GIG CYMRU NHS WALES | Iechyd Cyhoeddus Cymru Public Health Wales

5th September 2024

The role and use of Guidance documents: What to do when there are no breakpoints?

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EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING

European Society of Clinical Microbiology and Infectious Diseases

- 1st BP table published 2010

Organism groups

14 in 2010 → 37 in 2024

Organism	2010	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024
Enterobacteriaceae/ Enterobacterales	y	y	y	y	y	y	y	y	y	y	y	y	y	y
Pseudomonas spp.	y	y	y	y	y	y	y	y	y	y	y	y	y	y
Stenotrophomonas maltophilia		y	y	y	y	y	y	y	y	y	y	y	y	y
Acinetobacter spp.	y	y	y	y	y	y	y	y	y	y	y	y	y	y
Staphylococcus spp.	y	y	y	y	y	y	y	y	y	y	y	y	y	y
Enterococcu spp.	y	y	y	y	y	y	y	y	y	y	y	y	y	y
Streptococcus groups A, B, C and G	y	y	y	y	y	y	y	y	y	y	y	y	y	y
Streptococcus pneumoniae	y	y	y	y	y	y	y	y	y	y	y	y	y	y
Other streptococci	y													
Viridans group streptococci		y	y	y	y	y	y	y	y	y	y	y	y	y
Haemophilus influenzae	y	y	y	y	y	y	y	y	y	y	y	y	y	y
Moraxella catarrhalis	y	y	y	y	y	y	y	y	y	y	y	y	y	y
Neisseria gonorrhoeae	y	y	y	y	y	y	y	y	y	y	y	y	y	y
Neusseria meningitidis	y	y	y	y	y	y	y	y	y	y	y	y	y	y
Gram positive anaerobes	y	y	y	y	y	y	y	y	y	y	y	y		
Gram negative anaerobes	y	y	y	y	y	y	y	y	y	y	y	y		
Bacteroides spp.													y	y
Prevotella spp.													y	y
Fusobacterium necrophorum													y	y
Clostridium perfringens													y	y
Cutibacterium acnes													y	y
Clostridium/ Clostridioides difficile		y	y	y	y	y	y	y	y	y	y	y	y	y
Helicobacter pylori		y	y	y	y	y	y	y	y	y	y	y	y	y
Listeria monocytogenes		y	y	y	y	y	y	y	y	y	y	y	y	y
Pasteurella multocida/ Pasteurella spp.			y	y	y	y	y	y	y	y	y	y	y	y
Campylobacter jejuni and coli			y	y	y	y	y	y	y	y	y	y	y	y
Corynebacterium spp except C. diphtheriae				y	y	y	y	y	y	y	y	y	y	y
Corynebacterium diphtheriae and C. ulcerans														y
Aerococcus sanguinicola and urinae							y	y	y	y	y	y	y	y
Kingella kingae							y	y	y	y	y	y	y	y
Aeromonas spp.								y	y	y	y	y	y	y
Achromobacter xylosoxidane											y	y	y	y
Vibrio spp.													y	y
Bacillus spp. except B. anthracis											y	y	y	y
Bacillus anthracis														y
Brucella melitensis														y
Burkholderia pseudomallei										y	y	y	y	y
Burkholderia cepacia complex										y	y	y	y	y
Legionella. pneumophila										y	y	y	y	y
Mycobacterium tuberculosis					y	y	y	y	y	y	y	y	y	y

Species identified across Wales, 2023

		Blood Cultures		Tissues	
		Number	%age	Number	%age
Species reported	Covered by EUCAST	196	58.3	178	55.3
	Not covered by EUCAST	140	41.7	144	44.7
	TOTAL	336		322	
Organisms Reported to Species level	Covered by EUCAST	15,294	95.1	7,572	92.5
	Not covered by EUCAST	787	4.9	616	7.5
	TOTAL	16,081		8,188	

In 2013, only 139 different species reported from Blood Cultures

Abiotrophia	Eikenella	Micrococcus
Achromobacter	Elizabethkingia	Moraxella
Actinobaculum	Enterocloster	Myroides
Actinomyces	Erysipelothrix	Neisseria
Actinotignum	Eubacterium	Odoribacter
Aerococcus	Facklamia	Oligella
Aggregatibacter	Fannyhessea	Paenibacillus
Agrobacterium	Finegoldia	Paracoccus
Alcaligenes	Fusbacterium	Parvimonas
Anaerobiospirillium	Gemella	Pepticoccus
Anaerococcus	Globicatella	Peptoniphilus
Arcanobacterium	Gordonia	Peptostreptococcus
Atopbium	Granulicatella	Porphyromonas
Brevibacterium	Haemophilus	Propionibacterium
Brevundimonas	Helcococcus	Propionimicrobium
Campylobacter	Hungella	Rhodococcus
Capnocytophaga	Janibacter	Roseomonas
Chryseobacterium	Kocuria	Rothia
Clostridium	Lactabacillus	Ruminococcus
Delftia	Lancefieldella	Shewenella
Dermabacter	Leclercia	Solobacterium
Dermacoccus	Leptotrichia	Tissierella
Dialister	lysinibacillus	Veillonella
Eggerthella	Microbacterium	

