

Comments from the General Consultation on Revision of “EUCAST guidelines for detection of resistance mechanisms and specific resistances of clinical and/or epidemiological importance”

March - April, 2017

Changes from the previous consultation version are highlighted in yellow in the main document.

Comment from (name, contact details)	Comments	Responses
Ron A. Miller, US FDA Center for Veterinary Medicine	Section 1, 3 rd par: A sentence is needed here clarifying the terminology used in the text below. For example, when using the term 'resistant' this means clinically. Whereas when using the term 'decreased susceptibility' this means a deviation from wild-type that may or may not be clinically relevant. As such, we should be sure we use these terms correctly and consistently. For example: the word 'clinically' should be added before resistant at the end of this paragraph.	We agree that the document may be used for several purposes, not only clinical characterisation. We have added “clinically” as suggested in chapter 1.
Gregory Tyson, US FDA Center for Veterinary Medicine	Section 2, lead table: There needs to be a key to tell the reader what each of these categories means. E.g. 'public health' means that the bacteria described are of public health importance. Also, what does 'categorization' mean here? Categorized as having 'decreased susceptibility' or (clinically) 'resistant'?	We agree that this was not entirely clearly expressed and have tried clarifying throughout the document.
	2.2 1 st par: Should mention that carbapenemases in <i>P. aeruginosa</i> and <i>A. baumannii</i> will be discussed further in section 6 on page 28. Need to spell out 'CPE' when first used.	Since the heading of the chapter states that it pertains to Enterobacteriaceae we wanted to avoid including other species here. We have spelled out CPE in the text as suggested.
	2.2 2 nd par: IMP carbapenemases should also be	We have added a sentence about IMP-carbapenemases as suggested and a new relevant

	described.	reference. These are rather uncommon in Europe, but the document should be relevant in other locations also.
	3.4 Figure 1: in the bottom left of the figure, obviously, these are the three possibilities, but it would be useful to show what data would result in the interpretations in this figure.	We wanted to avoid making the figure too complex, and in the absence of a concrete suggestion for changes we decided to leave the figure as it is.
	3.4.3 last par: if 'molecular methods should be used for ESBL detection', appropriate methods should be discussed here.	The document is focused on phenotypic detection strategies. There is a plethora of both commercial and in-house assays that can be used, and also whole-genome sequencing with in silico mapping of resistance genes. We decided that making a comprehensive overview of all methods would not be possible. We could mention examples, but it could give an impression of an arbitrary selection that would maybe favour some commercial systems over other equally functional systems, as it is difficult to get an overview over all existing methods. Also, we are not specifically stating that it is important to do ESBL-characterisation in these situations.
	3.4.4: This section requires additional description. It is likely that with the increased use of WGS and other genotypic methods, standards or at least a brief review of available/acceptable methods would be useful.	See the response above. Additionally, we have added a reference to the recent EUCAST publication regarding the relationship between WGS and phenotypic AST. This document is scheduled for regular updates and for anyone looking for a state of the art update this should be sufficient source.
	4.2 2 nd par: The statement 'has remained far below that of ESBLs' requires additional context or caveats to refer specifically to Europe. Bacteria such as E. coli and Salmonella express AmpC beta-lactamases much more commonly than ESBLs in places such as the U.S.	We have added information about geographical location as suggested.
	5 Header: Suggest this be expanded to include other bacterial families to fit the listing in the table of contents	We agree that this is reasonable and have changed accordingly

	with the more encompassing term 'gram-negative bacilli'	
	5 4 th par: in the first sentence, it would be helpful to specify that colistin sulfate is the form of colistin that must be used.	We have added this information.
	7.3 2 nd par: the phrase 'detected by ceftazidime' is unclear as written-I believe this statement should be 'resistant to ceftazidime'?	Agreed. Changed as suggested.
	8 Header: Considering vancomycin is the only glycopeptide mentioned, I suggest using VRSA terminology instead of GRSA. This would also make it consistent with section 9 on VRE.	We have agreed and have changed the terminology throughout the text
	8.1 last par: If the last part of this sentence is true, perhaps these categories should be condensed into one. It seems to simply confuse the reader if they should all be treated the same. The description of VRSA can be expanded upon later by mentioning mechanistic differences contributing to resistance and how the various detection methods apply to each.	To some extent we agree, but for historical reasons we believe it is still important to mention the old terminology, and it will also in our opinion facilitate the understanding of the various mechanisms. We think the key part here is that the last sentence is included.
	8.4 1 st par: We should explain why disk diffusion can be used to test for GRSA. If the various resistance categories are condensed as suggested, an explanation can be added that only some mechanisms are appropriately identified without MIC determinations.	We have added a reference regarding detection of VRSA with disk diffusion.

