Treatment strategies and antibiotic pipeline for treatment of infections with resistant Gram-negative bacteria

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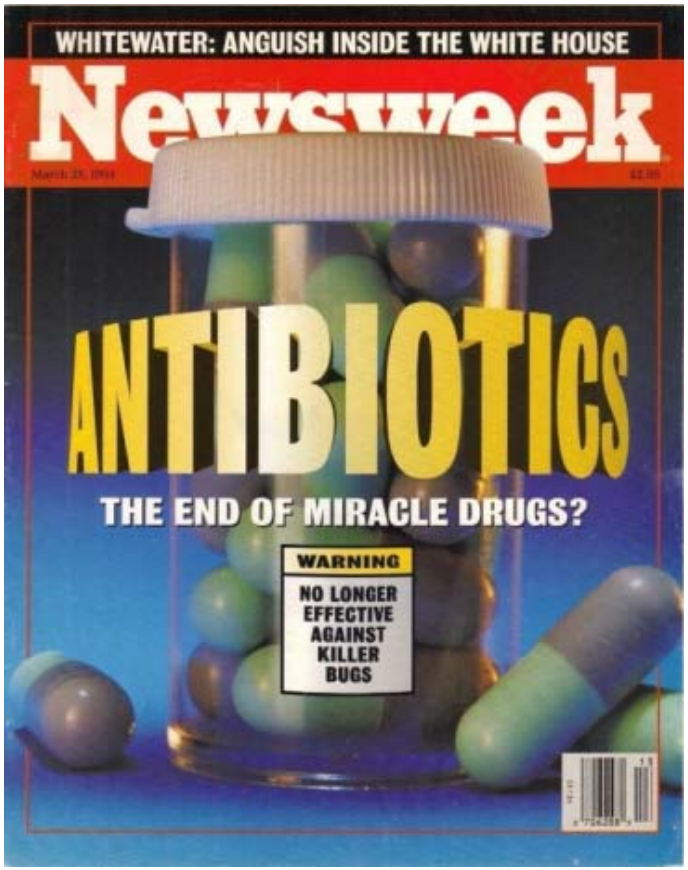
Infectious diseases were problematic in the past …

.. And treatment options were scarce … …

Are we in better shape today ?



How to optimise antibiotic usage?

Use available drugs appropriately

Examples of antibiotic misuses:

- Prescribing antibiotics unnecessarily
- Delaying administration of antibiotics in critically ill patients
- Spectrum of antibiotic therapy too narrow or too broad
- Dose of antibiotic too low or too high relative to that indicated for the patient
- Duration of antibiotic treatment is too short or too long
- Failure to review antibiotic treatment when microbiological culture data become available

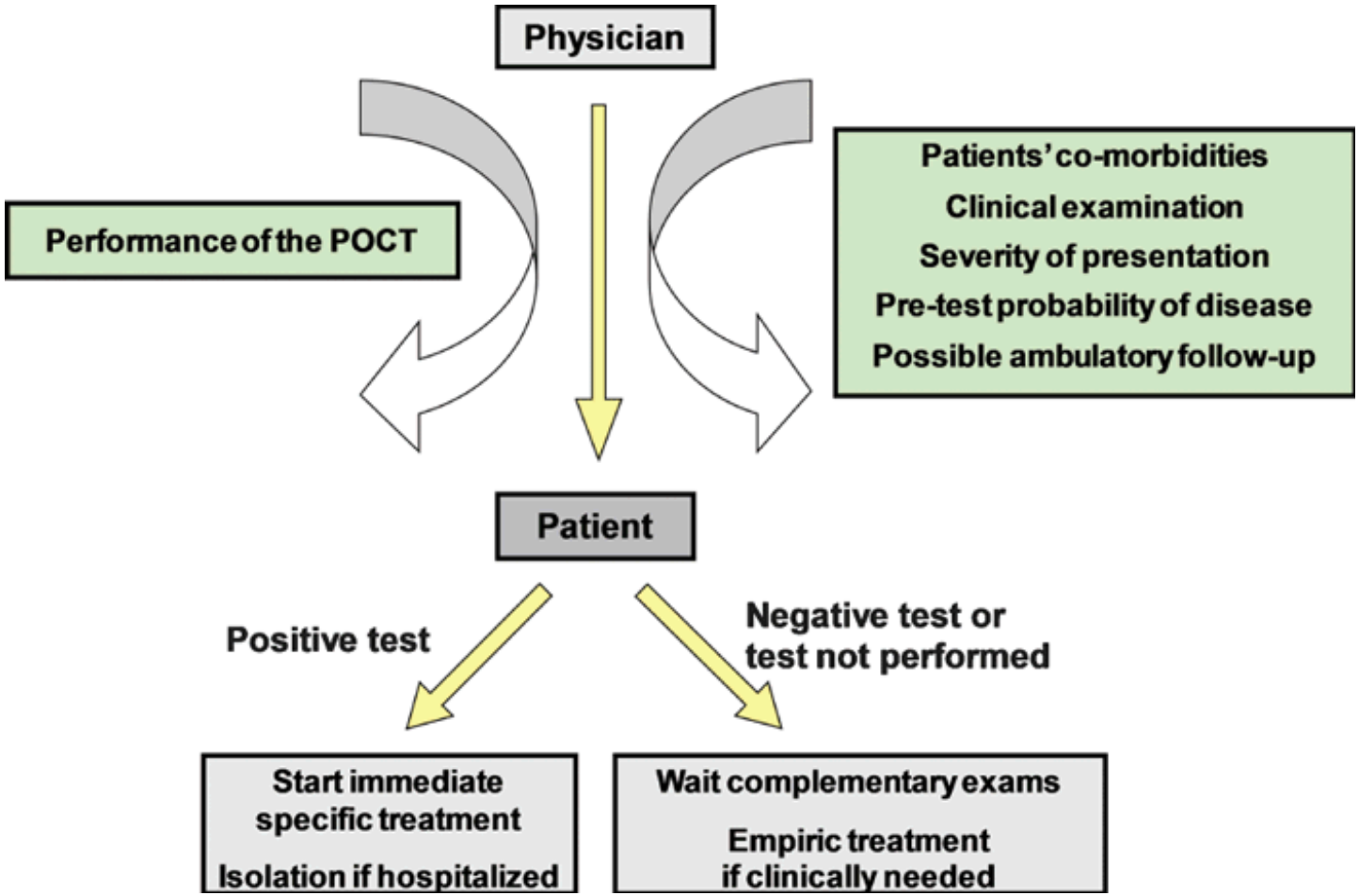
Dryden et al, JAC (2011) 66: 2441–43

Use antibiotics responsibly

- **right drug** → **Rapid diagnosis !**
  → Combinations ?
- right time → Appropriate initial therapy !
- right dose → PK/PD !
- right duration → Not too short, not too long !

Dryden et al, JAC (2011) 66: 2441–43

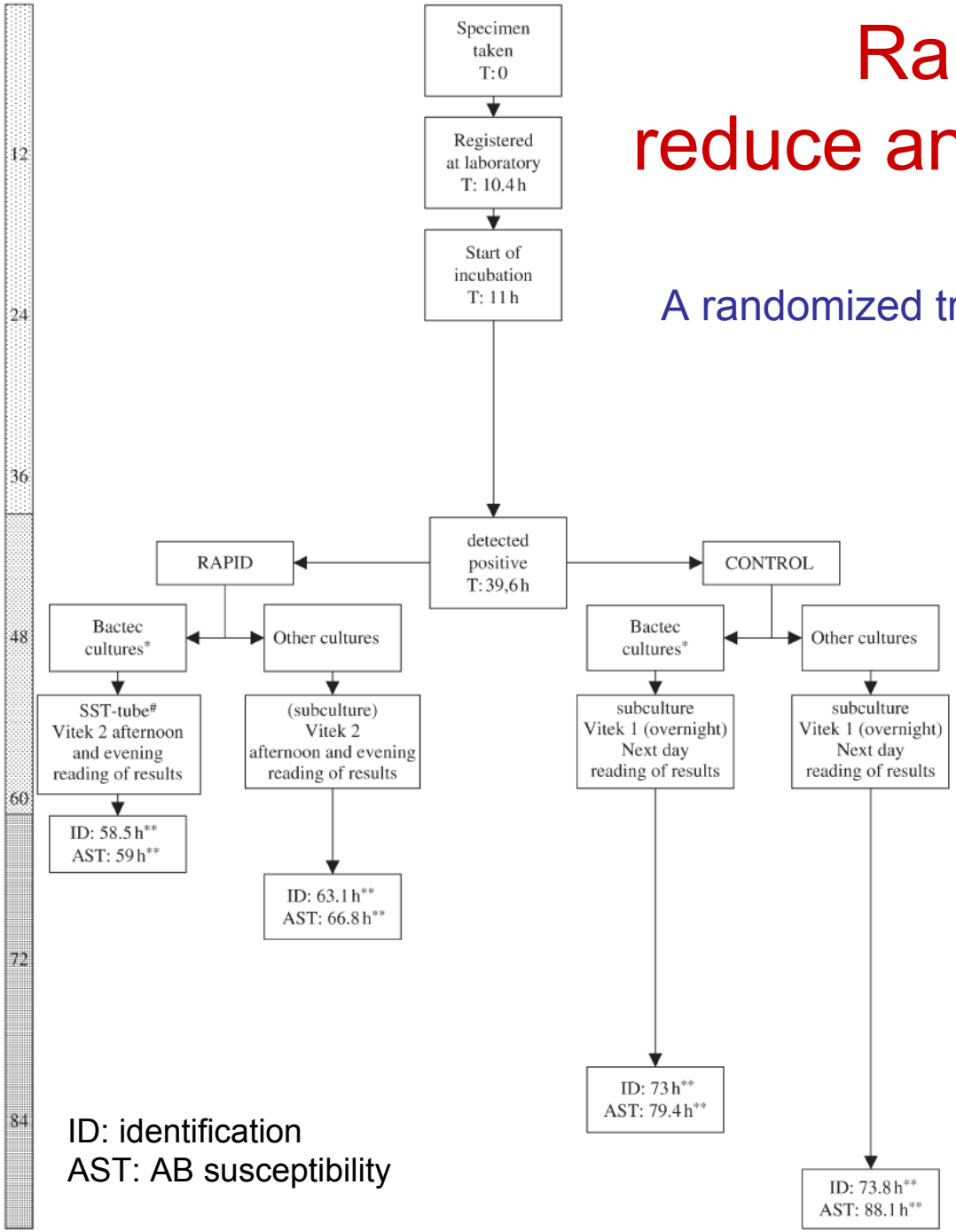
Rapid diagnostic tests as tools before prescription



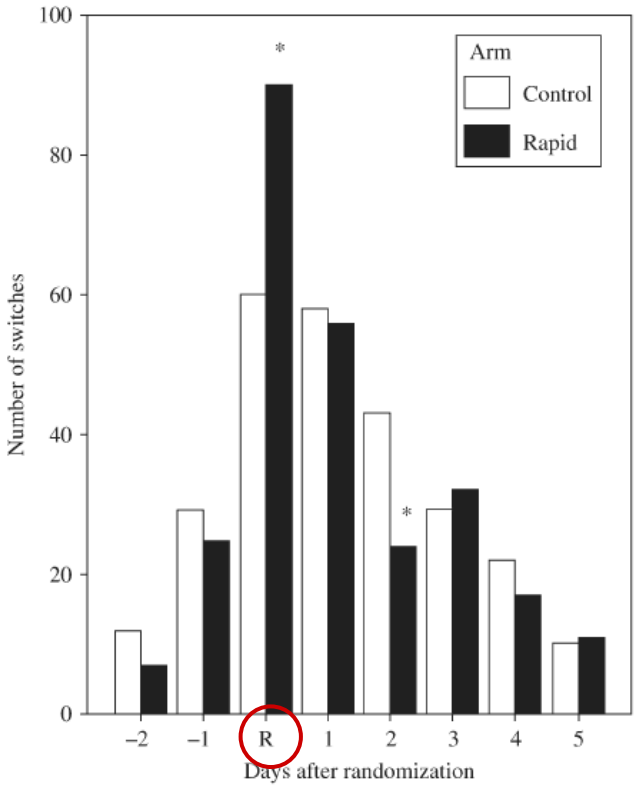
Clerc & Greub, CMI (2010) 16:1054-61

Rapid diagnostic tests reduce antibiotic prescription

A randomized trial: rapid vs conventional diagnostic



ID: identification
AST: AB susceptibility



Kerremans et al, JAC (2008) 61:428-35

Rapid diagnostic tests reduce antibiotic prescription

A randomized trial: rapid vs conventional diagnostic

Antibiotic use in average DDDs per patient in the secondary outcome subcohort

Antibiotic group	DDDs (SD)		*P* value*
	rapid arm ($n = 497$)	control arm ($n = 503$)	
Penicillins[a]	5.7 (13.0)	6.6 (14.7)	0.27
Penicillin and β-lactamase inhibitor[b]	4.5 (8.7)	5.0 (10.7)	0.32
Cephalosporins[c]	1.9 (4.6)	1.9 (5.2)	0.83
Carbapenems + monobactam[d]	1.1 (5.2)	1.3 (5.2)	0.053
Aminoglycosids[e]	1.2 (4.2)	1.1 (3.4)	0.85
Macrolides/lincosamides[f]	1.4 (5.5)	2.3 (8.1)	0.373
Quinolones[g]	5.7 (10.3)	6.1 (11.2)	0.67
Glycopeptides[h]	0.9 (3.6)	1.2 (4.4)	0.26
Other[i]	1.7 (5.6)	2.6 (7.9)	0.022
Total antibacterials	23.9 (21.5)	27.9 (24.7)	0.020
Antifungals[j]	2.7 (9.9)	4.9 (16.5)	0.050
Total antibacterials + antifungals	26.6 (24.5)	32.9 (31.9)	0.012

Clerc & Greub, CMI (2010) 16:1054-61

Rapid diagnostic tests start to be developed for resistance mechanisms

Rapid identification of carbapenemase producers

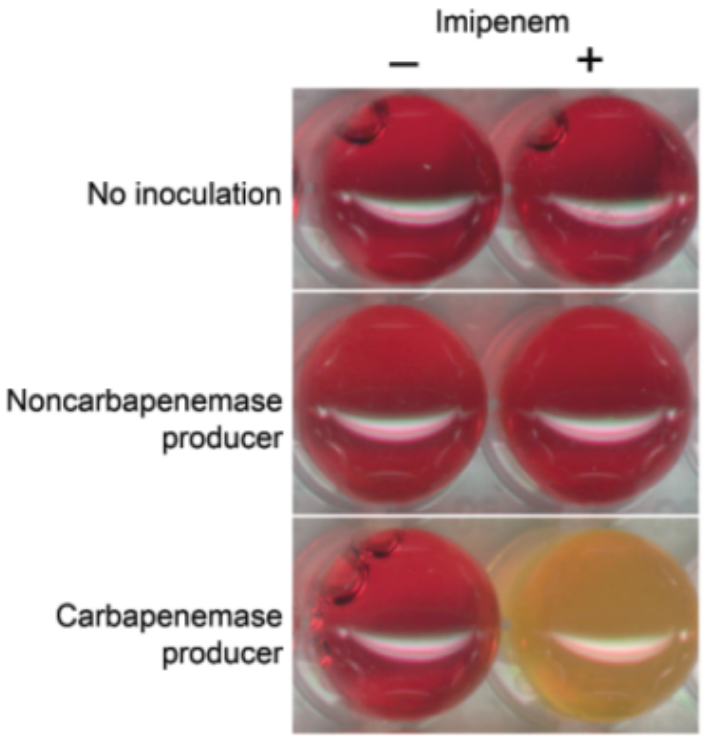


Figure 1. Representative results of the Carba NP test. The Carba NP test was performed with a noncarbapenemase producer (*Escherichia coli* producing the extended-spectrum β-lactamase CTX-M-15, upper panel) and with a carbapenemase producer (*Klebsiella pneumoniae*–producing New Delhi metallo-β-lactamase-1, lower panel) in a reaction medium without (left panel) and with (right panel) imipenem. Uninoculated wells are shown as controls. Photographs were taken after a 1.5-hour incubation.

