

Indication-specific breakpoints

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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
Ampicillin ^c when testing gram-negative enteric organisms and enterococci	10 µg	≤ 11	12-13	≥ 14	≥ 32 µg/mL	≤ 8 µg/mL
Ampicillin ^c when testing staphylococci ^d and penicillin G-susceptible microorganisms	10 µg	≤ 20	21-28	≥ 29	β-lactamase ^d	≤ 0.25 µg/mL
Ampicillin ^c when testing <i>Haemophilus</i> species ^e	10 µg	≤ 19	—	≥ 20	≥ 4 µg/mL	≤ 2 µg/mL
Bacitracin	10 units	≤ 8	9-12	≥ 13	—	—
Carbenicillin when testing the <i>Enterobacteriaceae</i>	100 µg	≤ 17	18-22	≥ 23	≥ 32 µg/mL	≤ 16 µg/mL
Carbenicillin when testing <i>Pseudomonas aeruginosa</i>	100 µg	≤ 13	14-16	≥ 17	≥ 256 µg/mL	≤ 128 µg/mL
Cefamandole ^f	30 µg	≤ 14	15-17	≥ 18	≥ 32 µg/mL	≤ 8 µg/mL
Cefo						
Ceph						
Chlo						
Clind						
Colis						
Eryth						
Gent						
Kana						
Meth						
Nafcillin^k	1 µg	≤ 10	11-12	≥ 13	≥ 8 µg/mL	≤ 2 µg/mL
Nalidixic Acid ^l	30 µg	≤ 13	14-18	≥ 19	≥ 32 µg/mL	≤ 12 µg/mL
Neomycin	30 µg	≤ 12	13-16	≥ 17	—	—
Nitrofurantoin ^l	300 µg	≤ 14	15-16	≥ 17	≥ 100 µg/mL	≤ 25 µg/mL
Oxacillin^k	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
Polymyxin B _i	300 units	≤ 8	9-11	≥ 12	≥ 50 units/mL	j
Streptomycin	10 µg	≤ 11	12-14	≥ 15	—	—
Sulfonamides ^{l,o}	250 or 300 µg	≤ 12	13-16	≥ 17	≥ 350 µg/mL	≤ 100 µg/mL
Tetracycline ^p	30 µg	≤ 14	15-18	≥ 19	≥ 12 µg/mL	≤ 4 µg/mL
Ticarcillin when testing <i>P. aeruginosa</i>	75 µg	≤ 11	12-14	≥ 15	≥ 128 µg/mL	≤ 64 µg/mL
Trimethoprim^{l,o}	5 µg	≤ 10	11-15	≥ 16	≥ 16 µg/mL	≤ 4 µg/mL
Trimethoprim-sulfamethoxazole ^o	1.25 µg, 23.75 µg	≤ 10	11-15	≥ 16	≥ 8/152 µg/mL	≤ 2/38 µg/mL
Tobramycin ^a	10 µg	≤ 12	13-14	≥ 15	≥ 8 µg/mL	≤ 4 µg/mL
Vancomycin	30 µg	≤ 9	10-11	≥ 12	—	≤ 5 µg/mL

NCCLS First Supplement, 1981
- “used for anything that would grow”

EUCAST perspectives

- For some infections and agents, to attain good **exposure** is
 - **easy (UTI)**
 - **more difficult (meningitis)**

and sometimes only a limited array of suitable agents are validated for use.

- These indications are evaluated separately by EUCAST.
- The AST numerical test-result is the same – the categorical interpretation may differ.
- To have different breakpoints for different indications is sometimes a challenge in the clinical laboratory:
 - Several agents are only used for uUTI so a misunderstanding is not likely
 - Other agents may be used for several fundamentally different purposes, and the **interpretation of results** will differ.

We will discuss different solutions to avoid misunderstandings.

