

Meet the Expert(s):

What to do when there are no breakpoints

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When there are no breakpoints in EUCAST tables!

- **Why are there no breakpoints?**
 - The species is not mentioned
 - *Francisella tularensis*, *Brucella melitensis*, *Erysipelothrix rhusopathiae*
 - The agent is not mentioned
 - Sparfloxacin, Josamycin, ...
 - New agent under development
 - There is a dash ("-") in the EUCAST tables
 - Enterobacterales and penicillin V, vancomycin, clindamycin
 - There is an "IE" in the EUCAST
 - Enterobacterales and netilmicin, Pseudomonas and ceftobiprole
 - There is "Note" (instead of a breakpoint)

Why are there no breakpoints in EUCAST tables!

The species is not mentioned

- *Francisella tularensis*, *Brucella melitensis*, *Erysipelothrix rhusopathiae*
- The species may be under consideration by EUCAST and breakpoints expected (*F.tularensis*, *B.melitensis*) – enquire with EUCAST
- The species is rare (*E. rhusopathiae*) and breakpoints may not be developed – enquire with EUCAST
 - Determine an MIC and follow guideline

Why are there no breakpoints in EUCAST tables!

The agent is not mentioned

- Sparfloxacin, Josamycin ...
 - New agent under development
-
- Enquire with EUCAST

Why are there no breakpoints in EUCAST tables!

There is a dash ("-") in the breakpoint tables

- Enterobacterales and penicillin V, vancomycin, clindamycin
- The agent is in every way unsuitable in the treatment of the species/group of species. "Resistance is the expected phenotype"
- If a report is needed – do not test, just report "R"

Why are there no breakpoints in EUCAST tables!

There is an "IE" in the breakpoint table

- Enterobacterales and netilmicin, Pseudomonas and ceftobiprole
- "IE" - is equivalent to "?" - insufficient evidence for a breakpoint. Perform an MIC and proceed with caution.
- There is "Note" (instead of a breakpoint)

Why are there no breakpoints in EUCAST tables!

There is a "Note" (instead of a breakpoint)

- A "Note" contains information on why no breakpoint is available and how to proceed.

A lack of EUCAST breakpoints among species and agents

- Nocardia spp
- Many anaerobic species
- Erysipelothrix rhusopathiae
- Campylobacter laridis
- *Brucella melitensis*, *Bacillus anthracis*, *Francisella tularensis* (currently being addressed)

- Josamycin
- Sparfloxacin
- Garenoxacin
- Spiramycin
-many cephalosporins

.....

When there are no breakpoints

- Determine the **MIC using broth microdilution** (if possible)
 - Is there a validated medium/method?
- Agar dilution is used by some
- Gradient tests – check with the manufacturer to ascertain that the test has been **validated for the species**.
- If the MIC is above common breakpoint values for other organisms, discourage the use of the agent
- If the MIC is equal to or below values for other microorganisms, avoid categorical reporting, but add a comment to explain that “the agent may be of value in the treatment of infections for which the agent is often used for other species”.

Reporting susceptibility when there are no breakpoints

When one of the techniques proposed above have been used to evaluate whether an isolate is or is not likely to respond to therapy with a specific agent, you want to report the result but can neither encourage or discourage the use of the agent:

You have **failed to develop a clear recommendation – use** one of the following comments:

- The MIC is X mg/L. "Categorising the susceptibility of the organism is not possible."
- The MIC is unknown and cannot be determined. "Categorising the susceptibility of the organism is not possible".

When the MIC can be determined, but breakpoints are not available:

If the aim is to **discourage** the use of an agent, you may or may not want to **add an R** to the report with a comment:

- Formal categorising of the susceptibility of the organism is not possible.
The MIC (of X mg/L) suggests that the agent should not be used for therapy.

If the aim is to **encourage** the use of an agent, you can add a comment:

- Formal categorising of the susceptibility of the organism is not possible.
The MIC (of X mg/L) suggests that the agent may be used for treatment.

TABLE 2. Zone Diameter Interpretive Standards and Approximate Minimum Inhibitory Concentration (MIC) Correlates

