



Stenotrophomonas maltophilia: testing and treatment

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Mentimeter question 1

Do you perform AST for *S. maltophilia*?

(only one possible)

- No, this is not clinically relevant
- No, this is too difficult
- Yes, but only for TMP-SMX
- Yes, TMP-SMX and other agents
- Not relevant (do not work in a lab)

Mentimeter question 2

Which other agents then TMP-SMX do you test?
(more than one possible)

- Cefiderocol, DD
- Cefiderocol, BMD
- Aztreonam-avibactam, BMD
- Aztreonam-avibactam, gradient test
- Minocycline, BMD
- Minocycline, gradient test
- Cipro- or levofloxacin, BMD
- Cipro- or levofloxacin, gradient test
- Something else

The shortest sheet in the breakpoint table has become more complicated

Stenotrophomonas maltophilia

EUCAST kliniske brytningspunkter v. 14.0, NordicAST v. 14.0, 2024-01-19

Expert Rules and Expected Phenotypes

For abbreviations and explanations of breakpoints, see the Notes sheet

Trimetoprim-sulfametoksazol er det eneste middelet som EUCAST har fastsatt brytningspunkter for. For mer informasjon, se EUCAST guidance document.

MIC determination (broth microdilution according to ISO standard 20776-1)
Medium: Cation-adjusted Mueller-Hinton broth (for cefiderocol, see <https://www.eucast.org/antimicrobials/methods/mic>)
Inoculum: 5×10^8 CFU
Incubation: Sealed plate
Reading: For trimethoprim-sulfamethoxazole, read the zone diameter that inhibits approximately 90% of the inoculum. For cefiderocol, see the Quality control, see the Notes sheet.

Disk diffusion (EUCAST standardised disk diffusion method)
Medium: Mueller-Hinton agar

Version 14.0:

Trimethoprim-sulfamethoxazole: breakpoints
Cefiderocol: insufficient evidence (IE)

Cephalosporins

Cefiderocol

Miscellaneous agents	MIC breakp			Disk content	Zone diamet			Kommentarer
	S \leq	R >	ATU		S \geq	R <	ATU	
Trimethoprim-sulfamethoxazole	0.001	4		1.25-23.75	50	16		Viltypen kategoriseres som "I – Følsom, økt eksponering", se tabell "Dosering". Trimetoprim-sulfametoksazol ratio 1:19. MIC-brytningspunktene uttrykkes som konsentrasjonen av trimetoprim. Isolater med enhver antydning til hemmingsone skal leses av og rapporteres i henhold til brytningspunktene, og vekst i hemmingsonen skal ignoreres. Innvekst i hemmingsonen kan variere fra et tynt slør til kraftig vekst (se bilder nedenfor). Trimetoprim-sulfametoksazolresistens hos <i>S. maltophilia</i> er uvanlig å skal bekreftes med en MIC-metode.

Stenotrophomonas maltophilia

EUCAST kliniske brytningspunkter v. 15.0, NordicAST v. 15.0, 2025-01-24

Expert Rules and Expected Phenotypes

For abbreviations and explanations of breakpoints, see the Notes sheet

For further information, see EUCAST Guidance Document for *S. maltophilia*.

Version 15.0:

Trimethoprim-sulfamethoxazole: breakpoints
Cefiderocol: Note (interpretive criteria)
Minocycline, Tigecycline: Note (used in combination)
Ciprofloxacin, Levofloxacin: Note (used in combination)
Aztreonam-avibactam: insufficient evidence (IE)

Ciprofloxacin	Note	Note			Note	Note			Kriterier for lappediffusjonstest mangler.
Levofloxacin	Note	Note			Note	Note			

Tetracyclines	MIC breakpoints (mg/L)			Disk content (µg)	Zone diameter breakpoints (mm)			Kommentarer
	S \leq	R >	ATU		S \geq	R <	ATU	
Minocycline	Note	Note			Note	Note		Tetracykliner har blitt brukt i kombinasjonsbehandling. ECOFF for tetracykliner i tabellen kan anvendes for å utelukke ervervede resistensmekanismer. Kriterier for lappediffusjonstest mangler.
Tigecycline	Note	Note			Note	Note		Gjelder kun i.v. behandling. Oral administrasjon gir ikke tilstrekkelig høy eksponering.

