

# Neue Antibiotika für gramnegative Bakterien

U. Theuretzbacher – **C**enter **f**or **A**nti-**I**nfective **A**gents, Vienna, Austria

# Gram-negative: Neue Antibiotika 2014/2015

6 neue Antibiotika zugelassen, 3 für Gram-negative Bakterien

- 1 Cephalosporin
- 2 Cephalosporine +  $\beta$ -Laktamase-Inhibitor

# Gram-negative: Neue Antibiotika

Drug	Focus	Company	Comments
Ceftobiprole (Zevtera)	MRSA	Roche→Basilea→J&J→ Basilea (Quintiles)	CAP, NAP (excl. VAP)
Ceftolozane+Tazobactam (Zerbaxa) FDA approved	Gram-Negative (incl. ESBL, AmpC)	Astellas→Calixa→ Cubist=Merck	cUTI, cIAI (+metronidazole) NAP/VAP (Phase 3 in 2014) Non-inferior to levofloxacin Non-inferior to meropenem
Ceftazidime+Avibactam (Avycaz) FDA approved (Ph2, 350 pat.)	Gram-Negative (incl. ESBL, AmpC, KPC)	Sanofi Aventis→Novoxel→ AstraZeneca (EU)/ Forest/Actavis (NA)	cUTI, cIAI (+metronidazole) Non-inferior to imipenem Non-inferior to meropenem Ph3 sNDA

# Ceftobiprole

- Ceftobiprole medocaril sodium (Zevtera 500 mg, Basilea)
- Austria, Belgium, Denmark, Finland, France, Germany, Italy, Luxemburg, Norway, Spain, Sweden, Switzerland, **UK**
- Approved by decentralised procedure, marketed by Quintiles in Europe
- Additional monitoring, report adverse reactions
- Indications
  - Community-acquired pneumonia (CAP)
  - Hospital-acquired pneumonia (HAP), excl. ventilator-associated pneumonia (VAP)
  - Withdrawn for cSSTI
- Administration
  - 500 mg every 8 hours via a slow infusion over 2 hours

# Activity of Ceftobiprole

## Target Attainment of Ceftobiprole

% fT > MIC	% of patients at MIC (mg/liter):						
	0.5	1	2	4	8	16	32
30	100	100	100	100	96.7	17.6	1.1
40	100	100	100	99.5	90.1	8.2	0.8
50	100	100	100	98.9	75.0	5.2	0.8
60	100	100	99.5	96.7	63.5	4.7	0.8
70	100	99.7	98.9	92.0	50.8	4.1	0.8
80	100	99.5	98.1	83.0	33.8	2.5	0.8
90	99.7	99.2	96.4	75.0	26.6	2.2	0.5
100	99.5	98.4	93.7	61.5	18.4	2.2	0.5

AE Muller et al AAC  
2013;57:2047-53

## Cumulative % distribution of ceftobiprole MICs, Europe 2005-2010

	MIC <sub>90</sub> (µg/ml)
MRSA	2
E. coli*	2
K. pneum.*	>8
Enterob.	>8
P. aerug.	>8

