow is visible at the bottom.

- Possibility 2

No infection site is introduced,

Both MIC's and Interpretations will be sent to LIS

LIS has to be programmed to receipt the right MIC/Interpretation, depending on the infection site.

# Introduction in BDXpert System

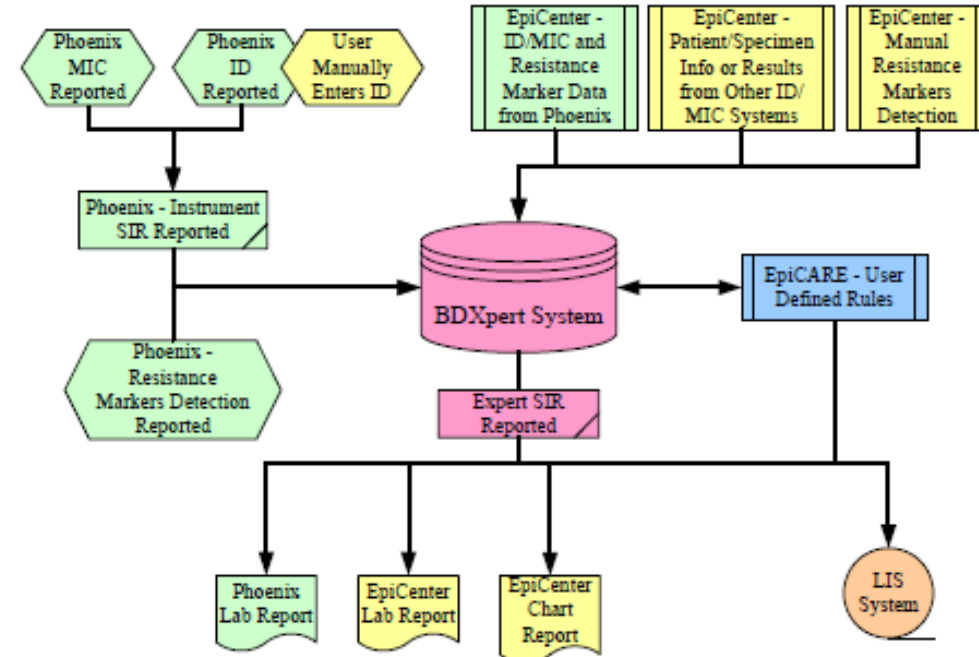


## BDXpert™ System User's Manual

For BD Phoenix™ and BD EpiCenter™

PUD 6.81

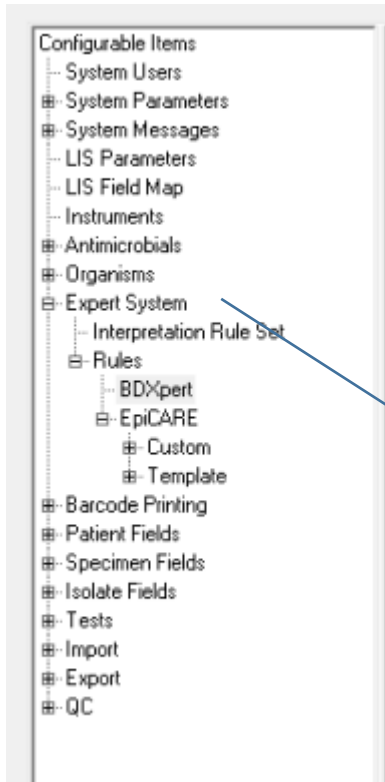
EUCAST Standard



\*Exposure is a function of how the mode of administration, dose, dosing time, as well as distribution and excretion of the antimicrobial agent will influence the infecting organism at the site of infection.

For wild-type organisms (organisms without phenotypically detectable resistance mechanisms to the agent), EUCAST has assigned an arbitrary, “off scale” MIC breakpoint of  $S \leq 0.001$ . These organism-agent combinations should never be reported as “Susceptible, standard dosing regimen” (S). To address these organism-agent combinations, a series of BDXpert rules (982 – 992) were created to change the interpreted SIR for any MIC below the resistant breakpoint to “Susceptible, increased exposure” (I).

