Treating ESBLs with beta-lactams - other than carbapenems

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We have to ask ourselves two Questions :

1. What is the effect/impact of an ESBL on susceptibility/efficacy?
   - In vitro
   - In vivo
2. Can that effect be countered?
   - In vitro
   - In vivo

   -How can doses of (combinations of) alternative agents be optimized?

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Part 1. Impact ESBL on drug activity

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Classes of BL with specific characteristics

BJ group	Class	Substrates	Representative enzymes
1	C	Cephalosporins	*E. coli* AmpC, P99, ACT-1, CMY-2, FOX-
1e	C	Cephalosporins	GC1, CMY-37
2a	A	Penicillins	PC1
2b	A	Penicillins, early cephalosporins	TEM-1, TEM-2, SHV-1
2be	A	Extended-spectrum cephalosporins,	TEM-3, SHV-2, CTX-M-15, PER-1, VEB-1
2br	A	Penicillins	TEM-30, SHV-10
2ber	A	Extended-spectrum cephalosporins,	TEM-50
2c	A	Carbenicillin	PSE-1, CARB-3
2ce	A	Carbenicillin,	RTG-4
2d	D	Cloxacillin	OXA-1, OXA-10
2de	D	Extended-spectrum	OXA-11, OXA-15
2df	D	Carbapenems	OXA-23, OXA-48
2e	A	Extended-spectrum	CepA
2f	A	Carbapenems	KPC-2, IMI-1, SME-1
3a	B (B1)	Carbapenems	IMP-1, VIM-1, CcrA, IND-1
	B (B3)		L1, CAU-1, GOB-1, FEZ-1
3b	B (B2)	Carbapenems	CphA, Sfh-1

Modified from Bassetti *et al* 2011

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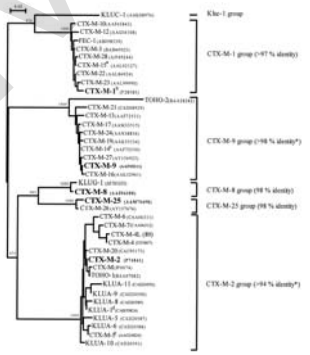
CTX-M family



Bonnet, AAC 2004

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Beta-lactams active against various BL

β-Lactam	MIC (μg/ml) Laboratory *E. coli* strains producing: CTX-M-3 (77)[f]	CTX-M-15 (77)	CTX-M-4 (40)	CTX-M-5 (20)	CTX-M-9 (14)	CTX-M-16 (14)	CTX-M-14 (15)	CTX-M-27 (15)	CTX-M-18 (74)	CTX-M-19 (74)
Amoxicillin	>512	>512	>512[e]	>128[e]	>2,048	>512	>512	>512	>512	>512
Amoxicillin + CLA[f]	128	32	8	32	8	8	8	4	128	128
Ticarcillin	>512	>512	128	>128	>512	>512	>512	>512	>512	>512
Ticarcillin + CLA	64	32		128	16	16	16	8	256	256
Piperacillin	512	>512	256	>128	256	256	256	256	>512	>512
Piperacillin + TZP[g]	2	4	2	1	2	2	2	2	16	8
Cephalothin	>512	>512			512	512	512	1,024	>512	>512
Cefuroxime	>512	>512	512		512	512	512	512	>512	>512
Cefotaxime	512	512	512	>128	16	16	16	16	64	4
Cefotaxime + CLA	2	2			0.06	0.06			0.5	0.5
Cefpirome	512	512			2	2	2	4		
Cefepime	128	64					0.5	1	16	4
Ceftazidime	32	256	2	16	1	8	1	8	2	128
Ceftazidime + CLA	2	2			0.25	0.25			0.5	16
Aztreonam	128	64	32	128	4	8	4	8	64	4
Aztreonam + CLA					0.06	0.06			0.25	0.12
Moxalactam	0.5	1							0.5	2
Cefoxitin	2	4		16					4	4
Imipenem	0.25	0.25		0.5					0.25	0.25

Bonnet, AAC 2004

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Activity / MICs (mg/L) differ by BL and BLA

	CTXM 3	CTXM 15	CTXM 4	CTXM 5	CTXM 19
Aztreonam	128	64	32	128	4
Moxalactam	0.5	1			2
Cefoxitin	2	4		16	4

Aftrer Bonnet, AAC 2004

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The big question: does an MIC of an ESBL strain reflect activity and predict efficacy?

