UiT The Arctic University of Norway

NordicAST new BL/BLI document- how to use it

Annual NordicAST workshop

Malmö, Sweden

May 12, 2026

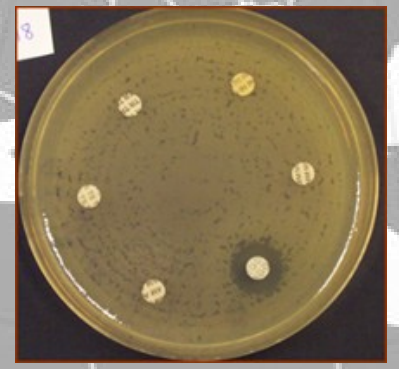
ARNFINN SUNDSFJORD

Centre for New Antibacterial Strategies (CANS: https://uit.no/research/cans)

***UiT** The Arctic University of Norway*

National Center for Detection of Antimicrobial Resistance (K-res: https://unn.no/fag-og-forskning/k-res)

University Hospital of Northern Norway, Tromsø



CANS Centre for New Antibacterial Strategies

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Outline

1. **Carbapenemase** producing organisms (CPO)
   - β-lactamase: groups and diversity
   - Epidemiology carbapenemase producing Enterobacterales **(CPE)**
2. **β-lactam β-lactamase inhibitor** (BLBLI) combinations
   - Inhibitor groups and mode of action
3. The **NordicAST BLBLI document** – how to use

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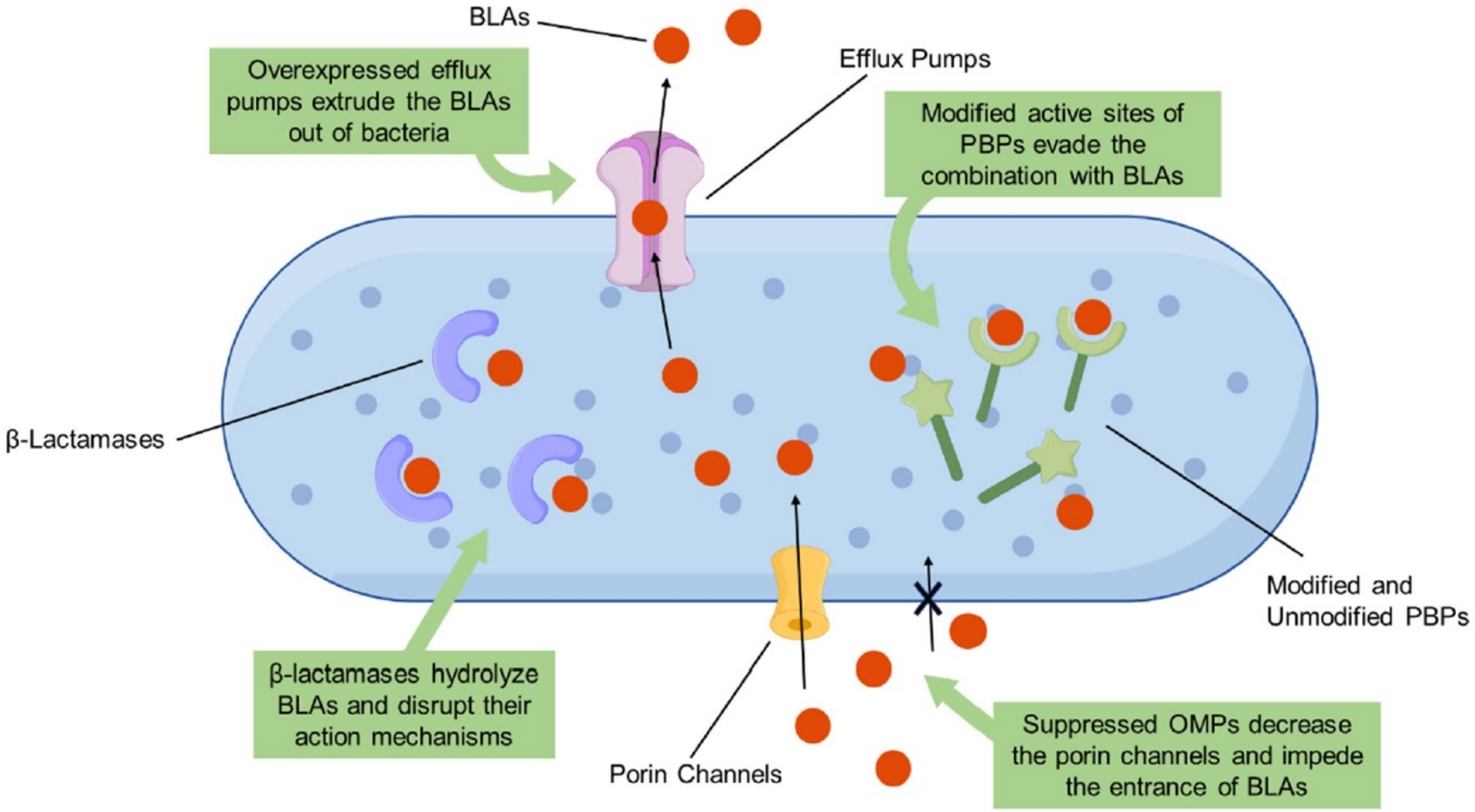
Resistance mechanisms to β-lactam antibiotics



