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In this document we include nomenclature from 2009 for ESBL (ESBL $_A$, ESBL$_{M-C}$ and ESBL$_{CARBA}$) (2), where *Enterobacterales* with ESBL$_{CARBA}$ is used as an alternative nomenclature to carbapenemase-producing *Enterobacterales* (CPE).

Background

Enterobacterales may have varying degrees of reduced susceptibility / resistance to carbapenems due to multiple different resistance mechanisms (1,2). Mechanisms include the production of acquired carbapenemases (ESBL$_{CARBA}$) as well as a combination of extended spectrum beta-lactamases (ESBL$_A$), plasmid-mediated AmpC (ESBL$_{M-C}$), chromosomal AmpC, and impaired permeability (porin loss).
An increasing global occurrence of CPE/ESBL$_{CARBA}$ is being reported, also from the Nordic countries. KPC (*Klebsiella pneumoniae* carbapenemase), MBL (metallo-beta-lactamase; VIM, NDM, IMP etc.) and OXA-48 variants are the most common enzymes in this group (see Table 1). With the exception of OXA-48 variants, carbapenemases usually confer resistance to the entire group of beta-lactam antibiotics, including carbapenems.
Detection of carbapenemase production in *Enterobacterales* is challenging due to the diversity of enzymes. This is further complicated by the fact that some CPE/ESBL$_{CARBA}$ remain clinically susceptible to carbapenems.

Table 1: Overview of the most common acquired carbapenemases (ESBLCARBA) in Enterobacterales

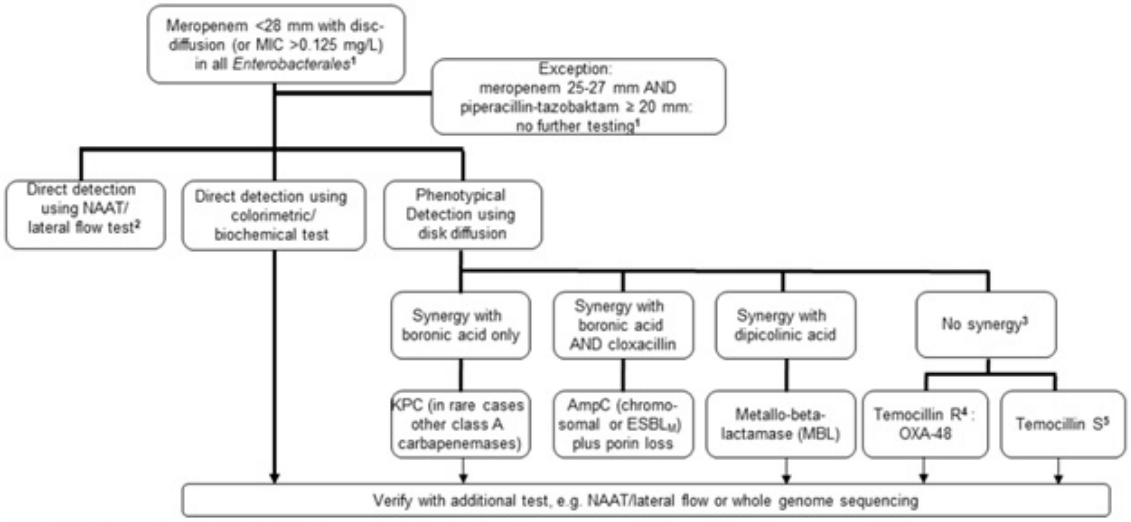
	Ambler Class A	**Ambler Class B**	**Ambler Class C**	**Ambler Class D**
Carbapenemase group	**KPC** (Klebsiella pneumoniae carbapenemase)	**MBL** (Metallo-beta-lactamase)	-	**OXA** (Carbapenem-hydrolysing class D betalactamases)
Important carbapenemase(s) within the group and main features	**KPC** Inactivates most beta-lactams including carbapenems **IMI** Chromosomal carbapenemase in E. cloacae, inactivates imipenem Rare: **GES, NMC, SME**	**NDM** **VIM** **IMP** Inactivate most beta-lactams except monobactams Rare: **SPM**	No carbapenemases in this Ambler class but AmpC+ porin loss can cause reduced susceptibility to carbapenems	A. **OXA-48 group** Often only slightly reduced susceptibility to carbapenems. Susceptible to cephalosporins. B. **OXA-23, -24/-40, -58** Inaactivate most beta-lactams including carbapenems
Common species (Rare species)	*Enterobacterales* *(P. aeruginosa)*	*Enterobacterales* *P. aeruginosa* *(A. baumannii*-group)	*Enterobacterales*	A. *Enterobacterales* B. *A. baumannii*-group
INHIBITED BY (used in phenotypical carbapenemase tests)	BORONIC ACID	DIPICOLINIC ACID and EDTA	CLOXACILLIN and BORONIC ACID	Inhibitor lacking (Temocillin[1])

[1]Temocillin >12 mm has been used as a phenotypical test to rule out OXA-48. Recently, new variants (e.g. OXA-244) have emerged which are not resistant to temocillin. Temocillin S can no longer be used to rule out carbapenemase production.

Detection of carbapenemases in *Enterobacterales* (ESBL$_{CARBA}$)

For the detection of carbapenemases in *Enterobacterales*, a meropenem screening cut-off of <28 mm for disk diffusion (or MIC >0.125 mg/L) is recommended (see Figure 1). Isolates with values below/over these mm/MIC cut-offs should be tested for the presence of carbapenemases using phenotypic and/or genotypic methods. This do not apply for isolates with zone diameters of 25-27 mm for meropenem AND a >20 mm for piperacillin-tazobactam, for such isolates no further testing is necessary. This additional testing for carbapenemases should not delay reporting according to clinical breakpoints to clinicians.
Phenotypic methods for detection of carbapenemases include the combination disk test, assays based on hydrolysis of carbapenems, and lateral flow assays. Genotypic testing can be performed using different 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 for gene detection.

Figure 1. Algorithm for detection of carbapenemases in Enterobacterales



[1] For laboratories using disk diffusion there is no added value in determining meropenem MIC regarding carbapenemase detection.
[2] NAAT (nucleic acid amplification test, e.g. PCR, LAMP)/lateral flow test should include the most common carbapenemases (OXA-48, NDM, VIM and KPC). 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 (e.g. IMP, IMI, GES) or whole genome sequencing.
[3] In rare cases highly resistant isolates with no synergy may harbor more than one carbapenemase.
[4] High levels of resistance to temocillin (>128 mg/L, zone <12 mm) may indicate OXA-48. OXA-48 producing isolates are also resistant to piperacillin-tazobactam and amoxicillin-clavulanic acid.
[5] Some new OXA-48 variants (e.g. OXA-244) do not cause resistance to temocillin. A phenotypical test using disc diffusion is not available to detect these variants and suscpetibility to temocillin can not be used to rule out carbapenemase production

Recommendations

NordicAST supports the EUCAST recommendations of using meropenem (for best balance of sensitivity and specificity) when screening for reduced susceptibility to carbapenems in order to detect carbapenemases in *Enterobacterales*. For laboratories using disk diffusion, there is no added benefit in determining meropenem MIC regarding carbapenemase detection. Isolates with suspected carbapenemase production should be reported as tested according to clinical breakpoints, and with a comment warning about possible CPE ($ESBL_{CARBA}$) whilst confirmation testing is carried out (either at a reference laboratory or in the local laboratory, depending on expertise and national guidelines).

References

1. EUCAST Detection of resistance mechanism version 2, 2017
2. Giske C et al. J Antimicrob Chemother. 2009;63:1-4.