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Some Controversies exist…

MIC= 0.125 mg/l Susceptible

ESBL positive

..And actually treating with it??

EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING
European Society of Clinical Microbiology and Infectious Diseases

Susceptible (S)

A micro-organism is defined as susceptible by a level of antmicrobial activity associated with a high likelihood of therapeutic success. A micro-organism is categorized as susceptible by applying the appropriate breakpoint in a defined phenotypic test system.

Note: This breakpoint may be altered with legitimate changes in circumstances

Intermediate (I)
A micro-organism is defined as intermediate by a level of antimicrobial activity associated with indetermiate therapeutic effect. A micro-organism is categorized as intermediate by applying the appropriate breakpoints in a defined phenotypic test system.
Note: This breakpoints may be altered with legitimate changes in circumstances.
Resistant (R)
bacteria are defined as resistant by a level of antimicrobial activity associated with a high likelihood of therapeutic failure. A micro-organism is categorized as resistant by applying the appropriate breakpoint in a defined phenotypic test system.
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There is no ESBL rule rendering strains Resistant
(As opposed to AmpC!)

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Pre-clinical Evidence

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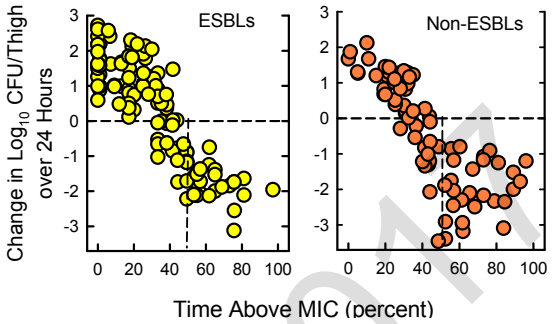
Activity of 4 Cephalosporins against Various Enterobacteriaceae with and without ESBLs



Craig & Andes ICAAC 2005

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Organism	Range of MICs (mg/L)	Q 6h Static Doses (mg/kg)	%T>MIC
E. coli	8->16	930->1600	41
K. pneumoniae	1->16	189->1600	23-35
E. cloacae	0.12->16	1.0-1424	22-36
S. marcescens	0.12->16	3.1->1600	25-42
Non-ESBLs	0.12->16	3.1->1600	22-38
ESBLs	1->16	71.3->1600	23-41

ESBL production in Enterobacteriaceae had no impact upon the $\%T_{>MIC}$ necessary for in-vivo efficacy with cefepime, ceftazidime, ceftriaxone and cefotaxime

Craig et al, ICAAC 2003 A-1318

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%fT>MIC predicts outcome irrespective of ESBL

Strain	ESBL	MIC (µg/ml)	ED80 %T>MIC	dCFU 70% T>MIC
ATCC 25922	none	0.06	23	-2.56
EC 120	none	0.5	23	-1.75
EC 242	TEM 12	0.75	26	-1.51
EC 243	TEM 26	256	11	-2.26
EC 285	TEM 10	4	24	-1.44
EC 273	UNKNOWN	2	41	-1.75

Maglio et al, ICAAC 2003 A-1317

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An MIC is nothing more than a reflection of overall drug activity – involving many different receptors and enzyme activities.

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An MIC is nothing more than a reflection of overall drug activity – involving many different receptors and enzyme activities.

-only one of these is an ESBL.

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Part 2. Can BLA activity be countered?

