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Aztreonam–avibactam and cefepime–enmetazobactam

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The toolbox – an overview

The “not-so-new”

- Ceftolozane–tazobactam
- Ceftazidime–avibactam

The fairly recent

- Meropenem–vaborbactam
- Imipenem–relebactam
- Cefiderocol

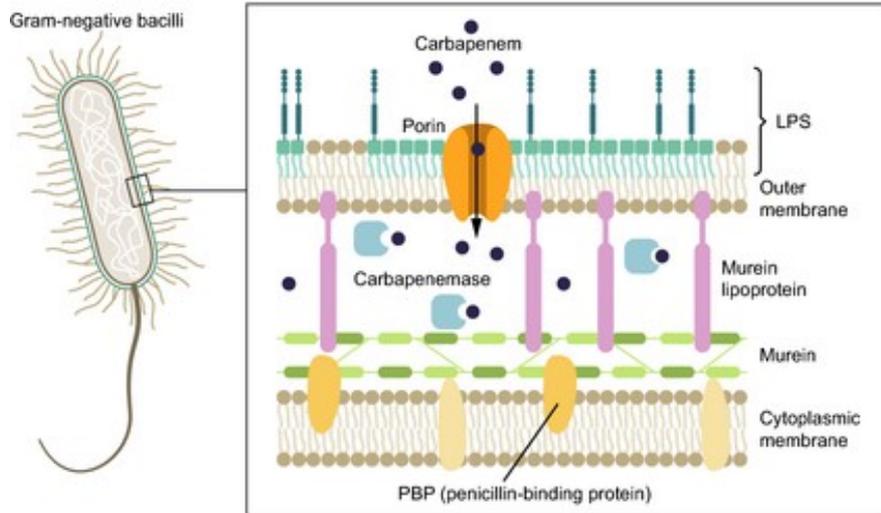
The brand new

- Aztreonam–avibactam
- Cefepime–enmetazobactam

Those in the pipeline

- Cefepime–zidebactam
- Cefepime–taniborbactam
- Sulbactam–durlobactam

Not only a matter of beta-lactamases...



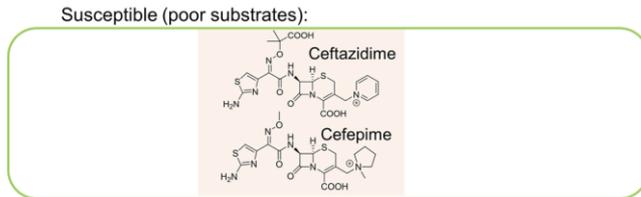
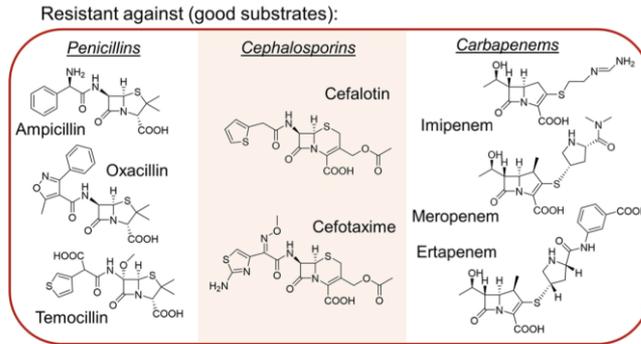
Beta-lactamases,
porins
efflux pumps, PBP-
changes

When developing new
drugs all have to be
considered

Tängdén T and Giske CG. J Intern Med. 2015;277(5):501-12.