# Expert rules epicenter Phoenix



- ❖ Expert system
  - \* Interpretation Rule Set
  - \* Rules:
    - °BDXpert
    - °EpiCARE
      - Custom
      - Template

**Enabled**  
**Disabled**

**Enabled**  
**Disabled**

**IF/AND/THEN**  
*Write it yourself*

# Breakpoints configuration Phoenix



RULE	IF	ORGANISM	AND	DRUG	AND		THEN	ACTION	AND	MESSAGE		
Logic Table by Organism						Enterobacterales					L009741(13) 2020-09	
Rule	IF:	Organism/Group	AND:	Drug(s)	AND:	Logic Criteria	THEN:	Action	AND:	Message Chartable Text	Application	Reference
984		Escherichia coli or Klebsiella species (except K. aerogenes) or Raoultella species or Proteus mirabilis		cefuroxime		S MIC <=8		1) Change any listed drug with SIR of S to SIR of I. 2) Print message.		For Escherichia coli, Klebsiella species (except K. aerogenes), Raoultella species and Proteus mirabilis, a cefuroxime MIC of <=8 mcg/mL should be considered "susceptible, increased exposure (I)."	Phoenix and EpiCenter	EUCAST 2020 (v10.0) Enterobacterales

BDXpert rules are categorized according to the following:

Rule Number	Standard
1-399, 2100+	CLSI
401-699	SFM
737-999	EUCAST

Rules applying to all standards:

Rule Series	Description
1000 series	Mostly intrinsic rules (note: does not apply to EUCAST)
1400 series	Resistance marker rules that can be disabled by the user
1500 series	Resistance marker rules that cannot be disabled by the user
1600 series	Resistance marker rules that the user must manually set in EpiCenter
1800 series	Rules for bug/drug combinations having no clinical indication or efficacy
2000 series	Miscellaneous rules



# Breakpoints configuration Phoenix



RULE	IF	ORGANISM	AND	DRUG	AND		THEN	ACTION	AND	MESSAGE		
------	----	----------	-----	------	-----	--	------	--------	-----	---------	--	--

Logic Table by Organism

Enterobacterales

L009741(13)  
2020-09

Rule	IF: Organism/Group	AND: Drug(s)	AND: Logic Criteria	THEN: Action	AND: Message Chartable Text	Application	Reference
984	Escherichia coli or Klebsiella species (except K. aerogenes) or Raoultella species or Proteus mirabilis	cefuroxime	S MIC <=8	1) Change any listed drug with SIR of S to SIR of I. 2) Print message.	For Escherichia coli, Klebsiella species (except K. aerogenes), Raoultella species and Proteus mirabilis, a cefuroxime MIC of <=8 mcg/mL should be considered "susceptible, increased exposure (I)."	Phoenix and EpiCenter	EUCAST 2020 (v10.0) Enterobacterales

Customize to LIS

DTG	Specimen Lab Report	Chart Report
A	YES	YES
B	YES	YES
C	YES	NO
U	YES, for urine specimen or unspecified	YES, for urine specimen
O	YES	NO
I	YES	NO
N	YES	NO

Drug Test Group

specimen source

Because some rules are applicable only for a specific specimen source, a standardized list of these has been established in EpiCenter ONLY. The only applicable specimen source descriptions referenced by BDxpert rules are: BLOOD (blood), CNS (central nervous system), EYE (eye), GI (gastrointestinal), RESP (respiratory), SBS (sterile body site), URINE (urine), and UNS (unspecified).



But sometimes it still stays a bit confusing...

Ceftazidime	0.001	8
Ceftazidime-avibactam, <i>P. aeruginosa</i>	8 <sup>2</sup>	8 <sup>2</sup>

I or S label for:

- Same molecule
- No inherent inhibitor activity for Pseudomonas
- BUT difference in dosage regimens

[Dosages \(v 11.0\) - file for printing and screen](#) (1 Jan, 2021)

	Standard dosage	High dosage	Uncomplicated UTI
Ceftazidime	1 g x 3 iv	2 g x 3 iv or 1 g x 6 iv	
Ceftazidime-avibactam	(2 g ceftazidime + 0.5 g avibactam) x 3 iv over 2 hours		

