EUCAST

European committee on antimicrobial susceptibility testing

ANTIBIOTIC RESISTANCE

Increasing year on year

↓

Agents to which pathogen is susceptible to are decreasing

BREAKPOINT

Determines if an organism is susceptible based on

Highest concentration of that antibiotic that can be achieved safely in a patient

BREAKPOINT

Predicts successful treatment against a specific organism

BREAKPOINT

Varies for different anatomical sites:-

C.S.F. versus Urinary Tract

DOSE

Dose important

↓

Eradication

Clinical Cure

CLASSICAL REPORTING ANTIBIOTIC SUSCEPTIBILITY

‘R’ Resistant

‘I’ Intermediate

‘S’ Susceptible

CLASSICAL 'INTERMEDIATE' IMPLIES:

1) Uncertain therapeutic effect

2) May work where high antibiotic levels attainable either due to anatomical site or higher dose

3) 'Buffer zone' for technical issues in the laboratory

NEW EUCAST guidelines

‘R’ Resistant

‘I’ Susceptible – increased exposure

‘S’ Susceptible, standard dose

CLINICAL RESPONSE TO 'I'

Previously = Avoid

Now – Ensure increased antibiotic concentration at infected site/s

INCREASED EXPOSURE HOW ?

- ↑ Dose
- ↓ Dosing interval
  Continuous infusion/oral to IV switch
- ↓ Excretion

EXPOSURE

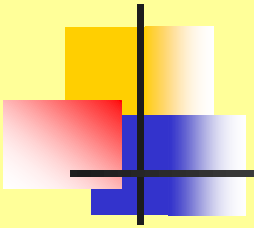
Concentration – time profile related to PK/PD of that antibiotic class

Pseudomonas spp

P. aeruginosa

P. fluorescens

P. putida



Pseudomonas spp

Opportunistic pathogens

but

Hard to treat

PSEUDOMONAS EUCAST BREAKPOINTS

Artificially decreased MIC values to 0.001 mg/L for some antibiotics to ensure they are never reported as susceptible with standard or traditional doses.

EUCAST – *Pseudomonas* sp

Breakpoints altered

↓

Gentamicin will always be reported as 'R'

GENTAMICIN USED FOR YEARS AGAINST *Pseudomonas* ?

Yes but typically in combination with a second antibiotic

THE PHARMACO–KINETICS OF TOBRAMYCIN SUPERIOR TO GENTAMICIN

∴ **Tobramycin is optimum aminoglycoside for *Pseudomonas* species**

TOBRAMYCIN

If treating a systemic infection always use in combination with a second antibiotic

MIC

Minimum inhibitory concentration

Where antibiotic causes visible cessation of growth in laboratory

PSEUDOMONAS

	Breakpoint
Piperacillin-tazobactam	≤ 0.00 1 mg/L
Ceftazidime	≤ 0.00 1 mg/L
Aztreonam	≤ 0.00 1 mg/L
Ciprofloxacin	≤ 0.00 1 mg/L

No longer will be reported as 'S'

Instead:- 'I – increased exposure'

Pseudomonas MAY BE 'S'

	Breakpoint
Meropenem	≤ 2 mg/L
Colistin	≤ 2 mg/L

CLINICAL

Reporting as 'I' ensures appropriate antibiotic use for clinical success

NEW EUCAST REPORTS

‘I’ or ‘S’ or ‘D’

“Increased exposure”

or

“Higher concentration”

or

Similar local comment

Children's Health Ireland at Crumlin - **Dept. of Microbiology**

Continuation Report for Lab No.: 21W01285 **INAB accredited testing lab Reg.no.375MT**

Name: | DOB: | Chart No.: | Source:

Susceptibility Result

1) Pseudomonas aeruginosa

	1)
Meropenem/Other	S
Tobramycin	S
Aztreonam	I
Ceftazidime	I
Cefepime	I
Ciprofloxacin	I
Imipenem	I
Levofloxacin	I
Pip/Tazo	I

Authorised by:

Sample Type: Swab of tracheostomy site ******INTERIM REPORT ******

Sample Taken: 05/04/21 , 22:00 Received: 06/04/21 , 07:02 Reported: 08/04/21 , 10:41

HOSPITAL ANTIBIOTIC FORMULARY

Recommended doses adjusted to reflect new EUCAST guidelines

Enterobacterales

Antibiotic	New Breakpoints	MIC	
Amoxicillin-clavulanic acid	1. Other infections	S ≤8	R >8
	2. Uncomplicated UTI only	S ≤32	R >32
Cefuroxime	1. IV *E. coli, Klebsiella spp. (except K. aerogenes), Raoultella spp. and P. mirabilis.*	S ≤0.001	R >8
	2. Oral (uncomplicated UTI only)	S ≤8	R >8
Cefotaxime **Ceftriaxone** **Meropenem**	New breakpoints specifically for meningitis (breakpoint for R category lowered)	S ≤1 S ≤1 S ≤2	R >1 R >1 R >2
Fosfomycin	1. Uncomplicated UTI only, E. coli	S ≤8	R >8
	2. IV (unchanged)	S ≤32	R >32

Cefuroxime

- Breakpoint for IV use artificially reduced to $\leq$ 0.001 mg/L
  - Ensures no longer reported as Susceptible at standard dose
- Will now be reported as "Susceptible increased exposure"
  - Higher dose of **1.5g TDS IV** should be used.

