

Background

Macrolides, lincosamides (clindamycin) and streptogramin B belong to the group of MLS_B antibiotics. They are bacteriostatic and act by binding to the ribosomal subunit 23S rRNA and thus inhibit protein synthesis. MLS_B antibiotics have overlapping binding sites on the ribosome, which explains that despite their various structures, cross-resistance occurs between them. Isolated resistance also occurs, for example, against macrolides or clindamycin alone. For susceptibility testing purposes, Erythromycin represents both 14-ring (erythromycin, clarithromycin, roxithromycin) and 15-ring (azithromycin) macrolides, except telithromycin, which must be independently tested.

Resistance linked to the *erm* gene is the most common MLS_B resistance. However, local variations occur.

Mechanisms

The following are the main resistance mechanisms for macrolide and MLS_B resistance:

- A. **Changed binding site at the ribosome** due to methylation of adenine at position 2058 in the 23S rRNA encoded by *erm* (erythromycin ribosomal methylase) genes. There are many *erm* genes where *ermA* and *ermC* are most commonly associated with staphylococci and *ermB* with streptococci. *erm* genes are expressed either constitutively (cMLS_B) or inducible (iMLS_B) in the presence of an inducer (i.e., macrolide). The latter is detected by the so-called "D-phenomenon" as shown below.
- B. **Active efflux** encoded by *mef* (macrolide efflux) genes in streptococci and *msr* (macrolide and streptogramin efflux) genes in staphylococci, only give rise to macrolide resistance (so-called M-type and MS_B-type resistance, respectively) against 14- and 15-ring macrolides and only to a limited extent to telithromycin. Clindamycin is not affected. MS_B-type resistance can cause inducible streptogramin B resistance.
- C. **Mutation in 23S rRNA and ribosomal protein** primarily L4 and L22 which results in clindamycin resistance without simultaneous erythromycin resistance and has been demonstrated in both staphylococci and streptococci, mainly in *S. pneumoniae*.
- D. ***Lnu* (formerly *Lin*) mediated resistance** via nucleotidyltransferase-modifying enzyme that inactivates clindamycin but not macrolides. This can be found among staphylococci, especially in animal-originated isolates.

Methods

Susceptibility to macrolides and clindamycin is tested by disk diffusion. Erythromycin is used as the test substance for all macrolides except telithromycin which must be independently determined. If erythromycin resistance is detected, inducible MLS_B resistance must be ruled out before reporting clindamycin susceptibility testing results. In addition, erythromycin sensitive isolates may be resistant to clindamycin as described above.

Inducible MLS_B resistance is demonstrated by placing a disk with erythromycin next to a disk with clindamycin on the agar plate with an edge to edge distance of 12-20 mm (staphylococci) and 12-16 mm (streptococci), respectively. The occurrence of antagonism, called "D-phenomenon" (see figure below), indicates that inducible clindamycin resistance is present.

Interpretation

Macrolides

Always report on the basis of the inhibition zone diameter.

Clindamycin

"D-phenomenon" has not been detected:

- Clindamycin is reported based on measured inhibition zone diameter regardless of results for erythromycin.

"D-phenomenon" has been detected:

- Report as resistant regardless of inhibition zone diameter for clindamycin. The following additional comment may be considered: "Inducible clindamycin resistance has been detected. Clindamycin may still be used for short-term therapy of less serious skin and soft tissue infections."
- When clindamycin is used in combination therapy with beta-lactam antibiotics for anti-toxin effect in severe

streptococcal infections, studies on the clinical significance of inducible clindamycin resistance are lacking, and there is no clear rationale for recommending that clindamycin therapy is discontinued.



Staphylococci: disk distance (edge to edge) 12-20 mm



Streptococci: disk distance (edge to edge) 12-16 mm

References

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Responsible for this document

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

Changes

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