ESCMID MANAGING INFECTIONS PROMOTING SCIENCE

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

How clinical breakpoints are set

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ESCMID Postgraduate Course, Tallinn

Breakpoints - the decision process

Why should you bother?

Enterobacteriaceae 1975 – 2001

Committee	Amoxicillin	Cefotaxime	Piperacillin-tazob.
BSAC (UK)	8 / 16	2 / 2	16 / 16
CA-SFM (F)	4 / 16	4 / 32	8 / 64
CRG (NL)	2 / 16	4 / 8	0.25 / 4
DIN (D)	2 / 8	2 / 8	0.12 / 1
NCCLS (USA)	8 / 16	8 / 32	16 / 64
NWGA (N)	0.5 / 8	1 / 2	8 / 16
SRGA (S)	1 / 8	0.5 / 1	16 / 16

Who are the stakeholders?

EUCAST*	EMA, Europe, ++
CLSI	USA, ++
FDA	USA
Colleagues who know better	Everywhere

*Organizing the national committees in Europe and elsewhere (USCAST, CanCAST, AusNAC, BrCAST, ChiCAST)

The process of setting breakpoints

Discussions behind closed doors

- Companies are not allowed to take part of the closed discussions
- Detailed minutes of the discussion will be shared
- Iterative process of comments and responses, which can go on for several months, and overlap with EMA's LoQ
- Ultimately, EUCAST makes a decision
- EUCAST does not conduct any voting
- When the agent has been approved by EMA, breakpoints will be published on the EUCAST website
- A rationale document will be published on the EUCAST website

EUCAST in brief

- Systematic review (and revision) process for all breakpoints
- Open consultation on all major decisions except on breakpoints for new agents where confidentiality is respected
- Rapid turnaround time on all decisions
  - 5 meetings per year; not restricted by industry or national agencies; turnaround time on questions normally 1 h – 24 h
- All output free of charge on website (www.eucast.org)
- Laboratory facilities for development

The EUCAST decision process

- EUCAST, EMA, ECDC, EFSA, Colleagues, Laboratories, Industry may all suggest topics and decisions
- Steering Committee (or subcommittee) will prepare decisions
- Once Steering Committee members agree, national breakpoint committees are consulted
- Suggestions from national breakpoint committees are discussed in the Steering Committee and a revised decision prepared
- All major decisions go to a 6 week open General Consultation published on the website with a document for comments
- Comments (from colleagues, institutions, companies, etc) are discussed and a response to each (and a modified decision) prepared.
  Anonymous comments are not accepted
- The final decision with comments and responses are published on the website
- Decisions on new agents are between EMA, EUCAST and the pharma company. Confidentiality issues prevent open consultation

EUCAST SOPs for breakpoints

EUCAST controlled document	EUCAST SOP 1.4
Date of issue: 2 December 2021	Page 1 of 16

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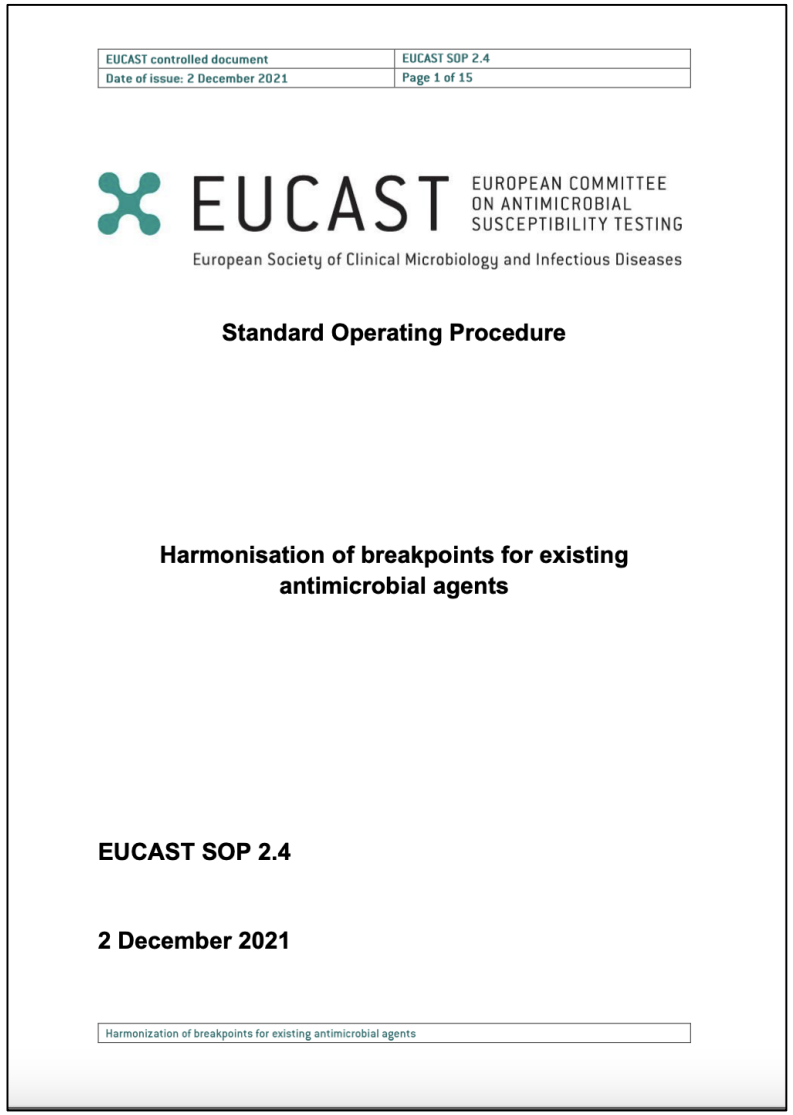
Standard Operating Procedure