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Inhibition of BL by tazobactam differs by strain Cefepime + Tazobactam

Max effect?

strainno.		0	0.031	0.063	0.125	0.25	0.5	1	2	4	8	16
kpn	44	16	8	8	16	4	16	8	4	2	4	0.25
ecl	68	16	16	8	8	8	1	4	4	4	2	0.5
ecl	18	>32	32	16	32	8	4	4	2	2	1	0.5
eco	73	>32	2	2	1	0.125	1	0.125	0.125	0.125	0.125	0.125
eco	81	>32	2	2	2	0.25	0.064	0.125	0.064	0.064	0.064	0.064
ecl	32	>32	4	4	4	8	1	1	0.25	0.125	0.125	0.125
eco	46	>32	4	8	4	2	0.125	2	2	0.064	0.064	0.064
eco	14	>32	8	4	8	4	0.25	0.25	0.125	0.064	0.064	0.25
eco	66	>32	8	4	4	4	2	0.25	0.125	0.125	0.125	0.064
ecl	33	>32	8	8	4	4	4	2	1	1	1	0.25
eco	16	>32	8	8	8	8	4	0.25	0.064	0.032	0.032	0.032
eco	56	>32	8	8	8	2	0.25	2	0.125	0.125	0.064	0.125
eco	78	>32	8	8	4	2	0.125	0.5	0.125	0.125	0.125	1
kpn	11	>32	8	8	8	8	1	0.125	0.125	0.064	0.032	0.016
ecl	72	>32	8	16	8	16	8	8	8	1	1	1
eco	34	>32	8	16	8	16	2	4	0.125	2	0.125	0.125
kpn	52	>32	16	8	16	16	8	16	32	4	1	0.5
kpn	53	>32	16	8	8	4	4	4	2	1	0.5	1
ecl	27	>32	16	16	16	16	4	1	2	0.5	0.5	0.5

Mouton et al, abstr 2251 ICAAC 2010; Melchers et al AAC 2016

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How much tazobactam in vitro is needed to render a strain susceptible?

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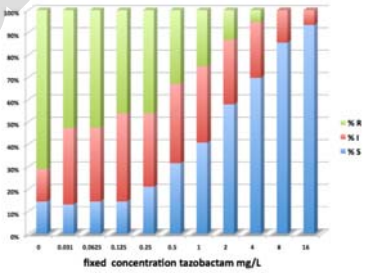
Susceptibility of cefepim depending on tazobactam concentration EUCAST criteria for cefepim



Mouton et al, abstr 2251 ICAAC 2010

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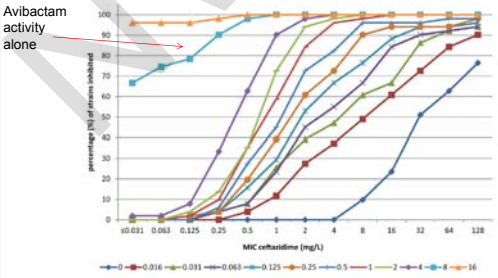
Cumulative Cumulative % inhibition of Avibactam 51 *Enterobacteriaceae*



Berkhout et al, AAC 2015

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Which Questions to answer for optimal dosing?

- Pharmacodynamic properties
- Exposure response relationship
- Pharmacodynamic targets

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Deriving doses and breakpoints

PKPD relationship single drug

↓

Pharmacodynamic target

↓

MIC breakpoint ⟷ Dosing Regimen

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Deriving doses and breakpoints

	Cefepime/ceftazidime
PKPD relationship single drug	$\%fT_{>MIC}$
↓	↓
Pharmacodynamic target	45-50%
↓	↓
MIC breakpoint (Dose Dependent)	4 mg/L 1g q8h

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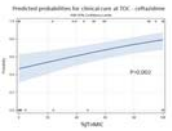
Pharmacodynamic Target

Ceftazidime in patients with nosocomial pneumonia

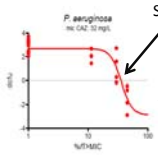
%fT>MIC breakpoint = 44.9 %

P< 0.0001

%fT>MIC	Success	Failure
>44.9	83 (90.2%)	9 (9.8%)
<44.9	31 (50%)	31 (50%)



Ceftazidime in mice



Static %fT>MIC 39.1 %

1log drop

2log drop

Muller et al, JAC 2013 68:900-906; Mouton unpubl.