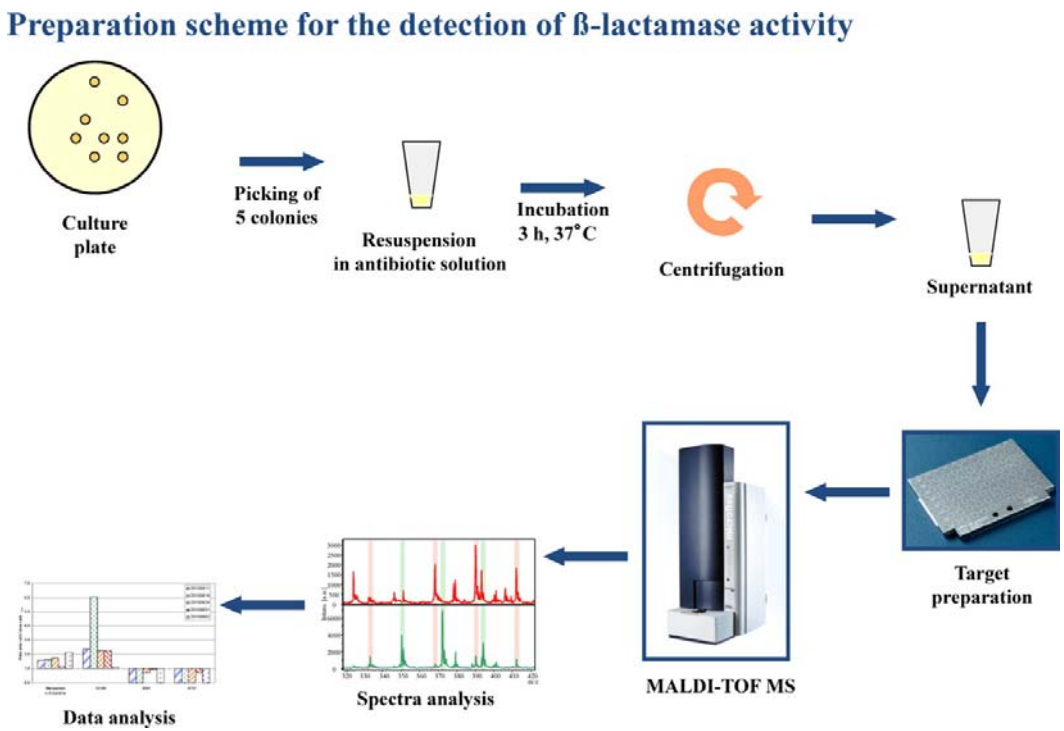
Phenol red added to the medium turns yellow if carbapenemase present due to acidification

Nordmann et al, EID (2012) 18:1503-07

Rapid diagnostic tests start to be developed for resistance mechanisms

MALDI-TOF for identification of bug and resistance mechanisms

- search for peaks corresponding to enzymes responsible for resistance (beta-lactamases)
- search for degradation production of antibiotics added to the sample (carbapenems & carbapenemases)
- MS profile specific of a given resistance phenotype (MRSA)



Hrabak et al, CMR (2013) 26:103-14, Ledeboer & Hodinka, JCM (2011) 49: S20-S24

Use antibiotics responsibly

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  → **Combinations ?**
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Dryden et al, JAC (2011) 66: 2441–43

Demonstrated advantages

1. Broader spectrum

- combination of
  - anti-Gram(+) + anti-Gram(-) [linezolid]
  - anti-aerobe + antianaerobe [metronidazole]
  - anti-« typcial » + anti-« atypical » [macrolide]
- better coverage in empiric therapy

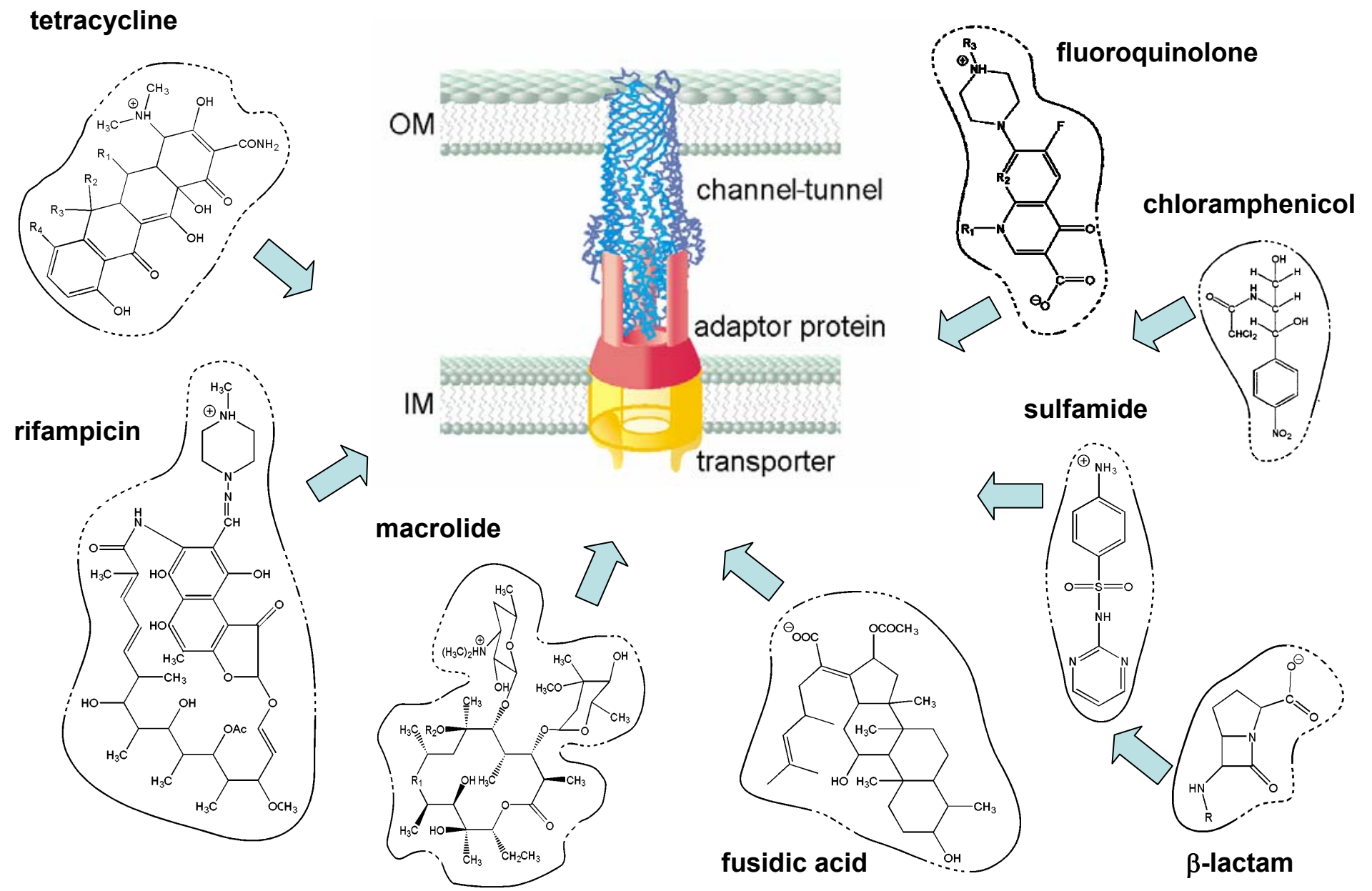
2. In vitro synergy … mainly shown in vitro!

- aminoglycoside + beta-lactam
- colistin + carbapenem, + glycopeptide !
- …

3. Prevention of resistance

- targets with high mutation frequency [rifampicin]
- drugs with different targets
- BUT mechanisms conferring co-resistance
  - MLS_B
  - efflux in Gram(-)
  - …

Efflux and multidrug resistance

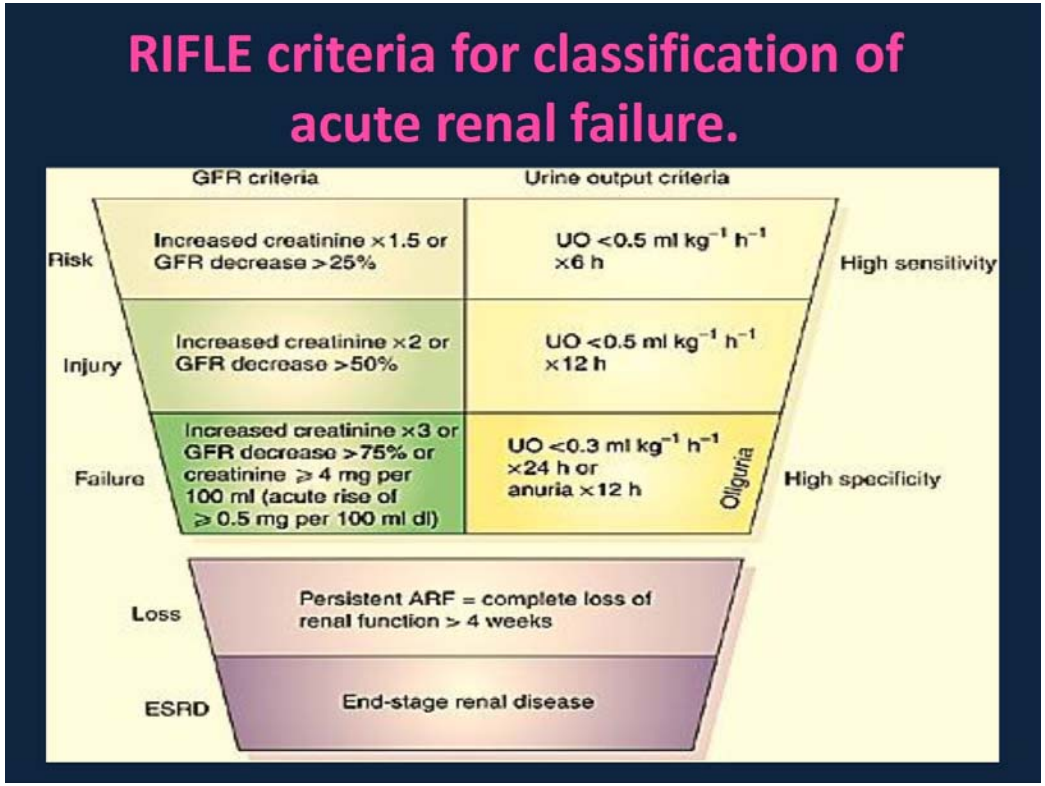


Possible drawbacks

1. Increased toxicity

- aminoglycoside + vancomycin: mainly small prospective studies
- colistin + aminoglycoside: no data ?

→ define nephrotoxicity using appropriate criteria
→ short treatment duration
→ monitoring



Possible drawbacks

2. Lack of clear demonstration of clinical impact

Bug identification is the priority ! Rapid diagnosis !

Combination Therapy for Treatment of Infections with Gram-Negative Bacteria

Pranita D. Tamma,[a] Sara E. Cosgrove,[b] and Lisa L. Maragakis[b]

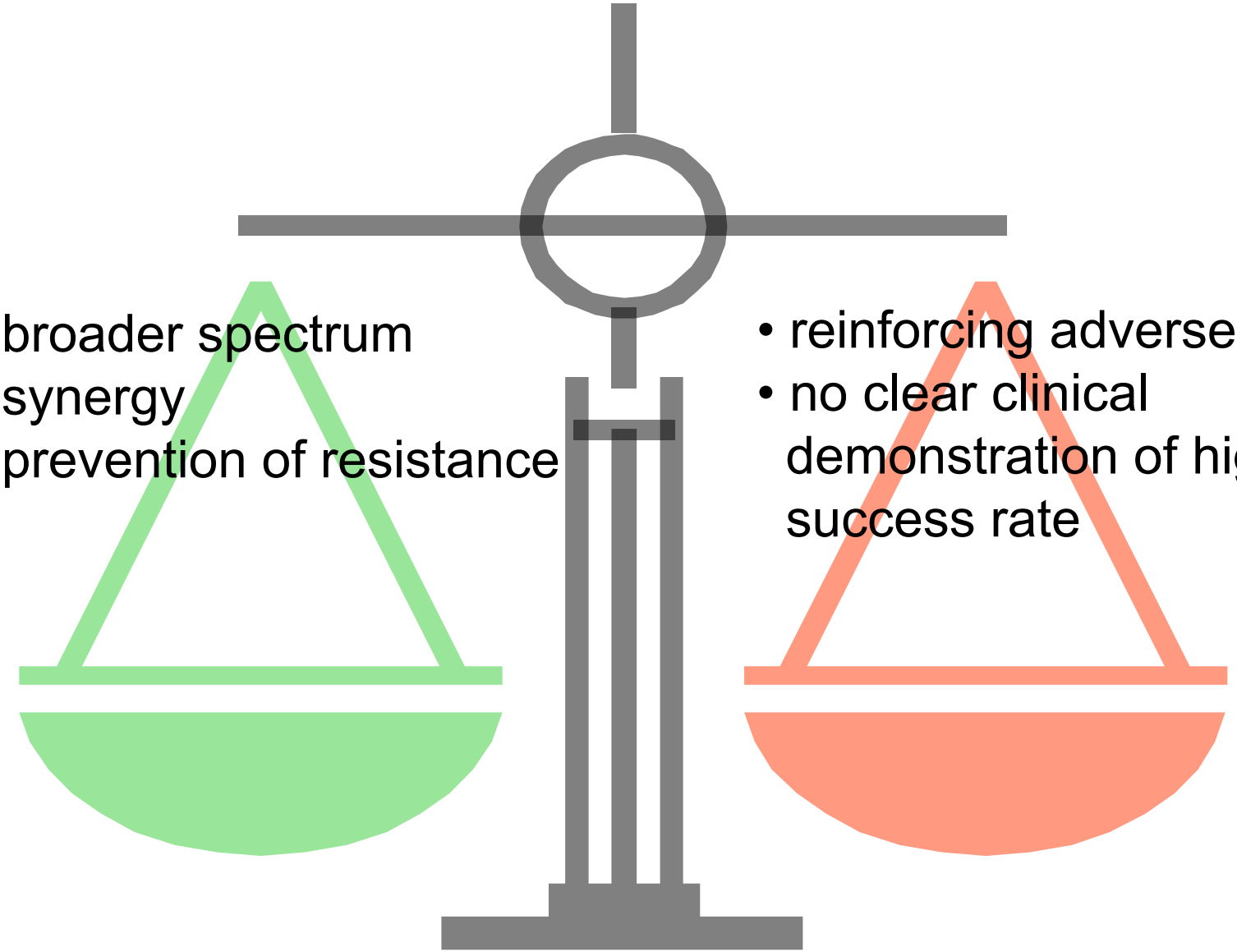
CMR
Journals.ASM.org

Although there are theoretical reasons why combination antimicrobial therapy may, in certain patients and situations, be superior to monotherapy for the treatment of infections with Gram-negative bacteria, the clinical data supporting these theories are neither overwhelming nor definitive. On the contrary, meta-analyses that have been conducted exclusively evaluating RCTs demonstrate no difference in clinical outcomes between the two treatment strategies for definitive management of infections with Gram-negative bacteria, but there are well-documented increased toxicities with combination therapy. This suggests that patients with infections with Gram-negative bacteria are served best by receiving definitive treatment with a single appropriate antibiotic.

In contrast, due to the greater mortality associated with delays in appropriate and effective antimicrobial treatment, initiating broad-spectrum empiric antimicrobial treatment (which often means combination therapy) at the first suspicion of infection in critically ill patients is prudent. For patients at risk of MDRGN infections, including patients with compromised immune systems, those with previous ICU admissions, or recent recipients of broad-spectrum antibiotics, empiric antimicrobial treatment should include coverage of pathogens that may be resistant to previously administered antibiotics, and empiric combination therapy may be appropriate. However, in attempts to avoid further emergence of resistance and adverse side effects such as *C. difficile* infection, nephrotoxicity, and ototoxicity, the antimicrobial regimen should be promptly narrowed or discontinued based on the patient's clinical course and culture and susceptibility profile results.

Tamma et al, CMR (2012) 25: 450-70

Antibiotic combinations : why ?



- broader spectrum
- synergy
- prevention of resistance

- reinforcing adverse effects
- no clear clinical demonstration of higher success rate

Tamma et al, CMR (2012) 25: 450-70

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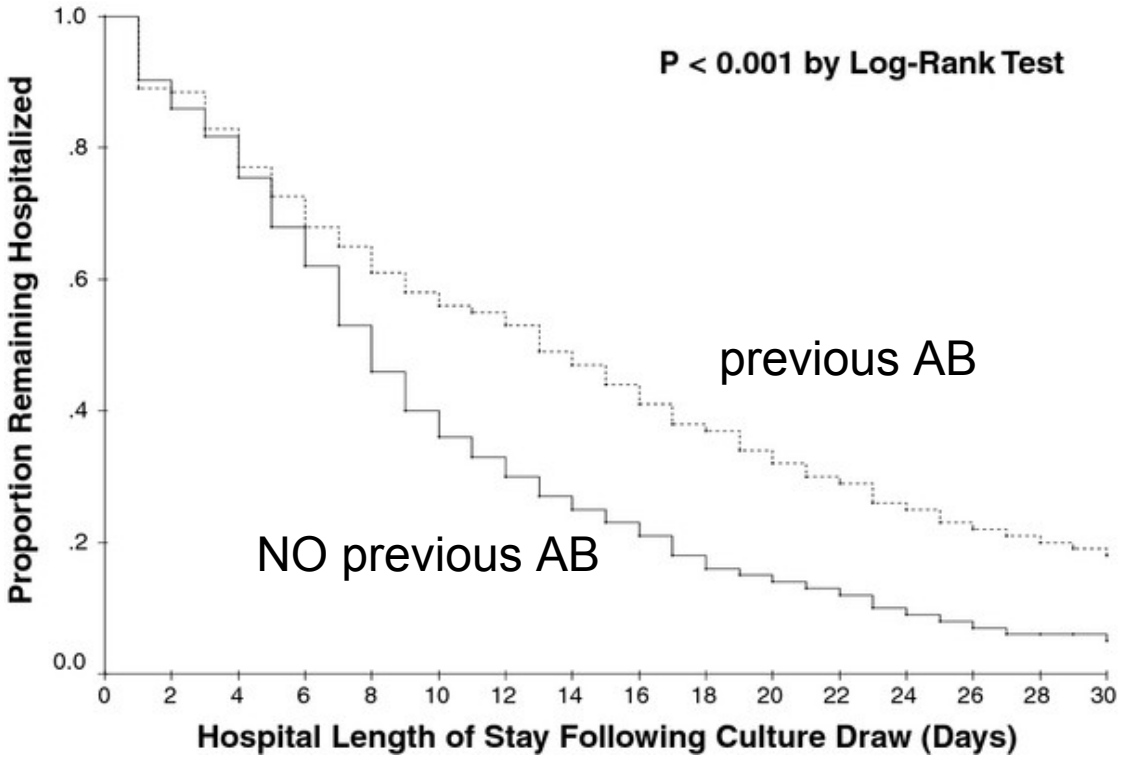
Dryden et al, JAC (2011) 66: 2441–43