Setting breakpoints for new antimicrobial agents

EUCAST SOP 1.4

2 December 2021

Setting breakpoints for new antimicrobial agents



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Standard Operating Procedure

Harmonisation of breakpoints for existing antimicrobial agents

EUCAST SOP 2.4

2 December 2021

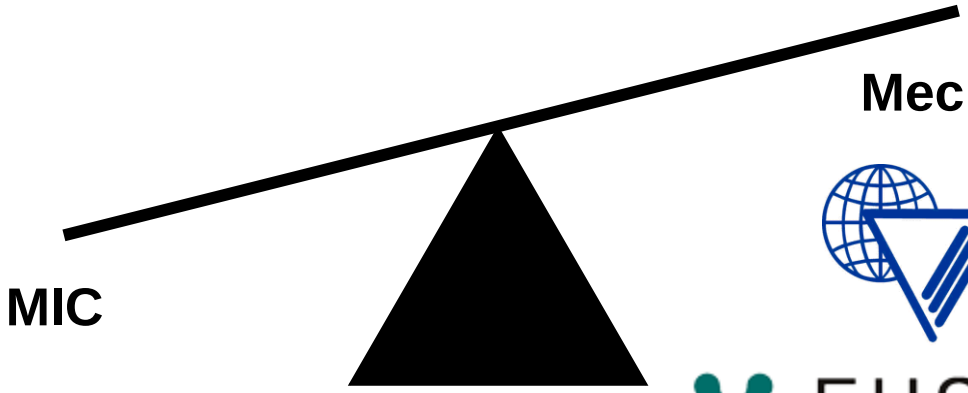
Harmonization of breakpoints for existing antimicrobial agents

Breakpoints – which data are considered?

The steps needed to set breakpoints

- Defining formulations, dosing regimens, indications, target microorganisms
- Establishing MIC-distributions for relevant species
- Defining pharmacokinetic (PK) data
- Defining pharmacodynamic (PD) targets (exposure vs response)
- Mathematical simulation of PD target attainments
- Considering clinical data related to exposure and/or MICs
- Considering important resistance mechanisms
- Integrating data
- Sometimes data are conflicting!