Miscellaneous agents	MIC breakpoints (mg/L)			Disk content	Zone diameter breakpoints (mm)			Kommentarer
	S \leq	R >	ATU		S \geq	R <	ATU	
Trimethoprim-sulfamethoxazole	0.001	2		1.25-23.75	50	16		Viltypen kategoriseres som "I – Følsom, økt eksponering", se tabell "Dosering". Trimetoprim-sulfametoksazol ratio 1:19. MIC-brytningspunktene uttrykkes som konsentrasjonen av trimetoprim. Isolater med enhver antydning til hemmingsone skal leses av og rapporteres i henhold til brytningspunktene, og vekst i hemmingsonen skal ignoreres. Innvekst i hemmingsonen kan variere fra et tynt slør til kraftig vekst (se bilder nedenfor). Trimetoprim-sulfametoksazolresistens hos <i>S. maltophilia</i> er uvanlig å skal bekreftes med en MIC-metode.

But there is guidance!



CMI COMMUNICATIONS 2 (2025) 105082

Guidance Document on *Stenotrophomonas maltophilia*



Contents lists available at [ScienceDirect](#)

CMI Communications

journal homepage: www.elsevier.com/locate/cmicom



Version 2, November 2024

Narrative Review

Rationale for contemporary antimicrobial treatment of *Stenotrophomonas maltophilia*: a narrative review



The organism

Stenotrophomonas maltophilia is a ubiquitous environmental

John Turnidge^a, Sören Gatermann^{b,c}, Gunnar Kahlmeter^{c,d}, Rafael Cantón^d, Mandy Wootton^e, Christian G. Giske^{f,g,*}, on behalf of the European Committee on Antimicrobial Susceptibility Testing

https://www.eucast.org/fileadmin/src/media/PDFs/guidance_documents/Stenotrophomonas_maltophilia_guidance_document.pdf

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Turnidge J et al. CMI Communications, 2025; 2(2):2105082



Agenda

- An environmental bacterium: clinical significance
- A very resistant bacterium: arsenal of resistance mechanisms
- Treatment options: more than trimethoprim-sulfamethoxazole
- Susceptibility testing: not easy

Clinical significance

Environmental Gram-negative rod, biofilm production

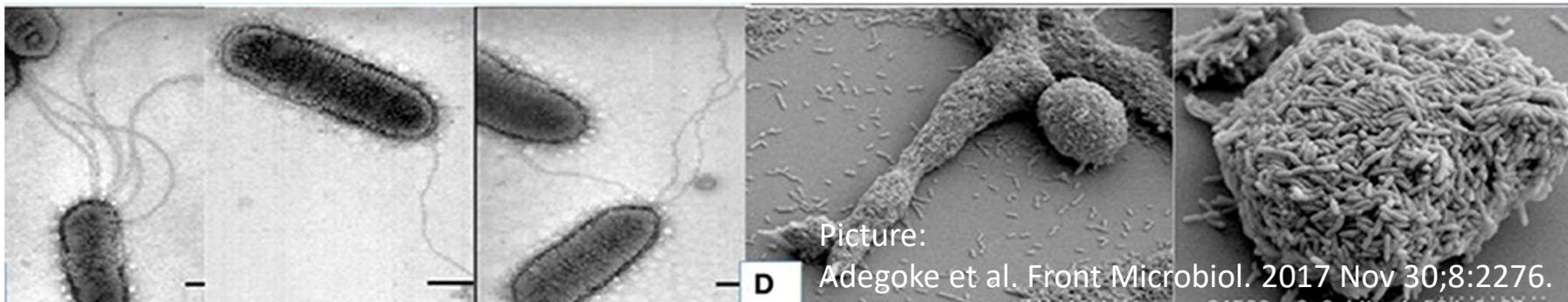
Opportunistic pathogen:

- in chronic lung disease

- foreign-body associated

- in immunocompromised patients

First question to ask: Should we perform and report AST in this specimen?