	8.4.3 Table 1 title: Is this supposed to say GRSA? Is there no GRSA strain suggested?	Correct as assumed. Thank you for spotting the error.
	10.4 1 st par: should the MIC methods that are suitable be expanded upon? Which are appropriate?	EUCAST always by default mean broth microdilution (except for species where agar dilution is the standard). If other methods are used it is the responsibility of the user to ensure that there are good data to support that this particular method is adequate. Lack of warnings on the EUCAST websites should not be interpreted as the method has been evaluated and shown to work properly. EUCAST never undertakes systematic investigations of commercial methods unless part of a specific project.
	10.4.1 Figure 1: Bottom right of figure- It is unclear what this means-no MIC is determined from a disk diffusion test. Does this mean that MIC determination is required as a subsequent step? If so, perhaps MIC-based methods should be emphasized as preferred for detecting this resistance phenotype.	It means that as a next step MIC-determination should be carried out.
Kristján Orri Helgason, Microbiology Dept., Landspítali University Hospital of Iceland.	<p>Section number: 3.4.1 ESBL-screening in Enterobacteriaceae</p> <p>Many isolates which would previously have been identified as <i>Klebsiella</i> sp. are now identified as <i>Raoultella</i> sp. As an example, Maldi-tof has difficulty differentiating</p>	We have added <i>Raoultella</i> spp. in the heading of the table.

	<p>between <i>K. oxytoca</i> and <i>Raoultella</i> sp. Can <i>Raoultella</i> sp. be included in group 1 for ESBL testing alongside <i>Klebsiella</i> sp.? If not it would be good to have some advice on how and when to test <i>Raoultella</i> sp for ESBL.</p> <p>Enterobacteriaceae ESBL-screening in Enterobacteriaceae</p>	
<p>Sören Gatermann, on behalf of the German NAK soeren.gatermann@rub.de</p>	<p>Page 31, GISA etc: “...., all of the above mentioned categories should be regarded as clinically resistant” – “should” or “could” – is there sufficient scientific and clinical evidence (by reliable studies) that EUCAST can recommend “should”? First "resistant" is defined as vanA positive.....later on it is defined as MIC >8. According to data from the Natl. Reference Centre for Staphylococci the term "Almost all isolates with elevated MIC (GISA) are MRSA...." is not suitable anymore - we see increasing numbers of MSSA with elevated MICs.</p>	<p>There is no evidence to suggest that hVISA or VISA can be treated with vancomycin. Also, it is important to consider that the dosage cannot be increased for toxicity reasons. For this reason we maintain “should”</p> <p>We were not able to find references suggesting that VRSA/VISA/hVISA is common in MSSA. We would be happy to modify if provided with references to support that this has changed.</p>
	<p>Page 33, Macro gradient test: Please add all the other non-standard conditions for the Etest Macro, only the higher inoculum is mentioned (e.g. BHI instead of MHA?; longer incubation of up to 48h before reading?)</p>	<p>We have added this information</p>

