

## Background

Investigation of high-grade aminoglycoside resistance (HLAR) in enterococci is relevant, when aminoglycosides are used in combination with other antibiotics to achieve synergy. Aminoglycosides in combination with cell wall active antibiotics are indicated for the treatment of enterococci and in some cases for viridans streptococci in severe infections such as endocarditis. Enterococci and viridans streptococci are intrinsically low-level resistant for aminoglycosides due to reduced intracellular uptake. However, synergy can be achieved when combining aminoglycosides with antibiotics that inhibit cell wall synthesis (betalactams and glycopeptides), provided the absence of HLAR and susceptibility to the cell wall active antibiotic in question. Among others, it has been shown that beta-lactam antibiotics increase intracellular uptake of aminoglycosides. A test to detect HLAR should always be performed when combination therapy may be relevant, e.g. for blood culture isolates. There is currently only documentation for combination therapy with gentamicin or streptomycin.

## Mechanisms for HLAR

Aminoglycoside resistance in enterococci and viridans streptococci is primarily caused by aminoglycoside modifying enzymes (AME). There are three main classes of AME: aminoglycoside acetyltransferases (AAC), aminoglycoside nucleotidyltransferases (ANT) and aminoglycoside phosphotransferases (APH). Some AMEs only affect a single aminoglycoside, while others affect several aminoglycosides. One of the most common AMEs is the bifunctional enzyme AAC (6')-I-APH (2'') which mediates HLAR against all aminoglycosides except streptomycin. *Enterococcus faecium* has a species-specific chromosomal-encoded AME (AAC (6')-II) that eliminates any synergy with aminoglycosides with the exception of gentamicin and streptomycin.

## Method

EUCAST disk diffusion method (gentamicin 30 µg; streptomycin 300 µg) and/or MIC method covering relevant concentrations. Control strain (HLAR positive): *Enterococcus faecalis* ATCC 51299

## Interpretation

*Enterococcus* spp.

	HLAR negative		HLAR positive	
	Inhibition zone	MIC	Inhibition zone	MIC
<b>Gentamicin</b>	≥8 mm	≤128 mg/L	<8 mm	>128 mg/L
<b>Streptomycin</b>	≥14 mm	≤512 mg/L	<14 mm	>512 mg/L

Isolates that are HLAR positive for gentamicin (zone <8 mm / MIC >128 mg/L) are also reported HLAR for netilmicin and tobramycin. In such cases, streptomycin can be used as a treatment alternative provided the isolate is not HLAR positive also for streptomycin (zone <14 mm, MIC >512 mg/L).

If an aminoglycoside other than gentamicin or streptomycin is used, HLAR should be tested for the relevant aminoglycoside as isolated HLARs for some aminoglycosides may occur, e.g. tobramycin, although the isolate was found to be HLAR negative for gentamicin and streptomycin. However, it is not known which MIC limit should apply to HLAR in these cases and clinical data on efficacy are lacking. It is therefore recommended to use gentamicin.

Viridans group streptococci

	HLAR negative	HLAR positive
<b>Gentamicin</b>	MIC ≤128 mg/L	MIC >128 mg/L

Isolates that are HLAR positive for gentamicin (MIC >128 mg/L) are also reported HLAR for other aminoglycosides (netilmicin and tobramycin), except streptomycin. However, there is no clear evidence on how to test viridans streptococci for streptomycin.

The following comments can be used:

1. High-grade aminoglycoside resistance has not been detected. Synergy for combination therapy of beta-lactam antibiotics and gentamicin may be expected.
2. High-grade resistance to all aminoglycosides except streptomycin has been detected. Synergy for combination

therapy of beta-lactam antibiotics and aminoglycoside can only be expected with streptomycin.

3. High-grade aminoglycoside resistance has been detected. Synergy for combination of beta-lactam antibiotics and aminoglycoside cannot be expected.

## References

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4. Hollenbeck BL and Rice LB. Intrinsic and acquired resistance mechanisms in enterococcus. Virulence. 2012; 3(5): 421–569.
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## Responsible for this document:

NordicAST representatives, subgroup for gram positive bacteria, see <http://www.nordicast.org/nordicasts-medlemma>

## Changes

Date	Changes
2021-03-29	Translation to English, new title (old title: "Høygradig aminoglykosid-resistens hos enterokokker"). Viridans streptococci and relevant reference included. Update of persons responsible for the document
2015-03-20	Uppdatering dokumentansvariga
2014-12-03	Nytt dokument