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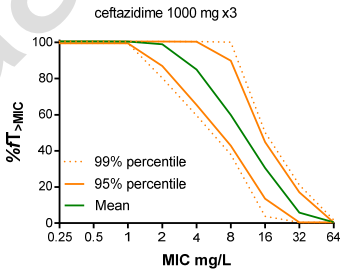
Monte Carlo Simulations : Target Attainment



EUCAST rationale document ceftazidime

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Purpose of BLI inhibitor

Restore the activity of the 'parent' drug

e.g. cefepime ceftazidime

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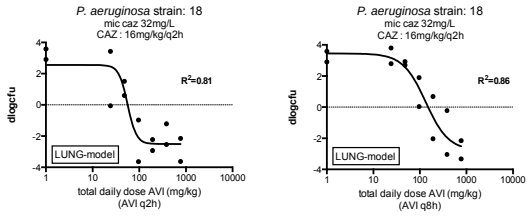
Time above Ct of Avibactam



Less frequent dosing : more inhibitor required

Berkhout *et al.*, AAC 2016

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PKPD index estimates of avibactam

Pneumonia	strain	MIC ceftazidime (mg/liter)	dose(mg/kg) avibactam q2h	dose(mg/kg) avibactam q8h	%$fT>C_T$ 1 q2h	%$fT>C_T$ 1 q8h
stasis	11 18	128 32	3.8 4.7	154.4 50.2	19.7 23.5	20.9 16.1
1 log kill	11 18	128 32	9.0 5.7	183.6 74.3	34.9 26.7	21.6 17.8
2 log kill	11 18	128 32	29.6 7.6	225.6 132.5	55.3 31.8	22.5 20.2

Berkhout et al. AAC 2016

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To summarize

- Dose of BL/BLI combination and Clinical Breakpoint Are based on the 'Parent Drug'
- Dose of BLI should restore Parent drug activity
  - Pharmacodynamic properties
  - Exposure response relationship
  - Pharmacodynamic targets

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Clinical Studies

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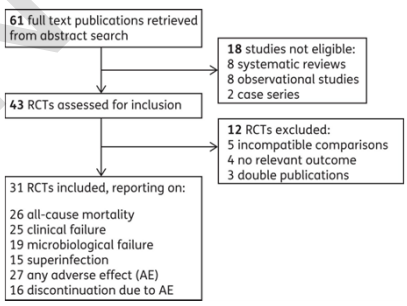
Meta-analysis BL/BLI vs Carbapenem RCTs in sepsis



Shiber et al, JAC 2015

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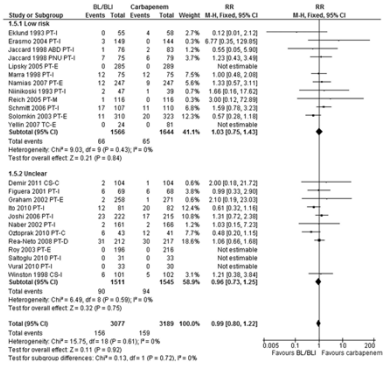

Shiber et al, JAC 2015

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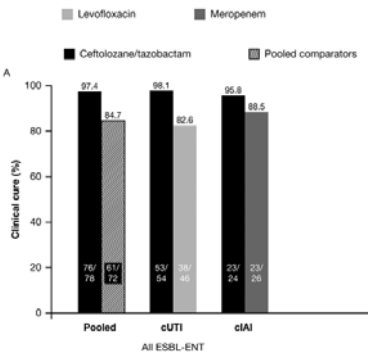
Pooled analysis of ceftolozane/tz vs levofloxacin/meropenem



Popejoy et al JAC 2017

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Other Options

BL with PBP2 and PBP3 activity (mecillinam, cefepime)

BL with enhancers (zidebactam, cefepime)

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Conclusions

- ESBLs can be treated with beta-lactams – just determine their activity
- BL/BLI combinations are effective – provided that the PKPD relationships have been sorted out
- Carbapenems can be spared!

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