Antimicrobial Agent	Disc Content	Resistant	Zone Diameter, nearest whole mm		Approximate MIC Correlates ^a	
			Intermediate ^a	Susceptible	Resistant	Susceptible
Amikacin ^b	30 µg	≤ 14	15-16	≥ 17	≥ 32 µg/mL	≤ 16 µg/mL
Amikacin ^b	30 µg	≤ 14	15-16	≥ 17	≥ 32 µg/mL	≤ 16 µg/mL
Amikacin ^b	30 µg	≤ 14	15-16	≥ 17	≥ 32 µg/mL	≤ 16 µg/mL
Amikacin ^b	30 µg	≤ 14	15-16	≥ 17	≥ 32 µg/mL	≤ 16 µg/mL
Bacitracin ^c	0.05 units	≤ 10	11-12	≥ 13	≥ 8 µg/mL	≤ 2 µg/mL
Carbenicillin ^d	30 µg	≤ 13	14-18	≥ 19	≥ 32 µg/mL	≤ 12 µg/mL
Cefazolin ^e	30 µg	≤ 12	13-16	≥ 17	—	—
Cefepime ^f	30 µg	≤ 14	15-16	≥ 17	≥ 100 µg/mL	≤ 25 µg/mL
Cefepime ^f	30 µg	≤ 14	15-16	≥ 17	≥ 100 µg/mL	≤ 25 µg/mL
Cefepime ^f	30 µg	≤ 14	15-16	≥ 17	≥ 100 µg/mL	≤ 25 µg/mL
Cefepime ^f	30 µg	≤ 14	15-16	≥ 17	≥ 100 µg/mL	≤ 25 µg/mL
Chloramphenicol ^g	30 µg	≤ 13	14-18	≥ 19	≥ 32 µg/mL	≤ 12 µg/mL
Cilastatin ^h	30 µg	≤ 12	13-16	≥ 17	—	—
Colistin ⁱ	4 units	≤ 10	11-12	≥ 13	≥ 8 µg/mL	≤ 2 µg/mL
Erythromycin ^j	15 µg	≤ 10	11-12	≥ 13	≥ 8 µg/mL	≤ 2 µg/mL
Genamycin ^k	10 units	≤ 20	21-28	≥ 29	β-lactamase ^d	≤ 0.1 µg/mL
Kanamycin ^l	30 µg	≤ 14	15-16	≥ 17	≥ 100 µg/mL	≤ 25 µg/mL
Mechillin ^m	10 units	≤ 11	12-21	≥ 22	≥ 32 µg/mL	≤ 1.5 µg/mL
Nafcillinⁿ	1 µg	≤ 10	11-12	≥ 13	≥ 8 µg/mL	≤ 2 µg/mL
Nalidixic Acid ^o	30 µg	≤ 13	14-18	≥ 19	≥ 32 µg/mL	≤ 12 µg/mL
Neomycin	30 µg	≤ 12	13-16	≥ 17	—	—
Nitrofurantoin ^p	300 µg	≤ 14	15-16	≥ 17	≥ 100 µg/mL	≤ 25 µg/mL
Oxacillin^q	1 µg	≤ 10	11-12	≥ 13	≥ 8 µg/mL	≤ 2 µg/mL
Penicillin G when testing <i>staphylococci</i> ^m	10 units	≤ 20	21-28	≥ 29	β-lactamase ^d	≤ 0.1 µg/mL
Penicillin G when testing other microorganisms ⁿ	10 units	≤ 11	12-21	≥ 22	≥ 32 µg/mL	≤ 1.5 µg/mL

In the beginning there was one table for everything.
 The zone diameter breakpoint was considered more exact than the MIC (which were relegated to approximate correlates).
 The breakpoint had no caveats!

NCCLS (later CLSI) First Supplement, 1981

Case 1

Male patient, admitted with fever

Positive blood culture (day 2) with *Finnegoldia magna*

Focus: hip osteomyelitis after osteosyntheses for proximal femur fracture, complicated by sacral decubitus ulcer

What is *Finnegoldia magna* and

How to perform AST on this isolate?

Finegoldia magna

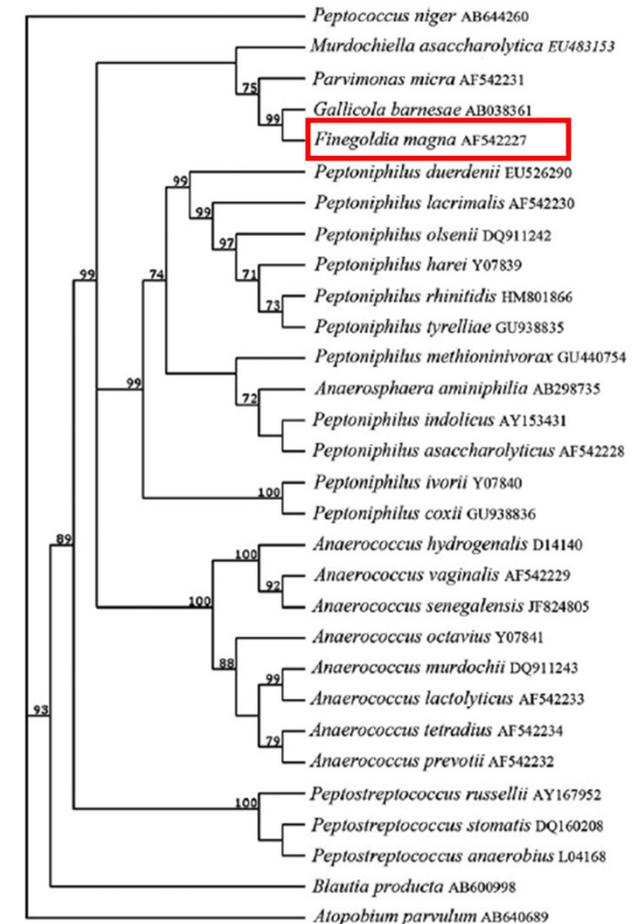
Gram-Positive Anaerobic Coccus (GPAC)