Appropriate initial therapy: influence of previous antibiotic exposure

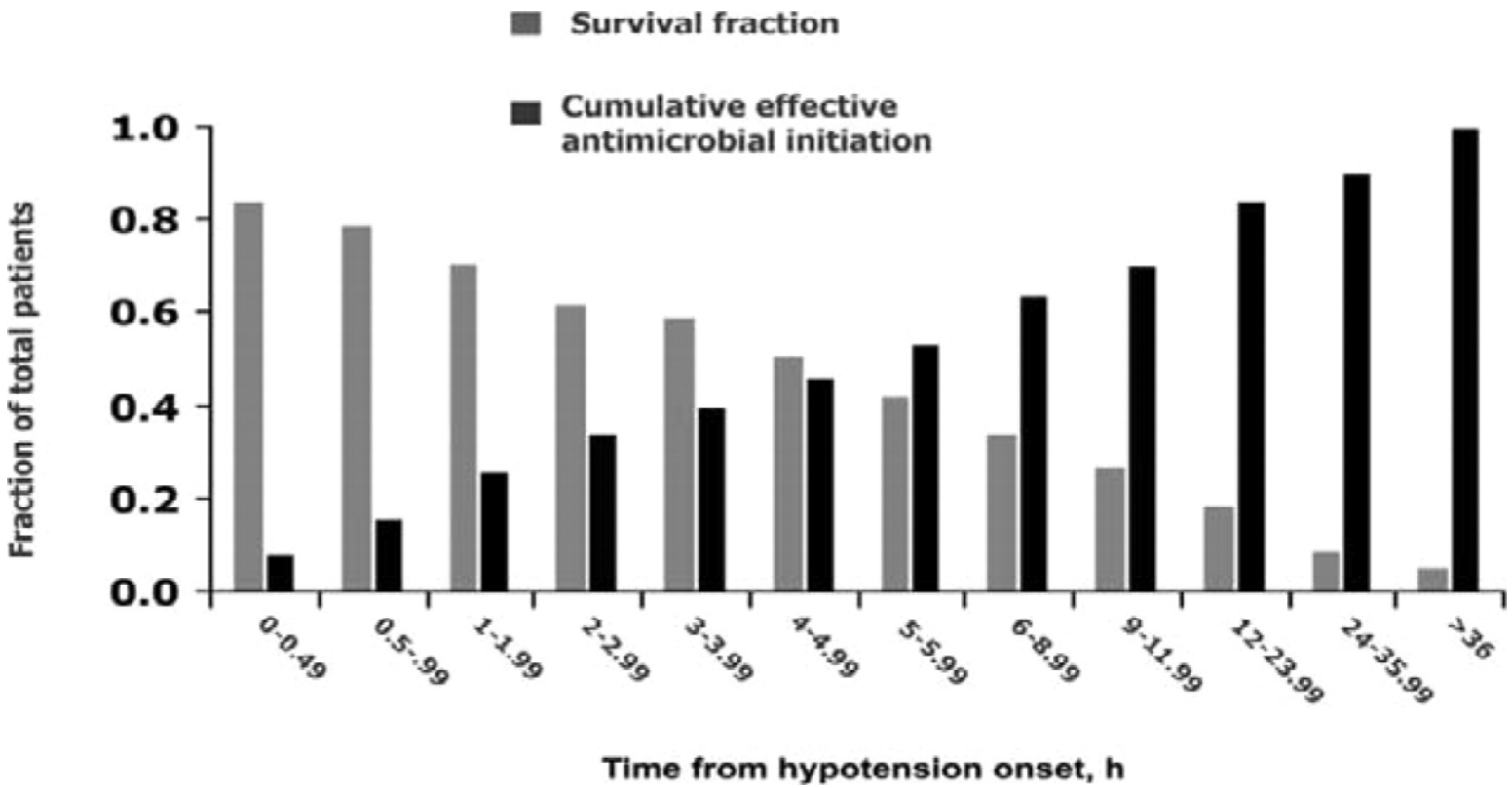
754 patients with Gram-negative bacteriemia



Micek et al, BMC Infect Dis. (2012) 12:56

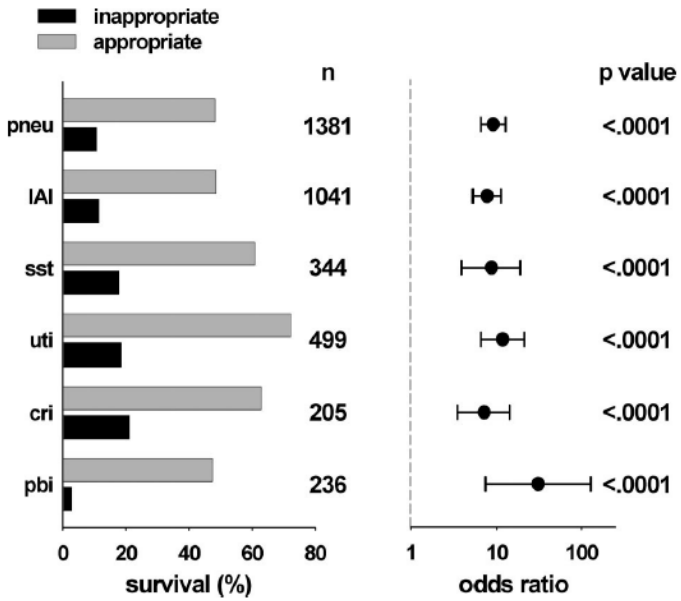
Appropriate initial therapy: impact on survival

2154 patients with septic shock



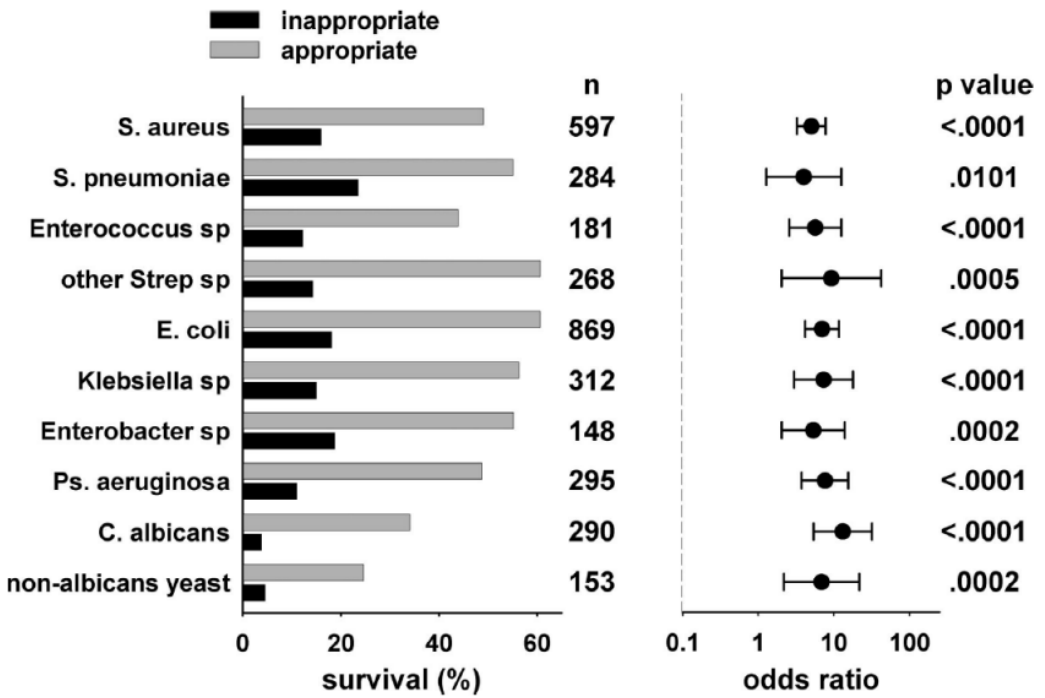
Kumar et al, Crit Care Med (2006) 34:1589-96

Appropriate initial therapy: impact on survival



Impact of antimicrobial appropriateness on survival in clinical infection subgroups.

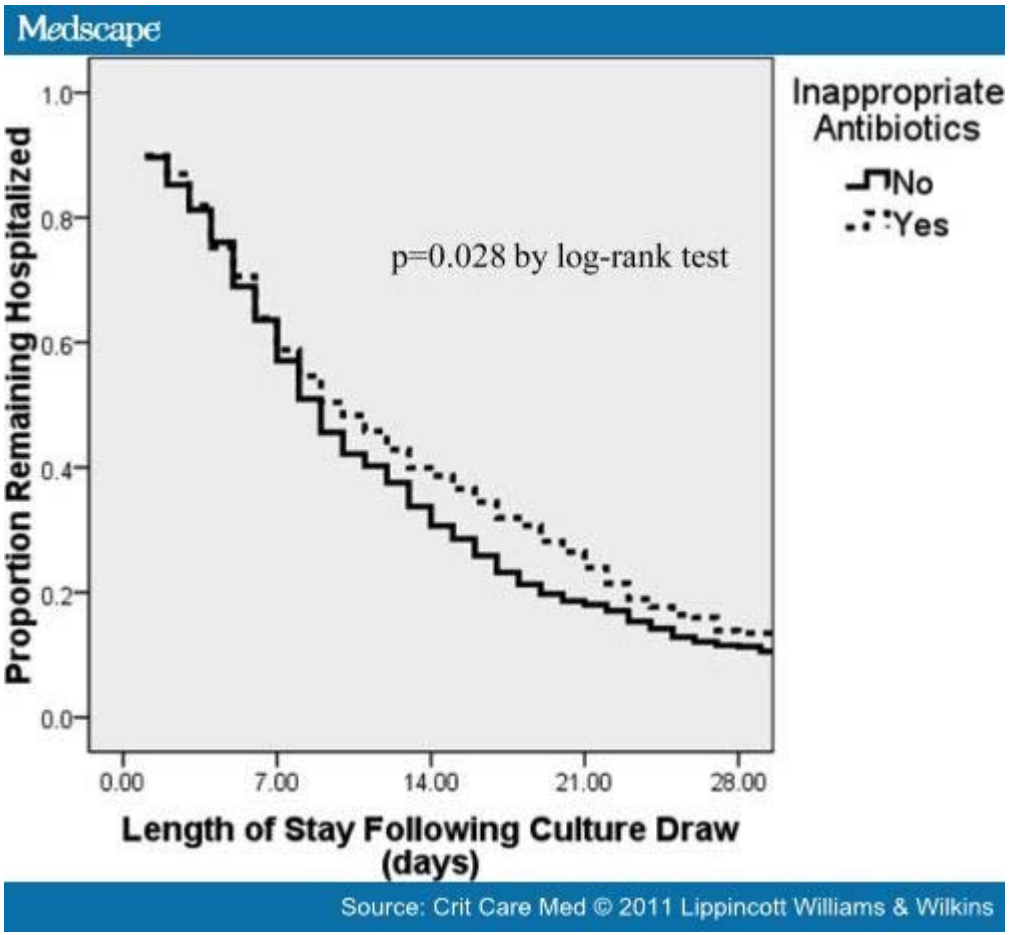
5715 patients with septic shock



Kumar et al, Chest (2009) 136:1237-48

Appropriate initial therapy: impact on length of stay

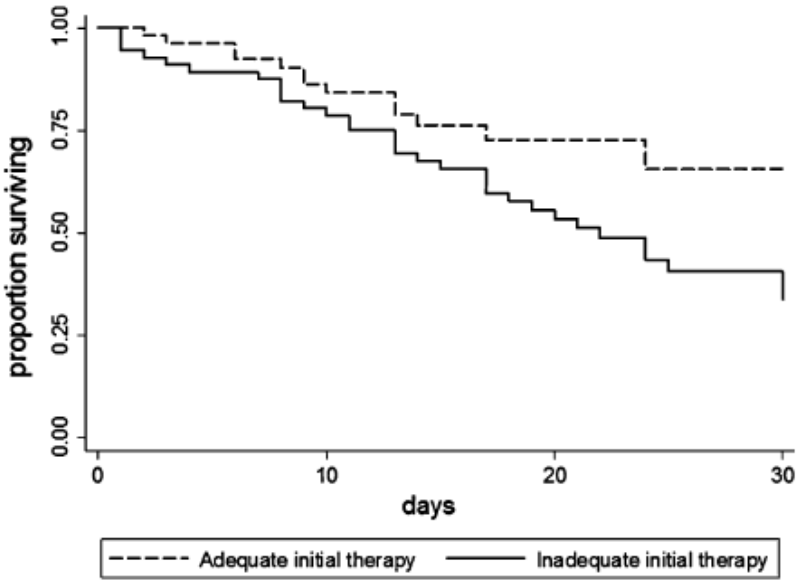
760 patients Gram-negative Sepsis

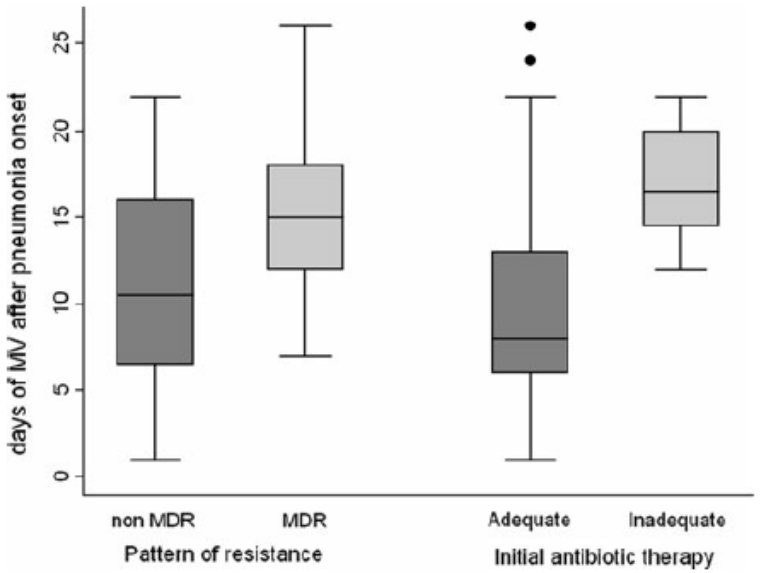


Shorr et al, Crit Care Med. (2011) 39:46-51.

Appropriate initial therapy: impact on survival and duration of ventilation

110 patients with *P. aeruginosa* VAP

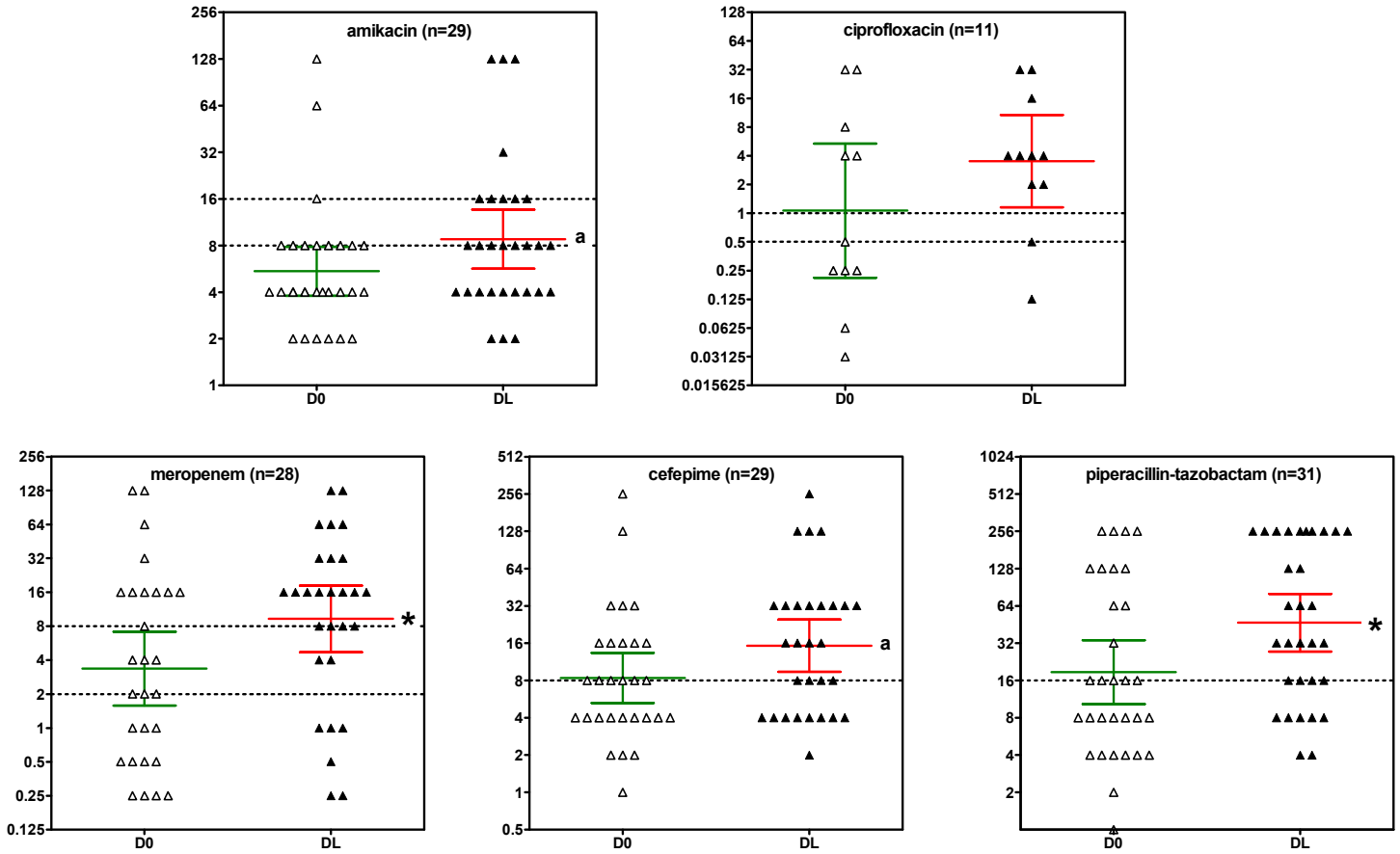




Tumbarello et al, Intensive Care Med (2013) 39:682–92

MICs change during treatment, follow up is needed!