71 organism groups from Blood Cultures/ Tissues with no EUCAST guidance

Organization
Public consultations
EUCAST News
Definitions of S, I and R
Clinical breakpoints and dosing
Rapid AST in blood cultures
Expert rules and expected phenotypes
Resistance mechanisms
Guidance documents
SOP
MIC and zone distributions and ECOFFs
AST of bacteria
AST of mycobacteria
AST of fungi
AST of veterinary pathogens
AST of phages
Frequently Asked Questions (FAQ)
Meetings
Rationale documents and publications
Presentations and statistics
Videos and online seminars
Warnings!
Translations
Information for industry
Links and Contacts

Website changes

Guidance Documents

EUCAST Guidance Documents

- Cefiderocol MIC broth microdilution guide (1 January, 2024). See also the Warning on cefiderocol susceptibility testing.
- When there are no breakpoints! (29 February, 2024). Previous version (30 June, 2023), Previous version (1 December 2021 - 30 June, 2023), Previous version (5 July, 2016 - 1 December 2021).
- Guidance on the use of fosfomycin intravenously (28 May, 2024); Previous version (5 December, 2023).
- ATU - the Area of Technical Uncertainty - Guidance to laboratories on how to deal with the antimicrobial susceptibility testing (originally published 2018; updated 2019, 2020, 2022, and 8 February 2024).
  Graphs to illustrate ATUs (Updated 5 February, 2024).
- Guidance on the use of ceftriaxone and cefotaxime in Staphylococcus aureus (8 February, 2023)
- Aminopenicillin breakpoints Enterobacterales following revision 2023 - guidance on implementation (14 January, 2023; an error in the flowchart was corrected on Sept 15, 2023).
- Setting breakpoints for agent-inhibitor combinations (14 December, 2021). Previous version of Setting breakpoints for agent-inhibitor combinations (2 October, 2017).
- Breakpoints in brackets in breakpoint tables (2 December 2021)
- Phenotypic screening tests to detect and exclude resistance of clinical relevance (update 22 August, 2022). Previous version (13 June, 2022). Previous version (2 Febr, 2022). Previous version (1 Dec 2021)
- Implementation and use of the 2022 revised colistin breakpoints (January, 2022; minor edits on previous version from Nov, 2021)
- Legionella pneumophila susceptibility testing (30 May, 2021); previous version Legionella pneumophila susceptibility testing (11 Dec, 2017)
- Implementation and use of the 2020 revised aminoglycoside breakpoints (first published 21 Jan, 2020; updated April 2020)
- Daptomycin in endocarditis and bloodstream infections caused by enterococci (also available in CMI as a EUCAST position paper; 2020)
- Breakpoints for topical use of antimicrobial agents (revised 12 April 2022, 21 Nov, 2019; 22 Dec, 2016)
- Guidance for industry on the working order between pharmaceutical industry, EMA and EU (5 May, 2019)
- Cefotaxime and ceftazidime disks with and without clavulanic acid for ESBL confirmation (12 February, 2019)
- Guidance on tigecycline dosing, 21 July, 2022. Previous version (23 December, 2018)
- The 2019 modifications of susceptibility categories S, I and R categories (22 October, 2018).
  This presentation also informs laboratories on how to implement the Area of Technical Uncertainty.
- EUCAST system for antimicrobial name abbreviations (January 2022). Previous version (13 July, 2018)
- Recommendations for colistin (polymyxin E) MIC testing - joint EUCAST and CLSI recommendation (22 March, 2016)
- Burkholderia cepacia complex (20 July, 2013)
- Stenotrophomonas maltophilia (1 Feb 2012)
- Oral cephalosporins and Enterobacterales breakpoints (14 July, 2020).
  Previous version (16 Feb 2012)
- Direct susceptibility testing (16 Feb 2012), See also "EUCAST Rapid AST directly from positive blood culture bottles"

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EUCAST guidance on

When there are no breakpoints in breakpoint tables?

2024-02-29

In breakpoint tables, there are some species/species groups and antimicrobial agents lacking numerical breakpoints to allow categorical interpretation to S, I or R or a dash to allow the reporting of “resistant” without testing.