The MIC paradigm: MIC>mechanism



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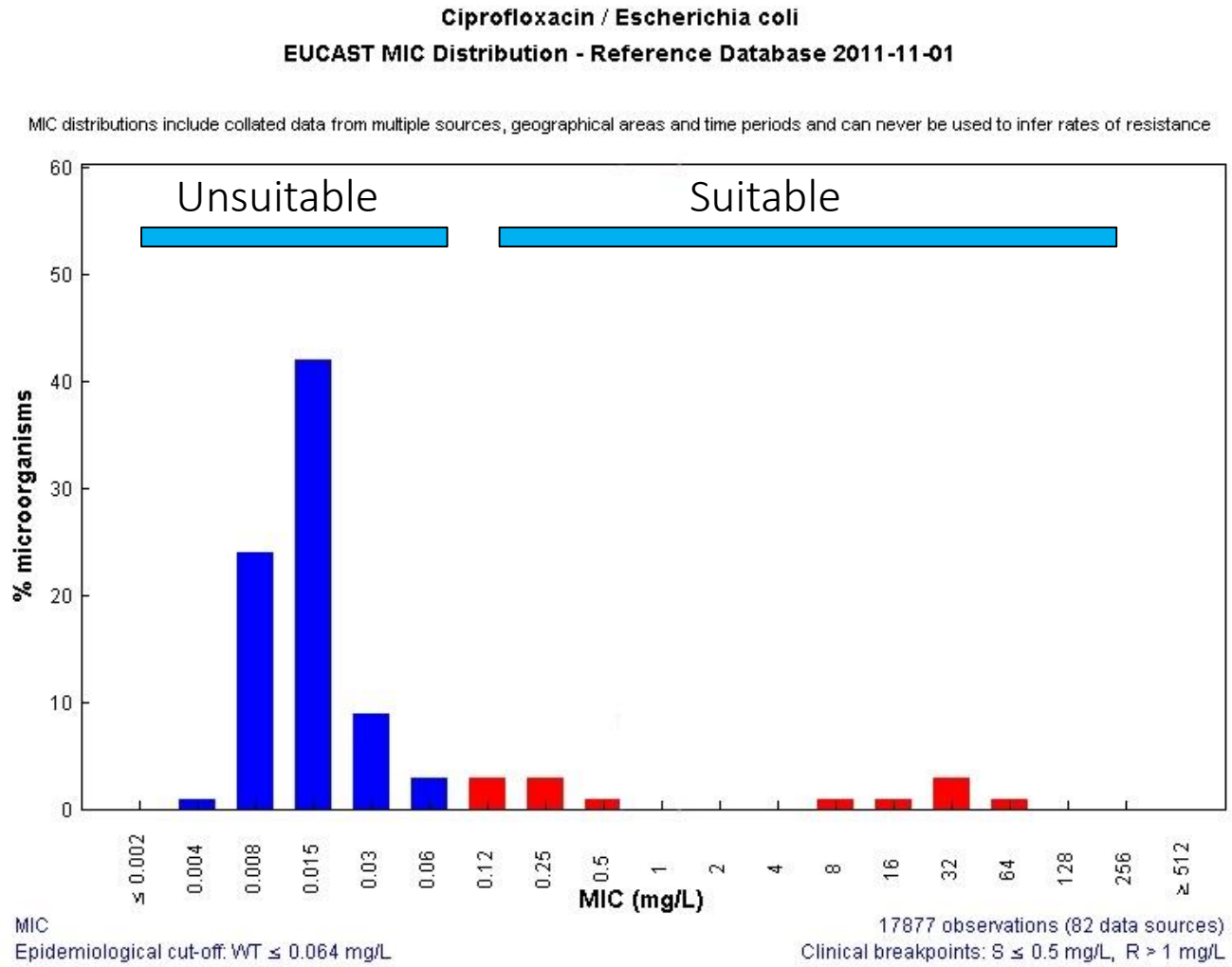
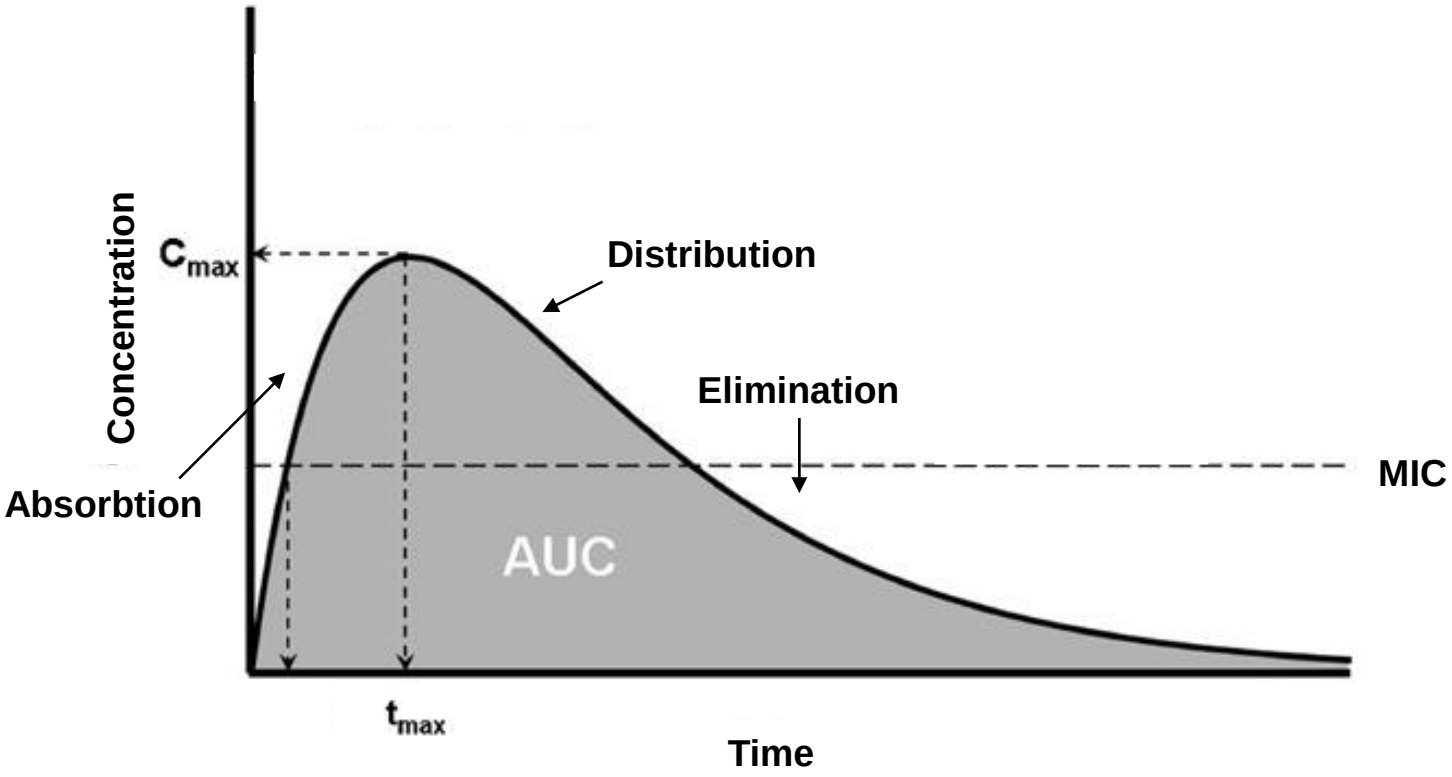
Where can the breakpoint be set?