Zhang et al. Antibiotics 2024, 13, 260.

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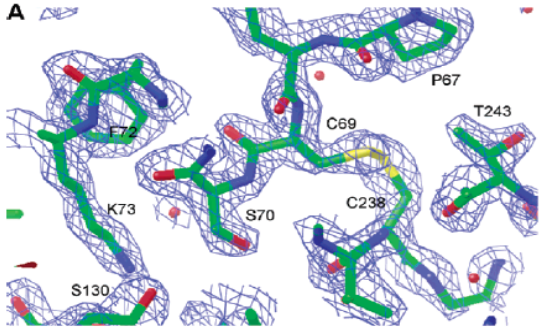
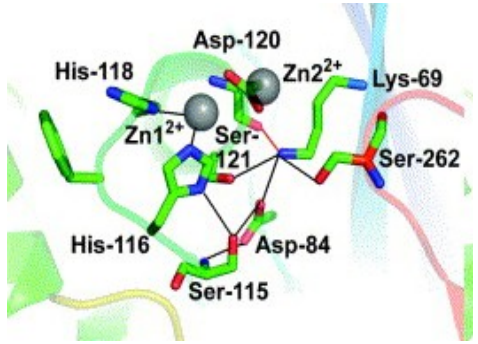
Classification of β-lactamases – carbapenemases in red

- Molecular classification **(Ambler)**

Serine β-lactamases



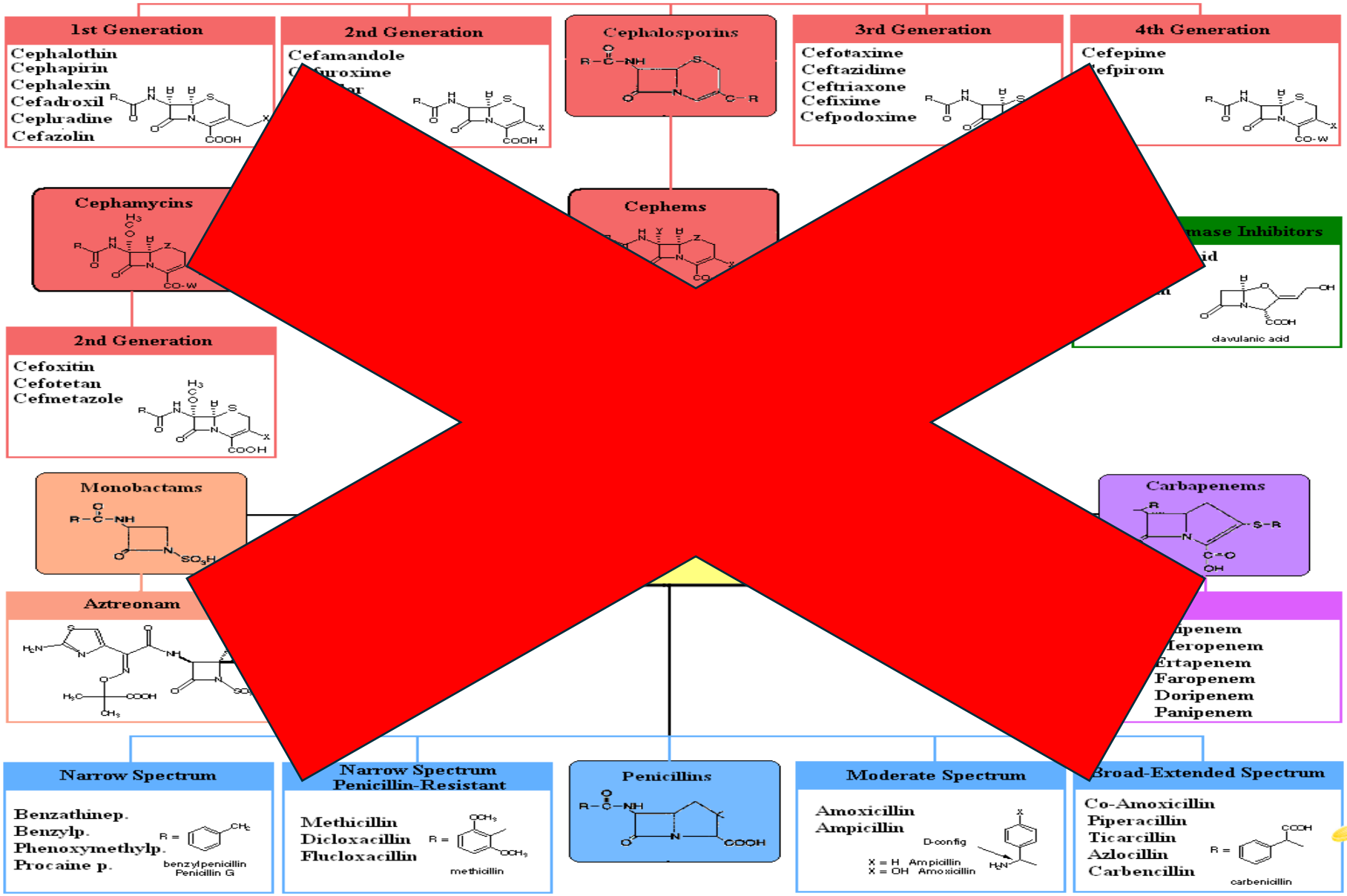
Metallo-β-lactamases (MBL)