Cefepime–enmetazobactam (Allegra)

- Phase 3 study
 - 2+0.5 g x 3 vs pip–tazo 4.5 g x 3 in cUTI
- Stable against ESBL, AmpC, KPC
- Activity against many MDR *Pseudomonas*

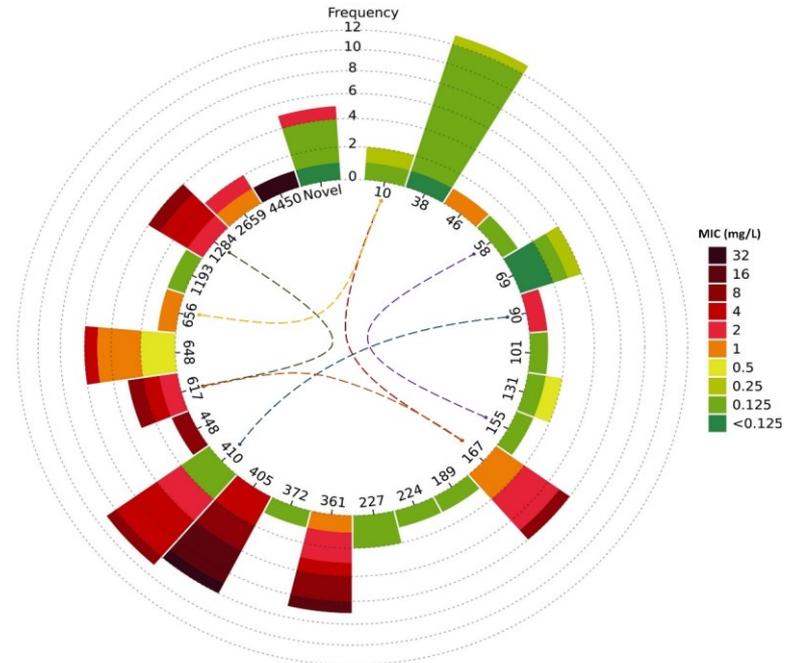


Stability vs OXA-48
Enmetazobactam does not inhibit, but cefepime is poorly hydrolysed

Hirvonen VHA. AAC 2021

Aztreonam-avibactam (Pfizer)

- ASSEMBLE: ATM-AVI vs best available therapy for treatment cIAI, HAP/VAP, cUTI, BSI caused by MBL-producing Gram-negatives
 - 15 patients included
 - 5/12 cure ATM-AVI (vs 0/3)
- REVIST: ATM-AVI +/- MZL vs MER +/- COL for treatment of cIAI, HAP/VAP caused by Gram-negatives (including MBL)
 - All-cause mortality 10.8 % vs 19.4% (422 pts in total)
- Dosing: 1.5+0.5 g x 4



102 clinical isolates of CP *E. coli* (unpubl.)
MIC>4 mg/L occurred among NDM-producers