Pharmacokinetics and – dynamics (PK-PD)



Pharmacodynamic targets

Antimicrobial	PD parameter	Target
Penicillins	%*f*T>MIC	50
Cephalosporins	%*f*T>MIC	50
Carbapenems	%*f*T>MIC	40
Fluoroquinolones	*f*AUC/MIC	Gram-positive: 40 Gram-negative: 80
Aminoglycosides	AUC/MIC	30-40
Tigecycline	AUC/MIC	Gram-positive: 12.5 Gram-negative: 7
Vancomycin	*f*AUC/MIC	180 (*S. aureus*)

Which drug has highest activity?

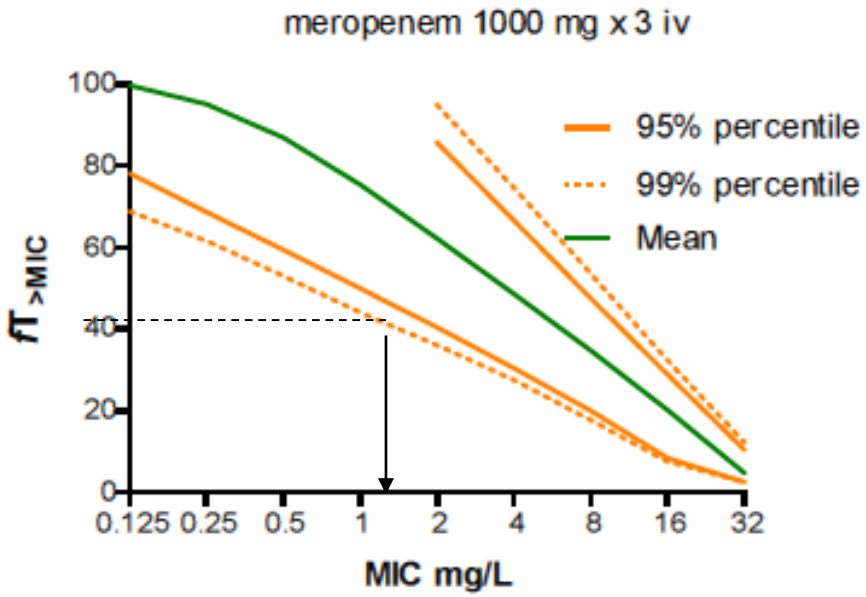
- Antimicrobial A: MIC 0.5 mg/L
- Antimicrobial B: MIC 8 mg/L

- Antimicrobial A: Area under serum concentration curve (AUC): 5
- Antimicrobial B: AUC 120