The most probable sequence of events in the laboratory is as follows (see also the flowchart):

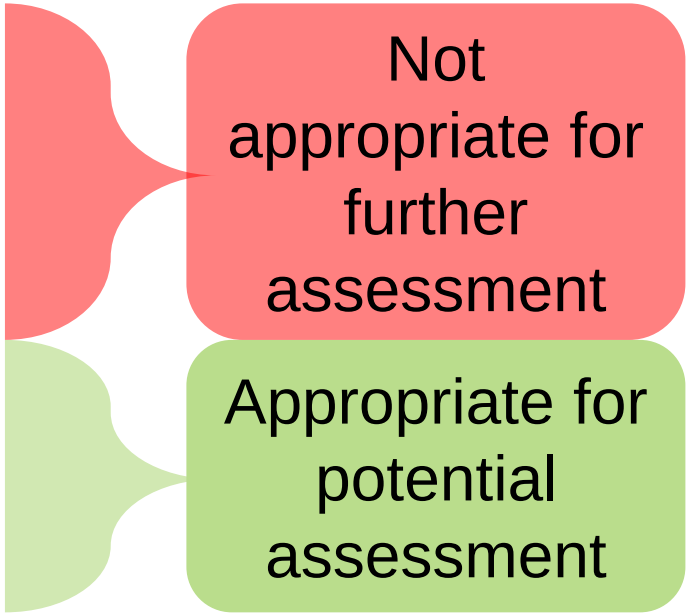
Why there is no BP?

- Organisms
  - Genus/Species not represented in BP tables
    - Less common organisms
      - *Erysipelothrix rhusiopathiae*,
      - *Streptomyces* spp.,
      - non-jejuni, non-coli, *Campylobacter* spp.
      - Many anaerobes

Appropriate for potential assessment

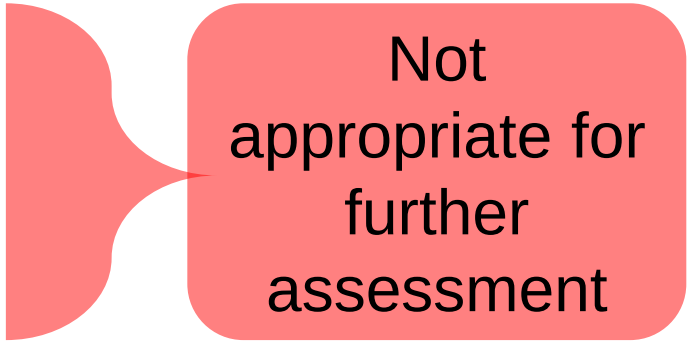
Why there is no BP?

- Organisms
  - Genus/Species present in BP tables but no BP for agent
    - Dash "-" means the agent is considered unsuitable for treatment of infections caused by this organism
    - IE means that there is insufficient evidence that the organism is a good target for therapy



Why there is no BP?

- Organisms
  - Genus/Species present in BP tables but no BP for agent
    - Organisms where reliable method not currently possible
      - *Stenotrophomonas maltophilia*
      - *Burkholderia cepacia* complex



Why there is no BP?

- Agents
  - New agents
    - Breakpoints for new agents are set as the agents go through their EMA application and are released if the agent is granted approval

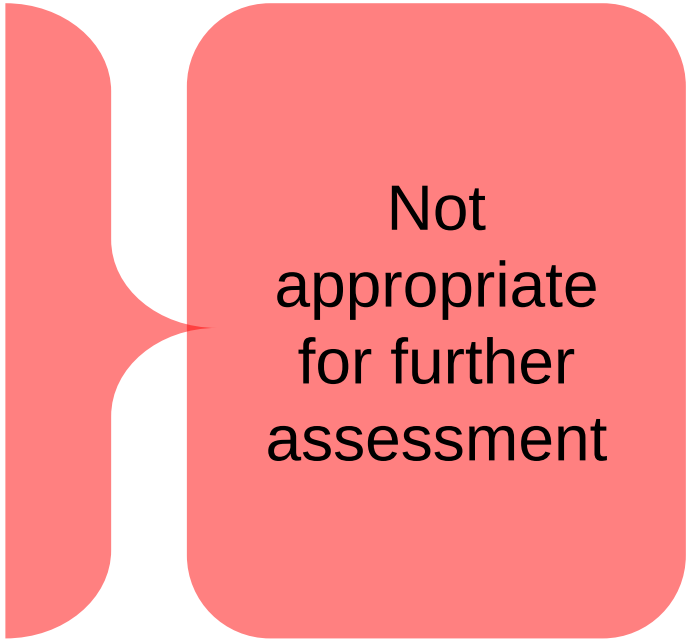
Appropriate for potential assessment

  - Old agents
    - Finding a new use due to developing resistance (e.g., temocillin, nitroxoline)

Appropriate for potential assessment

Why there is no BP?