# ATU: area of technical uncertainty

- ❖ Warning
- ❖ No mandatory action
- ❖ If lab decides to act on the warning, then:
  - Implementation in AST system
  - Implementation in LIS

# How can the ATU be implemented in laboratory practices?

- Laboratories **without IT support** (manual **S**, **I** and **R** categorisation on MIC or disk diffusion results)
  - List manually species/agents with ATUs and proposals on how to handle each.
- Laboratories **with IT support** (where **S**, **I** and **R** categorisation is performed automatically on entering MIC or disk diffusion results)
  - Develop the software to include IF/THEN algorithms such as:  
IF *S. aureus* and ceftaroline and MIC 1 mg/L (or zone 19-20 mm), THEN take ACTION\*..."  
IF *E. coli* and piperacillintazobactam MIC 16 mg/L (or zone 18 – 19), THEN take ACTION\*..."

The basic principle is the same irrespective of which methods are used, but there may be an ATU in only one system.

- Disk diffusion
- MIC determination
- Semi-automated AST devices

# MIC determination

- Automatic reading with computerized interpretation of full scale MIC determination.
  - Introduce ATU (species, agent, interval) to generate:
    - "Warning signal" (sound, light, asterisk in report protocol, ....)
    - Block automatic interpretation and force manual decisions.
- Manual reading of full scale MIC determination
  - print a manual list of ATUs or use EUCAST breakpoint table printout

# INTRODUCTION IN VITEK BIOART

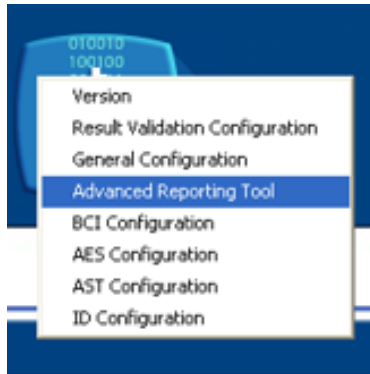


EUCAST breakpoints table V11 (2021)  
available at <http://www.eucast.org>



Fluoroquinolones	MIC breakpoints (mg/L)		
	S ≤	R >	ATU
Ciprofloxacin	0.25	0.5	0.5

# ADVANCED REPORTING TOOL - CONFIGURATION



Advanced Reporting Tool Configuration

Rules

- Custom
  - (2) staph kana
  - (3) VRE
  - (5) pseudo 2
  - (6) staph
  - (7) CRE
  - (8) mmm
  - (9) pseudo colistine
  - (10) esbl
  - (11) test comment
  - (13) shc
  - (14) TEST COMMENT 2
  - (15) sha
  - (16) ACISPP AMOX/CA AMP SUPPRESS
  - (17) Amp PL + Cron sak
  - (18) SAM PL + Cron sak
  - (19) TGC PL + Cron sak
  - (20) Copy of rule 5038 + Cron sak
  - (21) Copy of 5000 AM PL + Cron sak
  - (22) Copy of rule 5002 SAM PL +
  - (23) MRSA issue 1
  - (24) MRSA rule
  - (25) adasdasdasda
  - (26) ATU Cipro 0.5 - Enterobacteriaceae
  - (27) Off scale Cefuroxime
- Local
- Predefined
  - Product Limitation
    - Global European-based
    - Global CLSI-based
    - CLSI
    - VET:CASFM-based
    - VET:CLSI-based
    - EUCAST
  - Indications for Use

Rule: 26 Name: ATU Cipro 0.5 - Enterobacteriaceae Status: Enabled

Type: Custom

**IF**

Conditions

If these conditions are met:

- Organism is Enterobacteriaceae
- And Antibiotic is Ciprofloxacin, MIC = 0.5, Antibiotic Type: Tested

Other 'conditions' available.

**Then**

Actions

Then take these actions:

- Stop for review
- And Add comment: Free text, for example:  
MIC Cipro 0.5 ATU  
1. repeat test if suspicion of technical problem  
2. perform an alternative MIC or genotypic test, if only few therapeutic alternatives  
3. downgrade the susceptibility category if there are other therapeutic alternatives  
4. include the uncertainty as part of the report  
5. omit an uncertain result
- And Suppress from reporting Ciprofloxacin

Other 'actions' available.