Renamed/-classified 1999

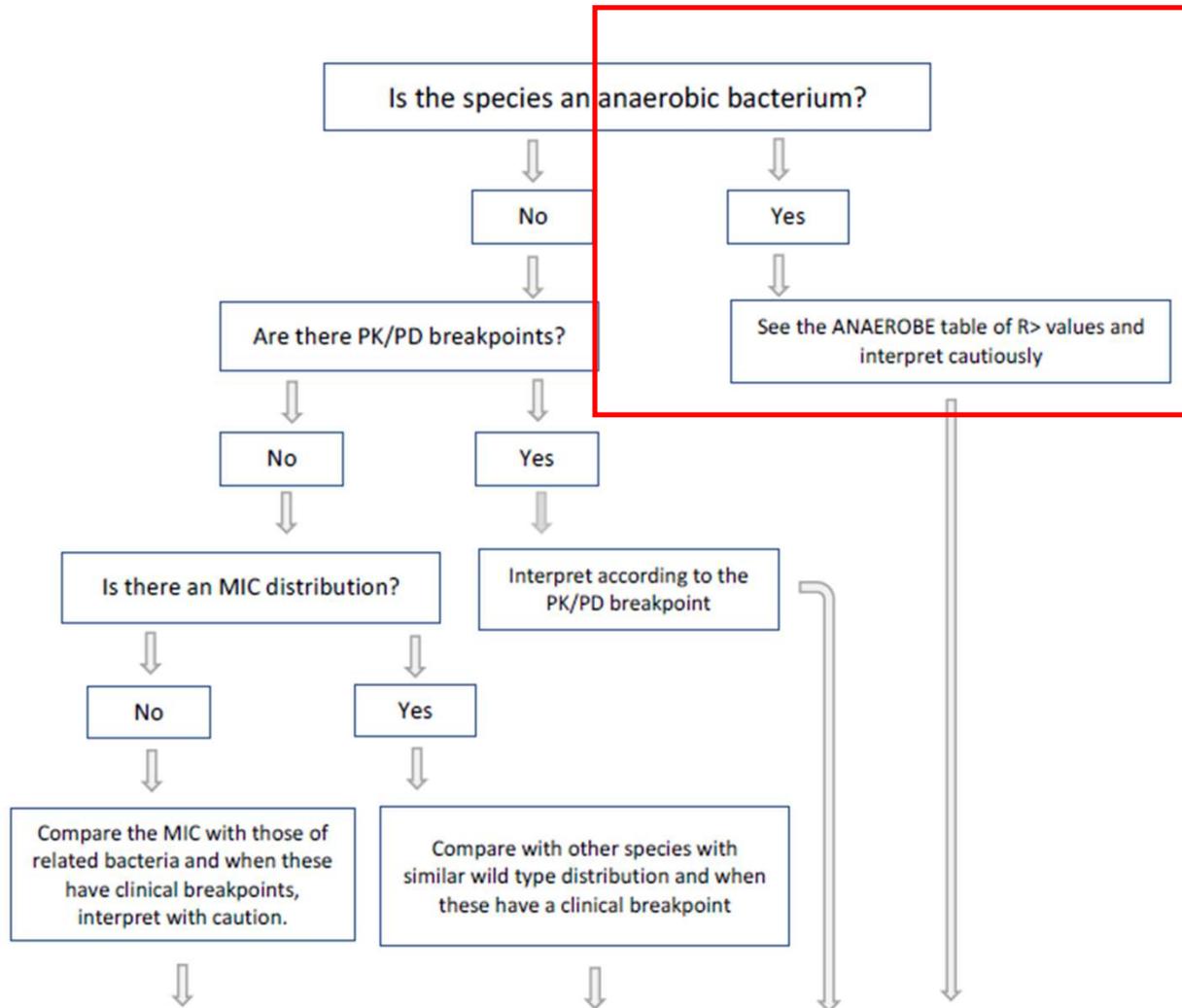
(previous *Peptostreptococcus magnus*)

“most common species of GPAC in human clinical specimens and probably the most pathogenic”

Clinical significance: typically soft-tissue abscesses, wound infections, bone and prosthetic joint infections



Murphy EC and Frick IM. FEMS Microbiol Rev 2013;37(4):520-53.
Murdoch DA. Clin Microbiol Rev. 1998 Jan;11(1):81-120.



EUCAST Guidance Document: Antimicrobial susceptibility tests on groups of organisms or agents for which there are no EUCAST breakpoints; Updated 1 December 2021

What we did:

Gradient test (E-test) on ~~FAA~~ McFarland 1, anaerobic environment, 35-37°C, 18±2h

Benzylopenicillin MIC 0,06 mg/L

Meropenem MIC 0,03 mg/L

Clindamycin MIC 0,25 mg/L

Metronidazole MIC 0,06 mg/L

Expected? How to report?