Why EUCAST disease specific breakpoints

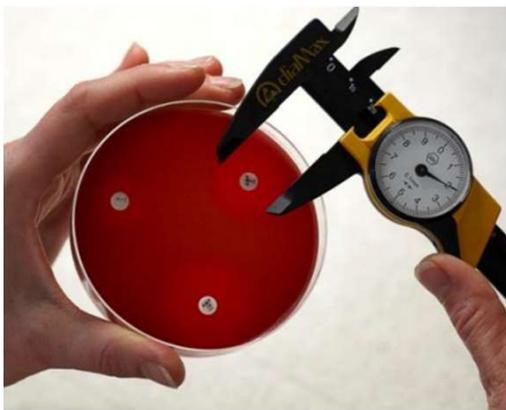
- The agent may be suitable for one indication only (uUTI, UTI, infections originating from the urinary tract)
 - Fosfomicin
 - Nitrofurantoin
 - Norfloxacin
 - Pivmecillinam
 - Trimethoprim
- The agent may be suitable for two very different indications (general systemic infections and a very difficult or special target: meningitis, endocarditis)
 - Benzylpenicillin
 - Ampicillin
 - Meropenem
 - Cefotaxime
 - Ceftriaxone

The laboratory perspective: Challenges

1. How much clinical information do we have?

2. (How do we make it work in the laboratory information system?)

3. Communication



Microbiology report
S. pneumoniae
Benzylpenicillin R
Ceftriaxone S



Example: *S. pneumoniae* blood isolate

***S. pneumoniae* blood isolate**

Oxacillin: 13 mm (screen positive)

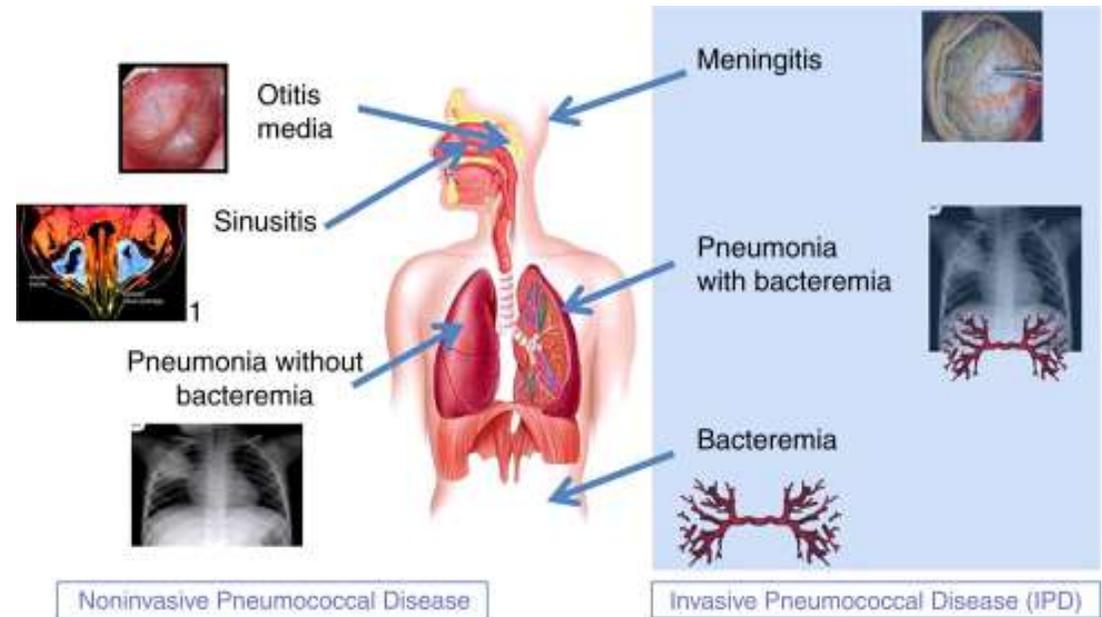
Benzylopenicillin (MIC 0,25 mg/L)