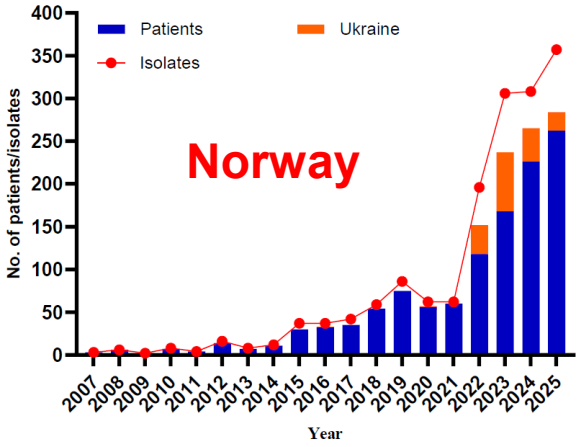
Class A	Class C	Class D	Class B
KPC IMI GESv		OXA-48-like (Enterobacterales) OXA-23/-24/-40/-58/ -143-like (*A. baumannii*)	NDM VIM IMP

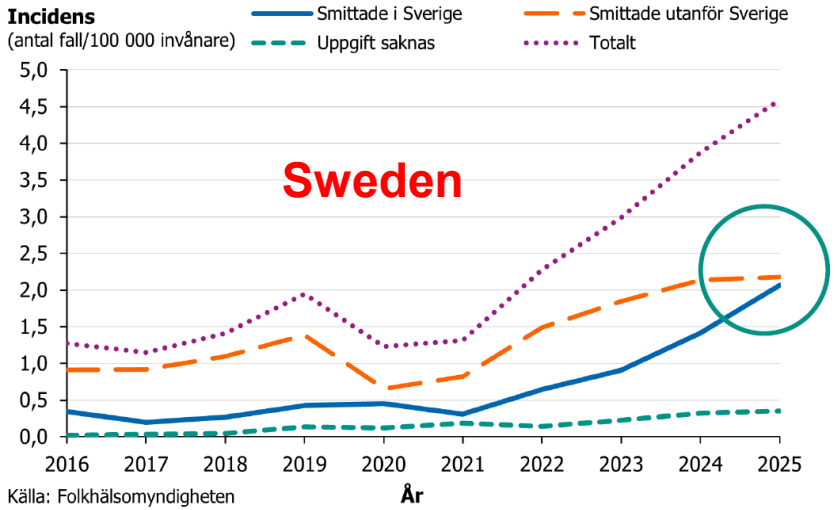
Ambler RP. Philos. Trans. R. Soc. Lond. B. Biol. Sci. 1980; Bush K, Bradford PA. CMR 2020