1. Not validate automatically this result
2. Internal comment: Free text add to result  
(or External comment to LIS)
3. Suppress for reporting

# RESULT SCREEN



VITEK 2 Systems Web

https://localhost/vitek/viewer/#/isolate?id=21244

### Isolate Detail

1 of 1

**To be reviewed** 1.

**Accession ID** 6034

**Organism Origin** VITEK 2

**Organism** K.pneum.pneumoniae

**AES Findings** Consistent

**Phenotypes Selected for Review**

BETA-LACTAMS

[ESBL + IMPERMEABILITY \(CEPHAMYCINS\)](#)

[EXTENDED SPECTRUM BETA-LACTAMASE](#)

**Card Comments:**

**Advanced Reporting Tool Comments:**

**Internal Comments:**

Free text, for example:  
MIC Cipro 0.5 ATU

1. repeat test if suspicion of technical problem
2. perform an alternative MIC or genotypic test, if only few therapeutic alternatives
3. downgrade the susceptibility category if there are other therapeutic alternatives
4. include the uncertainty as part of the report
5. omit an uncertain result

**AST-N041**

Antibiotic	MIC	INT
<input type="checkbox"/> ESBL	POS	+
<input type="checkbox"/> Ampicillin	≥32	R
<input type="checkbox"/> Amoxicillin/ Clavulanic Acid	8	S
<input type="checkbox"/> Piperacillin	≥128	R
<input type="checkbox"/> Piperacillin/ Tazobactam	8	S
<input type="checkbox"/> Cefazolin	(-)	(-)
<input type="checkbox"/> Cefoxitin		

**GN**

Antibiotic	MIC	INT
<input type="checkbox"/> Cefotaxime	4	R
<input type="checkbox"/> Ceftriaxime	16	R
<input type="checkbox"/> Cefepime	≤1	S
<input type="checkbox"/> Imipenem	≤1	S
<input type="checkbox"/> Amikacin	≤2	S
<input type="checkbox"/> Gentamicin	≥16	R
<input type="checkbox"/> Netilmicin	≤1	S

**Advanced Reporting Tool Comments:**

**Internal Comments:**

Free text, for example:  
MIC Cipro 0.5 ATU

1. repeat test if suspicion of technical problem
2. perform an alternative MIC or genotypic test, if only few therapeutic alternatives
3. downgrade the susceptibility category if there are other therapeutic alternatives
4. include the uncertainty as part of the report
5. omit an uncertain result

**3.**

Antibiotic	MIC	INT
<input checked="" type="checkbox"/> Ciprofloxacin	0.5	S
<input type="checkbox"/> Norfloxacin	2	R
<input type="checkbox"/> Tetracycline	(-)	(-)
<input type="checkbox"/> Nitrofurantoin		
<input type="checkbox"/> Trimethoprim/ Sulfamethoxazole	≤20	S

# Introduction BDXpert system



RULE	IF	ORGANISM	AND	DRUG	AND		THEN	ACTION	AND	MESSAGE		
Logic Table by Organism					Enterobacterales					L009741(13) 2020-09		
Rule	IF:	Organism/Group	AND:	Drug(s)	AND:	Logic Criteria	THEN:	Action	AND:	Message Chartable Text	Application	Reference
959		Enterobacterales		ciprofloxacin		MIC is 0.5 mcg/mL		Print message		For <b>Enterobacterales</b> , a ciprofloxacin MIC of 0.5 mcg/mL is in an area of technical uncertainty (ATU) where reproducible interpretation cannot be achieved. Confirmation with another method is suggested.	Phoenix and EpiCenter Default MANUAL	EUCAST 2020 (V10.0) Enterobacterales
Customize to LIS												

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2000 series	Miscellaneous rules



# FOLLOW-UP

- bioMérieux will organise a webinar for VITEK users end October 2021
- BD Life Science provides support with planned software updates to individual clients

# Special thanks to:

- Cécile Malentjer, bioMérieux
- Jurgen Vandamme, bioMérieux
- Lut Van den Broecke, BD Life Science
- Eric Nulens, AZ Sint-Jan Brugge
- EUCAST: slides used for this presentation can be found in their original form at [www.eucast.org](http://www.eucast.org)