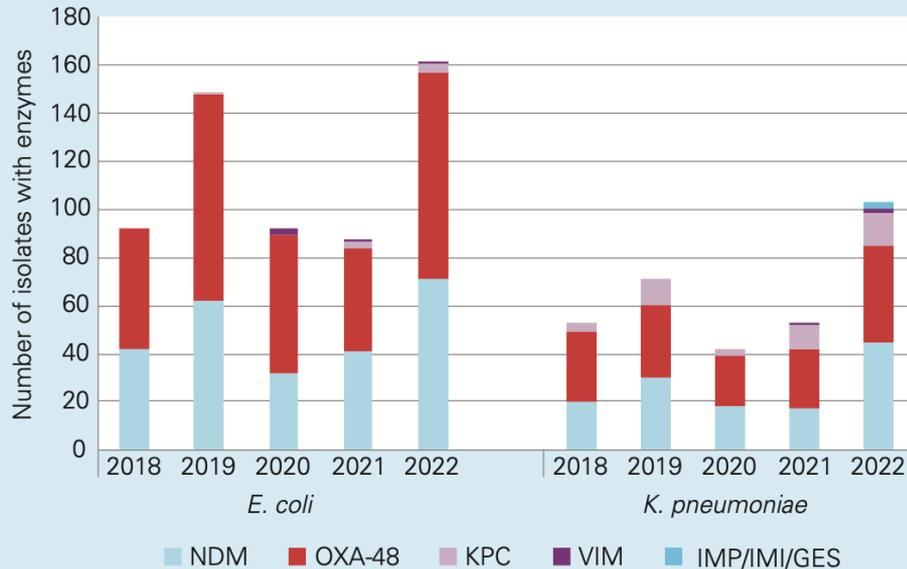
New breakpoints

- *Enterobacterales*
 - Aztreonam-avibactam: S \leq 4 mg/L, R $>$ 4 mg/L
 - Cefepime-enmetazobactam: S \leq 4 mg/L, R $>$ 4 mg/L
- *P. aeruginosa*
 - Aztreonam-avibactam: IE (ECOFF is 16 mg/L....)
 - Cefepime-enmetazobactam: IE (inhibitor does not add clinical benefit)
- *Acinetobacter* and *S. maltophilia*
 - Lacks clinically useful activity
- Disk diffusion criteria are in preparation

Enterobacterales

Which are the encountered carbapenemases?

Figure 3.7. Number of isolates and enzyme types of ESBL_{CARBA} in Enterobacterales in Sweden 2013-2022.



Source: The Public Health Agency of Sweden

Strong dominance of NDM and OXA-48

Influx from Ukraine has shifted towards more NDM

Treatment of KPC-producers (absence of acq. resistance)

Antimicrobials	Activity
Ceftolozane-tazobactam	⊖
Ceftazidime-avibactam	✓
Meropenem-vaborbactam	✓
Imipenem-relebactam	✓
Cefiderocol	✓
Aztreonam-avibactam	✓
Cefepime-enmetazobactam	✓

Development of resistance can occur to all mentioned agents
Meropenem-vaborbactam has fairly high stability to resistance mechanisms

Treatment of OXA-48-producers (absence of acq. resistance)

Antimicrobials	Activity
Ceftolozane-tazobactam	⊖
Ceftazidime-avibactam	✓
Meropenem-vaborbactam ¹	⊖
Imipenem-relebactam	⊖
Cefiderocol	✓
Aztreonam-avibactam	✓
Cefepime-enmetazobactam ¹	⊖

MER-VAB and FEP-ENM can have activity, but not due to the inhibitor

Treatment of MBL-producers (absence of acq. resistance)

Antimicrobials	Activity (<i>in vitro</i>)
Ceftolozane-tazobactam	⊖
Ceftazidime-avibactam	⊖
Meropenem-vaborbactam	⊖
Imipenem-relebactam	⊖
Cefiderocol	✓
Aztreonam-avibactam ¹	✓
Cefepime-enmetazobactam	⊖

¹So far given as (ceftazidime)-avibactam+aztreonam, but now approved in Europe

P. aeruginosa

Treatment of MDR *P. aeruginosa*

Antimicrobials	Chromosomal	MBL	KPC
Ceftolozane-tazobactam	✓	⊖	⊖
Ceftazidime-avibactam	✓	⊖	Weak
Meropenem-vaborbactam ¹	✓	⊖	Weak
Imipenem-relebactam	✓	⊖	Unknown
Cefiderocol	✓	✓	✓
Aztreonam-avibactam	Weak	Weak	Weak
Cefepime-enmetazobactam ¹	✓	⊖	Unknown

¹No increased activity vs the parent beta-lactam

A. baumannii-group

Treatment of MDR *A. baumannii*-group

Antimicrobials	OXA-carbap.	MBL
Ceftolozane-tazobactam	⊖	⊖
Ceftazidime-avibactam	⊖	⊖
Meropenem-vaborbactam ¹	⊖	⊖
Imipenem-relebactam ¹	⊖	⊖
Cefiderocol	✓	✓
Aztreonam-avibactam	⊖	⊖
Cefepime-enmetazobactam ¹	⊖	⊖

¹No increased activity vs the parent beta-lactam