Antimicrobial agent relevant for the treatment of anaerobic bacteria	Resistance (R>) for species lacking specific breakpoints*	our <i>Finegoldia magna</i> isolate:
Benzylopenicillin	0.5	0,06 mg/L
Piperacillin-tazobactam	8	
Meropenem	2	0,03 mg/L
Vancomycin	2	
Clindamycin	0.5	0,25 mg/L
Metronidazole	4	0,06 mg/L

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Any other reports on susceptibility pattern?

Lund, retrospective study

9 patients with *F. magna* orthopedic infections, 2004-2016

5 monomicrobial, 4 polymicrobial

most treated with regimens containing benzylpenicillin or amoxicillin

Gradient tests (Etest / moxifloxacin: Liofilchem) on FAA

0.5 McFarland; incubation 36°C, anaerobic conditions, 5 days

TABLE 1 Distribution of MIC values for eight antibiotics, using *Finegoldia magna* isolated from patients with orthopedic implant-associated infections ($n = 9$)

Antimicrobial agent ^a	No. of isolates with MIC ($\mu\text{g/ml}$):													
	0.002	0.004	0.008	0.016	0.032	0.064	0.125	0.25	0.5	1.0	2	4	8	>32
PG				4	2	3								
AC				1	2	4	1		1					
CM					2	1	2	2	1	1				
MZ				2	4	1	2							
LZ							1		1	1	5		1	
RI	3	1				3		1						1
VA							2	7						
MXF				1	1	3		1				1		2

^aPG, benzylpenicillin; AC, amoxicillin; CM, clindamycin; MZ, metronidazole; LZ, linezolid; RI, rifampin; VA, vancomycin; MXF, moxifloxacin.

France, multicentre (9 hosp.), 2016-2020

Invasive isolates:

Bacteremia

bone and joint infections

deep-seated soft-tissue infections

Agar dilution (according to CLSI 2018 guidelines, Brucella agar)

EUCAST 2020 Gram-positive anaerobe breakpoints

Antibiotic (Clinical BP) ^a	MIC (mg/L)	<i>Anaerococcus</i> spp. ^b (n = 10)	<i>F. magna</i> (n = 49)	<i>P. micra</i> (n = 33)	<i>Peptoniphilus</i> spp. ^c (n = 30)	<i>P. anaerobius</i> (n = 11)
Amoxicillin (≤4/>8)	MIC ₅₀	≤0.03	0.25	0.06	0.12	2
	MIC ₉₀	0.25	0.5	0.5	0.5	16
	Range	≤0.03–0.25	≤0.03–2	≤0.03–2	≤0.03–0.5	0.25–16
	Susceptibility (%)	100	100	100	100	55
Piperacillin (≤8/>16)	MIC ₅₀	0.12	0.25	0.25	0.06	16
	MIC ₉₀	2	1	2	2	32
	Range	≤0.03–4	≤0.03–16	≤0.03–4	≤0.03–4	0.25–32
	Susceptibility (%)	100	98	100	100	45
Cefotaxime (≤1/>2)	MIC ₅₀	0.5	8	0.12	0.12	8
	MIC ₉₀	16	16	1	2	8
	Range	≤0.03–>16	0.12–>16	≤0.03–8	≤0.03–4	0.25–8
	Susceptibility (%)	80	10	97	87	45
Imipenem (≤2/>4)	MIC ₅₀	≤0.03	0.06	≤0.03	≤0.03	1
	MIC ₉₀	0.12	0.25	0.12	0.06	2
	Range	≤0.03–0.12	≤0.03–1	≤0.03–0.25	≤0.03–0.12	≤0.03–2
	Susceptibility (%)	100	100	100	100	100
Clindamycin (≤4/>4)	MIC ₅₀	0.06	1	0.12	1	0.5
	MIC ₉₀	16	32	1	>32	1
	Range	≤0.03–>32	≤0.03–>32	≤0.03–>32	≤0.03–>32	≤0.03–>32
	Susceptibility (%)	80	76	94	53	91
Vancomycin (≤2/>2)	MIC ₅₀	2	2	2	0.5	2
	MIC ₉₀	2	2	2	2	2
	Range	0.5–2	1–2	0.5–4	0.5–2	1–2
	Susceptibility (%)	100	100	91	100	100
Linezolid (≤2/>4)	MIC ₅₀	1	2	1	1	0.5
	MIC ₉₀	1	2	1	2	0.5
	Range	0.5–2	0.25–4	0.5–2	0.25–2	0.5–2
	Susceptibility (%)	100	100	100	100	100
Moxifloxacin (≤1/>2)	MIC ₅₀	1	0.5	0.25	0.25	0.12
	MIC ₉₀	2	8	0.5	4	8
	Range	0.25–8	≤0.03–>16	0.03–8	0.06–>16	0.06–8
	Susceptibility (%)	80	57	91	87	82
Rifampicin (≤4/>16)	MIC ₅₀	≤0.03	0.5	≤0.03	≤0.03	≤0.03
	MIC ₉₀	>32	>32	≤0.03	1	≤0.03
	Range	≤0.03–32	≤0.03–>32	≤0.03–8	≤0.03–>32	≤0.03–0.5
	Susceptibility (%)	80	88	97	97	100
Metronidazole (≤4/>4)	MIC ₅₀	1	0.5	0.25	1	0.5
	MIC ₉₀	2	1	0.5	2	1
	Range	0.25–2	0.25–4	≤0.12–1	0.12–4	0.25–1
	Susceptibility (%)	100	100	100	100	100