Arsenal of resistance mechanisms

Antimicrobial ^a	Genetics and description	Reference(s)
β -Lactams	<i>bla</i> _{SHV} , <i>bla</i> _{CTX-M-GP1} , <i>bla</i> _{PERV} , <i>bla</i> _{NDM-1} , <i>bla</i> _{OXA1-like} , <i>bla</i> _{OXA48-like} , <i>bla</i> _{L1,L2} , <i>mrcA</i> , lytic transglycosylase D1, CreBC two-component system, AmpNG-AmpD ₁ -NagZ-AmpR circuit, NagZ-dependent and NagZ-independent mechanisms, and mutation of TonB gene	114, 177, 178, 2343
Aminoglycosides	<i>aac(6')</i> -Iak and protease <i>dpA</i> and <i>htpX</i>	303, 304, 308
Quinolones	<i>qnrA</i> , <i>qnrB</i> , <i>qnrS</i> , <i>oqxA</i> , <i>oqxB</i> , SmQnr genes, <i>aac(6')</i> -Ib-cr, <i>aadA2</i> , and mutation of <i>smeT</i>	178, 294, 295, 331, 348, 346
TMP-SMX	Class 1 integrons, <i>dfra</i> , <i>sul1</i> , and <i>sul2</i> genes	178, 307, 309, 341, 346
MDR efflux pumps		
ABC family		
Aminoglycosides, macrolides, polymyxins	MacABCsm (<i>macRS-macABCsm</i> cluster)	311
Fluoroquinolones, tetracycline	<i>SmrA</i> (<i>smrA</i>)	315
MFS family		
Erythromycin, nalidixic acid	<i>EmrCABsm</i> (<i>emrCABsm</i>)	316
Fluoroquinolones, paraquat	<i>MfsA</i> (<i>soxR-mfsA</i> system)	317-319
RND family		
Quinolones, β -lactams, aminoglycosides	<i>SmeABC</i> (<i>smeABC</i>)	320, 326
Quinolones, tetracycline, chloramphenicol, TMP-SMX, macrolides	<i>SmeDEF</i> (<i>smeT-smeDEF</i> system, association with the <i>smeRySy</i> operon and <i>smeYZ</i>)	294, 295, 321-326, 331, 334
Quinolones, macrolides, chloramphenicol, polymyxin B, tetracycline, some β -lactams	<i>SmeGH</i> (<i>smeGH</i> , <i>tolCsm</i> , mutations of <i>smeH</i>)	292, 313
Ciprofloxacin, levofloxacin, minocycline, tetracycline	<i>SmeIJK</i> (<i>smeIJK</i> , association with <i>smeZ</i>)	327, 328
Nalidixic acid, doxycycline, macrolides, aminoglycosides, chloramphenicol, TMP-SMX	<i>SmeOP-ToIC</i> (<i>tolCsm-pem-smeRo-smeO-smeP</i> cluster)	312, 314
Quinolones, tetracycline, chloramphenicol	<i>SmeVWX</i> (<i>smeRv-smeVWX</i> system, association with vitamin K ₃ inducers)	294, 329-331, 338
TMP-SMX, aminoglycosides	<i>SmeYZ</i> (<i>smeYZ</i> , association with <i>smeRySy</i> system, association with <i>smeJK</i> , inducers, association with <i>rplA</i> mutation)	327, 332-334, 338
Fusaric acid	<i>FuaABC</i> (<i>fuaR-fuaABC</i>)	336
Biocides	<i>qacK</i> , <i>qacL</i> , biocide binding to <i>SmeT</i> , relationship with fitness cost	307, 339

two inducible chromosomal beta-lactamases:
L1 (metallo-beta-lactamase)
& L2 (serine-beta-lactamase)

chromosomal aminoglycoside modifying enzymes

chromosomal SmQnr genes (FQ)