109 patients with VAP from 5 Belgian hospitals,
collect of two successive, clonal isolates of *P. aeruginosa*



Riou et al, IJAA (2010) 36:513-22

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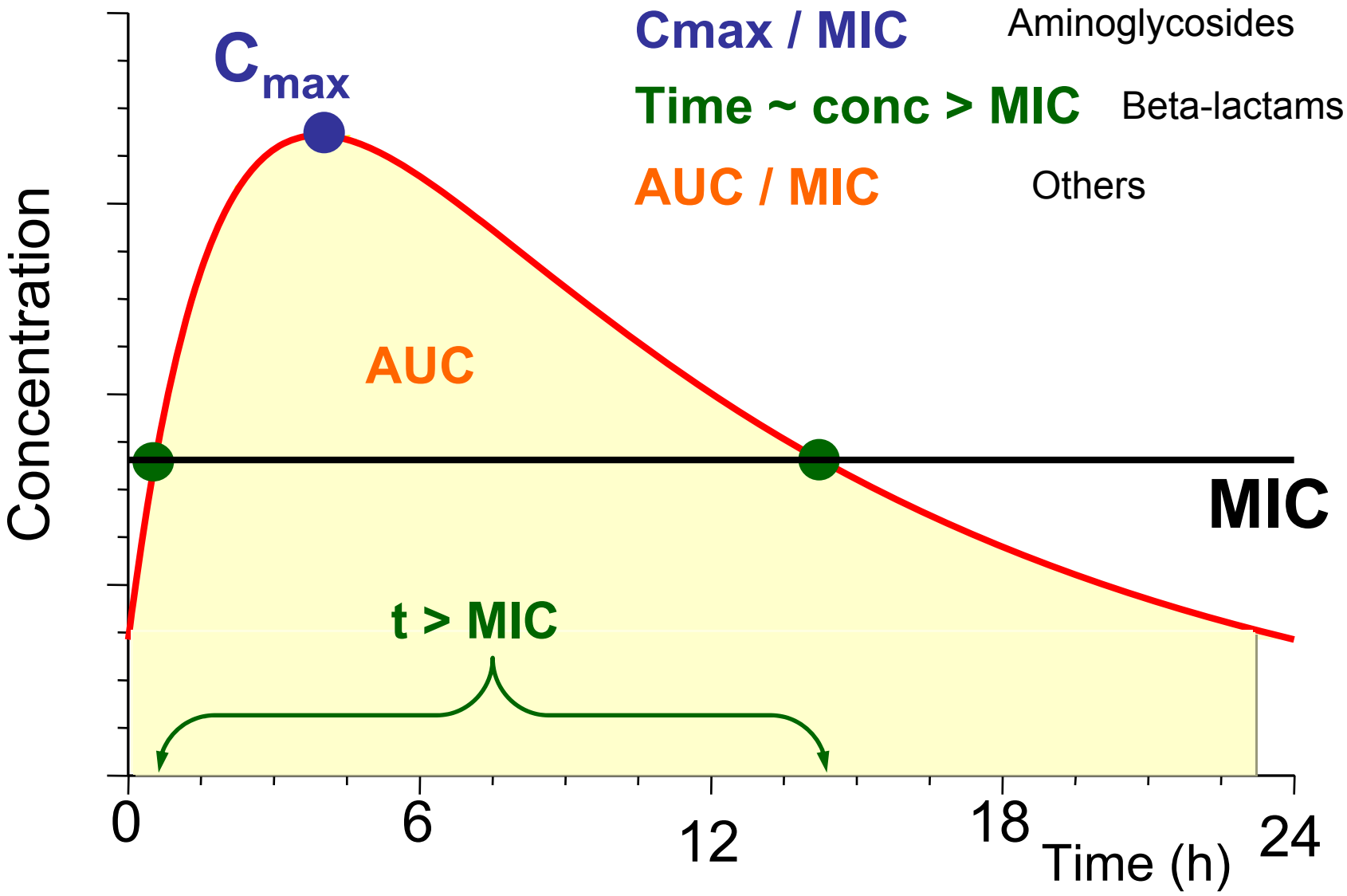
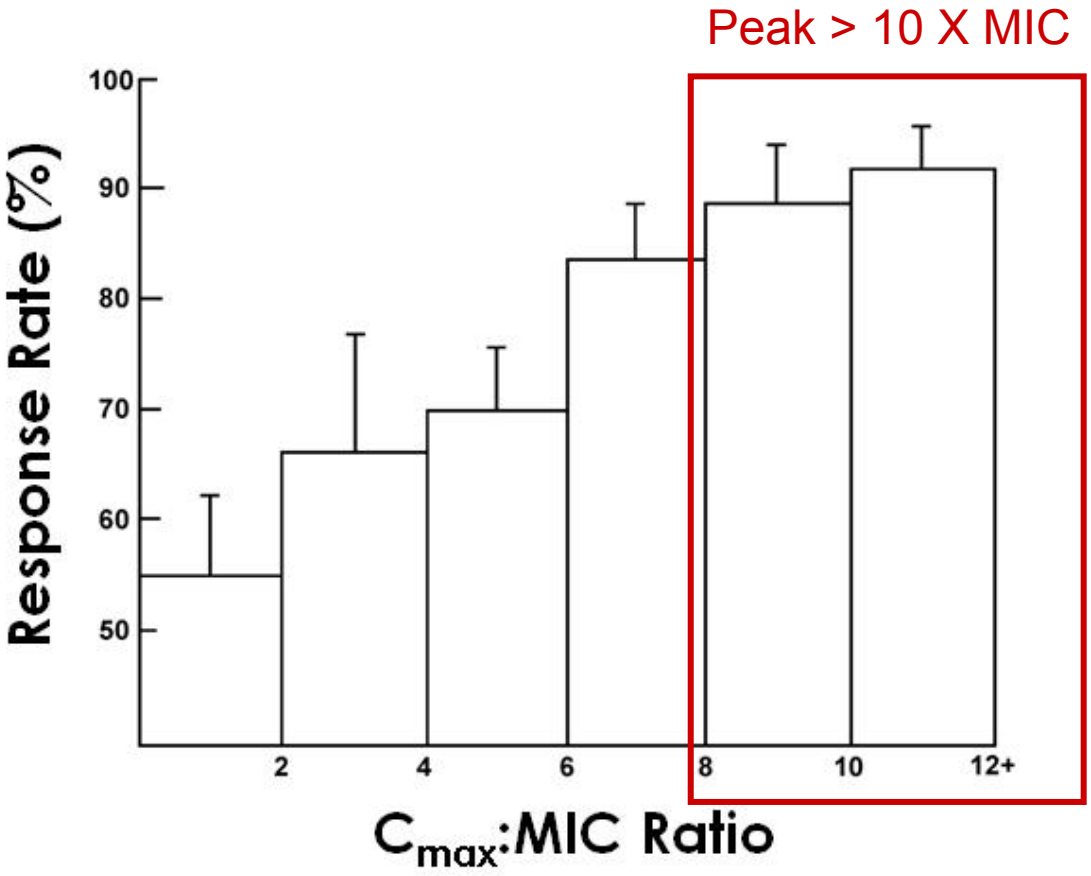
Dryden et al, JAC (2011) 66: 2441–43

PK/PD profiles



Aminoglycosides : peak to the max!

236 patients with Gram-negative infections



Moore et al, JID (1987) 155:93-9

Aminoglycosides : peak to the max!

2 case reports from Erasme hospital, ULB

Patient 1:
100 kg (BMI 35)
K. pneumoniae MDR
MIC amikacin: 16 mg/L

→ Amika 2500 mg (25 mg/kg)

Patient 2:
120 kg (BMI 39)
P. aeruginosa MDR
MIC amikacin: 16 mg/L

→Amika 3000 mg (25 mg/kg)
increased to 6000 mg at day 4

Peak ~ 8-10 x MIC

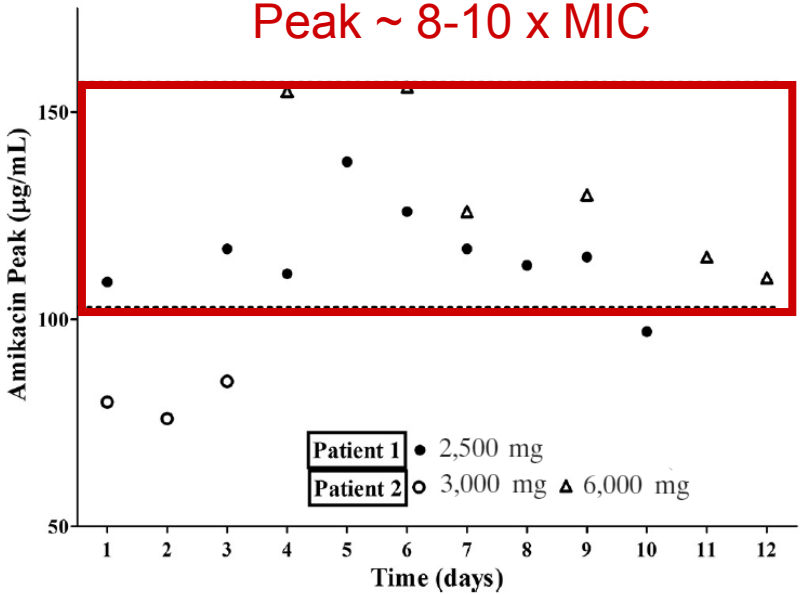


FIG. 1. Peak concentrations of amikacin in patient 1 (daily dose of amikacin, 2,500 mg [black circles]) and patient 2 (daily dose of amikacin, 3,000 mg [white circles], and then 6,000 mg following day 4 [white triangles]). Dotted lines indicate amikacin levels between 108 and 160 µg/ml, corresponding to 8 to 10 times the MIC (MIC = 16 µg/ml) for the isolated *Pseudomonas* strains.

Concentration matters, not the dose !

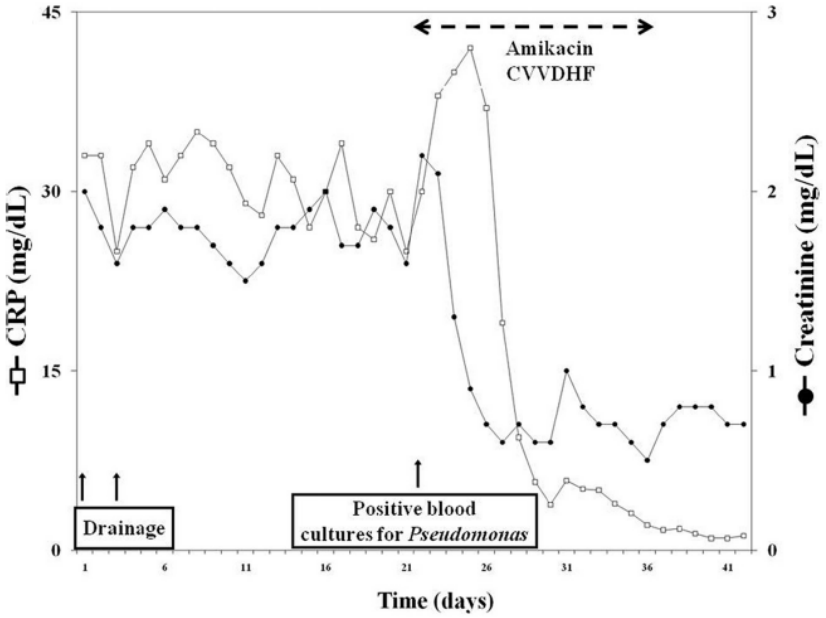
*Layeux et al, AAC (2010) 54:*4939–41

Aminoglycosides : peak to the max!

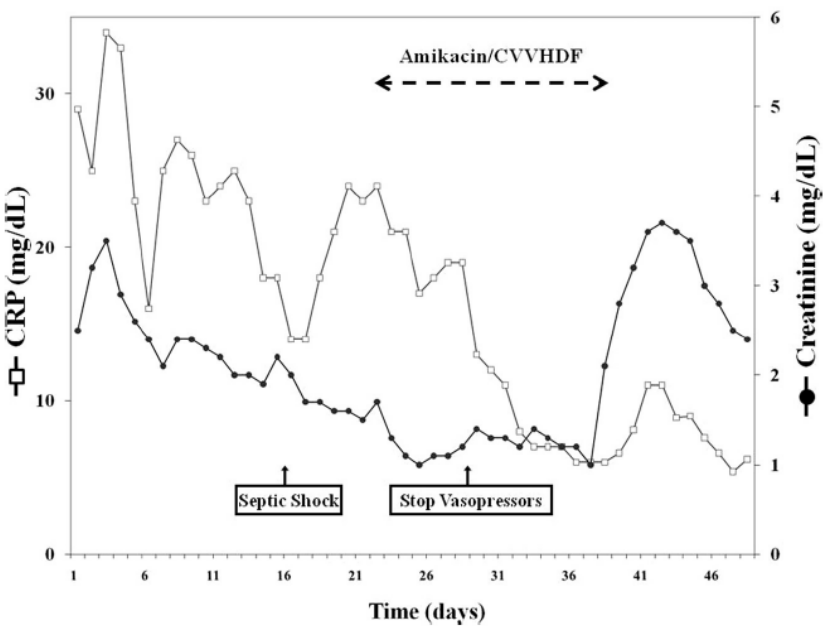
2 case reports from Erasme hospital, ULB

Toxicity ??? → Elimination by hemodialysis 2 h after administration

Evolution of patient 1:

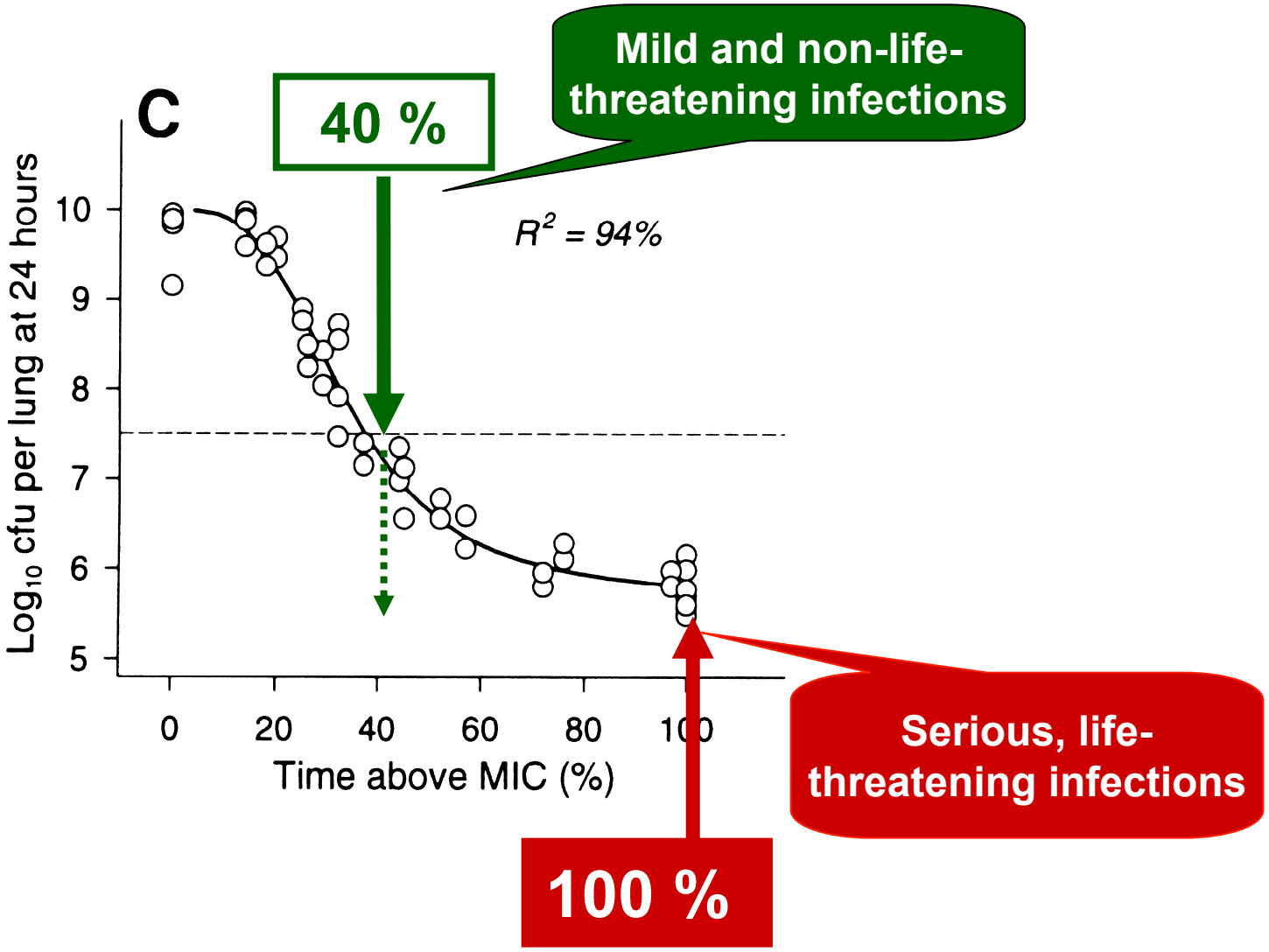


Evolution of patient 2:



Moore et al, JID (1987) 155:93-9

Beta-lactams : bringing them to the max!



