Först publicerad: 2022-09-15 12:37
Uppdaterad: 2022-09-15 12:37
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Utskriven av: anonym
Utgåva: 1
Revision: 0
2025-12-19

In this document, we include nomenclature from 2009 for ESBL (ESBL $_A$, ESBL$_{M-C}$, and ESBL$_{CARBA}$) (1), where *P. aeruginosa* with ESBL$_{CARBA}$ is used to describe carbapenemase-producing *P. aeruginosa*.

Background

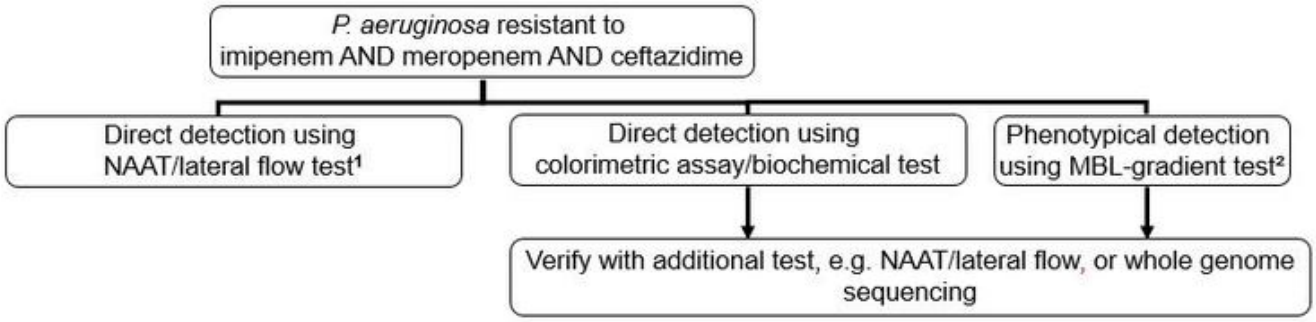
Carbapenem resistance in *P. aeruginosa* is normally caused by decreased permeability (porin deficiency), derepressed AmpC-expression, active drug efflux and/or production of horizontally transmitted (often by plasmids) carbapenem-hydrolyzing beta-lactamases (carbapenemases) (2). The mechanisms can occur in combination and can modulate resistance levels. Carbapenemases are considered particularly relevant from a public health point of view due to their high propensity for horizontal and clonal dissemination. In the Nordic countries, the most common mechanisms of carbapenem resistance are combinations of porin deficiency, increased AmpC-expression and efflux, but carbapenemases occur sporadically, usually related to hospitalization outside the Nordic countries.

The most common carbapenemases in *P. aeruginosa* are metallo-beta-lactamases (MBL; class B) (3). MBLs can hydrolyze almost all beta-lactams, with the exception of aztreonam and to a large extent the novel siderophore cephalosporin cefiderocol (4). The main MBL types in *P. aeruginosa* are VIM and NDM, but IMP and some others may occur. Class A carbapenemases, including KPC, can also be found, particularly in South America and China (5). Class D carbapenemases have occasionally been described in Europe (6).

Detection of carbapenemases in *P. aeruginosa* (ESBL$_{CARBA}$)

For detection of carbapenemases in *P. aeruginosa* NordicAST recommends testing isolates that are resistant to imipenem, meropenem and ceftazidime (see flowchart below). A susceptible disk diffusion result with ceftolozane-tazobactam (or imipenem-relebactam) can be used as an additional test to rule out MBL since MBL-producing isolates always lead to resistance to these two agents, while they are largely stable against increased AmpC expression and several efflux mechanisms (5).
Phenotypic methods for detection of carbapenemases include MBL gradient tests, assays based on hydrolysis of carbapenems and lateral flow assays. Genotypic testing can be performed using NAAT methods, often multiplex PCR with probe-based detection, LAMP or commercial microarray technology. Carbapenemase genes can also be identified from whole-genome sequencing data using open-source databases.

The diagnostic algorithm for carbapenemase confirmation is shown below.



¹NAAT (nucleic acid amplification test, e.g. PCR, LAMP)/lateral flow test should include the most common carbapenemases (NDM, VIM og IMP). If the test is negative, but the isolate is still suspected to be carbapenemase producing (e.g. due to laboratory or epidemiological reasons), consider additional testing for rarer carbapenemases or whole genome sequencing.
² Disk diffusion with ceftolozane-tazobactam can be used as an additional test to rule out MBL. MBL-producing isolates are always R.

Recommendations

Isolates with suspected carbapenemase production should be reported as tested according to clinical breakpoints, with a comment warning about possible carbapenemase-production (ESBL$_{CARBA}$) whilst confirmatory testing is carried out (in a reference laboratory or locally, depending on expertise and national guidelines).

Responsible for this document

NordicAST representatives, subgroup for gram negative bacteria in 2022, see http://www.nordicast.org/nordicasts-medlemmar

References

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Changes

2022-09-14	New document, replaces/based on “Pseudomonas aeruginosa og karbapenemaser (ESBLCARBA)”, last updated 2015-03-20.