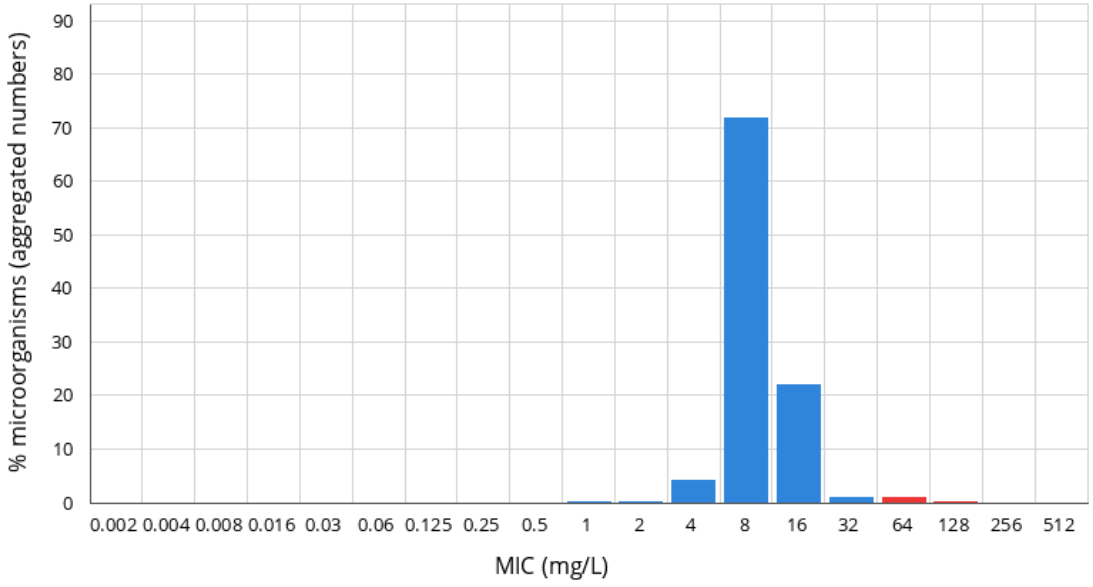
- Agent vs Organism
  - EUCAST has determined BPs for some species within a genus/family
    - Enterobacterales
      - Temocillin
      - Mecillinam
      - Cefazolin
      - Cefuroxime
      - Imipenem
      - Tigecycline
      - Fosfomycin
      - Nitrofurantoin



Miscellaneous agents	MIC breakpoints (mg/L)			Disk content (µg)	Zone diameter breakpoints (mm)		
	S ≤	R >	ATU		S ≥	R <	ATU
Chloramphenicol	-	-			-	-	
Colistin	-	-			-	-	
Daptomycin[1]	IE	IE			IE	IE	
Fosfomycin iv	-	-			-	-	
Fosfomycin oral	-	-			-	-	
Fusidic acid	-	-			-	-	
Lefamulin	Note[2]	Note[2]			Note[A]	Note[A]	
Metronidazole	-	-			-	-	
Nitrofurantoin (uncomplicated UTI only), *E. faecalis*	64	64		100	15	15	

Nitrofurantoin / Enterococcus faecalis
International MIC distribution - Reference database 2022-09-27
Based on aggregated distributions

MIC distributions include collated data from multiple sources, geographical areas and time periods and can never be used to infer rates of resistance