Continuous infusion of β-lactams in clinical practice: literature review *

drug	no. of studies	main indications	main conclusions
1. controlled studies with clinical end-point(s)			
piperacillin	5 [a]	cIAI / VAP / septicaemia / various infections	equivalence but superiority if ↗ MIC
ceftazidime	2 [b]	VAP / pneumonia/ melioidosis/ cystic fibrosis	superiority mainly with resistant isolates
cefriaxone	1 [c]	sepsis	superiority
meropenem	1 [d]	VAP	superiority

* Full papers in peer-reviewed Journals only with evaluable clinical end-point(s)
a Grant 2002; Buck 2005; Lau 2006; Rafati 2006; Lorente 2009
b Rappaz 2000; Angus 2000; Nicolau 2001; Lorente 2007; Hubert 2009
d Lorente 2006 (Note: meropenem is unstable and may, therefore, not be recommended for continuous infusion without specific precautions)

Continuous infusion of β-lactams in clinical practice: literature review *

drug	no. of studies	main indications	main conclusions
2. non-controlled studies with clinical end-point(s)			
penicillin G	1 [a]	serious infections	favorable
oxacillin	1 [b]	burn wound cell.	faster cure
ampicillin	2 [c]	septicemia (infants)	equivalence or superiority (practical)
ceftazidime	3 [d]	neutropenic fever and infections	favorable (2) unfavorable (1)

* Full papers in peer-reviewed Journals only with evaluable clinical end-point(s)

[a] Walton 2007

[b] Schuster 2009

[c] Colding 1982; Colding 1982

[d] Daenen 1995; Vinks 1997; Marshall 2000

Continuous infusion of β-lactams in clinical practice: literature review *

drug	no. of studies	type of patients	main conclusions
3. PK/PD studies in humans (no clinical end-point)			
ampicillin	1 [a]	colorectal surgery	equivalence
piperacillin	1 [b]	VAP.	favorable
temocillin	1 [c]	non *Ps*. Gram (-)	pharmacokinetic super.
ceftazidime	5 [d]	ICU, cIAI, neutropenia, VAP	pharmacokinet. super.
cefepime	4 [e]	nosocom. pneum. and severe Gram(-) infect.	equivalence or superiority (practical)
imipenem	1 [f]	surgery (various indic.)	equivalence
meropenem	3 [g]	neutropenic fever and infections	favorable (2) – unfavorable (1)

* Full papers in peer-reviewed Journals only with evaluable clinical end-point(s)

[a] Martin 1998 -- [b] Boselli 2008 -- [c] De Jongh, 2008

[d] Lipman 1999; Buyck 2002; Dalle 2002; Cousson 2005; Mariat 2006

[e] Georges 1999; Jaruratanasirikul 2002; Boselli 2003; Roos 2006 (Note: cefepime solutions develop color upon storage and may not be suitable for human use)

[f] Sakka 2007; [g] Thalhammer 1999; Langgartner 2008; Roberts 2009 (Note:both imipenem and meropenem are unstable and may, therefore, not be recommended for continuous infusion without special precautions)

Beta-lactams : prolonge to the max!

Continuous infusion ?

- The exact role of continuous infusion of β-lactam antibiotics in the treatment of severe infections remains unclear...
- However, increasing evidence is emerging that suggests potential benefits
  - better attainment of pharmacodynamic targets for these drugs
  - More reliable pharmacokinetic parameters in seriously ill patients
  - when the MIC of the pathogen is ≥4 mg/L (empirical therapy where the susceptibility of the pathogen is unknown)
- Clinical data supporting continuous administration are less convincing, but
  - Some studies have shown improved clinical outcomes from continuous infusion
  - none have shown adverse outcomes.
  - clinical and bacteriological advantage are visible in seriously ill patients requiring at least 4 days of antibiotic therapy.
- **Seriously ill patients with severe infections requiring significant antibiotic courses (≥4 days) may be the subgroup that will achieve better outcomes with continuous infusion.**

Roberts et al, IJAA (2007) 30:11-8

Use antibiotics responsibly

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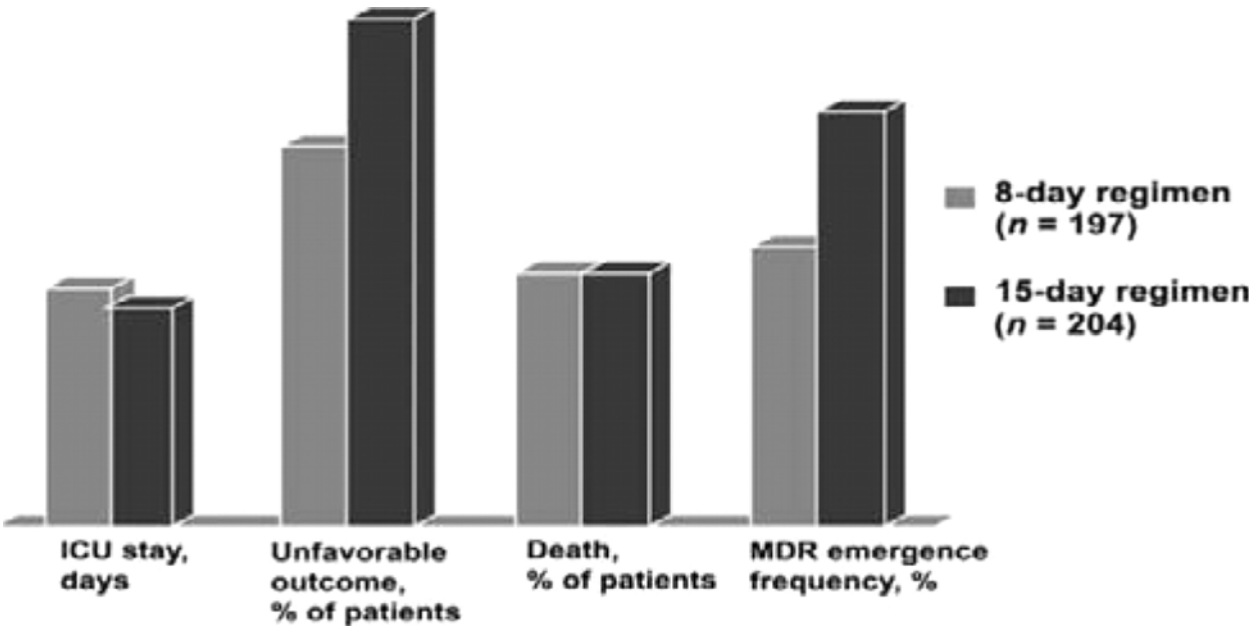
- **right duration → Not too short, not too long !**

Dryden et al, JAC (2011) 66: 2441–43

Reduce treatment duration ?

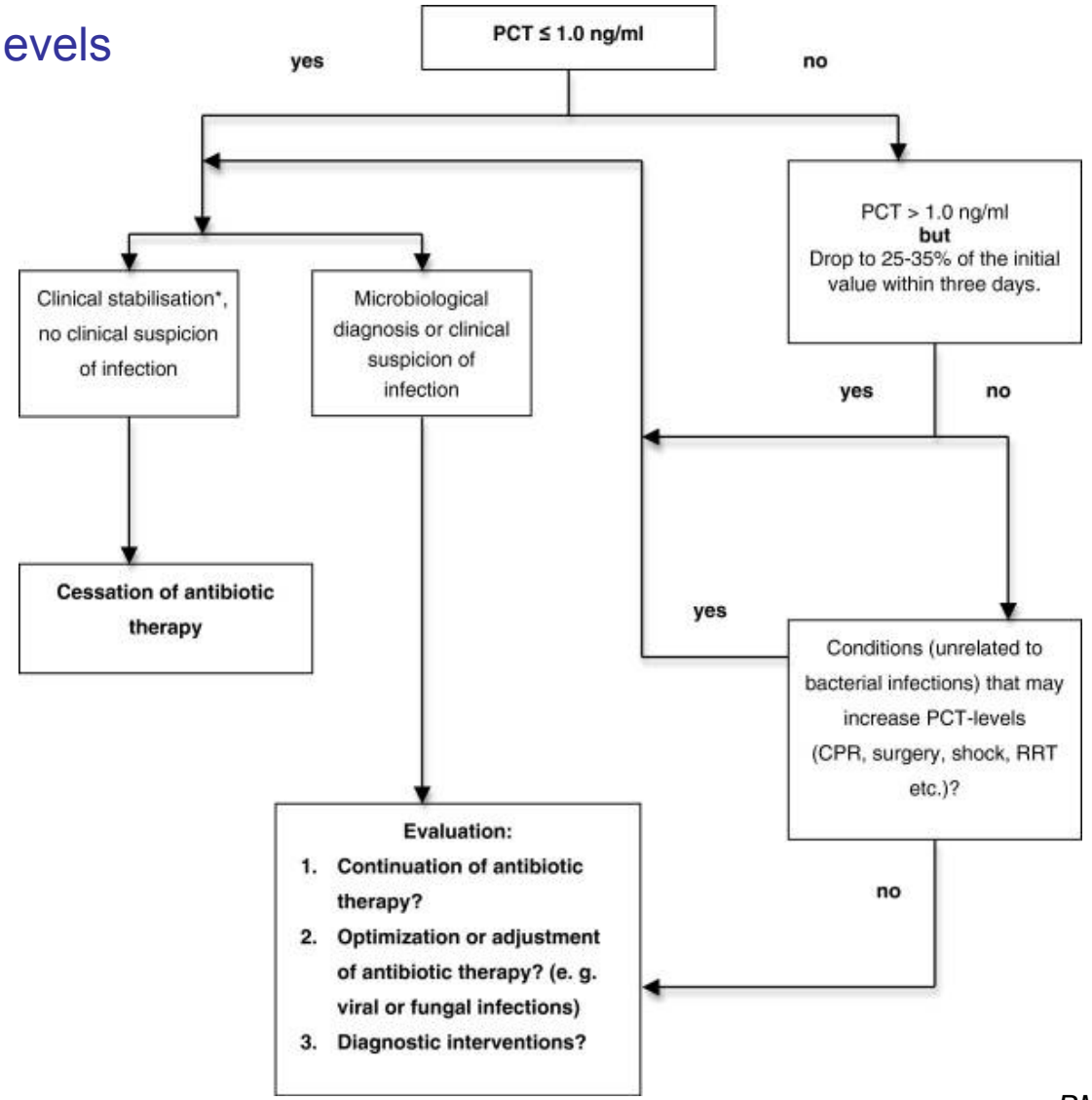
400 patients with ventilator associated pneumonia



Chastre et al, JAMA (2003) 290:2588-9

Biomarkers as a guide for shortening treatment duration

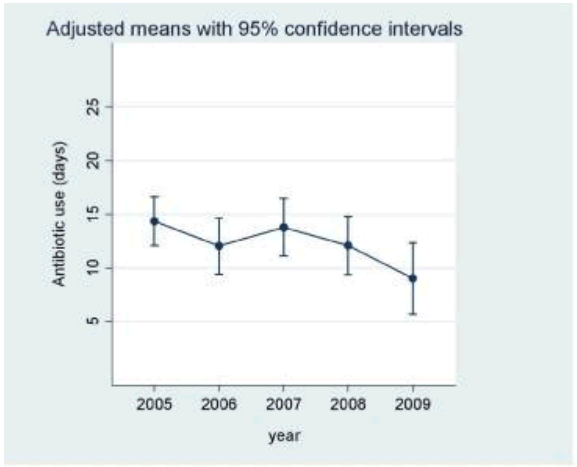
Procalcitonin levels



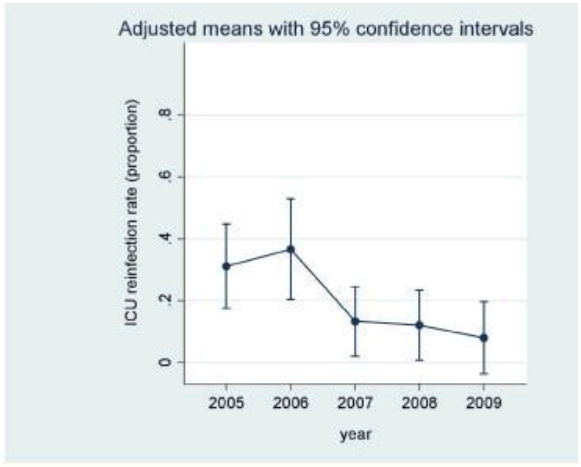
Hohn et al,
BMC Infect Dis. (2013) 13:158

Biomarkers as a guide for shortening treatment duration

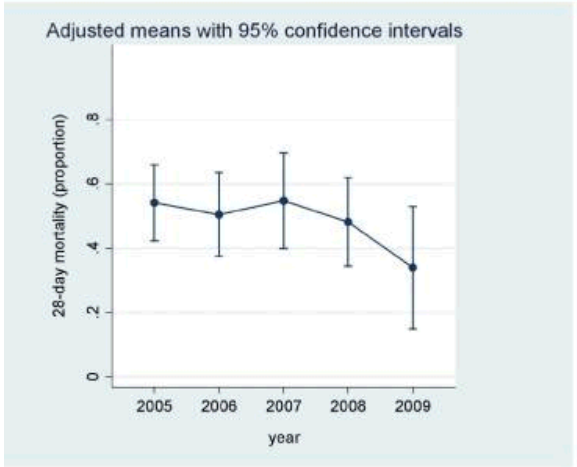
Procalcitonin levels used after 2005 to decide about antibiotic need



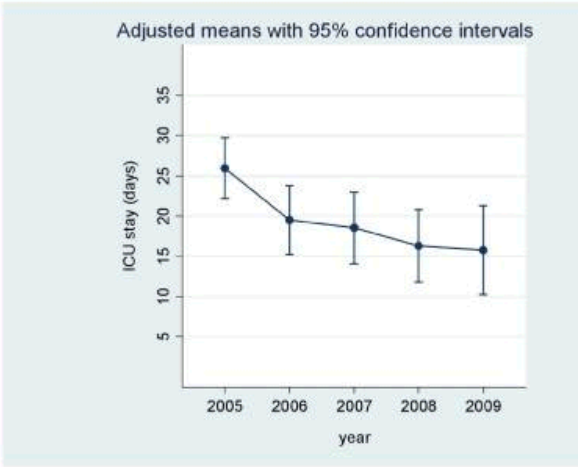
Days of antibiotic use



ICU reinfection rate



ICU mortality (28 days)



Length of stay in the ICU

Hohn et al,
BMC Infect Dis. (2013) 13:158

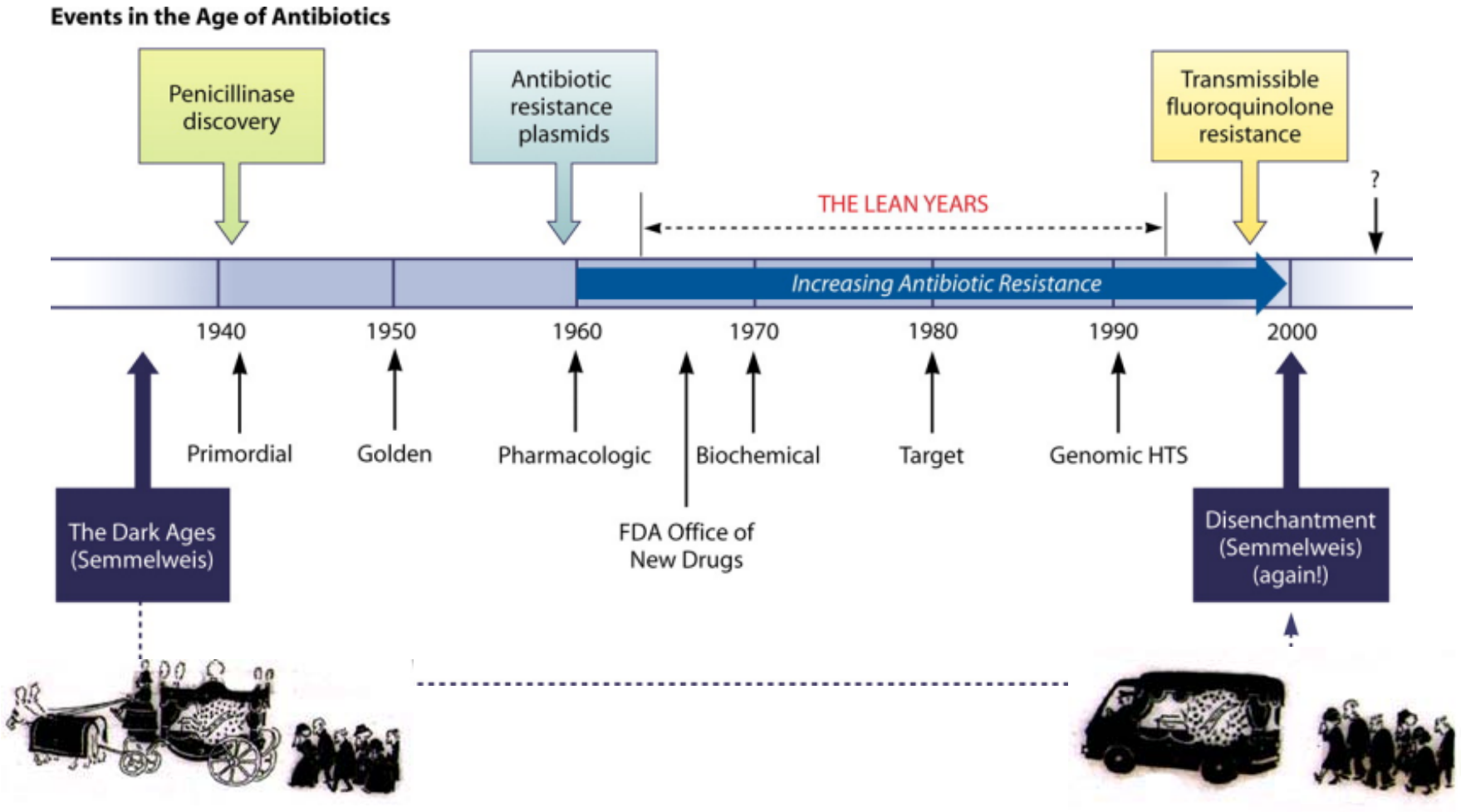
How to treat today: Summary

- right drug → Rapid diagnosis !
  → Combinations ?
- right time → Appropriate initial therapy !
- right dose → PK/PD !
- right duration → Not too short, not too long !