Efflux pumps (affecting e.g. FQ, tetracyclines)

Treatment options: IDSA Guidance, 2024

Moderate to severe infections: 2 approaches

Two of the following agents: cefiderocol, minocycline, TMP-SMX, or levofloxacin (listed in order of preference)

Rationale: combination, because limited data to support any individual agent
or

combination ceftazidime-avibactam & aztreonam

Acknowledging: limited available clinical data

Tamma PD et al. Clin Infect Dis. 2024 Aug 7:ciae403. doi: 10.1093/cid/ciae403.
PMID: 39108079



Treatment options: EUCAST Guidance, 2025

PKPD targets from *in vitro* and animal model data included in Monte Carlo simulations

Antibiotic	PK/PD Breakpoint	Clinical Breakpoint		ECOFFs ^a
		CLSI	EUCAST	
Cotrimoxazole (trimethoprim/sulfamethoxazole) 240/1200 mg q6h 320/1600 mg q8h 320/1600 mg q6h				
Levofloxacin 500 mg q24h 500 mg q12h 750 mg q24h				
Minocycline 100 mg q12h	0.5	<4	n.d.	1
200 mg q12h	1			
Tigecycline 50 mg q12h	0.5	n.d.	n.d.	4
100 mg q12h	1			
Cefiderocol 2 g q8h	4			0.125
Aztreonam/avibactam 1500/500 mg q6h	2	n.d.	n.d.	8 ^d

PK/PD cut-off < ECOFF

Even with high doses, the wild type population cannot be treated.

Exeption:
(minocycline)
Cefiderocol

^a: Epidemiological cut-off values according to EUCAST; ^b: trimethoprim component; ^c: susceptible, increased exposure; ^d: tentative ECOFF (TECOFF). n.d.: not defined.

Treatment options: EUCAST Guidance, 2025

Clinical data:

	Comparison	Type of analysis	Infection types	Conclusion
Ko 2019	TMP-SMX vs FQ (mainly ciprofloxacin and levofloxacin)	Meta-analysis (14 studies)	All	FQ superior to TMP-SMX in terms of 30-day mortality.
Maraolo 2023	FQ vs TMP-SMX	Meta-analysis	All	FQ superior to TMP-SMX in terms of 7 to 30-day all-cause
Junco 2021	TM m	<div style="border: 2px solid red; padding: 10px;"> <p>Heterogeneous data No clear conclusions regarding first line treatment</p> <p>“comparing suboptimal agents with suboptimal agents?”</p> </div>		cycline than
Hevia 2023	M m			f minocycline 0.3 [0.1 to d with TMP-
Alhayani 2023	Doxycycline or Minocycline vs TMP-SMX			2-centre retrospective
Almangour 2024	TMP-SMX vs levofloxacin	4-centre retrospective	All	No difference between levofloxacin and TMP-SMX in terms of clinical failure or 30-day mortality rates
Graves 2025	TMP-SMX versus minocycline as monotherapy	Single centre retrospective	Pneumonia	No difference in clinical outcomes. Higher in-hospital mortality with TMP-SMX but lower recurrent pneumonia

TMP-SMX: Trimethoprim-sulfamethoxazole
FQ: Fluoroquinolones

Table modified from: Turnidge J et al. CMI Communications, 2025; 2(2):2105082

Treatment options: Cefiderocol

Registration trials

- CREDIBLE-CR: 5 in cefiderocol group, 0 in best available treatment group
- APEKS-NP: 1 in cefiderocol group, 3 in meropenem group

~~Retrospective studies of real world effectiveness and safety:~~

“EUCAST assessment is that cefiderocol is the best alternative treatment, but that further clinical evidence is required for EUCAST to determine clinical breakpoints. Due to the importance of this agent, some interpretive criteria have been published (...)”

Turnidge J et al. CMI Communications, 2025; 2(2):2105082

70% clinical cure, 50% 28-day mortality

- ...

