EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING

European Society of Clinical Microbiology and Infectious Diseases

Guidance on the Implementation of Revised Aminopenicillin Breakpoints for *Enterobacterales* January 2023

Introduction

With increasing information on the PK/PD of aminopenicillins, EUCAST became aware that certain adjustments were required to some aminopenicillin breakpoints. As a result, the aminopenicillin section of the *Enterobacterales* breakpoint table has become more complex. This guidance document provides the rationale for the changes and gives examples of how these changes can be implemented in the laboratory.

Rationale

Several factors must be considered in setting breakpoints for aminopenicillins:

- The range of agents with varying clinical availability and use around the world: ampicillin, ampicillin-sulbactam, amoxicillin and amoxicillin-clavulanic acid
- Differences in systemic exposure between oral and intravenous formulations
- The inability to achieve sufficient exposure with oral formulations for the treatment of systemic infections
- The use of ampicillin testing for predicting susceptibility to both ampicillin and amoxicillin
- The range of conditions, from minor to life-threatening, where aminopenicillins are traditionally used

As described in the consultation [1], there are major differences in exposure between intravenous and oral formulations of all aminopenicillins. This is complicated by the notably lower bioavailability of oral ampicillin compared to oral amoxicillin, and the fact that amoxicillin oral bioavailability is saturable, with no significant increase in exposure beyond 750 mg 8-hourly using the high dose regimens listed in the Dosages tab [2].

EUCAST analyses showed that the maximum achievable exposure with oral amoxicillin ± clavulanic acid could only cover pathogens with MICs up to 2 mg/L [3]. The ECOFF of the most common species of *Enterobacterales* is 8 mg/L

Aminopenicillins have high urinary excretion and hence are suitable for the treatment of *uncomplicated urinary tract infection* (uUTI). Most countries rely on amoxicillin ± clavulanic as oral agents to treat infection. In uUTI, clinical evidence supports the raising of the breakpoints for oral amoxicillin-clavulanic acid to S≤ 32, R> 32 mg/L, but there is insufficient clinical evidence to support raising the breakpoints for oral amoxicillin alone, oral ampicillin or oral ampicillin-sulbactam for uUTI. Nevertheless, these agents can safely be used when they test as susceptible at ≤ 8 mg/L.

Aminopenicillins are also important for the treatment of *infections originating from the urinary tract*, most commonly bacteraemic acute pyelonephritis. These infections have better outcomes than other bacteraemic infections and hence can be managed with oral amoxicillin ± clavulanic acid as oral stepdown for instance.

Maximum exposure with oral amoxicillin ± clavulanic acid is inadequate for other forms of systemic infection caused by *Enterobacterales.* Clinical evidence as monotherapy is generally lacking but they may still be used for a specific indication or in combination with another active agent or other measure (e.g. surgical intervention). This recommendation does not apply to *Enterobacterales* with expected resistance phenotype to amoxicillin ± clavulanic acid [4].

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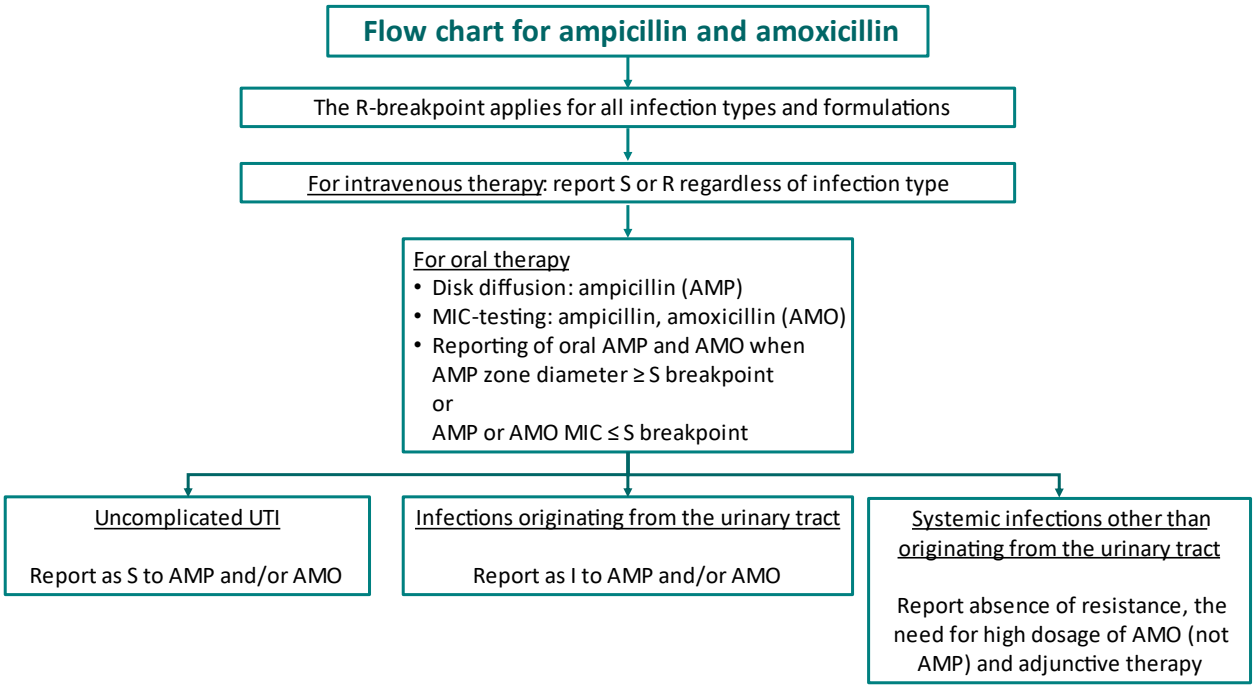
Implementing the revised breakpoints

