Background

Methicillin- or oxacillin-resistant staphylococci, both *Staphylococcus aureus* (MRSA) and coagulase negative staphylococci (CoNS), cause a wide range of infections including severe infections. MRSA is a significant problem internationally, while the number of MRSA infections in the Nordic countries remains limited. Methicillin-resistance is significantly more common in CoNS than in *S. aureus*. These strains are often multidrug-resistant in addition to being methicillin resistant and thus can cause difficult-to-treat infections, especially foreign body-related infections.

Mechanisms

Methicillin resistance is due to the formation of an additional penicillin binding protein (PBP2a, PBP2b, or PBP2c) (1-3). PBP2a/2c has a low affinity for and therefore results in resistance to all β-lactam antibiotics except the new class of anti-MRSA cephalosporins ceftaroline and ceftobiprole. PBP2a is encoded by *mecA*, PBP2b by *mecB,* and PBP2c by *mecC* (1-3). Only one *S. aureus* carrying the *mecB gene* has been described (3) and this mechanism will not be discussed further. The *mec* gene is located in the Staphylococcal cassette chromosome *mec* (SCC*mec*) element. The expression of *mecA*/*mecC* and thus PBP2a/2c is highly variable so that some strains have very low MICs for oxacillin. A similar phenomenon is seen to a lesser extent with cefoxitin. Cefoxitin can be used as a very reliable screening agent for detecting MRSA (very high sensitivity and specificity) and to a certain degree also for methicillin-resistant CoNS (high sensitivity, lower specificity). NordicAST therefore recommends that cefoxitin is used for detection of methicillin resistance.
Some *S. aureus* isolates exhibit low resistance to oxacillin but not to cefoxitin and are *mecA*/*mecB*/*mecC* and PBP2a/2b/2c negative. These are known as "borderline susceptible *S. aur*eus (BORSA)". The resistance mechanism of these is most often poorly characterized / unknown but may include hyperproduction of β-lactamases or alteration of the existing PBPs (4).
The increased use of molecular methods has led to reports on *mecA*-positive *S. aureus* that are oxacillin (and cefoxitin) susceptible (OS-MRSA) (5). Several recent studies have reported on the mechanisms for silenced *mecA*-expression in *S. aureus* and the ability to revert to a clinically methicillin resistant phenotype during antibiotic selection mediating treatment failure (5). A combination of both geno- and phenotypic screening test are needed for the detection of OS-MRSA, presently such isolates are presumed to be rare in the Nordic countries. OS-MRSA is likely to increase with increasing MRSA prevalence (6). OS-MRSA should be reported as MRSA.

Methods

Methicillin resistance can be detected both phenotypically with disk diffusion (using cefoxitin screening) or genotypically with nucleic acid amplification testing (7,8). In CoNS, genotypic testing should be carried out in severe infections in case the test result for *S. epidermidis* is in the range of the area of technical uncertainty. Note that there are differences in species-specific zone breakpoints. See breakpoint table.

Phenotypic detection

- Disk diffusion: Standard EUCAST disk diffusion method with cefoxitin. QC strain: *S. aureus* ATCC 29213
- Broth microdilution: For cefoxitin, standard EUCAST method
- Latex agglutination kits for detecting the PBP2a protein. It should be noted that PBP2c is not detected by agglutination kits for detecting the PBP2a protein. Follow the manufacturer's instructions. There is good correlation to *mecA* for MRSA, the correlation is poorer for methicillin-resistant CoNS.

Genotypic detection

Genotypic detection of *mecA* and/or *mecC* genes by PCR. Both commercial as well as in-house methods can be used. It should be noted that commercial kits most often do not use gene sequences from the *mecA* or the *mecC* gene, but instead gene sequences from the SCC*mec* cassette. This can give rise to both false positive and false negative results. If your own laboratory does not perform *mecC* PCR, cefoxitin screening positive *S. aureus* isolates should be sent to the region / reference laboratory.
MRSA isolates must be *mecA* / *mecC* confirmed and sent to the national reference laboratory.

Interpretation

For cefoxitin resistant strains, the following antibiotics can be reported as R without further testing: penicillins (including beta-lactamase inhibitor combinations and beta-lactamase-stable penicillins), cephalosporins (except ceftaroline and ceftobiprole, which have to be tested separately) and carbapenems.

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NordicAST representatives, subgroup for Gram-positive bacteria, see NordicAST homepage.

Changes

Date	Changes
2021-05-11	Translation to English, new title (old title: “Stafylokokker / Påvisning av methicillinresistens”). Update of persons responsible for the document.
2015-03-20	Uppdatering av dokumentansvariga
2014-03-06	Förtydligande i tabell om tolkning av oxacillin MIC
2013-08-26	Nytt dokument