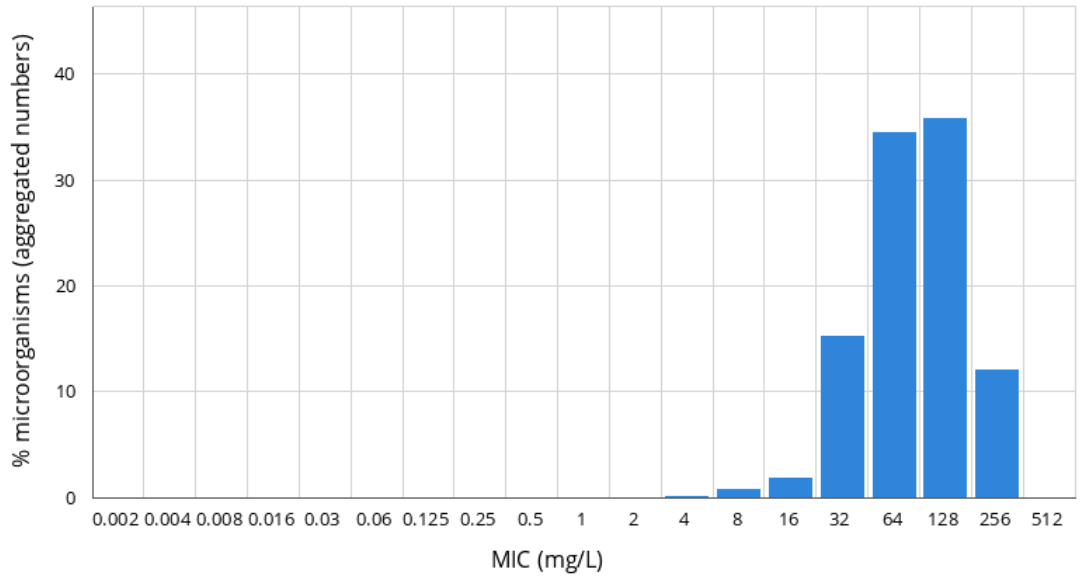


MIC
Epidemiological cut-off (ECOFF): (32) mg/L
Wildtype (WT) organisms: ≤ 32 mg/L

Confidence interval: -
746 observations (3 data sources)

Nitrofurantoin / Enterococcus faecium
International MIC distribution - Reference database 2022-09-27
Based on aggregated distributions

MIC distributions include collated data from multiple sources, geographical areas and time periods and can never be used to infer rates of resistance



MIC
Epidemiological cut-off (ECOFF): 256 mg/L
Wildtype (WT) organisms: ≤ 256 mg/L

Confidence interval: -
2185 observations (13 data sources)

Process if no published BP

- Aim to provide guidance to encourage or discourage use of an agent
  - Do not report categorical (S, I, R) results in general

Review the literature

- Clinical relevance of the species
- Antimicrobials that may be expected to be active and relevant to test
- Species growth characteristics

Absolute requirement

- Reliable reproducible MIC performed by a reference method
  - Broth microdilution for aerobes using MH or MH-F
  - Agar dilution for anaerobes using FAA-HB
  - **NOT** disc diffusion
  - **NOT** gradient tests (unless validated for species by manufacturer)

Refer to EUCAST MIC distribution website

- If non-wild type, implies resistance mechanism

Include a comment to discourage therapy

- If wild type, do not immediately consider the isolate susceptible to the agent, …
- If impossible to determine whether the isolate belongs to the wild type, …

Follow guidance below

- Numerical values determined from
  - a compromise between current EUCAST susceptible (S or I) breakpoints for anaerobic species already in the tables,
  - wild type distributions for microorganisms when available and
  - PK/PD cut-off values

Table 1: Aerobic Bacteria

	MIC-values above which therapy with the agent should be discouraged		
Agents and notes for aerobic bacteria	**Gram-positive organisms**	**Gram-negative organisms**	**Notes**
Benzylpenicillin	0.25	0.5	If a beta-lactamase is detected, report resistant without further testing.
Ampicillin, Amoxicillin, Ampicillin-sulbactam, Amoxicillin-clavulanic acid (IV only)	0.5	8	The breakpoint of 8 mg/L pertains to intravenous high dose administration. If a beta-lactamase is detected, the value is only valid for amoxicillin-clavulanic acid and ampicillin-sulbactam.
Piperacillin-tazobactam	1	8	Species specific breakpoints for gram-positive organisms are 0.25 – 1 mg/L, and for gram-negative organisms 8 – 16 mg/L
Cefotaxime	0.5	0.5	Cefotaxime and ceftriaxone – resistance to either excludes the use of both.
Ceftriaxone	0.5	0.5	Cefotaxime and ceftriaxone – resistance to either excludes the use of both.
Ceftazidime	-	4	This is the Enterobacterales R-breakpoint.
Imipenem	2	2	Species specific breakpoints are often 2 mg/L.
Meropenem	2	2	Species specific breakpoints are 0.25 – 2 mg/L
Ciprofloxacin	0.25	0.25	Species specific breakpoints are 0.25 – 1 mg/L.
Levofloxacin	0.5	0.5	Species specific breakpoints are 0.25 – 1 mg/L.
Moxifloxacin	0.25	0.25	Species specific breakpoints are 0.125 – 0.5 mg/L
Clindamycin	0.5	NA	Species specific breakpoints are 0.25 – 0.5 mg/L.
Tetracycline (test tetracycline, report doxycycline, minocycline)	2	2 For Gram-negative organisms other than Enterobacterales	Tetracycline (as a representative for tetracycline, doxycycline, and minocycline) species specific breakpoints are 0.5 – 2 mg/L.
Trimethoprim-sulfamethoxazole	1	1	Species specific breakpoints are 0.5 – 2 mg/L.
Tigecycline	0.5	NA	Species specific breakpoints are 0.125 – 0.5 mg/L.
Rifampicin	0.125	NA	Species specific breakpoints are 0.06 – 0.125 mg/L.
Linezolid	2	NA	Species specific breakpoints are 2 - 4 mg/L
Vancomycin	2	NA	Species specific breakpoints are 2 mg/L.
Dalbavancin	0.125	NA	Species specific breakpoints are 0.125 mg/L.
Daptomycin	1	NA	Species specific breakpoints are 1 mg/L.