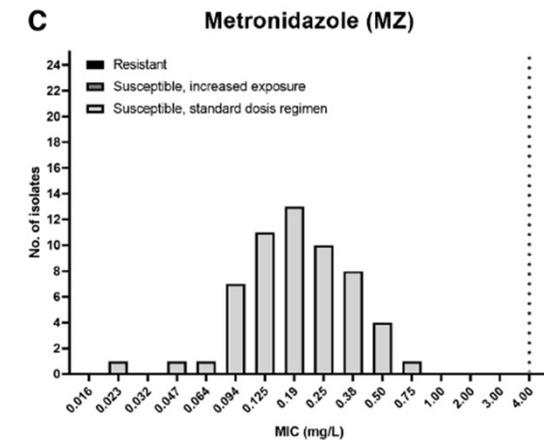
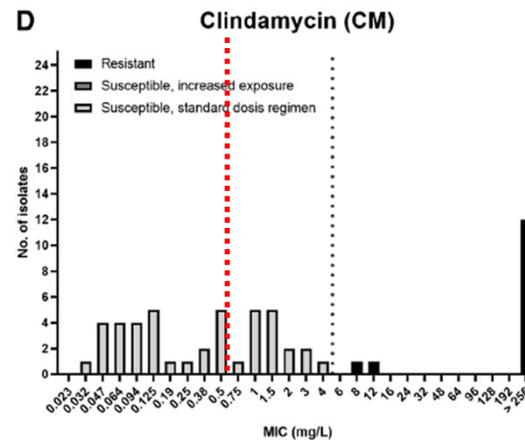
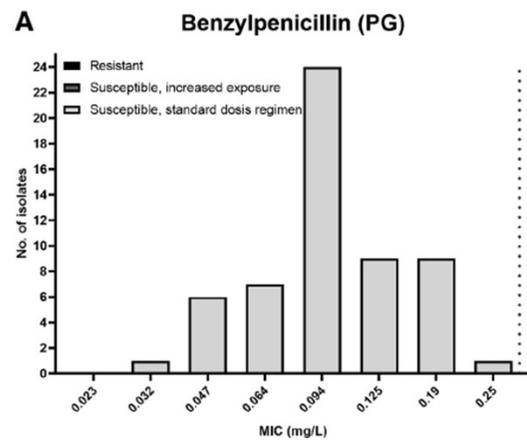
Zürich, 2019/20

57 *F. magna* clinical isolates

Etest, Brucella agar, McF 1, anaerobic incubation 48h

EUCAST 2020 Gram-positive anaerobe breakpoints

EUCAST GD 2021:
R>0,5



Case 1, cont.: Surgical revision

Culture results from bone specimen:

- *Finegoldia magna*
- *Peptostreptococcus* sp.
- *Peptoniphilus* sp.
- *Bacteroides fragilis*
- *Prevotella corporis*
- *Proteus mirabilis*

Perform testing on all isolates?

When we culture 5 different anaerobes, how many did we fail to culture?

Case 1, for discussion

- Media selection
 - According to manufacturer's instructions
- Communicating results
 - Avoid SIR-categorization
- Choose wisely which isolates to perform AST on

Case 2

Male patient in his eighties, with biological aortic valve prosthesis, admitted with fever and malaise for a couple of weeks.

Blood culture positive with *Granulicatella adiacens* (in 5 sets)