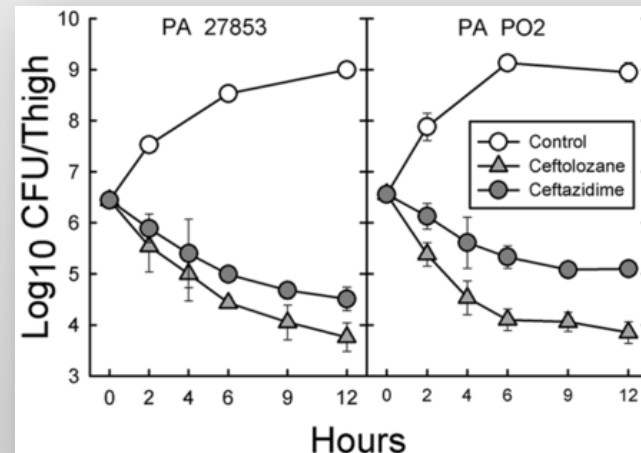
DJ Farrell et al AAC  
2014; 58:3882-8

\* Not active against ESBL-producing strains

# Ceftolozane + Tazobactam

- Ceftolozane/tazobactam (Zerbaxa, 1 g/0.5 g, Cubist)
- Approved by FDA
- EMA has accepted MAA submission
- Indications
  - cUTI, cIAI (+metronidazole)
- Administration
  - every 8 hours over 1 hour

Neutropenic mouse thigh model: *P. aerug*



W. Craig, D. Andes: AAC 2013, 57:1577-1582

# Ceftazidime + avibactam

- Ceftazidime + avibactam (Avycaz, 2/0.5 g, Actavis/AstraZeneca)
- Approved by FDA based on Phase II data (350 pat.), MAA expected 1Q/2015
- Indication
  - cUTI and cIAI + metronidazole
- Administration
  - 2/0.5 g administered every 8 hours over 2 hours

# Ceftolozane/Tazobactam vs Ceftazidime/Avibactam

	Ceftolozane/Tazobactam	Ceftazidime/Avibactam
Dosing	1 g/0.5 g q8h (1h)	2/0.5 g q8h (2h)
Indication	cUTI, cIAI (+metronidazole)	
β-lactamase-inhibitor	Tazobactam (ESBL)	Avibactam (+ KPC, OXA48, AmpC)
Activity	Gram-Negatives	
Res. Pseud.	Permeability, drug efflux, overproduction of β-lactamases	

β-Lactamases		
Class	Examples	Frequent in
A	ESBL, <b>KPC</b>	Enterobacteriaceae
B	<b>NDM, IMP, VIM</b>	Klebsiella, other enterobacteriaceae, Pseudomonas
C	AmpC	Enterobacter, Citrobacter, Serratia, Morganella
D	OXA ( <b>OXA48</b> )	Acinetobacter, enterobacteriaceae

## Carbapenemases

	Tazobactam	Avibactam	
<b>KPC</b>	-	+	Class A
<b>OXA 48</b>	-	+	Class D
<b>NDM</b>	-	-	Class B
<b>VIM</b>	-	-	
<b>IMP</b>	-	-	

Carbapenemases

AAC 2011;55:390-394

CENTER FOR  
ANTI-INFECTIVE  
AGENTS



# Gram-negative: Neue Antibiotika - Ausblick

Drug	Phase	Class	Company	Comments
Ceftolozane+Tazobactam	approved	$\beta$ -lactam+BLI	Astellas/Calixa/ Cubist=Merck	cUTI, cIAI (+metronidazole) NAP/VAP (Phase 3)
Eravacycline	Phase 3	Tetracycline	Tetraphase	cUTI, cIAI
Plazomicin	Phase 3	Aminoglycosid	Isis-Achaogen	Serious inf. due to gram-neg.e bacteria (CRE vs colistin)
Meropenem+Carbavance	Phase 3	$\beta$ -lactam+ boronic BLI	Rempex/The Medicines Company	cUTI, serious bacterial inf. due to gram-negative bacteria (150 pat., CRE vs best available therapy)
Ceftaroline+Avibactam	Phase 2	$\beta$ -lactam+BLI	Avibactam: Sanofi Aventis- Novoxel-AstraZeneca- Forest/Activa	cUTI
Aztreonam+Avibactam	Phase 2	$\beta$ -lactam+BLI	AstraZeneca-Forest/Activa IMI	Serious inf. caused by Gram- neg. bacteria proven or susp. to be caused by MDR bacteria incl. metallo- $\beta$ -lactamase prod.
Imipenem+Relebactam	Phase 2	$\beta$ -lactam+BLI	Merck	cUTI, cIAI