Cefotaxime MIC 0,06 mg/L

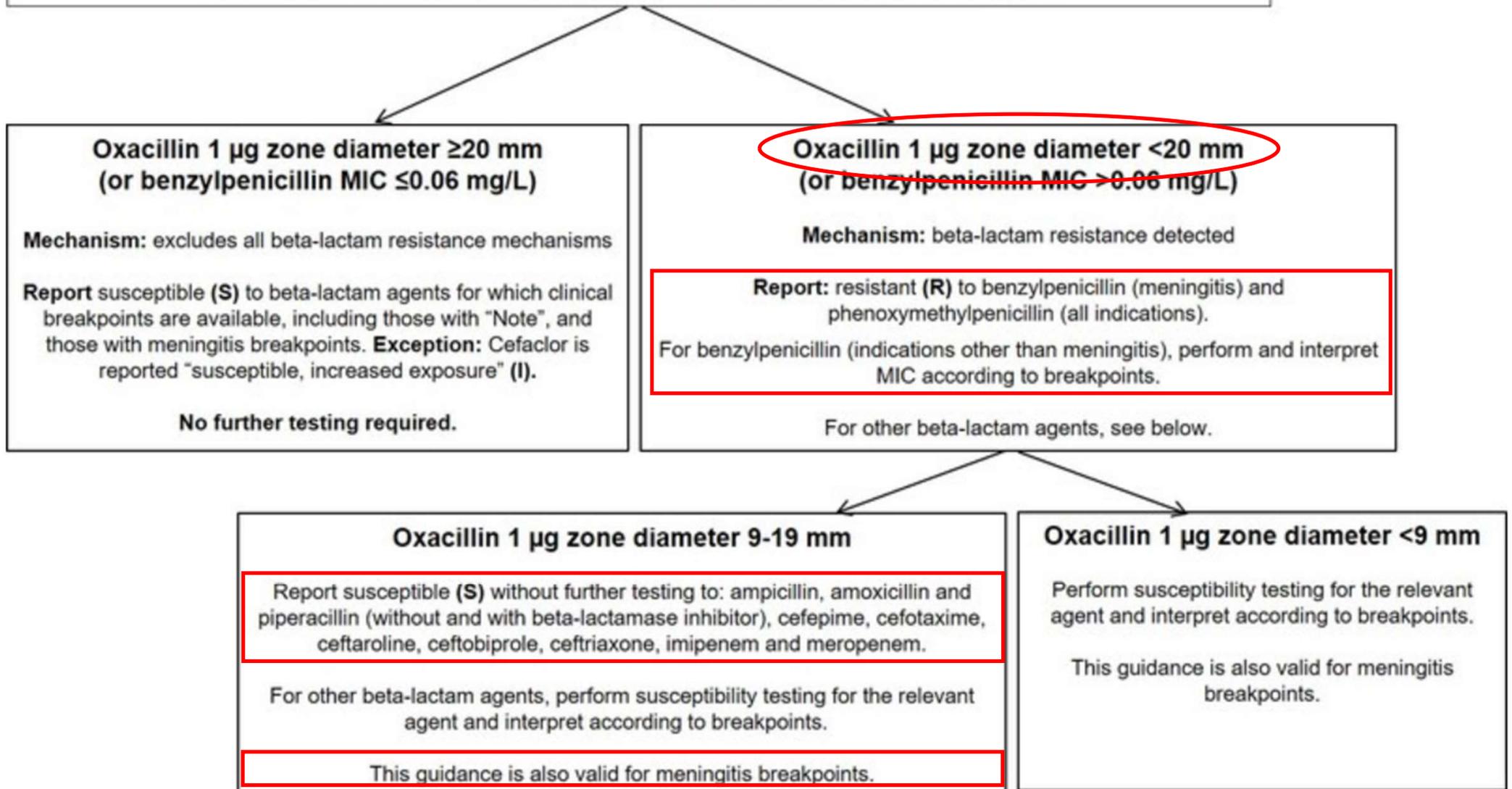
Ceftriaxone MIC 0,06 mg/L

Meropenem MIC 0,06 mg/L

How to report?



Flow chart based on the oxacillin screen test for beta-lactam resistance mechanisms to reduce the number of specific tests for beta-lactam agents



Example: *S. pneumoniae* blood isolate

***S. pneumoniae* blood isolate**

Oxacillin: 13 mm (screen positive)

Benzylopenicillin (MIC 0,25 mg/L)

Cefotaxime MIC 0,06 mg/L

Ceftriaxone MIC 0,06 mg/L

Meropenem MIC 0,06 mg/L

Meningitis:

Benzylopenicillin **R**

Cefotaxime **S**

Ceftriaxone **S**

Meropenem **S**

Other indications:

Benzylopenicillin **I**

Cefotaxime **S**

Ceftriaxone **S**

Meropenem **S**

Example: *S. pneumoniae* blood isolate

***S. pneumoniae* blood isolate**

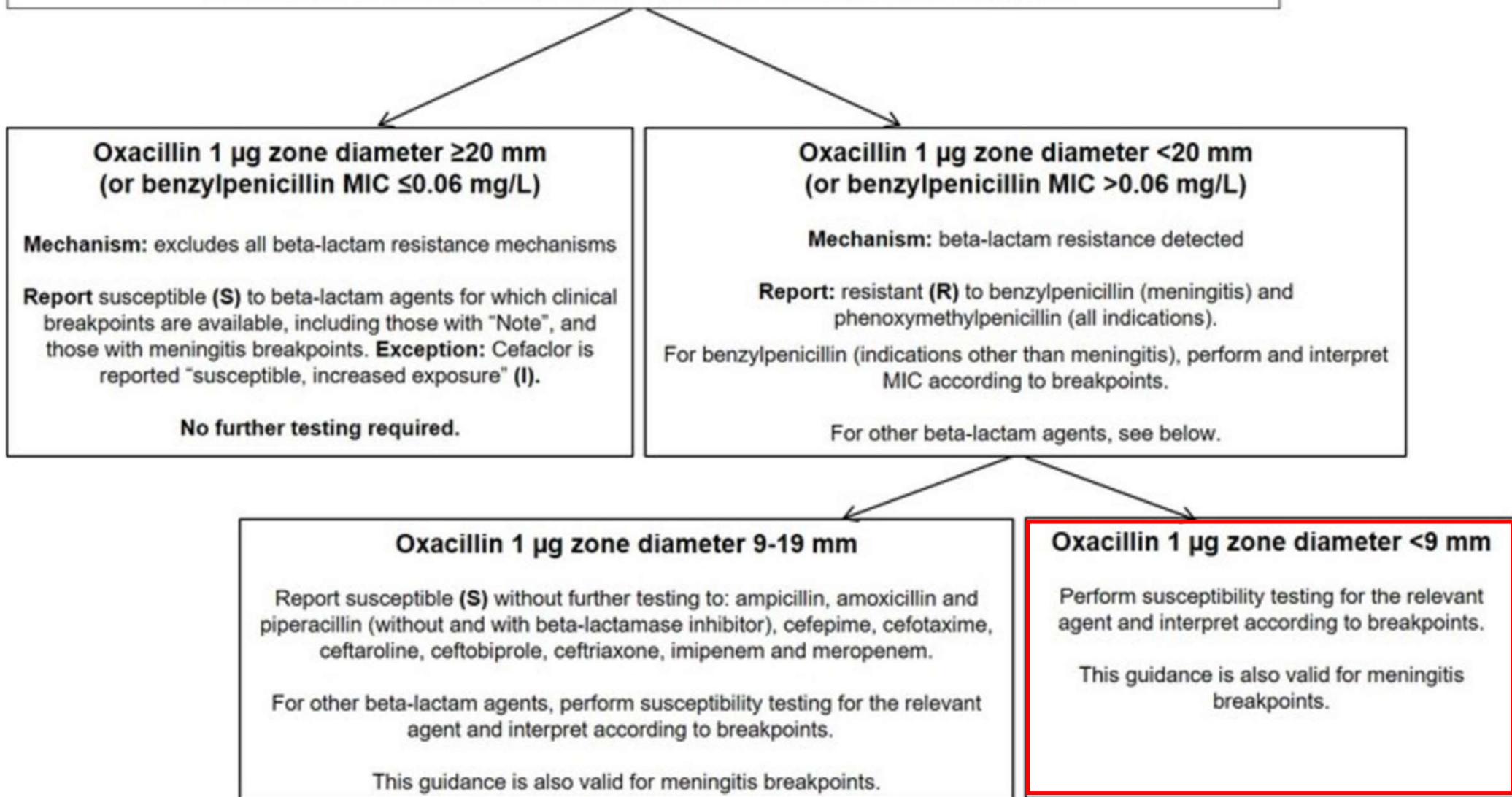
Oxacillin: 6 mm (screen positive)

Benzylopenicillin MIC 2 mg/L

Ceftriaxone MIC 0,5 mg/L

How to report?