First transesophageal echocardiography negative

Second transesophageal echocardiography: infective endocarditis

Granulicatella adiacens

Nutritionally variant streptococcus

Normal oropharyngeal and gastrointestinal flora

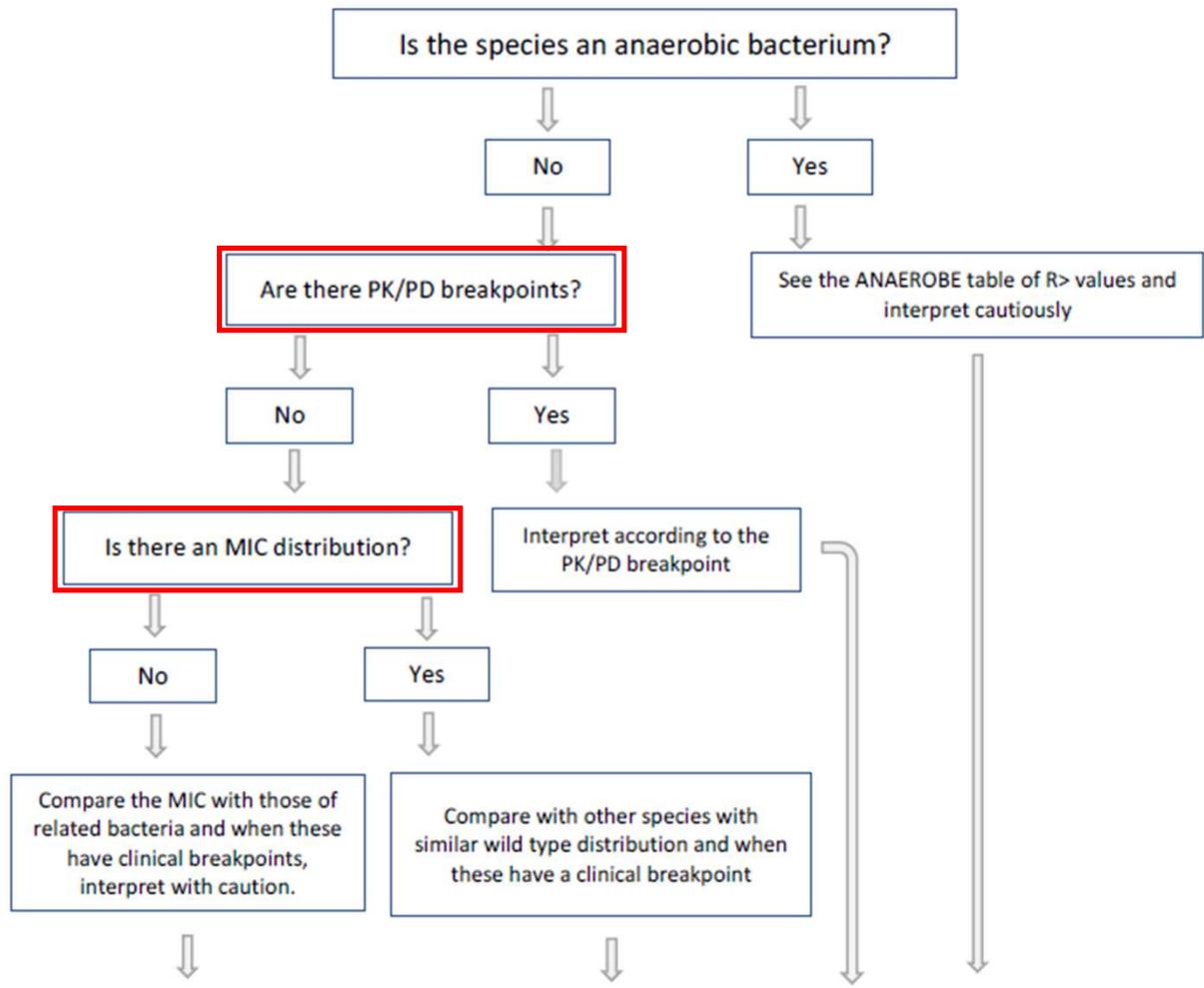
Clinical significance: infective endocarditis, abscesses, ...

How we performed AST:

E-test (columbia blood agar, control *S. pneumoniae* ATCC 49619)

- Benzylpenicillin 0,125 mg/L
- Ampicillin 0,06 mg/L
- Ceftriaxon 0,25 mg/L
- Gentamicin 16 mg/L
- Moxifloxacin 0,125 mg/L
- Rifampicin 0,004 mg/L

How to interpret and report?



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No EUCAST MIC distribution for *Granulicatella* spp.:

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

Species...

Fusobacterium mortiferum
Fusobacterium necrophorum
Fusobacterium nucleatum
Fusobacterium varium
Haemophilus aphrophilus
Haemophilus influenzae
Haemophilus influenzae ATCC 49247
Haemophilus influenzae ATCC 49766
Haemophilus influenzae NCTC 8468
Haemophilus parainfluenzae
Haemophilus parasuis
Hafnia alvei
Helicobacter pylori
Histophilus somni
Kingella kingae
Klebsiella aerogenes
Klebsiella oxytoca
Klebsiella ozaenae
Klebsiella pneumoniae
Klebsiella pneumoniae ATCC 700603

<https://mic.eucast.org/search/>

MIC distributions from one US study:

90 *Granulicatella adiacens* isolates (+ 37 *Abiotrophia defectiva*, 5 *G. elegans*)

