Guidance for the testing and reporting of Aminopenicillin susceptibility for Enterobacterales.

Situation

In Version 13.0 of the EUCAST method (January 2023), there was an amendment to the interpretive criteria for aminopenicillins for Enterobacterales following a review of clinical, pharmacokinetic-pharmacodynamic and microbiological evidence. The changes pose challenges for the reporting of results in diagnostic laboratories as they provide separate clinical breakpoints for oral and intravenous therapy, urinary and non-urinary sources of infection and complicated and uncomplicated urine infection syndromes. Most laboratories will not have access to the necessary information to use these different breakpoints or their LIMS may not support such reporting.

Background.

The previous MIC and Zone Diameter guidance for Enterobacterales are shown in the table below. There were generally single breakpoints for each agent and an additional breakpoint for amoxicillin-clavulanic acid (co-amoxiclav) in uncomplicated UTI.

Table1: Aminopenicillin Breakpoints from EUCAST Version 12

Penicillins	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

In 2021, EUCAST undertook a review of aminopenicillins to account for the

- mode of delivery (oral versus iv) and
- site of infection (uncomplicated UTI, complicated UTI ± associated bacteraemia, and other systemic infection sites).

This led to a consultation in 2022:
https://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Consultation/2021/Aminopenicillins_and_Enterobacterales_General_consultation_November_2021.pdf

This reviewed pharmacokinetic and pharmacodynamic data for common doses, plus published clinical data.

The main findings of the review were,

- Pharmacodynamic modelling suggested that even higher doses of oral amoxicillin or co-amoxiclav could only predictably treat organisms with MICs up to 1 mg/L, wild-type E. coli typically having an MIC in the range 1 – 8 mg/L.
- The was very little published clinical data to support the use of oral amoxicillin for the treatment of infections outside the urinary tract caused by Enterobacterales.
- The was very little published clinical data to support the use of co-amoxiclav for the treatment of infections outside the urinary tract caused by Enterobacterales. There was some evidence suggestive of a possible role of high-dose co-amoxiclav following intravenous therapy for lung abscess, or for the treatment of skin and soft tissue infections.

Following the review and consultation, the new breakpoints for aminopenicillins in EUCAST v 13.0 are given in Table 2.

Table2: Aminopenicillin Breakpoints from EUCAST Version 13

Penicillins	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		**10**	14	14	
Ampicillin-sulbactam iv	8	8		**10-10**	14	14	
Ampicillin-sulbactam oral (uncomplicated UTI only)	8	8		**10-10**	14	14	
Amoxicillin iv	8	8		-	Note[B]	Note[B]	
Amoxicillin oral (infections originating from the urinary tract)	0.001	8		-	Note[C]	Note[C]	
Amoxicillin oral (uncomplicated UTI only)	8	8		-	Note[B]	Note[B]	
Amoxicillin oral (other indications)	(8)	(8)		-	Note[D,E]	Note[D,E]	
Amoxicillin-clavulanic acid iv	8	8		**20-10**	19	19	19-20
Amoxicillin-clavulanic acid oral (infections originating from the urinary tract)	0.001	8		**20-10**	50	19	19-20
Amoxicillin-clavulanic acid oral (uncomplicated UTI only)	32	32		**20-10**	16	16	
Amoxicillin-clavulanic acid oral (other indications)	(8)	(8)		**20-10**	(19)D	(19)D	19-20

Note B: Susceptibility inferred from ampicillin (iv or oral).

Note C: Isolates susceptible to ampicillin (iv or oral) can be reported "susceptible, increased exposure" (I) to "amoxicillin oral (infections originating from the urinary tract)". Isolates resistant to ampicillin (iv or oral) can be reported resistant to "amoxicillin oral (infections originating from the urinary tract)".

Note D: For information on how to use breakpoints in brackets, see https://www.eucast.org/eucastguidancedocuments/.

Note E: Infer from ampicillin oral, but the report should explain the meaning of breakpoints in brackets.

Assessment

The BSAC Standing Committee for Antimicrobial Susceptibility Testing recognises that there is little evidence that amoxicillin and co-amoxiclav are effective/appropriate for the treatment of Enterobacterales infections originating from outside the urinary tract.

Practice in the UK has been that these agents have been used variously to 'cover'/treat a number of infections where Enterobacterales may be cultured and may have a role. BNF/NICE recommends the use of oral co-amoxiclav in a number of non-urinary indications such as exacerbation of bronchiectasis, community acquired pneumonia, hospital acquired pneumonia, acute diverticulitis and leg ulcer infection

In the context of antimicrobial susceptibility testing and reporting, it is appropriate that if Enterobacterales are reported from a sample originating from outside the urinary tract, that there are suitable efficacy and dosing warnings included in any report that includes susceptibility test results for aminopenicillins.

Many laboratories may have difficulties in the implementation of the EUCAST guidance in full due to constraints of their laboratory information systems or concern regarding the clarity of reports to clinical colleagues.

Recommendations

In order to provide clear and safe results to clinicians, an approach to reporting is suggested in Table 3.

Table 3: Approach to reporting aminopenicillin susceptibility results for Enterobacterales.

Source of isolate	Penicillins	MIC breakpoints (mg/L)			Disk content (µg)	Zone diameter breakpoints (mm)			Notes
		S ≤	R >	ATU		S ≥	R <	ATU	
Blood Culture isolates	**Amoxicillin**	8	8		**10**	Note	Note		Report as Tested. Optional Report Comment that oral follow-on treatment should be given at high dose.
	Amoxicillin-clavulanic acid	8	8		**20-10**	19	19	19-20	
Urinary isolates	**Amoxicillin**	8	8		**10**	Note	Note		Report as Tested.
	Amoxicillin-clavulanic acid	8	8		**20-10**	19	19		Report as Tested. Option to report that for isolates with MIC of 16-32mg/L (zone size 16-18mm) oral co-amoxiclav remains a treatment option for **uncomplicated UTI only.** This can be indicated as a comment or separate interpretation.
Isolates from other samples	**Amoxicillin**	8	8		**10**	Note	Note		Report as Tested Add Report Comment that oral therapy should be given at high dose* and may not be effective as monotherapy.
	Amoxicillin-clavulanic acid	8	8		**20-10**	19	19	19-20	

*High Dose should be at least amoxicillin 500mg TDS or co-amoxiclav 625mg TDS