Flow chart based on the oxacillin screen test for beta-lactam resistance mechanisms to reduce the number of specific tests for beta-lactam agents



Example: *S. pneumoniae* blood isolate

S. pneumoniae blood isolate

Oxacillin: 6 mm (screen positive)

Benzylpenicillin MIC 2 mg/L

Ceftriaxone MIC 0,5 mg/L

	MIC breakpoints (mg/L)			Disk content (µg)	Zone diameter breakpoints (mm)		
	S ≤	R >	ATU		S ≥	R <	ATU
Benzylicillin (indications other than meningitis)	0.06	2			Note	Note	
Benzylicillin (meningitis)	0.06	0.06			Note	Note	
Oxacillin (screen only)	NA	NA		1	20	Note	
Cefotaxime (indications other than meningitis)	0.5	2			Note	Note	
Cefotaxime (meningitis)	0.5	0.5			Note	Note	
Ceftriaxone (indications other than meningitis)	0.5	2			Note	Note	
Ceftriaxone (meningitis)	0.5	0.5			Note	Note	
Meropenem (indications other than meningitis)	2	2			Note	Note	
Meropenem (meningitis)	0.25	0.25			Note	Note	

Principle: no I-category for meningitis breakpoints!

Meningitis:

Benzylicillin **R**

Ceftriaxone **S**

Other indications:

Benzylicillin **I**

Ceftriaxone **S**

Example: *S. pneumoniae* blood isolate

Meningitis versus other indications

- Cerebrospinal fluid isolate might be available
- DK: Positive blood cultures are communicated to treating clinician by phone
- DK: For meningitis patients direct contact between clinical microbiologist and infectious disease specialist in the vast majority of cases

But: Not all meningitis cases are presented to the lab as meningitis cases, and we need to assume the worst case – eg. a warning on all oxa-screen positive isolates needs to be added.

Example: Indication "uncomplicated UTI" / *Enterobacterales*

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.

	MIC breakpoints (mg/L)		Disk content (µg)	Zone diameter breakpoints (mm)	
	S ≤	R >		S ≥	R <
Amoxicillin-clavulanic acid p.o. (uncomplicated UTI only) <i>E. coli</i> , <i>Klebsiella</i> spp. (except <i>K. aerogenes</i>), <i>Raoultella</i> spp. and <i>P. mirabilis</i>	32	32	20-10	16	16
Mecillinam p.o. (pivmecillinam) (uncomplicated UTI only) , <i>E. coli</i> , <i>Citrobacter</i> spp. <i>Klebsiella</i> spp., <i>Raoultella</i> spp., <i>Enterobacter</i> spp. and <i>P. mirabilis</i>	8	8	10	15	15
Cefadroxil (uncomplicated UTI only) <i>E. coli</i> , <i>Klebsiella</i> spp. (except <i>K. aerogenes</i>), <i>Raoultella</i> spp. and <i>P. mirabilis</i>	16	16	30	12	12
Cefalexin (uncomplicated UTI only) <i>E. coli</i> , <i>Klebsiella</i> spp. (except <i>K. aerogenes</i>), <i>Raoultella</i> spp. and <i>P. mirabilis</i>	16	16	30	14	14
Cefixime (uncomplicated UTI only) <i>E. coli</i> , <i>Klebsiella</i> spp. (except <i>K. aerogenes</i>), <i>Raoultella</i> spp. and <i>P. mirabilis</i>	1	1	5	17	17
Cefpodoxime (uncomplicated UTI only) <i>E. coli</i> , <i>Klebsiella</i> spp. (except <i>K. aerogenes</i>), <i>Raoultella</i> spp. and <i>P. mirabilis</i>	1	1	10	21	21
Cefuroxime p.o. (uncomplicated UTI only) , <i>E. coli</i> , <i>Klebsiella</i> spp. (except <i>K. aerogenes</i>), <i>Raoultella</i> spp. and <i>P. mirabilis</i>	8	8	30	19	19
Norfloxacin (uncomplicated UTI only)	0.5	0.5	10	22	22
Fosfomycin p.o. (uncomplicated UTI only) , <i>E. coli</i>	8	8	200	24	24
Nitrofurantoin (uncomplicated UTI only) , <i>E. coli</i>	64	64	100	11	11
Trimethoprim (uncomplicated UTI only)	4	4	5	15	15

Example: Indication "uncomplicated UTI" / *Enterobacterales*

No I-category

Refers to dosing table:

Dosages				EUCAST Clinical Breakpoint Tables v. 12.0, valid from 2022-01-01
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 considered a guidance for dosing in clinical practice, and does not replace specific local, national, or regional 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		<p>Meningitis caused by <i>S. pneumoniae</i>: For a dose of 2.4 g (4 MU) x 6 iv, isolates with MICs ≤ 0.06 mg/L are susceptible.</p> <p>Pneumonia caused by <i>S. pneumoniae</i>: 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.</p>
Ampicillin	2 g x 3 iv	2 g x 4 iv		Meningitis: 2 g x 6 iv
Ampicillin sulbactam	(2 g ampicillin + 1 g sulbactam) x 3 iv	(2 g ampicillin + 1 g sulbactam) x 4 iv		
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	3 g x 4 iv	3 g x 6 iv		
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.