- Numerical values determined from
  - a compromise between current EUCAST susceptible (S or I) breakpoints for anaerobic species already in the tables,
  - wild type distributions for microorganisms when available and
  - PK/PD cut-off values

Table 2: Anaerobic Bacteria

Agents and notes for anaerobic bacteria	MIC-values above which therapy with the agent should be discouraged	
Benzylpenicillin	0.5	Breakpoints for anaerobic bacteria in the breakpoint table are 0.06 – 0.5 mg/L. If a beta-lactamase is detected, report resistant without further testing.
Amoxicillin	0.5	Breakpoints for anaerobic bacteria in the breakpoint table are 0.25 – 0.5 mg/L. If a beta-lactamase is detected, report resistant without further testing.
Amoxicillin-clavulanic acid	0.5	Breakpoints for anaerobic bacteria in the breakpoint table are 0.25 – 0.5 mg/L.
Ampicillin-sulbactam	0.5	Breakpoints for anaerobic bacteria in the breakpoint table are 0.25 – 0.5 mg/L.
Piperacillin-tazobactam	2	Breakpoints for anaerobic bacteria in the breakpoint table are 0.5 – 2 mg/L.
Meropenem	1	Breakpoints for anaerobic bacteria in the breakpoint table are 0.03 – 1 mg/L.
Imipenem	1	Breakpoints for anaerobic bacteria in the breakpoint table are 0.03 – 1 mg/L
Ertapenem	0.25	Breakpoints for anaerobic bacteria in the breakpoint table are 0.06 – 0.5 mg/L
Clindamycin	0.5	Breakpoints for anaerobic bacteria in the breakpoint table are 0.25 mg/L.
Metronidazole	4	Breakpoints for anaerobic bacteria in the breakpoint table are 0.5 - 4 mg/L.
Vancomycin (Gram-positive)	2	Only relevant for a few gram-positive anaerobic bacteria. A breakpoint of 2 mg/L is common for targeted species.
Rifampicin (Gram-positive)	0.125	Breakpoints for species already in the EUCAST breakpoint tables are 0.06 – 0.125 mg/L.
Linezolid (mixed infections)	Pending	Linezolid has been used in the treatment of mixed infections where anaerobic bacteria were considered causative, but rarely for targeted therapy of anaerobic infections.
Moxifloxacin (mixed infections)	Pending	Moxifloxacin has been used in the treatment of mixed infections where anaerobic bacteria were considered causative, but rarely for targeted therapy of anaerobic infections.

Reporting

- If unable to determine an MIC:
  - "An MIC could not be determined and characterising the susceptibility of the microorganism is impossible"

- An MIC could be determined:
  - The analysis suggests discouraging the use of the agent.
    - "Formal categorising of the susceptibility of the organism is not possible. The MIC suggests that the agent should not be used for therapy".
    - The MIC-value may be added.
    - Consider reporting as "R" in obvious cases.
  - The analysis suggests cautiously encouraging the use of the agent.
    - "Formal categorising of the susceptibility of the organism is not possible. A cautious interpretation suggests that the agent may be considered for therapy."
    - The MIC-value may be added.

Case Report

Rothia mucilaginosa Meningitis in a Child with Myelodysplastic Syndromes

Ochi F, et al. Case Reports in Paediatrics (2021)

Case Report

Rothia mucilaginosa Meningitis in a Child with Myelodysplastic Syndromes

- Literature review
  - Review of 16 cases – recommended high-dose ampicillin plus rifampicin
  - All sensitive to penicillin, meropenem, vancomycin – 33% oxacillin resistant
  - Bacteraemia isolates resistant to beta-lactams, sensitive to vancomycin
  - Report sensitivity rates of 3% penicillin, 0% oxacillin, 76% cefazolin, 73% meropenem, 100% vancomycin
  - Recommendation of vancomycin

Case Report

Rothia mucilaginosa Meningitis in a Child with Myelodysplastic Syndromes

Agent	MIC (mg/L)
Benzylpenicillin	0.06
Piperacillin-tazobactam	<0.25
Ceftriaxone	0.25
Linezolid	1
Meropenem	0.5
Vancomycin	1

Ochi F, et al. Case Reports in Paediatrics (2021)

Case Report

Rothia mucilaginosa Meningitis in a Child with Myelodysplastic Syndromes

Antimicrobial wild type distributions of microorganisms

Mic distributions include collated data from multiple sources, geographical areas and time periods and can never be used to infer rates of resistance

Search database

Method ◉ **MIC** ○ **Disk diffusion**

Antimicrobial Antimicrobial ...