	<p>Page 35, chapter 9.2: A more recent paper is missing about teicoplanin “breakthrough” resistance in VanB VRE under therapy: Holmes et al., 2013 J Antimicrob Chemother. 2013 Sep;68(9):2134-9. (PMID: 23612571; DOI:10.1093/jac/dkt130). In contrast to the text written, 4 cases of therapy failure due to TPL therapy for VanB-VRE infections were described. We interpret these findings as NOT to recommend TPL for therapy of VanB VRE infections.</p>	<p>We have added the reference and some accompanying text. We do not believe the body of evidence is strong enough to warrant reporting them as resistant. There could also be a significant publication bias, with successful cases not being reported.</p>
	<p>Page 36, chapter 9.4, third paragraph: Do the biochemical assays in fact still have a deeper role for enterococcal species ID? The majority of species ID for diagnostics is done by MALDI TOF MS. So we doubt the relevance of a hint regarding biochemical assays for species characterization. At least, one should start the paragraph with the last comment on MALDI and then maybe specify discriminating assays (Motility, arabinose utilization).</p>	<p>We agree that MALDI-TOF has largely replaced biochemical methods, but the document should be applicable also in settings where this technology is not available. We have as suggested reversed the order.</p>
	<p>Page 36, chapter 9.4.1: The Etest Macro has a good sensitivity for <i>E. faecium</i> with vanB, but has a low specificity for <i>E. faecalis</i> in general. About 30% of VAN susceptible <i>E. faecalis</i> showed a VAN MIC >4 in Etest Macro (Etest Macro: BHI instead of MHA; 2.0 McFarland inoculum, 48h incubation before reading; unpublished data, but presented as a conference abstract/poster [Werner et al.]).</p>	<p>We have removed the text about using the Etest macro method for this purpose.</p>

	Page 37, chapter 9.4.4. genotypic test: The sentence says “can be performed” – Should EUCAST at least “recommend” confirming a phenotypic VRE result by a vanA/vanB PCR?	We decided to leave the text as it is, as we do not see compelling evidence to always conduct genotypic confirmation. In many settings this will be done, but we have opted against making it a clear recommendation.
Inga Fröding, Clinical microbiology, Karolinska University Hospital, inga.froding@sll.se	Table page 7. Inconsistency with text – reads temocillin <12 mm in one place and <11 mm in another place.	We have changed to <11 mm.
	Could ertapenem be integrated to the screening algorithm for CPE somehow? Could it be stated that if meropenem is 25-27 mm isolates should only be subjected to screening if they are ertapenem resistant or non-susceptible? One problem with piperacillin-tazobactam is the lack of specificity and not all labs test temocillin.	In future versions ertapenem could be introduced, but this would have to be based on published evidence. At this stage we have not found clear evidence to suggest that adding ertapenem would be helpful.
NWGA, Christoffer Lindemann, pc-linde@online.no	<p>Chapter 9, VRE: Table 1 These are typical MICs of glycopeptides for enterococci that express vanA and vanB. Both vanA and vanB genotype strains either silenced or not so well induced may show MICs for vancomycin as low as 1 mg/L.</p> <p>We suggest to change Table 1 heading to; Typical MICs of glycopeptides for enterococci expressing <i>vanA</i> and <i>vanB</i>. 9.3 last paragraph should also mention low MIC vanB. We suggest following modified paragraph;</p> <p>Vancomycin variable enterococci (VVE) is a term used for VRE where the expression of <i>van</i> genes is phenotypically silenced by genetic rearrangements, which may be reversed under glycopeptide selection pressure (11, 12). Moreover, low-MIC VRE is a term used for <i>vanB</i> isolates</p>	<p>We agree with the first suggestion and have changed to “express”</p> <p>We have added the suggested sentence regarding low-MIC VRE.</p> <p>The suggested reference for breakpoint agars has been added.</p>

	<p>that due to initial poor ability to be induced by vancomycin have a low expression of <i>vanB</i> genes giving MIC levels below the clinical breakpoint. These low-MIC VRE may increase their MIC to above the breakpoint upon longer exposure to vancomycin (Grabsch et al., 2008. Improved Detection of <i>vanB2</i>-Containing <i>Enterococcus faecium</i> with Vancomycin Susceptibility by Etest Using Oxgall Supplementation. J. Clin. Microbiol 46; 1961-4). Both VVE and low-MIC VRE strains can often only be detected by molecular analysis. Their current prevalence in different geographical regions is unknown.</p> <p>9.4.3 Breakpoint agars Please refer to reference 17 in first sentence.</p>	
--	---	--