Aminoglycosides

- For systemic infections, aminoglycosides must be used in combination with other active therapy.
- When reporting include a comment in the report:

  "Aminoglycosides are often given in combination with other agents, either to support the activity of the aminoglycoside or to broaden the spectrum of therapy. In systemic infections, the aminoglycoside must be supported by other active therapy."

Tobramycin versus Gentamicin for the treatment of *P. aeruginosa* infections

1. Dosage
2. MIC distributions and ECOFF values
3. PK/PD
4. Clinical data

Dosage

- Current EUCAST breakpoints based on
  - Tobramycin 6-7 mg/kg/day single dose
  - Gentamicin 6-7 mg/kg/day single dose

MIC distributions and ECOFF values for *P. aeruginosa*

- Tobramycin ECOFF= 2mg/L, WT ≤ 2
- Gentamicin ECOFF= 8mg/L, WT ≤ 8
- Amikacin ECOFF =16mg/L ,WT ≤ 16

- "Tobramycin is significantly more potent against *P. aeruginosa* than the other agents"

Rationale for the EUCAST clinical breakpoints, version 2. 30 April, 2020. Tobramycin. Gentamicin

PK/PD

- Gentamicin & Tobramycin have sufficiently similar PK & PD properties to receive same breakpoints both throughout.
- Gentamicin slightly lower volume of distribution, unlikely significant.

Clinical data

- Tobramycin is recommended over gentamicin in CF patients[1]
  - Increased renal toxicity with gentamicin in comparison to tobramycin [2]
  - Lack of studies showing efficacy with gentamicin

1. Pediatr Pulmonol . 2013 Nov;48(11):1047-61. Epub 2013 Sep 2. Optimization of anti-pseudomonal antibiotics for cystic fibrosis pulmonary exacerbations: V. Aminoglycosides
2 Smyth A, Lewis, S, Bertenshaw C, Choonara I, McGaw J, Watson A. Case-control study of acute renal failure in patients with cystic fibrosis in the UK. Thorax 2008; 63:532–535.

Clinical data – CF guidelines

- Eradication therapy (in combination) inhaled for 28 days
- Chronic infection – inhaled for 28 days alternating cycles

ECFS best practice guidelines: the 2018 revision. Journal of Cystic Fibrosis, Volume 17, Issue 2, March 2018, Pages 153-178

Mogayzel PJ, Naureckas ET, Robinson KA, Mueller G, Hadjiliadis D, Hoag JB, et al. Cystic fibrosis pulmonary guidelines. Am J Respir Crit Care Med 2013;187:680–9. https://doi.org/10.1164/rccm.201207-1160OE.

Clinical data – other patients

- Historic data
- Some evidence that tobramycin causes nephrotoxicity less frequently than gentamicin (19 v. 9, 26% v 12%) [1]
- Similar clinical efficacy [2]

1. N Engl J 1980 May 15;302(20):1106-9. doi: 910.1056/NEJM198005153022002. Double-blind comparison of the nephrotoxicity and auditory toxicity of gentamicin and tobramycin.
2. Antimicrob Agents Chemother. 1974 Feb; 5(2): 133–138. doi: 10.1128/aac.5.2.133 Comparative Clinical Study of Tobramycin and Gentamicin

EUCAST Piperacillin-tazobactam dosing changes

Date	Standard dose	Increased dose	Special circumstances
2020	(4 g piperacillin + 0.5g tazobactam) x 3 iv	(4 g piperacillin + 0.5 g tazobactam) x 4 iv	
2021	(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.

Dosing proposal

Situation	Proposed piperacillin-tazobactam dosing regimen
Cystic fibrosis patients with *Ps.aeruginosa* colonisation	High dose 4.5g QDS extended infusion over 3 hours
Any systemic infection where *Ps.aeruginosa* is a pathogen	As above
Any respiratory infection where piperacillin-tazobactam is indicated	4.5g QDS over 30-60 minutes
Infections involving Enterobacterales resistant to cephalosporins and non ESBL	4.5g QDS over 30-60 minutes
Intra-abdominal infection with inadequate drainage/source control	4.5g QDS over 30-60 minutes
Other indications	4.5g TDS over 30-60 minutes

Ref: Personal communication HMD with Prof Gunnar Kahlmeter, Prof Christian Giske, Prof John Turnidge EUCAST Steering Committee members

Haemophilus influenzae

- Screen for beta-lactam resistance mechanisms following EUCAST guidelines/algorithm.
- Report susceptibility based on phenotypic results
- Exceptions

1. oral amoxicillin and co-amoxiclav which will be reported as “susceptible, increased exposure”

2. Meropenem IV for treatment of *H. influenzae* meningitis

Antimicrobial	MIC		Dose
	S	R	
Amoxicillin oral	≤0.001	> 2	750mg – 1000mg TDS
Co-amoxiclav oral	≤0.001	> 2	875mg/125mg tablet TDS
Meropenem IV (other than meningitis)	≤2	>2	1g TDS
Meropenem IV (meningitis)	≤0.25	>0.25	2g TDS (over 30 minutes or infuse over 3 hours)