Example:

Indication "uncomplicated UTI" / *Enterobacterales*

The easy ones: agents only used for uncomplicated UTI

Do not need any comment / further explanation (?)

(Microbiology reports is interpreted in relation to treatment guidelines)

The difficult ones: agents also used for other indications, namely complicated UTI

Danish perspective: only relevant for amoxicillin/clavulanic acid

Enterobacterales

Current breakpoints

Penicillin	MIC breakpoints (mg/l)			Disk content (µg)	Zone diameter breakpoints (mm)		
	S ≤	R >	ATU		S ≥	R <	ATU
Ampicillin	8	8		10	14	14	
Ampicillin-sulbactam	8	8		10-10	14	14	
Amoxicillin	8	8		-	Note ^B	Note ^B	
Amoxicillin-clavulanic acid	8	8		20-10	19	19	19-20
Amoxicillin-clavulanic acid (uncomplicated UTI only)	32	32		20-10	16	16	

Note B: Susceptibility inferred from ampicillin

Proposed breakpoints to come 2023

Penicillin	MIC breakpoints (mg/l)			Disk content (µg)	Zone diameter breakpoints (mm)		
	S ≤	R >	ATU		S ≥	R <	ATU
Ampicillin iv	8	8		10	14	14	
Ampicillin oral, uncomplicated UTI only	8	8			14	14	
Ampicillin-sulbactam iv	8	8		10-10	14	14	
Ampicillin-sulbactam oral, uncomplicated UTI only	8	8			14	14	
Amoxicillin iv	8	8		-	Note ^B	Note ^B	
Amoxicillin oral, complicated UTI	<0.001	8			Note ^B	Note ^B	
Amoxicillin oral, uncomplicated UTI only	8	8			Note ^B	Note ^B	
Amoxicillin oral, other indications	(8) ¹	(8) ¹			Note ^{A B}	Note ^{A B}	
Amoxicillin-clavulanic acid iv	8	8		20-10	19	19	19-20
Amoxicillin-clavulanic acid oral, complicated UTI	<0.001	8			19	19	
Amoxicillin-clavulanic acid oral, (uncomplicated UTI only)	32	32		20-10	16	16	
Amoxicillin-clavulanic acid oral, other indications	(8)	(8)			16	16	

Solution: comment or "two separate agents?"

Fosfomycin, oral for uUTI vs. Fosfomycin, IV

Consultation re. Fosfomycin IV breakpoints now on website; proposed change from 32/32 to 8/8 mg/L.

- Alternative 1. Proposed new IV breakpoints 8/8 mg/L (=breakpoints for oral fosfomycin) – no need for specific action.
- Alternative 2. Current IV breakpoint 32/32 mg/L is different from the oral breakpoint 8/8 mg/L.
 - The report would need two agents – for example:
Fosfomycin oral: S
Fosfomycin IV: R

Alternative solutions

- Agree with clinical colleagues and clarify in local treatment guidelines that some agents are valid only for UTI:
 - Fosfomicin, oral
 - Nitrofurantoin
 - Nitroxoline
 - Norfloxacin
 - Pivmecillinam
 - Trimethoprim

Alternative solutions

- Add "new" antibiotics to the list of agents:
 - Benzylpenicillin, meningitis
 - Benzylpenicillin, non-meningitis
 - Fosfomicin, IV -if different breakpoints
 - Fosfomicin, oral
 - Amoxicillin-clavulanic acid, UTI
 - Amoxicillin-clavulanic acid, systemic infections

Alternative solutions

- General comment:
 - AST interpretations only valid for non-meningitis. Contact the laboratory for alternative interpretations.
- Comment related to a specific antibiotic