Bassetti M et al. Lancet Infect Dis 2021; 21: 226–40

Wunderink RG et al. Lancet Infect Dis 2021; 21: 213–25

Clancy C et al. Infect Drug Resist 2024;17:4427–43. 15.

Marcella S et al. Open Forum Infect Dis 2023;10(Suppl 2). 27ofad500.2363.

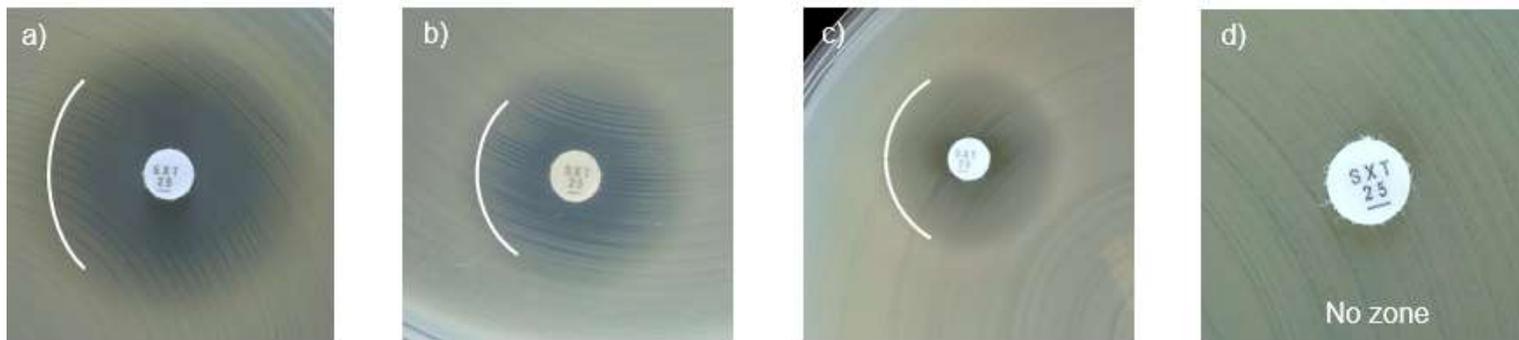
Torre-Cisneros J et al. Eur J Clin Microbiol Infect Dis 2025 Mar 24; Online ahead of print

Susceptibility testing: Trimethoprim-sulfamethoxazole

Clinical breakpoint $S \leq 0.001; R > 2$ (v15.0: R-breakpoint lowered to ECOFF)

Disk diffusion: difficult to read, overcalls resistance

→ Note: Trimethoprim-sulfamethoxazole resistance in *S. maltophilia* is rare and should be confirmed with an MIC test.

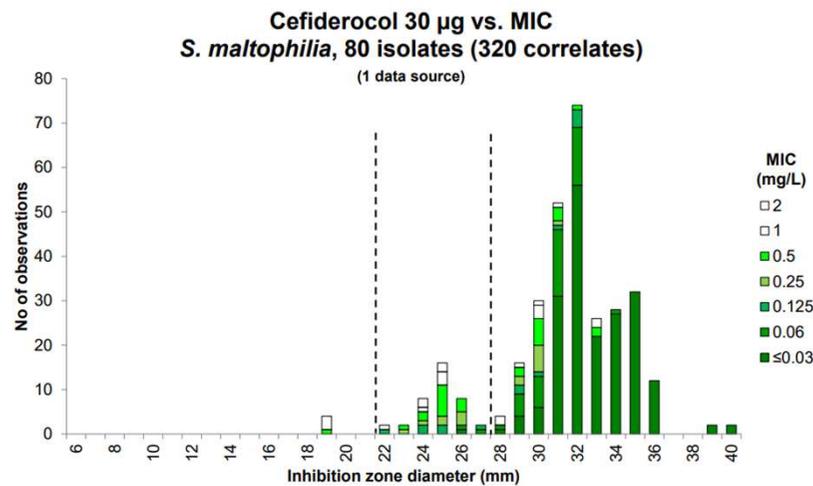


Examples of inhibition zones for *Stenotrophomonas maltophilia* with trimethoprim-sulfamethoxazole.

a-c) An outer zone can be seen. Read the outer zone edge and interpret according to the breakpoints.

d) Growth up to the disk **and** no sign of inhibition zone. Report resistant.