2008 – 2014, Los Angeles

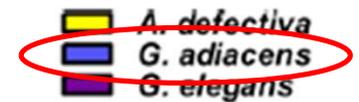
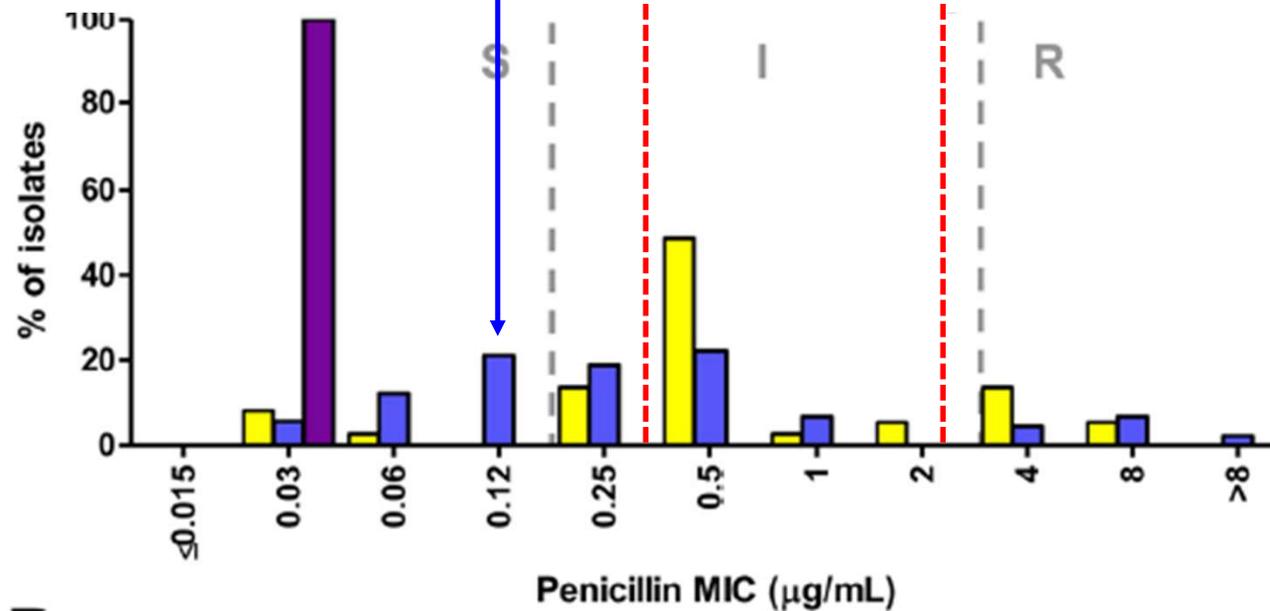
Broth microdilution according to CLSI standard (Mueller-Hinton broth + 2.5% lysed horse blood + 1 µg/ml pyridoxal hydrochloride)