Dryden et al, JAC (2011) 66: 2441–43

Is the sky bright for tomorrow ?

The antibiotic saga …

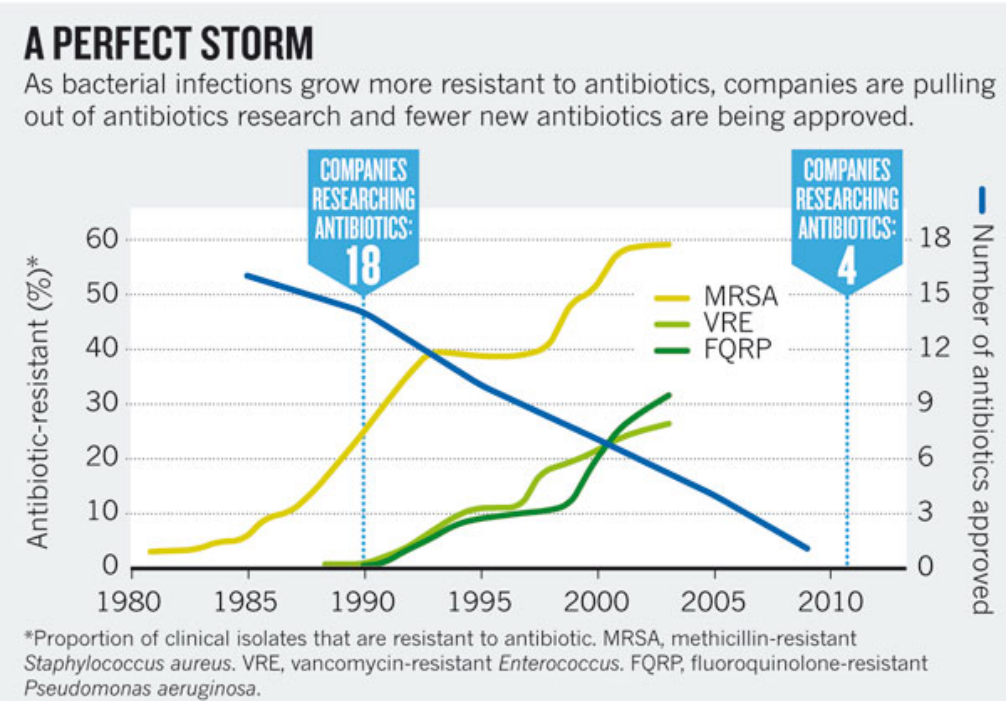


« avant la découverte de la pénicilline »
De Konk – Le Monde 1975

« après la découverte de la pénicilline »
De Konk – Le Monde 1975

Davies & Davies, Microbiol. Mol. Biol. Rev. (2010) 74:417-33

How does Industry address the problem ?



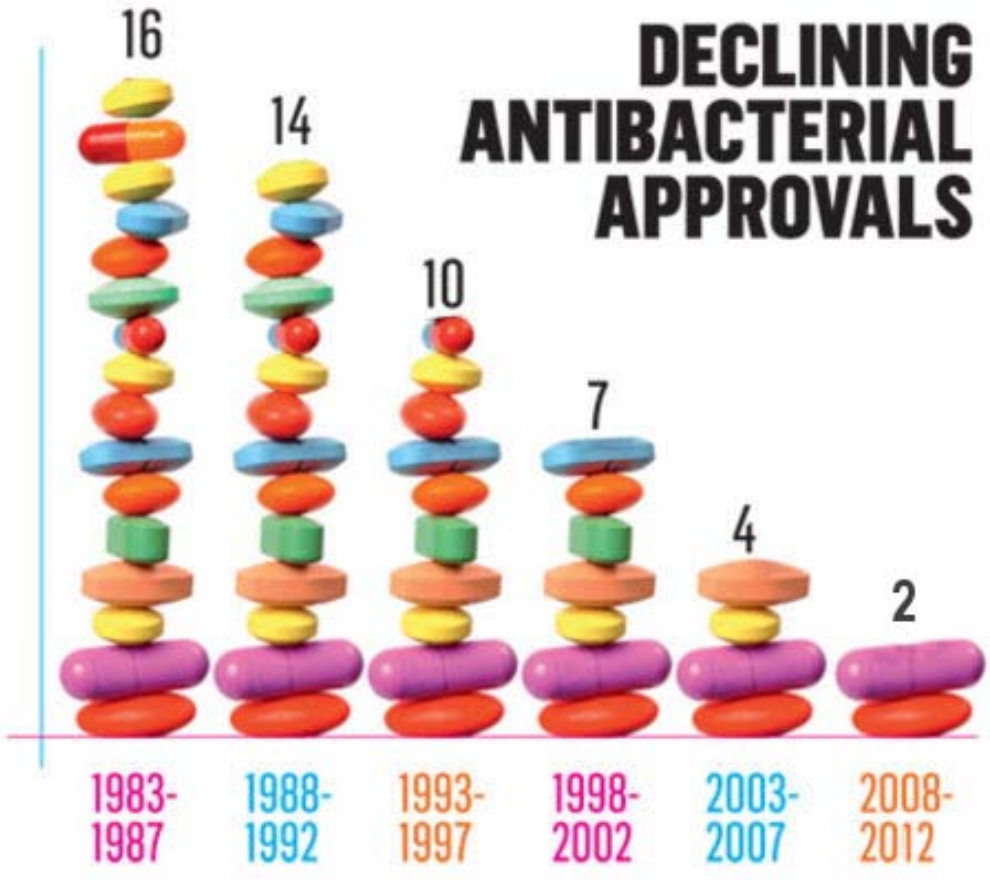
Big Pharma:
- GlaxoSmithKline
- AstraZeneca
- Merck & Co
- (Pfizer)

Antibacterial Pipeline (Anti–Gram Positive and Anti–Gram Negative), Big Pharma

Company	Since 1998	Phase 2/3
Abbott Laboratories	0	0
AstraZeneca	0	2
Bayer	0	0
GlaxoSmithKline	0	1
Lilly	0	0
Merck/Schering-Plough	1	1
Novartis	0	0
Ortho McNeil/Johnson & Johnson	1	0
Pfizer/Wyeth	2	0
Roche	0	0
Sanofi	0	0

Cooper, Nature (2011) 472: 32; Boucher et al. CID (2013) 56:1685-94

… as a result …



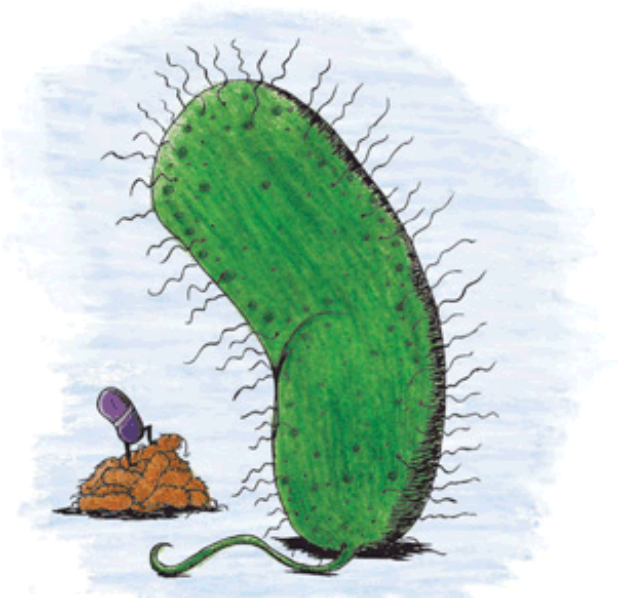
telavancin

ceftaroline

… No ESKAPE ! …

***E**. faecium*

***E.** aerogenes*



***S**. aureus*

***P**. aeruginosa*

***K**. pneumoniae*

***A.** baumannii*

… No ESKAPE ! …

IDSA

Bad Bugs Need Drugs

10x'20

Ten new ANTIBIOTICS by 2020

imi efpia

ND4BB : New Drugs for Bad Bugs

Anti Gram-positive agents in the pipeline

company	drug	status	MRSA	MDR S. pneumo	VRE
Rib-X	delafloxacin	III (ABSSSI)			
TaiGen	nemonoxacin	II (CAP/diabetic foot)			
Trius	tedizolid	III (ABSSSI)			
Rib-X	radezolid	II (ABSSSI/CAP)			
Adv. Life Sci.	cethromycin	III (CAP) / anthrax			
Cempra	solithromycin	III (CAP)			
The MedCo	oritavancin	III (ABSSSI)			
GSK	1322322	II (ABSSSI/CAP)			
Polymedix	brilacidin	II (ABSSSI)			

Adapted from *Gould et al. Virulence (2013) 4:185–91*

Anti Gram-positive agents in the pipeline

company	drug	status	MRSA	MDR S. pneumo	VRE
Rib-X	delafloxacin	III (ABSSSI)	quinolones		
TaiGen	nemonoxacin	II (CAP/diabetic foot)			
Trius	tedizolid	III (ABSSSI)	oxazolidinones		
Rib-X	radezolid	II (ABSSSI/CAP)			
Adv. Life Sci.	cethromycin	III (CAP) / anthrax	ketolides		
Cempra	solithromycin	III (CAP)			
The MedCo	oritavancin	III (ABSSSI)	lipoglycopeptides		
GSK	1322322	II (ABSSSI/CAP)	peptide deformylase		
Polymedix	brilacidin	II (ABSSSI)	peptide defense protein mimetic		

is this really « new » ?

Adapted from *Gould et al. Virulence (2013) 4:185–91*

Anti Gram-negative agents in the pipeline

company	drug	status	Enterobact.			P. aeruginosa			Acinetob.	
			ESBL	sCBP	mCBP	WT	MDR	mCBP	WT	MDR
Cubist	ceftolozane/ tazobactam	III cUTI/cIAI I HAP/VAP								
Astra/ Cerexa	ceftazidime/ avibactam	III cIAI								
Astra/ Cerexa	ceftaroline/ avibactam	II cUTI/cIAI								
Merck	imipenem/ MK7655	II cUTI/cIAI								
Achaogen	plazomicin	II cUTI								
Tetraphase	eravacycline	II cIAI								

sCBP: serine-carbapenemase; mCBP: metallo-carbapenemase

Boucher et al. CID (2013) 56:1685-94

Anti Gram-negative agents in the pipeline

company	drug	status	Enterobact.			P. aeruginosa			Acinetob.	
			ESBL	sCBP	mCBP	WT	MDR	mCBP	WT	MDR
Cubist	ceftolozane/ tazobactam	III cUTI/cIAI I HAP/VAP	β-lactams + β-lactamase inhibitors							
Astra/ Cerexa	ceftazidime/ avibactam	III cIAI								
Astra/ Cerexa	ceftaroline/ avibactam	II cUTI/cIAI								
Merck	imipenem/ MK7655	II cUTI/cIAI								
Achaogen	plazomicin	II cUTI	aminoglycoside							
Tetraphase	eravacycline	II cIAI	glycylcycline							

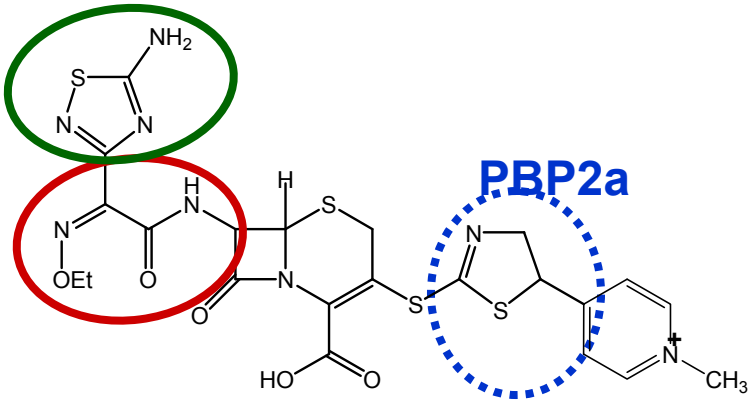
is this really « new » ?

Boucher et al. CID (2013) 56:1685-94

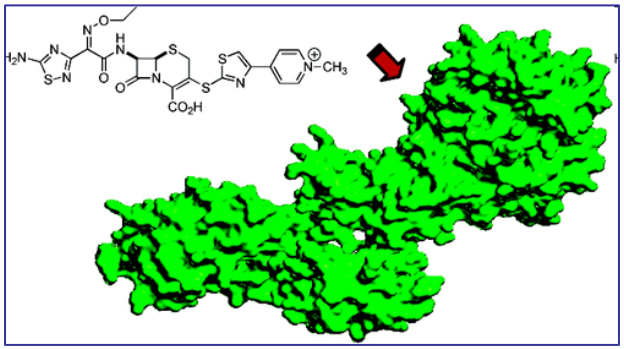
CEFTAROLINE

Gram-neg

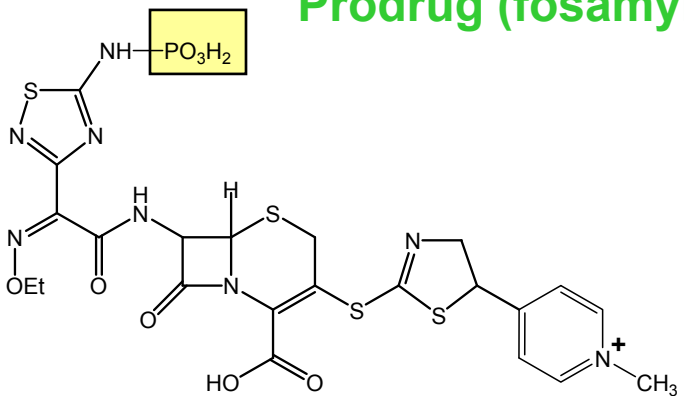
β-lactamases



PBP2a



Prodrug (fosamyl) **TAK-599**



TAK-91825

Ishikawa et al., Bioorg Med Chem. (2003) 11:2427-37

MICs distributions: *S. pneumoniae* and *S. aureus* (MRSA)

Comparisons of ceftaroline MIC values with those of selected other agents for organisms of various species commonly occurring during the FOCUS 1 and 2 Phase III clinical trials;[32] data derived from the ceftaroline 2008 surveillance study results in the USA

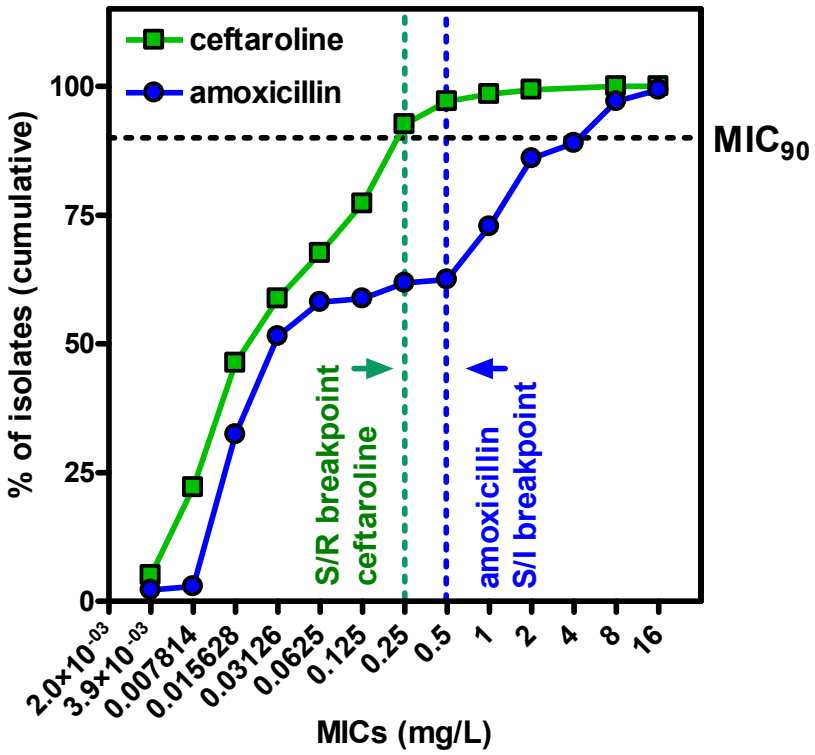
Pathogen (no. tested)/ antimicrobial agent	MIC (mg/L)			Percentage by category, susceptible/resistant[a]
	50%	90%	range	
Streptococcus pneumoniae (894)				
ceftaroline	0.015	0.12	≤0.008–0.5	—[b]/— (100.0)[c]
ceftriaxone	≤0.25	1	≤0.25–8	90.8/2.2
amoxicillin/clavulanate	≤1	8	≤1–16	83.3/13.2
penicillin (≤2 mg/L)	≤0.03	4	≤0.03–>4	86.5/1.0
erythromycin	≤0.25	>2	≤0.25–>2	61.6/38.0
clindamycin	≤0.25	>2	≤0.25–>2	79.3/20.5
levofloxacin	1	1	≤0.5–>4	99.4/0.4
TMP/SMX	≤0.5	>2	≤0.5–>2	66.3/24.9
vancomycin	≤1	≤1	≤1	100.0/—
MRSA (215)				
ceftaroline	1	1	0.25–2	—/— (100.0)[f]
ceftriaxone	>32	>32	4–>32	0.0/100.0
imipenem	1	>8	≤0.12–>8	0.0/100.0
erythromycin	>2	>2	≤0.25–>2	1.9/96.7
clindamycin	0.5	>2	≤0.25–>2	49.8/49.8
levofloxacin	>4	>4	≤0.5–>4	14.4/85.6
linezolid	2	2	0.25–4	100.0/0.0
TMP/SMX	≤0.5	≤0.5	≤0.5–>2	98.6/0.9
vancomycin	1	1	0.5–2	100.0/0.0

Jones et al., JAC (2011) 66 Suppl 3:iii69-80

MICs distributions: *S. pneumoniae* and *S. aureus* (MRSA)