Species Rothia mucilaginosa

Elements per page 50

MIC distributions for Rothia mucilaginosa, 2024-09-01

Species: Rothia mucilaginosa (Method: MIC)

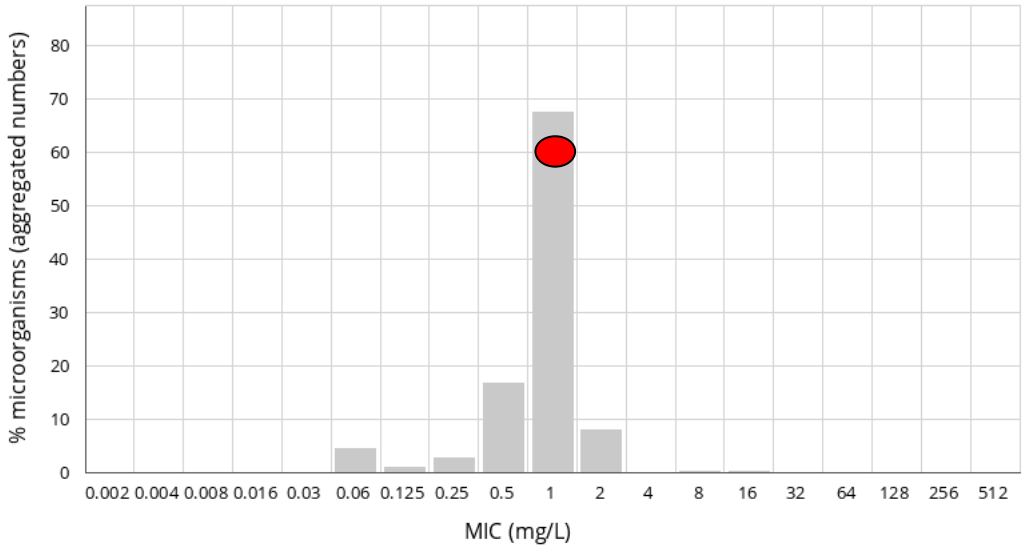
	0.002	0.004	0.008	0.016	0.03	0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	512	Distributions	Observations	(T)ECOFF	Confidence interval
Ceftriaxone	0	0	0	65	41	229	114	117	115	92	48	27	6	10	0	0	0	0	0	2	864	-	
Clindamycin	0	0	0	24	61	72	104	150	150	122	58	109	0	0	0	0	0	0	0	2	850	ID	
Doxycycline	0	0	0	0	0	0	66	175	149	44	11	15	53	33	0	0	0	0	0	1	546	ID	
Erythromycin	0	0	0	0	0	0	639	47	50	26	17	12	54	0	0	0	0	0	0	2	845	-	
Gentamicin	0	0	0	0	0	0	45	35	106	193	375	56	28	8	0	0	0	0	0	2	846	-	
Levofloxacin	0	0	0	0	0	0	0	77	153	47	17	24	57	178	0	0	0	0	0	1	553	ID	
Linezolid	0	0	0	0	0	0	22	81	435	299	9	0	0	0	0	0	0	0	0	2	846	-	
Rifampicin	0	0	0	0	0	0	0	290	540	3	2	1	7	0	0	0	0	0	0	2	843	-	
Trimethoprim-sulfamethoxazole	0	0	0	0	0	85	29	214	93	73	91	263	0	0	0	0	0	0	0	2	848	-	
Vancomycin	0	0	0	0	0	37	8	23	141	571	66	0	1	1	0	0	0	0	0	2	848	-	

Case Report

Rothia mucilaginosa Meningitis in a Child with Myelodysplastic Syndromes

Vancomycin / Rothia mucilaginosa
International MIC distribution - Reference database 2022-09-27
Based on aggregated distributions

MIC distributions include collated data from multiple sources, geographical areas and time periods and can never be used to infer rates of resistance