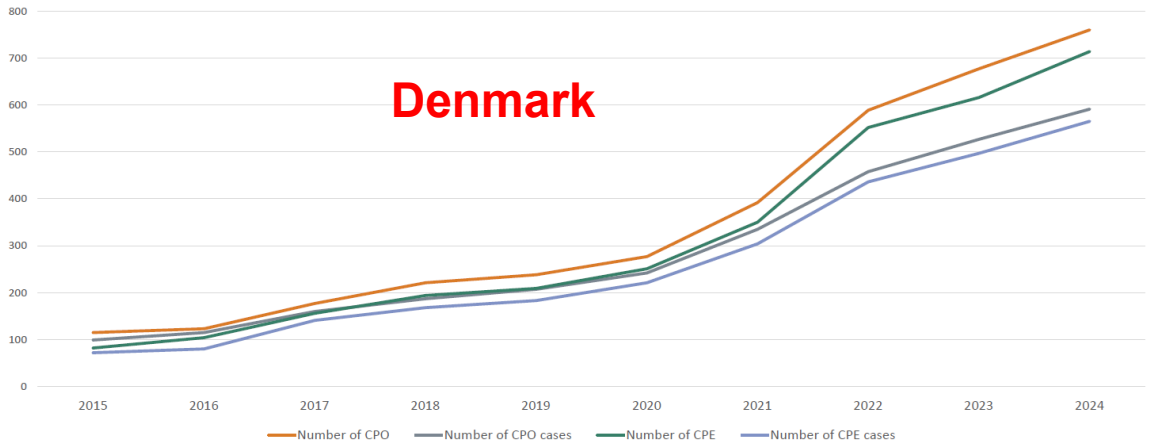
Carbapenemases «eat» β-lactams



CPE epidemiology – Nordic 2025 data







- **Increase in CPE cases**
  - 4-6/100.000 inhabitants
- **Strains**
  - *E.coli* > *K. pneumoniae*
  - Global clones
- **Carbapenemase**
  - OXA-48 like
  - NDM
- **Clusters**
  - Intra-/interhospital spread
- **Community spread?!**
  - *E.coli* OXA-48-like

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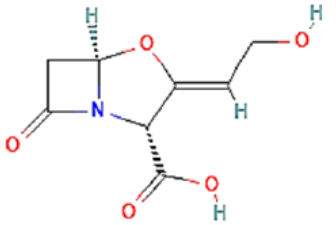
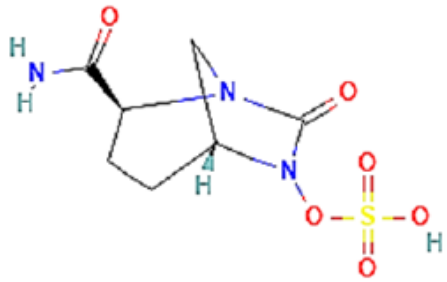
β-lactamase inhibitors

Clavulanic acid



- **β-lactam-based inhibitors**
  - Clavulanic acid, tazobactam, sulbactam, and enmetazobactam
  - Inhibit serine betalactamases by acylation
  - «Suicidal» inhibitors binding irreversibly to the betalactamase (1:1)
  - Minimal intrinsic antibacterial effect – except sulbactam (*Acinetobacter*)
- **Non-β-lactam inhibitors**
  - **DBOs** (diazabicyclooctanes): avibactam, durlobactam, relebactam, zidebactam ++
    - Covalent reversible inhibitors – inhibit, dissociate, and recycle
      - One inhibitor molecule inhibits multiple β-lactamase molecules
    - Some have intrinsic antibacterial activity (synergy)
      - Particular PBP2 binding activity
  - **Boronic acid-based:** vaborbactam ++
    - Covalent reversible inhibitor - inhibit, dissociate and recycle
    - Vaborbactam has no significant intrinsic antibacterial activity

Avibactam



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NordicAST BLBLI document

- **Aim**: Guide laboratories in the expected activity of BLBLIs combinations + cefiderocol against various β-lactamases
  - Guide susceptibility testing, interpretation and consulting
- **DO NOT**
  - Provide clinical treatment guidelines
  - Replace antimicrobial susceptibility testing
- **Structure**
  - **Tables 1.1-3:** Expected BLBLI and cefiderocol activities against Enterobacterales, *Pseudomonas* spp., and *Acinetobacter baumannii* complex
  - **Table 2:** Expected β-lactamase inhibitors (BLIs) activities on specific groups of β-lactamases