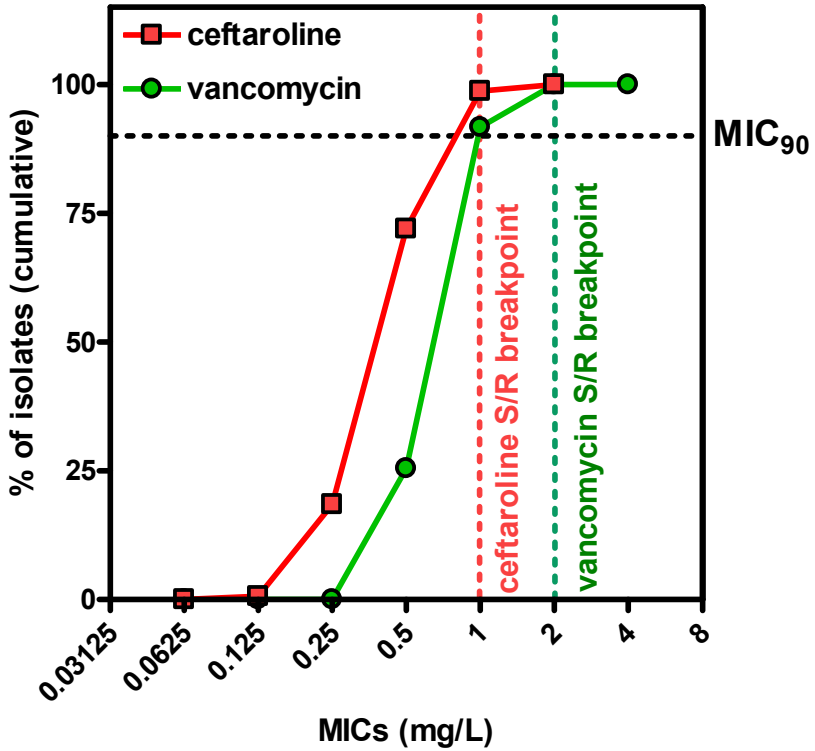
Belgian data

***S. pneumoniae* (n = 136)**



EUCAST breakpoints
- **amoxicillin: S ≤ 0.5 – R > 2**
- **ceftaroline: S ≤ 0.25 – R > 0.25**

MRSA (N = 157)



EUCAST breakpoints
- **ceftaroline: S ≤ 1 – R > 1**
- **vancomycin: S ≤ 2 – R> 2**

Lemaire et al., ICC (2013) P106

MICs distributions: Gram-negative bacteria

In vitro activity (μg/mL) of ceftaroline, ceftaroline-avibactam and comparator antimicrobial agents against aerobic Gram-negative isolates recovered from infected diabetic foot wounds.

Organism (No.) Antimicrobial agent	Range	MIC_{50}	MIC_{90}
Enterobacteriaceae (42) [a]			
Ceftaroline	≤0.03–>32	0.06	0.5
Ceftaroline-avibactam	≤0.015–0.5	0.03	0.125
Ceftriaxone	≤0.015–>32	0.06	0.5
Clindamycin	32–64	>64	>64
Ertapenem	≤0.015–>32	≤0.015	0.125
Levofloxacin	≤0.015–16	0.06	0.5
Piperacillin-tazobactam	≤0.03–>64	1	4
Pseudomonas aeruginosa (10)			
Ceftaroline	0.06–>32	2	>32
Ceftaroline-avibactam	≤0.015–32	2	32
Ceftriaxone	0.06–>32	4	>32
Clindamycin	0.25–>64	>64	>64
Ertapenem	≤0.015–>32	2	>32
Levofloxacin	0.06–16	0.5	16
Piperacillin-tazobactam	≤0.03–>64	1	>64
Non-fermenting, Gram-negative rods (10) [b]			
Ceftaroline	0.06–>32	2	>32
Ceftaroline-avibactam	≤0.015–32	2	32
Ceftriaxone	0.06–>32	4	>32
Clindamycin	0.25–>64	>64	>64
Ertapenem	≤0.015->32	2	>32
Levofloxacin	0.06–16	0.5	16
Piperacillin-tazobactam	≤0.03–>64	1	>64

Goldstein et al., DMID (2013) doi: 10.1016/j.diagmicrobio.2013.03.019

Pharmacokinetic profile

	Multiple-dose administration					
	300 mg every 12 h		600 mg every 12 h		800 mg every 24 h	
Parameter	first dose	day 14	first dose	day 14	first dose	day 7
C_{max} (mg/L)	10±0.76	8.5±1.85	19.0±0.71	21.3±4.10	29.7±4.97	31.5±2.39
$t_{1/2}$ (h)	2.56±0.47	2.62±0.41	1.6±0.38	2.66±0.4	2.16±0.15	2.63±0.24
$AUC_{0-\infty}$ (h·mg/L)	25.8±3.8	—	56.8±9.3	—	72.4±8.7	—
AUC_{ss} (h·mg/L)	—	24.3±3.7	—	56.2±8.9	—	74.2±14.2
CL/F_m (mL/min)	174.6±27.0	184.9±26.9	159.7±30.9	160.1±23.3	164.6±18.9	164.3±35.2
CL_R (mL/min)	92.8±69.3	75.3±19.9	68.8±19.8	118.9±72.8	78.0±23.2	66.1±20.2
Urinary recovery (%)	51.4±36.8	40.6±8.8	42.1±9.8	73.9±45.9	45.7±9.1	40.1±8.9
Metabolic ratio	23.9±7.7	23.0±8.1	20.3±9.0	24.5±8.9	30.4±3.2	26.5±9.5

C_{max}, maximum concentration; $t_{1/2}$, terminal half-life; $AUC_{0-\infty}$, AUC from time zero extrapolated to infinity; AUC_{ss}, AUC at steady-state; CL/F_m, metabolic clearance, where F_m is the fraction of the dose metabolized; CL_R, renal clearance.

Laudano, JAC (2011) 66 Suppl 3:iii11-18

PK/PD breakpoint

Table 1: Interpretive Criteria Proposed by Agency versus those proposed by Applicant for S. aureus, S. pneumoniae* and *H. influenzae

Indication	Pathogen	FDA Proposed Interpretive Criteria			Applicant Proposed Interpretive Criteria		
		S	I	R	S	I	R
cSSSI	*S. aureus* (includes methicillin-resistant isolates)	≤0.5	—	—	≤2[a]	—	—
CABP	*S. aureus* (excluding methicillin-resistant isolates)	≤0.25	—	—			
CABP	*S. pneumoniae*	≤0.008	—	—	≤0.5	—	—
CABP	*H. influenzae*	No interpretive criteria			≤0.25[b]	—	—

[a]Applicant only proposed interpretive criteria for *S. aureus* regardless of indication
[b]Applicant proposed interpretive criteria for *Haemophilus* spp.

Figure 3: Monte Carlo Simulation Predicted Probability (%) of Target Attainment for the 600 mg q12h dose as a function of MIC for MSSA and MRSA

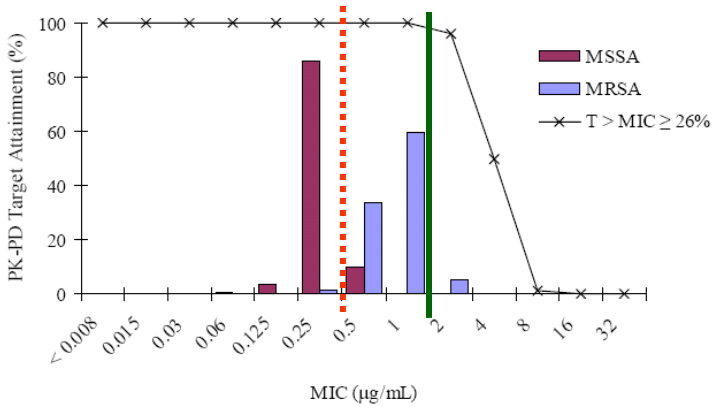
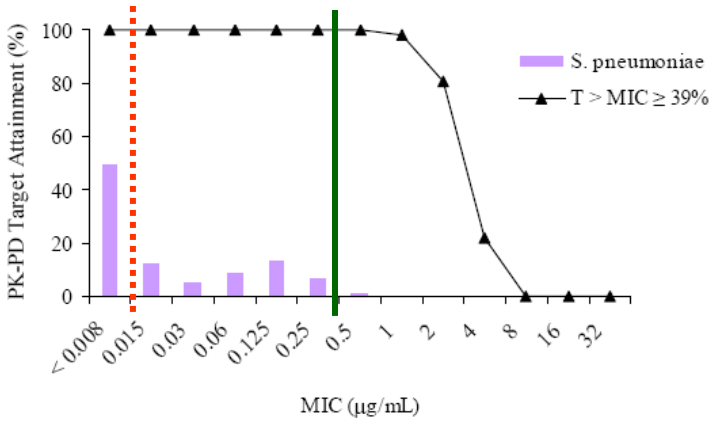


Figure 4: PK/PD Target Attainment for S. pneumoniae as a Function of MIC

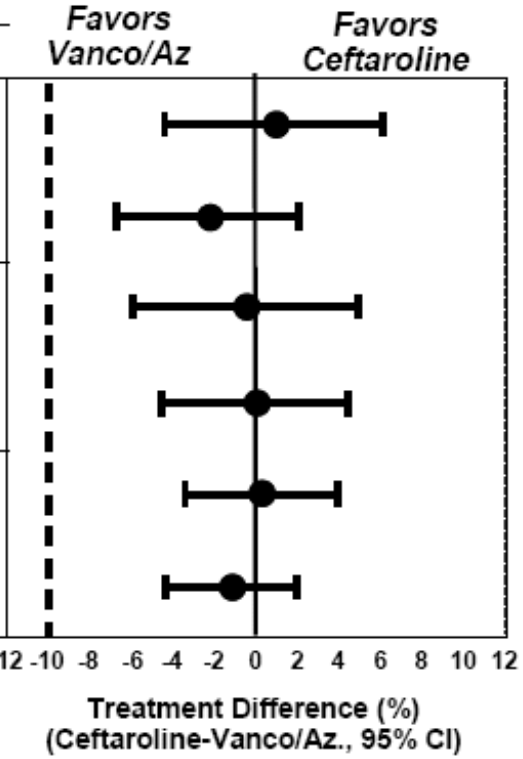


FDA breafing document; september 2010

Complicated skin/skin structure infections

Figure 7.6–1. **Clinical Response and Confidence Intervals for the Difference in Clinical Cure Rates at Test of Cure, Phase 3 Complicated Skin and Skin Structure Studies—MITT and CE Populations**

Study/Population		Clinical Response at TOC % (n/N) Ceftaroline	Clinical Response at TOC % (n/N) Vanco/Az
P903-06	MITT	**86.6** (304/351)	**85.6** (297/347)
	CE	**91.1** (288/316)	**93.3** (280/300)
P903-07	MITT	**85.1** (291/342)	**85.5** (289/338)
	CE	**92.2** (271/294)	**92.1** (269/292)
COMBINED	MITT	**85.9** (595/693)	**85.5** (586/685)
	CE	**91.6** (559/610)	**92.7** (549/592)

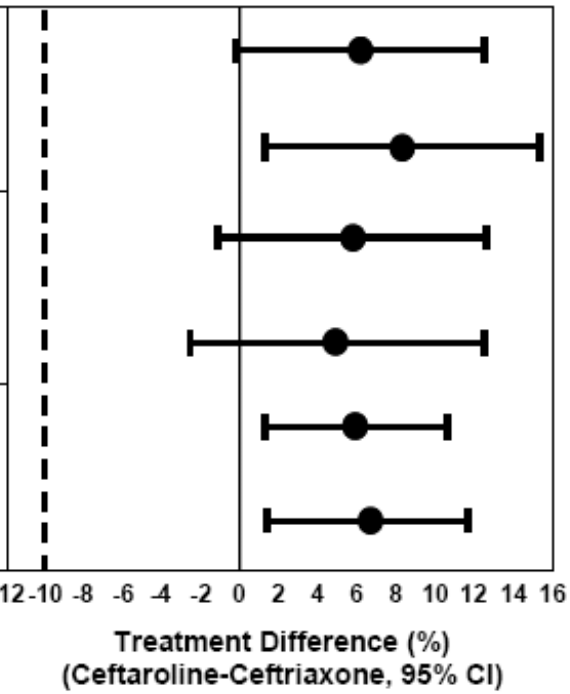


FDA breafing document; september 2010

Community-acquired pneumonia

Figure 6.6–1. **Clinical Response and Confidence Intervals for the Difference in Clinical Cure Rates at Test of Cure, Phase 3 Community-acquired Bacterial Pneumonia Studies—MITTE and CE Populations**

Study/Population		Clinical Response at TOC % (n/N) Ceftaroline	Ceftriaxone
P903-08	MITTE	**83.8** (244/291)	**77.7** (233/300)
	CE	**86.6** (194/224)	**78.2** (183/234)
P903-09	MITTE	**81.3** (235/289)	**75.5** (206/273)
	CE	**82.1** (193/235)	**77.2** (166/215)
COMBINED	MITTE	**82.6** (479/580)	**76.6** (439/573)
	CE	**84.3** (387/459)	**77.7** (349/449)



FDA breafing document; september 2010

Safety profile (Phase III)

Table 4: Adverse Reactions Occurring in ≥ 2% of Patients Receiving Teflaro in the Pooled Phase 3 Clinical Trials

System Organ Class/ Preferred Term	Pooled Phase 3 Clinical Trials (four trials, two in ABSSSI and two in CABP)	
	Teflaro (N=1300)	Pooled Comparators[a] (N=1297)
Gastrointestinal disorders		
Diarrhea	5 %	3 %
Nausea	4 %	4 %
Constipation	2 %	2 %
Vomiting	2 %	2 %
Investigations		
Increased transaminases	2%	3 %
Metabolism and nutrition disorders		
Hypokalemia	2 %	3 %
Skin and subcutaneous tissue disorders		
Rash	3%	2%
Vascular disorders		
Phlebitis	2%	1%

[a] Comparators included vancomycin 1 gram IV every 12h plus aztreonam 1 gram IV every 12h in the Phase 3 ABSSSI trials, and ceftriaxone 1 gram IV every 24h in the Phase 3 CABP trials.

CEFTAROLINE: current indications

EMA approved indications (2012):

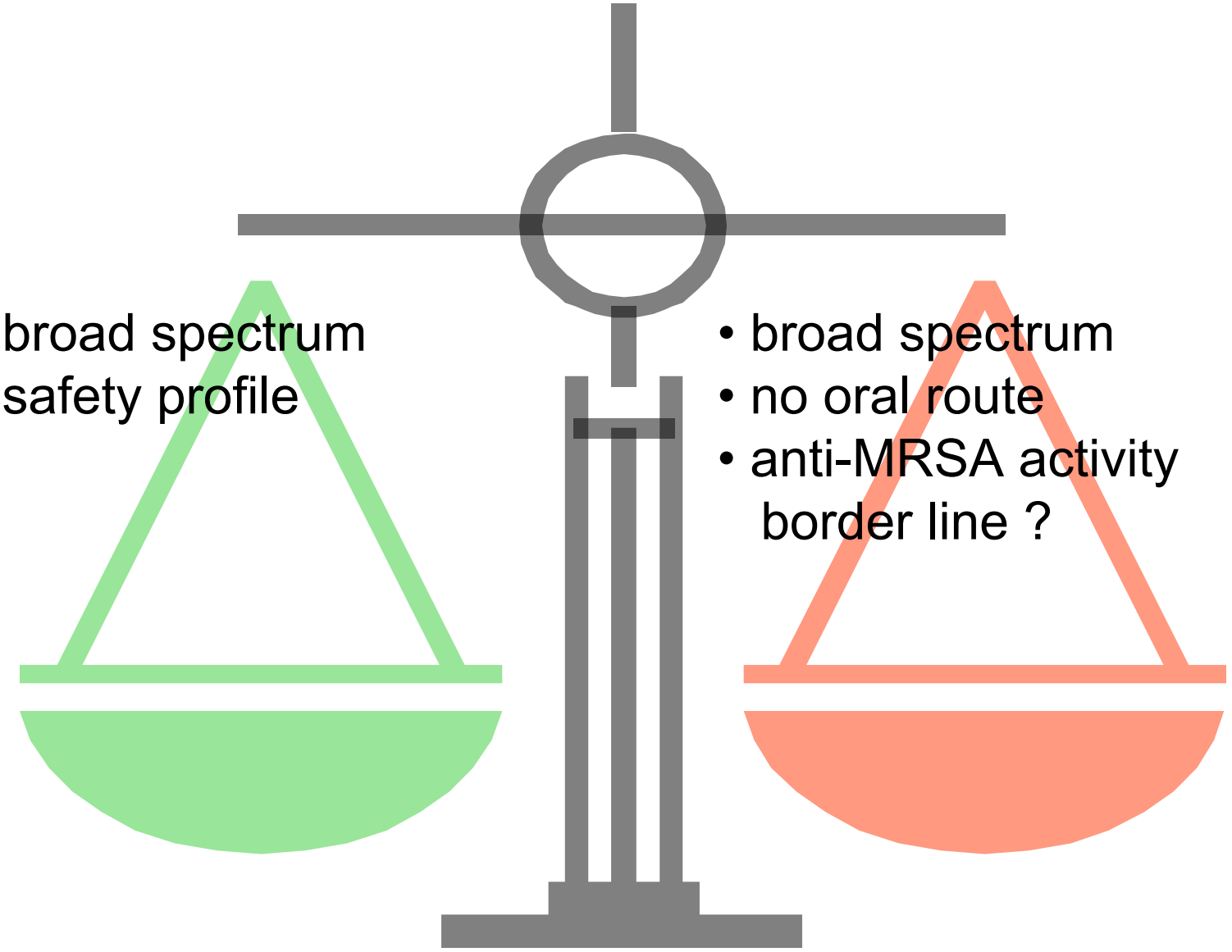
treatment of adults
- with community acquired pneumonia
- complicated skin and soft tissue infection