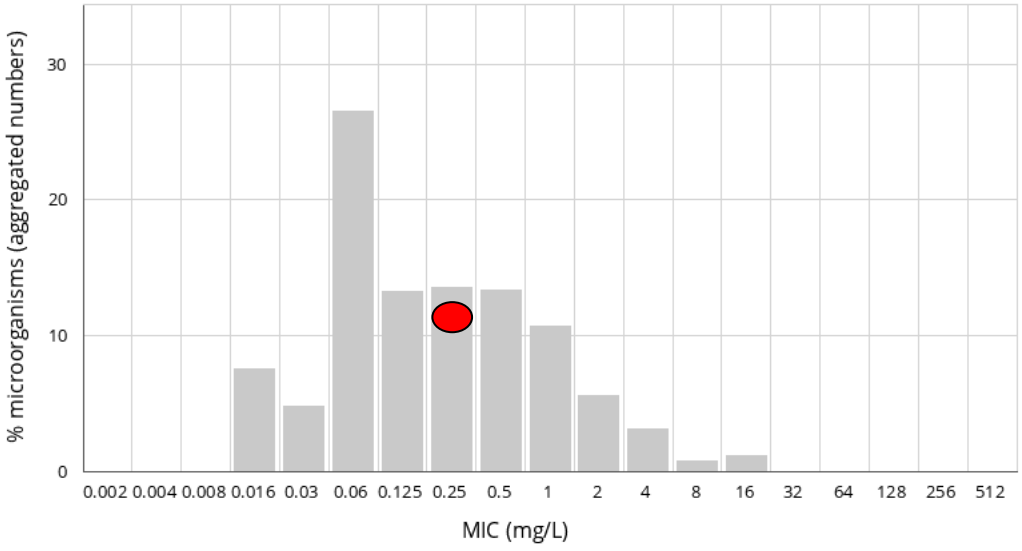


MIC
Epidemiological cut-off (ECOFF): -

Confidence interval: -

Ceftriaxone / Rothia mucilaginosa
International MIC distribution - Reference database 2022-09-27
Based on aggregated distributions

MIC distributions include collated data from multiple sources, geographical areas and time periods and can never be used to infer rates of resistance

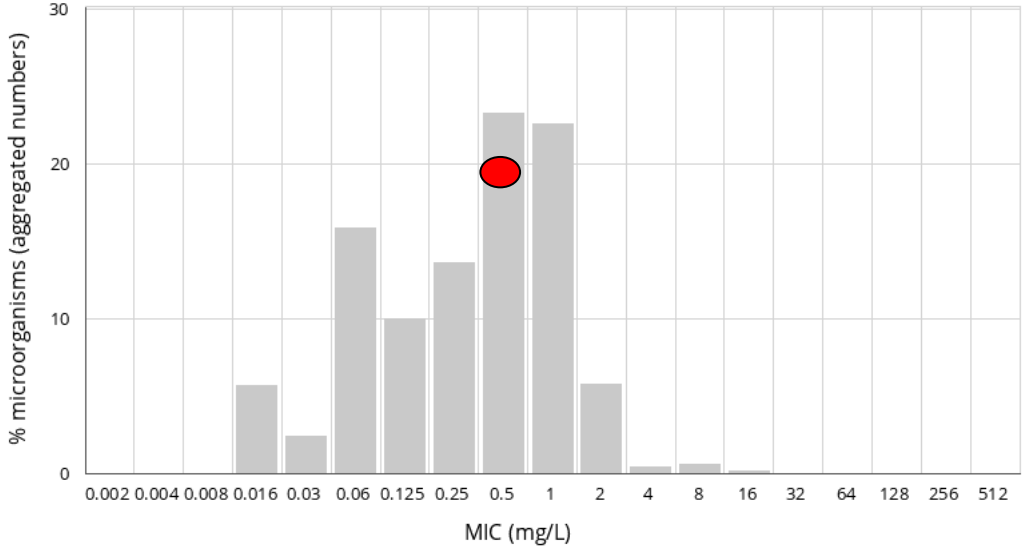


MIC
Epidemiological cut-off (ECOFF): -
Wildtype (WT) organisms: -

Confidence interval: -
864 observations (2 data sources)

Meropenem / Rothia mucilaginosa
International MIC distribution - Reference database 2022-09-27
Based on aggregated distributions

MIC distributions include collated data from multiple sources, geographical areas and time periods and can never be used to infer rates of resistance



MIC
Epidemiological cut-off (ECOFF): -
Wildtype (WT) organisms: -

Confidence interval: -
852 observations (2 data sources)

Case Report

Rothia mucilaginosa Meningitis in a Child with Myelodysplastic Syndromes

Agent	MIC (mg/L)	Wild Type
Benzylpenicillin	0.06	-
Piperacillin-tazobactam	<0.25	-
Ceftriaxone	0.25	?y
Linezolid	1	?y
Meropenem	0.5	?y
Vancomycin	1	?y

Ochi F, et al. Case Reports in Paediatrics (2021)

Case Report

Rothia mucilaginosa Meningitis in a Child with Myelodysplastic Syndromes

Agent	MIC (mg/L)	Wild Type	MIC above which discourage use	Assessment
Benzylpenicillin	0.06	-	0.25	Encourage
Piperacillin-tazobactam	<0.25	-	1	Encourage
Ceftriaxone	0.25	?y	0.5	Encourage
Linezolid	1	?y	2	Encourage
Meropenem	0.5	?y	2	Encourage
Vancomycin	1	?y	2	Encourage

Cautions

- NOT possible if reliable reproducible MIC not available
  - AST methods likely to give a result but may not be reliable
- Lack of expert rules likely
- Always correlate with clinical evidence where possible