1. Benzylpenicillin

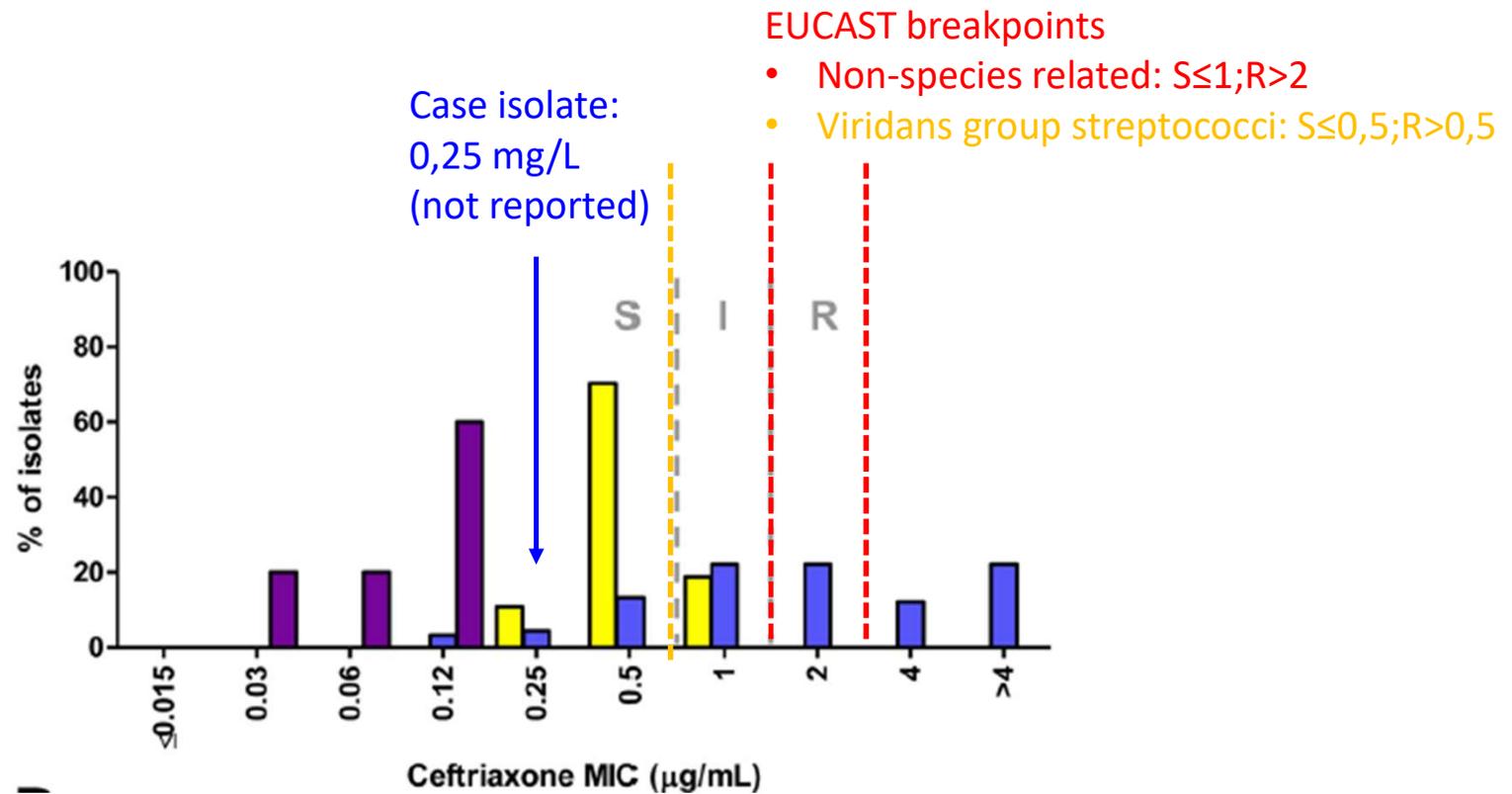
Case *C. adiacens* isolate:
0,125 mg/L

EUCAST breakpoints

- Non-species related $S \leq 0,25; R > 2$
- Viridans group streptococci $S \leq 0,25; R > 2$



2. Ceftriaxone

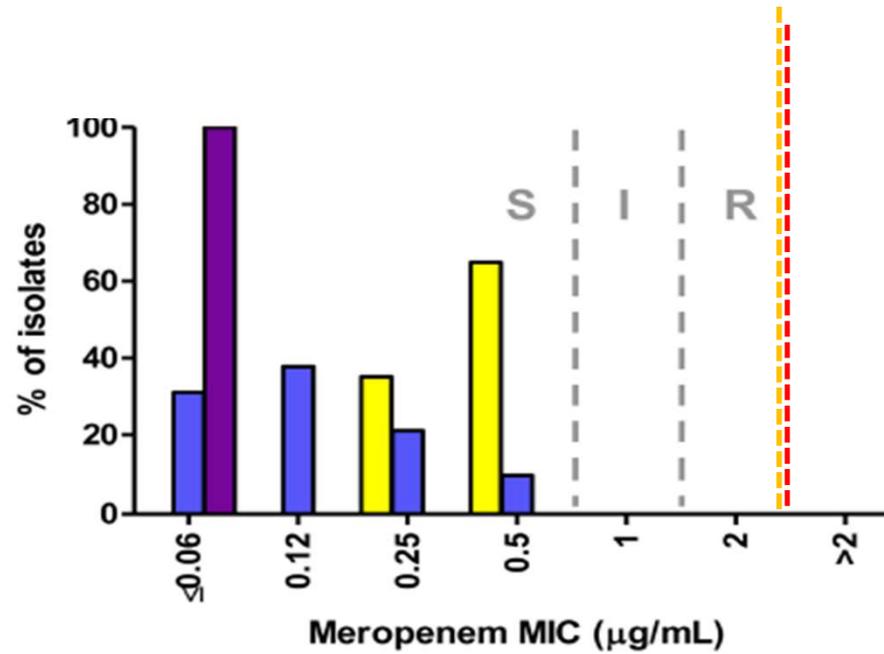


3. Meropenem

(Case isolate not tested)

EUCAST breakpoints

- Non-species related: S≤2;R>8
- Viridans group streptococci: S≤2;R>2



3. Other agents

Case *C. adiacens* isolate:

Gentamicin 16 mg/L	No PKPD-breakpoints. Viridans group streptococci: acquired high-level resistance if MIC >128 mg/L
Moxifloxacin 0,125 mg/L	No PKPD-breakpoints. Viridans group streptococci: acquired resistance if MIC >0,5 mg/L
Rifampicin 0,004 mg/L	No PKPD-breakpoints. Viridans group streptococci: acquired resistance if MIC >0,25 mg/L

All 3 MICs could be reported and all 3 agents could be considered as combination therapy in endocarditis.

For discussion /case 2

- Perform AST or treat according to expected phenotype?

Perform MIC to detect acquired resistance, but do not report MICs below the non-species-related breakpoint, if this breakpoint lies within the wild type distribution (ex. Ceftriaxone)

- How to communicate these complex results to the clinician?

Here: report MICs, discuss via phone or in person

Conclusions

- When formal breakpoints are lacking:
 - If "dash", the species is considered naturally resistant by
 - If "IE", the clinical data available is insufficient for a clinical breakpoint, but a successful result is not ruled out – proceed with caution.
 - EUCAST has not dealt with the species/agent in question.
 - An accepted AST method is not defined/available
- Choose wisely whether to test and what to test for
- Reporting
 - avoid SIR categorization – use comments or direct contact with the clinician in charge of the patient.