Implementing the revised breakpoints is obviously a little more complex than previously. Put as simply as possible, for situations other than amoxicillin-clavulanic acid in uncomplicated UTI, the resistant breakpoint R>8 mg/L is valid for all aminopenicillins with or without inhibitor and for all situations. Report such isolates as resistant. The “susceptible“ breakpoint S≤ 8 mg/L is also valid throughout, but for oral therapy the report should be modified or accompanied by a comment.

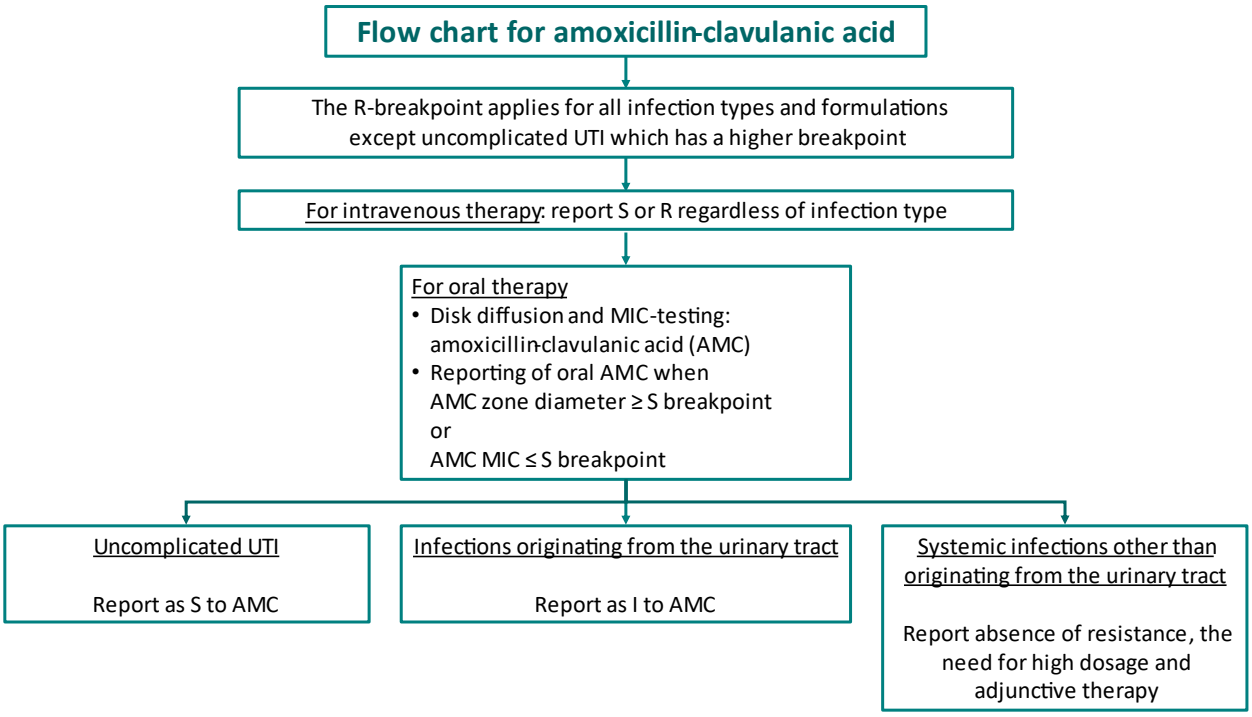
The breakpoint table represents the EUCAST view on how reporting should be performed but this may have to be modified in accordance with national guidelines and traditions and/or the limitations imposed by local health care and laboratory information systems. It is important to at least add a comment to explain the limitation and possible inadequacy of oral administration of ampicillin and amoxicillin (with and without inhibitor) in any situation beyond their use in uncomplicated urinary tract infections

Some laboratories might wish to develop a simple flowchart that will be of assistance to those reading and reporting the susceptibility testing results at the bench. Examples of such flow charts are shown below. It is recognised that implementation and any flow charts must be tailored to the availability of the agents and local clinical practice.

Possible flowcharts for implementing aminopenicillin breakpoints for *Enterobacterales*



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References

[1] Aminopenicillin breakpoints for *Enterobacterales* https://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Consultation/2021/Aminopenicillins_and_Enterobacterales_General_consultation_November_2021.pdf

[2] de Velde F, de Winter BCM, Koch BCP et al. Non-linear absorption pharmacokinetics of amoxicillin: consequences for dosing regimens and clinical breakpoints. J Antimicrob Chemother 2016; 71:2929-2917.

[2] Oral dosing of amoxicillin and amoxicillin-clavulanic acid in *S. pneumoniae* and *H. influenzae*. https://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Consultation/2018/Consultation_Amox_amp_Hi_Sp_oral_breakpoints_20180207.pdf

[3] Expected phenotype. https://www.eucast.org/expert_rules_and_expected_phenotypes

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