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Expected inhibitor activity

Table 2. Expected inhibitor activity of BLIs on clinically relevant β-lactamases[1]

β-lactamase inhibitor	ESBL (CTX-M)	Chromosomal/ plasmid-mediated AmpC (CMY, DHA)	Class A carbapenemases (KPC, IMI)	Class B carbapenemases (NDM, VIM, IMP)	Class D carbapenemases[2] (OXA-48, OXA-181, OXA-244)	Class D carbapenemases[3] (OXA-23-/24-/58-like)
Avibactam	+	+	+	-[4]	+	(+)
Clavulanic acid	+	-	-	-	-	-
Durlobactam	+	+	+	-	+	+
Enmetazobactam	+	-	(+)	-	-	-
Relebactam	+	+	+	-	-	-
Sulbactam	+	-	-	-	-	-
Tazobactam	+	-	-	-	-	-
Vaborbactam	+	+	+	-	-	-
Zidebactam	+	+	+	-[5]	-[5]	-

[1] +: activity to be expected; -: no activity to be expected; (+) uncertain or insufficient activity.

[2] Class D carbapenemases mainly associated with Enterobacterales but also found occasionally in *P. aeruginosa*.

[3] Class D carbapenemases mainly associated with *A. baumannii* complex. These are rare among Enterobacterales, except for some reports mainly in *P. mirabilis*. The activity of avibactam and taniborbactam is uncertain against these β-lactamases.

[4] Activity is to be expected against MBL-producing Enterobacterales in combination with aztreonam, as aztreonam is not a target for MBL.

[5] Activity is to be expected against Enterobacterales and *P. aeruginosa* in combination with cefepime due to the synergistic bactericidal effect arising from complementary PBP inhibition by zidebactam and cefepime.

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Enterobacterales and relevant BLBLI

Table 1.1. Enterobacterales – expected activity of BLBLIs and cefiderocol [1]

Antimicrobial	ESBL (CTX-M)	Chromosomal/ plasmid-mediated AmpC (CMY, DHA)	Class A carbapenemases (KPC, IMI, GES)	Class B carbapenemases (NDM, VIM, IMP)	Class D carbapenemases (OXA-48-like)
Amoxicillin-clavulanic acid[2]	+	-	-	-	-
Ampicillin-sulbactam[2]	+	-	-	-	-
Aztreonam-avibactam	+	+	+	+[3]	+
Cefepime-enmetazobactam	+	+[4]	-	-	+[4]
Cefepime-zidebactam	+	+	+	+[5]	+[5]
Cefiderocol	+	+	+	+/-	+
Ceftazidime-avibactam	+	+	+	-	+
Ceftolozane-tazobactam	+	-	-	-	-
Imipenem-relebactam[6]	+	+	+	-	-
Meropenem-vaborbactam	+	+	+	-	-
Piperacillin-tazobactam	+	-	-	-	-

[1] +: activity to be expected; -: no activity to be expected; +/-: variable activity to be expected.

[2] Relevant for *E. coli, Klebsiella* spp. (except *K. aerogenes*), *Raoultella* spp. and *P. mirabilis*. Not relevant for AmpC-producing Enterobacterales.

[3] The activity of the combination is due to the lack of class B carbapenemase (metallo-β-lactamases – MBLs) hydrolytic activity against aztreonam and avibactam's inhibitory activity against ESBLs/AmpCs that are frequently found in class B carbapenemase-producing isolates. Avibactam has no inhibitory activity against class B carbapenemases.

[4] The activity of the combination is due to the limited OXA-48/AmpC-hydrolytic activity against cefepime and enmetazobactam's inhibitory activity against ESBLs that are frequently found in OXA-48-like-producing isolates (7, 10).

[5] The activity of the combination is mainly due to the synergistic bactericidal effect arising from complementary PBP inhibition by zidebactam and cefepime, rather than restoration of cefepime activity through β-lactamase inhibition. Direct inhibitory activity of zidebactam against class B/OXA-48-like carbapenemases is not expected.

[6] BLBLI relevant for Enterobacterales except *Morganellaceae* which has reduced susceptibility to imipenem.