Susceptibility testing: Cefiderocol



Isolates with **MIC values ≤ 0.5 mg/L (zone diameter ≥ 28 mm)** are mostly devoid of **resistance mechanisms**. Isolates with MICs 1-2 mg/L have acquired resistance mechanisms which may result in impaired clinical response. Isolates with **MIC values > 2 mg/L (zone diameter < 22 mm)** will likely be resistant.

Susceptibility testing: other agents

Monobactams	MIC breakpoints (mg/L)			Disk content (µg)	Zone diameter breakpoints (mm)			Notes Numbered notes relate to general comments and/or MIC breakpoints. Lettered notes relate to the
	S ≤	R >	ATU		S ≥	R <	ATU	
Aztreonam	-	-			-	-		Aztreonam-avibactam: IE
Aztreonam-avibactam	IE	IE			IE	IE		

Fluoroquinolones	MIC breakpoints	Disk	Zone diameter	Notes
Ciprofloxacin				Ciprofloxacin, Levofloxacin: have been used in combination therapy. ECOFF to exclude acquired resistance
Levofloxacin				

Tetracyclines	MIC breakpoints	Disk	Zone diameter	Notes
Minocycline				Minocycline, Tigecycline: have been used in combination therapy. ECOFF to exclude acquired resistance
Tigecycline				

A. Disk diffusion criteria are not available.

Question from a participant

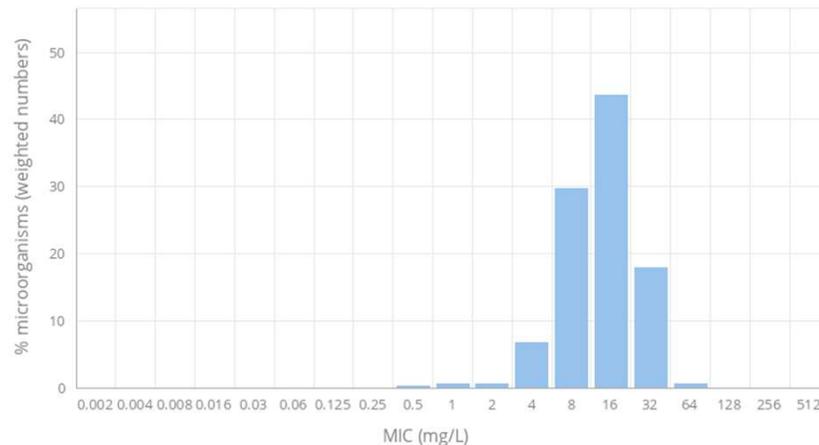
"Stenotrophomonas and **minocycline AST**: is there any data on the **performance of gradient tests** for this drug-bug combination?"

In the 'When there is no breakpoint document', it is recommended to **test tetracycline and infer from that minocycline**. There is though a MIC distribution for Stenotrophomonas and minocycline in the EUCAST database.

What is your recommendation?"