- Antimicrobial A: AUC/MIC=5/0.5=10
- Antimicrobial B: AUC/MIC=120/8=15

Simulation of target attainments

- PK-data from relevant patient populations and healthy volunteers are used
- Mathematical simulation to increase variability in the dataset
- Calculate probability of reaching a predefined target (e.g. T>MIC)
- 95% of the population should reach the target
- Always applies for one specific dosing regimen



Assessing clinical data

- Different types of clinical data:
  - Trust my bro – it always worked for me – my patients always do fine
  - Mostly the drug seems to work for the wild type (supports ECOFF bp)
  - MIC vs outcome data – with reference MIC (bp can be higher than ECOFF)
  - AUC/MIC or T>MIC vs outcome data
- Observational data showing good outcome in combination therapy: can't be used to support developing a breakpoint
- Unfortunately, many old clinical datasets are not useful for setting breakpoints – at most they will support ECOFF-based breakpoints

Rationale documents to support decisions

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Tigecycline: Rationale for EUCAST Clinical Breakpoints

Current version	**3.0**	**April 2023**
Previous versions	2.0 1.0	July 2022 March 2006

Introduction

Tigecycline is an injectable antibacterial derived from the tetracyclines and classified by the manufacturer as a glycylcycline. Its in vivo potency is similar to tetracyclines with the exception that it is active against many bacterial strains which are resistant to existing tetracyclines. It is available only in an intravenous formulation. Tigecycline is licenced for use in complicated skin and skin structure infections (CSSSI), complicated intra-abdominal infection (IAI).

This version is extracted from version 2.0, and will be format for future updates. Previous versions are available on request.

Dosages related to clinical breakpoints

Standard dosage: 50 mg x 2 iv, preceded by a 100 mg loading dose
High dosage: See Guidance document (https://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Guidance_documents/Tigecycline_Guidance_document_v2_20220720.pdf)

MIC distributions and epidemiological cut-off (ECOFF) values

MIC distributions and ECOFFs can be found at https://mic.eucast.org/Eucast2/SearchController/search.jsp?action=init

All breakpoints are dose-related

Dosages used to define breakpoints

EUCAST Clinical Breakpoint Tables v. 13.0, valid from 2023-01-01

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 used as a guidance for dosing in clinical practice as dosages can vary widely by indication. It does not replace specific national, regional or local 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 iv	(2 g ampicillin + 1 g sulbactam) x 3 iv	(2 g ampicillin + 1 g sulbactam) x 4 iv		
Ampicillin-sulbactam oral	None	None	0.75 g x 2 oral	
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 30-minute infusion or x 3 iv 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, 30-minute infusion, 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~~				
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	Dosages vary by indication		
Cloxacillin	0.5 g x 4 oral or 1 g x 4 iv	Dosages vary by indication		**Meningitis:** 2 g x 6 iv
Dicloxacillin	0.5-1 g x 4 oral or 1 g x 4 iv	Dosages vary by indication		
Flucloxacillin	1 g x 3 oral or 2 g x 4 iv (or 1 g x 6 iv)	Dosages vary by indication		**Meningitis:** 2 g x 6 iv
Mecillinam oral (pivmecillinam)	None	None	0.2-0.4 g x 3 oral	

If another dose is used, the breakpoints are not applicable

Now you will be the judge for some tricky decisions

Case 1

- ECOFF is 2 mg/L
- PK-PD suggests a breakpoint at 1 mg/L would be suitable
- Clinical data: non-reference MIC-data suggests a breakpoint at 1 mg/L would be suitable
- Dosing: not possible to increase dosing
- Which value do you select – 1 or 2 mg/L?
- Discuss in groups of 2-3

Case 2

- ECOFF is 2 mg/L
- PK-PD suggests a breakpoint at 0.5 mg/L would be suitable
- Clinical data: suggest that the drug works when focus in the urinary tract
- Dosing: not possible to increase dosing
- Which value do you select – 0.5? 2? Other value?
- Discuss in groups of 2-3

Concluding remarks

- The EUCAST system for setting breakpoint is described in publicly available standard operating procedures (SOPs)
- The rationale for individual breakpoints can be found in rationale documents on the EUCAST website
- EUCAST has a system with public consultations where anyone can respond (not anonymously)
- The main components in breakpoint setting are: definition of dosing regimens and target bacteria, assessment of clinical data, establishing MIC-distributions, and PK-PD
- Sometimes data with different methods are conflicting
- The breakpoint is never allowed to split the wild type population

Acknowledgements

- Colleagues in EUCAST – past and present

Karolinska Institutet, South Campus

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