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Table 1.2. *Pseudomonas* spp. – expected activity of BLBLIs and cefiderocol[1]

Antimicrobial resistance in *Pseudomonas aeruginosa* is driven by a combination of chromosomal mutations, transferable resistance determinants, and the global spread of multidrug-resistant (MDR) and extensively drug-resistant (XDR) epidemic lineages (17). The remarkable ability of *P. aeruginosa* to develop mutation-driven resistance against newer β-lactams, β-lactamase inhibitors, and siderophore-conjugated antibiotics (e.g., cefiderocol) introduces greater uncertainty in the expected activity profile of β-lactam/β-lactamase inhibitor (BLBLI) combinations compared to Enterobacterales. This uncertainty is particularly associated with mutations affecting the chromosomal AmpC β-lactamase, prevalent OXA-2/10 β-lactamases, penicillin-binding protein 3 (PBP3), the MexAB-OprM efflux pump, and iron transporters (17).

Antimicrobial	ESBL (CTX-M, GES, PER)	Chromosomal AmpC	Class A carbapenemases (KPC, GES-variants)	Class B carbapenemases (NDM, VIM, IMP)	Class D[2] carbapenemases (OXA-48-like, OXA-23-like, OXA-58-like)
Aztreonam-avibactam[3]	(+)	(+)	(+)	(+)	(+)
Cefepime-zidebactam	+	+	+	+[4]	+[4]
Cefiderocol	+[5]	+	+	+/-	+
Ceftazidime-avibactam	+	+	+	-	-
Ceftolozane-tazobactam	+	+[6]	-	-	-
Imipenem-relebactam	+	+	+/-[7]	-	-
Meropenem-vaborbactam	+	+	+/-[7]	-	-
Piperacillin-tazobactam	+	-	-	-	-

[1] +: activity to be expected; -: no activity to be expected; +/-: variable activity to be expected; (+): potential activity in combination therapy

[2] Class D carbapenemases are rare in *Pseudomonas* spp. and the clinical efficacy of relevant BLBLIs is uncertain (15).

[3] EUCAST has no clinical breakpoints for aztreonam-avibactam against *Pseudomonas* spp. due to high MICs compared to the potential exposure.

[4] The activity of the combination is mainly due to the synergistic bactericidal effect arising from complementary PBP inhibition by zidebactam and cefepime, rather than restoration of cefepime activity through β-lactamase inhibition. Direct inhibitory activity of zidebactam against class B/OXA-48 carbapenemases is not expected.

[5] Cefiderocol activity can be compromised by the presence of SHV- (SHV-12), PER-, VEB-, and BEL-like β-lactamases (8).

[6] The activity of the combination is mainly due to the lack of AmpC-hydrolytic activity against ceftolozane and stability against mutation-driven resistance (17).

[7] Recent *in vitro* studies have shown that relebactam and vaborbactam resulted in poor augmentation of the partner carbapenem activity, imipenem and meropenem, respectively, in class A carbapenemase-producing *P. aeruginosa* (9, 17).

Acinetobacter and relevant BLBLI

Table 1.3. *A. baumannii* complex – expected activity of BLBLIs and cefiderocol[1]

Cephalosporins and monobactams, even when combined with β-lactamase inhibitors (BLIs), except cefiderocol and cefepime-zidebactam, are not deemed clinically relevant due to insufficient evidence supporting their efficacy in treating infections caused by the *A. baumannii* complex.

Antimicrobial	Class A carbapenemases (KPC)[2]	Class B carbapenemases (NDM, VIM, IMP)	Class D carbapenemases (OXA-23-like, OXA-24/40-like, OXA-58-like)
Cefepime-zidebactam	Uncertain		
Cefiderocol[3]	(+)	+/-	+
Imipenem-relebactam	(+)	-	-
Meropenem-vaborbactam	(+)	-	-
Sulbactam-durlobactam	(+)	-	+

[1] +: activity to be expected; -: no activity to be expected; +/-: variable activity to be expected; (+): potential activity in combination therapy.

[2] Class A carbapenemases are rare in *A. baumannii* complex and the clinical efficacy of relevant BLBLIs is uncertain (14).

[3] EUCAST has not established clinical breakpoints (only a note) for cefiderocol against the *A. baumannii* complex. The EUCAST note reads: *Isolates with MIC values ≤0.5 mg/L (zone diameter ≥21 mm) are mostly devoid of resistance mechanisms and are likely to be a target for treatment with this agent. Isolates with MICs 1-2 mg/L have some acquired resistance mechanisms. Little clinical data exists regarding clinical outcome for these isolates; however, they may still be a target for treatment with this agent if there are limited treatment options. Isolates with MIC values >2 mg/L (zone diameter <17 mm) have acquired resistance mechanisms and are likely to be resistant to this agent.*

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Thanks

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