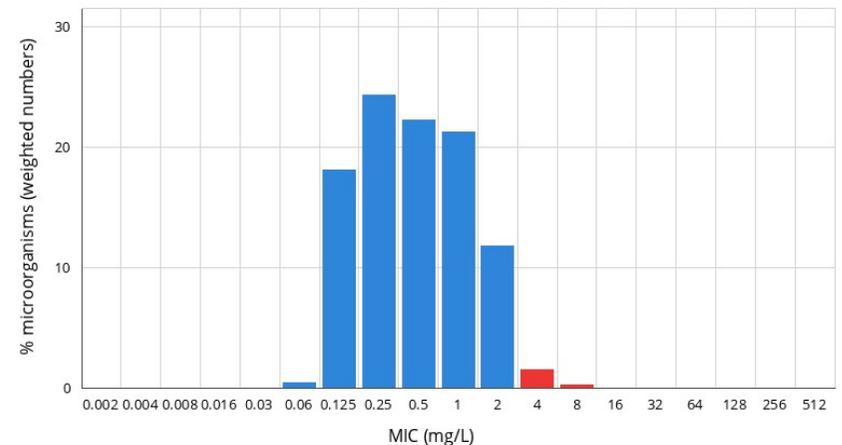
Infer minocycline from Tetracycline? NO

Tetracycline / *Stenotrophomonas maltophilia*
International MIC distribution - Reference database 2025-05-24
Based on aggregated distributions where each distribution has equal weight *
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): 64 mg/L
Wildtype (WT) organisms: ≤ 64 mg/L
Confidence interval: 32 - 128
193 observations (6 data sources)
* individual distributions were converted to percentages of their individual total and then aggregated

Minocycline / *Stenotrophomonas maltophilia*
International MIC distribution - Reference database 2025-05-24
Based on aggregated distributions where each distribution has equal weight *
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): 2 mg/L
Wildtype (WT) organisms: ≤ 2 mg/L
Confidence interval: 0.125 - 4
432 observations (8 data sources)
* individual distributions were converted to percentages of their individual total and then aggregated

GD “When there are no breakpoints”:
MIC-values above which therapy with the agent
should be discouraged : 2 mg/L

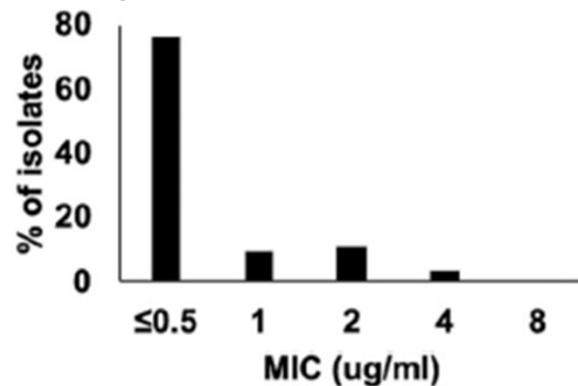
EUCAST v 15.0 Minocycline Notes:

1. Tetracyclines have been used in combination therapy. **The ECOFF can be used to exclude acquired resistance mechanisms.**
2. Pertains to intravenous therapy. Oral therapy will lead to insufficient exposure.

Performance of gradient tests

109 blood isolates

Minocycline MIC distribution (BMD):



CLSI breakpoints

(M100-ED30, 2020): S≤4, I=8, R≥16 mg/L

(M100-ED35, 2025): S≤1, I=2, R≥4 mg/L

Categorical agreement for gradient test results:

Antimicrobial	Isolate group	n	No. (%) with indicated value							
			Etest				MTS			
			CA	VME	ME	MI	CA	VME	ME	MI
MIN	Overall	109	101 (92.7)	NA	0	8 (7.3)	108 (99.1)	NA	0	1 (0.9)
	≥R + 2	0		NA	NA	0		NA	NA	0
	I ± 1	4		NA	0	3 (75.0)		NA	0	0
	≤I - 2	105		NA	0	5 (4.8)		NA	0	1 (1.0)

Etest: 8 isolates testet I (MIC = 8)

MTS: 1 isolates testet I (MIC = 8)

- No resistant isolates included according to the applied breakpoints, thus VME could not appear.
- Essential agreement not calculated (large number off-scale MICs)

Conclusion: not enough data to support use of gradient tests.

Conclusions

- A difficult bug, both in terms of treatment and testing
- Often a colonizer: chose wisely when to test and treat
- Trimethoprim-sulfamethoxazole is no longer the best treatment option, although only agent with numerical EUCAST breakpoint
- Cefiderocol has good *in vitro* activity and is an alternative treatment for severe infections. EUCAST has published interpretive criteria, although no clinical breakpoint.
- Other treatment options are minocycline or fluoroquinolones (levofloxacin, ciprofloxacin)