FDA approved indications (2010):

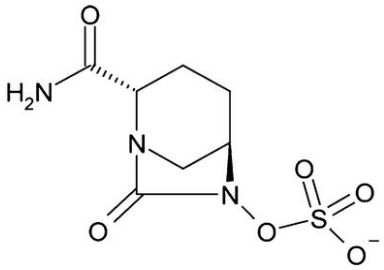
•community-acquired bacterial pneumonia (CABP) caused by susceptible isolates of the following Gram-positive and Gram-negative microorganisms: *Streptococcus pneumoniae* (including cases with concurrent bacteremia), *Staphylococcus aureus* (methicillin-susceptible isolates only), *Haemophilus influenzae*, *Klebsiella pneumoniae*, *Klebsiella oxytoca*, and *Escherichia coli.*

• acute bacterial skin and skin structure infections (ABSSSI) caused by susceptible isolates of the following Gram-positive and Gram-negative microorganisms: *Staphylococcus aureus* (including methicillin-susceptible and -resistant isolates), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Escherichia coli*, *Klebsiella pneumoniae*, and *Klebsiella oxytococa*

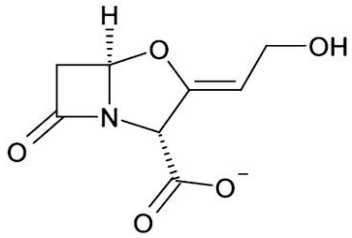
Ceftaroline : pros and cons



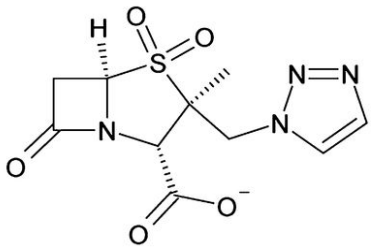
AVIBACTAM



Avibactam



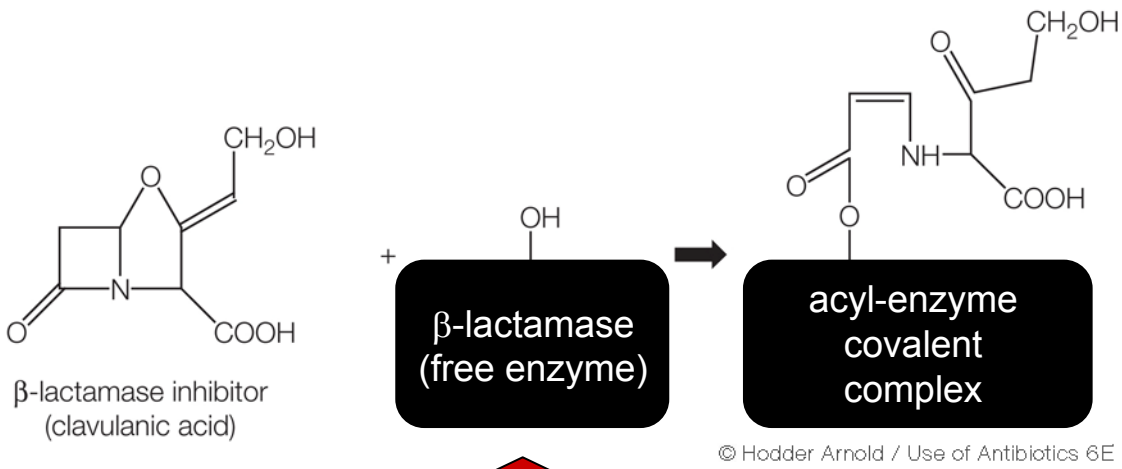
Clavulanic acid

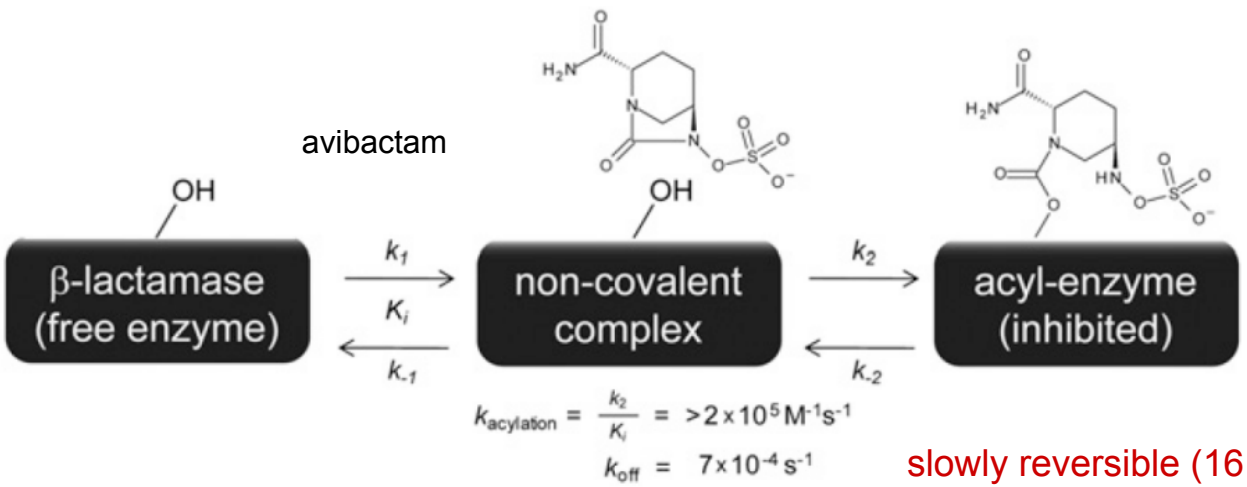


Tazobactam

Amber class	Active site	avibactam	clav. acid	tazobactam
A (TEM, KPC, CTX-M)	Serine			
B (VIM, NDM)	Zn^{2+}			
C (AmpC)	Serine			
D (OXA)	Serine	OXA-48		
		OXA-10, 23, 40, 53		

Mechanism of action of avibactam

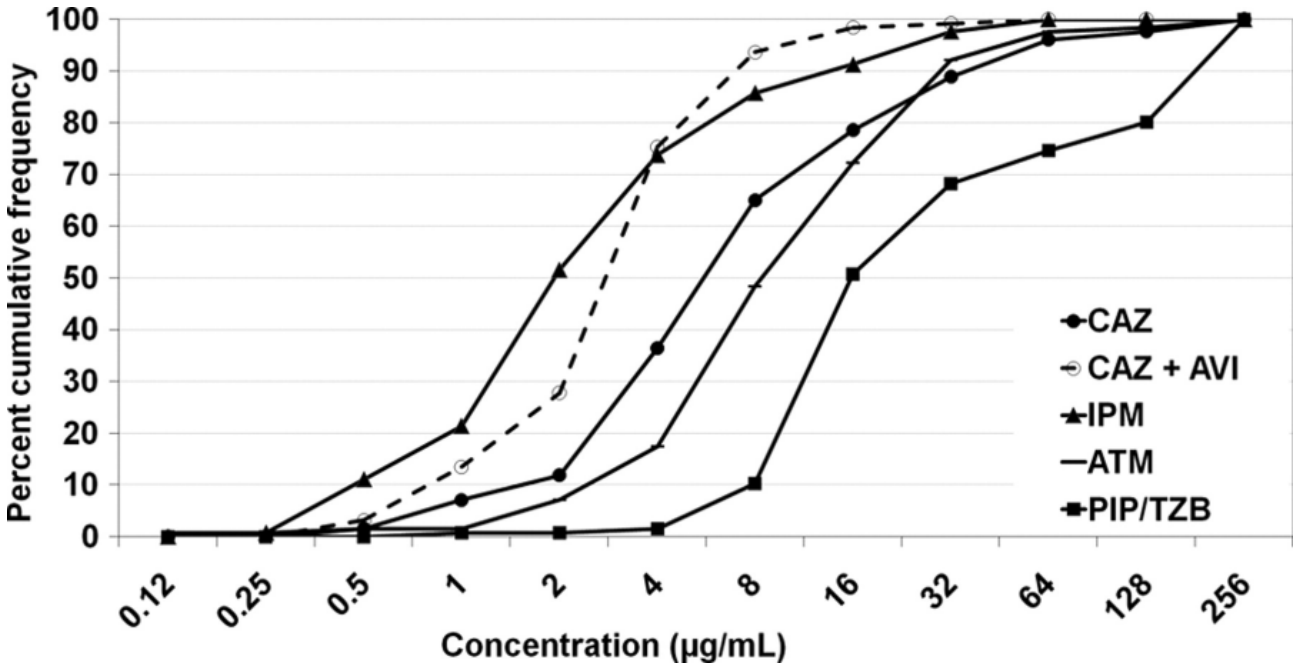




slowly reversible (16 min)

Ehmann et al, PNAS (2012) 109:11663–8

In vitro activity : avibactam/ceftazidime



MIc distribution ~ carbapenems

Levasseur et al, AAC (2012) 56:1606-8

In vitro activity : avibactam/cephalosoprins

TABLE 2. MIC_{50}, MIC_{90}, MIC_{90} reduction, range, and percentage of isolates susceptible to various β-lactam drugs in combination with NXL104

Strain (no. of isolates)	Antibiotic(s)[a]	MIC_{50} (μg/ml)	MIC_{90} (μg/ml)	MIC_{90} reduction (fold)[b]	Minimum (μg/ml)	Maximum (μg/ml)	%S[c]
ESBL-producing *E. coli* (161)	NXL	8	8		4	128	NA
	FEP	8	64		0.06	>64	67.7
	FEP-NXL	0.03	0.06	1,024	≤0.015	0.25	100
	CAZ	16	64		0.5	>64	65
	CAZ-NXL	0.12	0.25	256	≤0.004	2	100
	CRO	64	>64		0.5	>64	1.2
	CRO-NXL	0.03	0.06	>1,024	≤0.015	0.5	100
	MEC	1	2		0.06	32	97.5
	MEC-NXL	0.06	0.12	16	≤0.008	4	100
	MEM	0.03	0.06		0.015	0.12	100
	MEM-NXL	≤0.001	0.008	4	0.015	0.06	100
AmpC-hyperproducing *E. coli* (94)	NXL	8	16		4	1,024	NA
	FEP	0.25	0.5		0.03	4	100
	FEP-NXL	0.03	0.12	4	≤0.015	0.25	100
	CAZ	16	64		1	>64	35.1
	CAZ-NXL	0.12	0.5	128	0.004	2	100
	CRO	16	32		0.06	>64	28.7
	CRO-NXL	0.06	0.12	256	<0.015	1	100
	MEC	0.5	2		0.12	>32	93.6
	MEC-NXL	0.06	0.25	8	0.12	>32	97.9
	MEM	0.03	0.06		0.015	0.25	100
	MEM-NXL	0.008	0.015	4	≤0.001	0.12	100

Lagacé-Wiens et al, AAC (2011) 55: 2434–37

In vitro activity : avibactam/aztreonam

species		Beta-lactamases produced	MIC aztreonam	
			- AVI	+ AVI
Enterobacteriaceae				
E. coli	EC395	AmpC, OXA-2,CTX-M-15, CMY-4, NDM-1, OXA-1, TEM-1	> 256	4
	EC394	AmpC, NDM-1, CTX-M-15, TEM-1, OXA-2, CMY-6	> 256	8
Klebsiella	KP427	NDM-1, TEM-1, CTX-M-15, SHV-2a, DHA-1	128	0.125
	KP449	NDM-type, TEM-1, OXA-1, CTX-M-15	256	0.5
P. aeruginosa	PSA1472	VIM-type	16	16
	PSA1474	IMP-type	16	16

Crandon et al, AAC (2013) PMID: 23650162

In vitro activity : avibactam/ceftaroline

species		ceftaroline		ceftaroline/ avibactam		ceftazidime	
		MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}
Enterobacteriaceae		0.12	32	0.06	0.25	0.12	8
E. coli	total	0.12	16	≤0.03	0.06	0.12	2
	ESBL	> 32	> 32	0.06	0.12	16	>32
Klebsiella	total	0.12	> 32	0.06	0.12	0.12	8
	ESBL	> 32	> 32	0.06	0.12	32	> 32
E. cloacae	total	0.25	> 32	0.12	0.25	0.25	> 32
	cefta R	> 32	> 32	0.25	1	> 32	> 32
P. aeruginosa		16	> 32	4	16	2	> 32

Sader et al, AAC (2013) 57: 1982–88

Avibactam: data from clinical studies

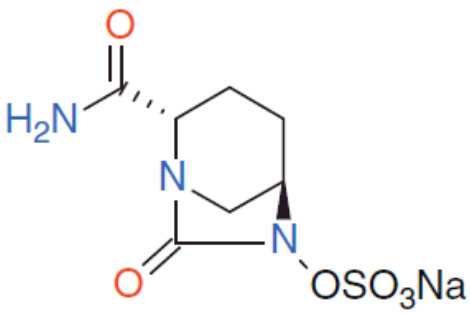
Clinical trials of ceftazidime/avibactam

Trial (clinicaltrials.gov ID)	Number of patients (clinically evaluable)	Dosage regimen (number treated)	Microbiological response	Clinical response
Phase II treatment of complicated intra-abdominal infection in hospitalized adults (NCT00752219)	203 (144)	Ceftazidime-avibactam + metronidazole: 2,000/500 mg + 500 mg, IV, q8 h (101)	Ceftazidime-avibactam: 91.2 % eradication	Ceftazidime-avibactam: 91.2 % favourable outcome
		Standard therapy: meropenem 1,000 mg + placebo, IV, q8 h (102)	Meropenem: 93.4 % eradication	Meropenem: 93.4 % favourable outcome
Phase II treatment of complicated urinary tract infection in hospitalized adults (NCT00690378)	137 (64)	Ceftazidime-avibactam: 500/125 mg, IV, q8 h (68)	Ceftazidime-avibactam: 70.4 % eradication	Ceftazidime-avibactam: 85.7 % favourable outcome
		Standard therapy: imipenem/cilastatin 500 mg, IV, q6 h (67)	Imipenem: 71.4 % eradication	Imipenem: 80.6 % favourable outcome

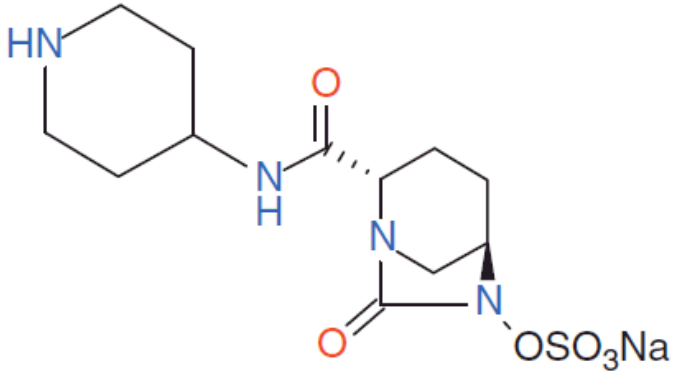
IV intravenous, *qxh* every x hours

Zhanel et al, Drugs (2013) 73:159-77

MK7655



Avibactam



MK-7655

Inhibition profile of marketed β-lactamase inhibitors and diazabicyclooctanes (IC50 in μM)

Enzyme	Class	Source	Clavulanic acid	Tazobactam	Avibactam	MK-7655
TEM-1	A	*E. coli*	0.026	0.012	0.008	0.031
KPC-2	A	*K. pneumoniae*	5.1	43	0.170	0.208
KPC-3	A	*K. pneumoniae*	5.4	27	NR	0.197
SHV-1	A	*K. pneumoniae*	0.012	0.067	NR	0.029
SHV-4	A	*K. pneumoniae*	0.004	0.055	0.003	NR
SHV-5	A	*K. pneumoniae*	0.0012	0.007	NR	0.361
IMP-1	B	*P. aeruginosa*	>20	>200	NR	>50
AmpC	C	*A. baumannii*	>500	18	NR	4.063
AmpC	C	*P. aeruginosa*	>500	1.491	0.128	0.465
P99	C	*E. cloacae*	>250	12	0.100	0.134
OXA*	D	*A. baumannii*	28	58	NR	>50

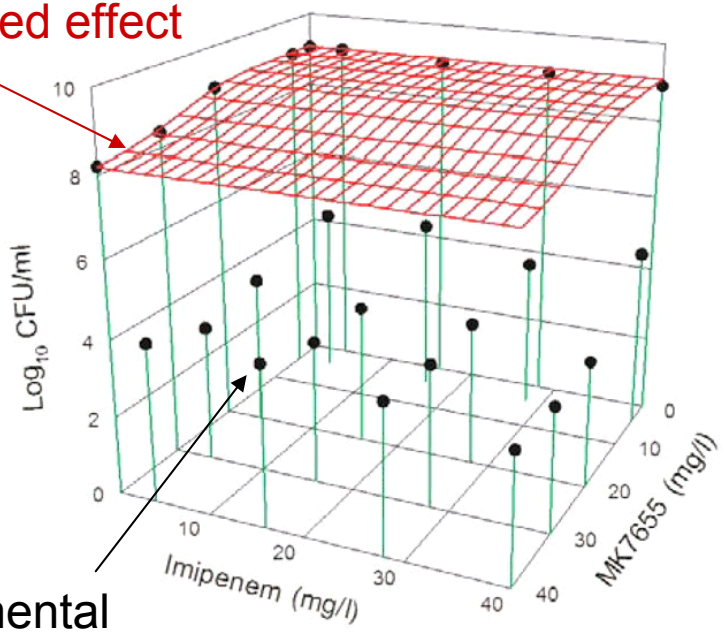
Coleman, Curr Op Microbiol (2011) 14:550–55

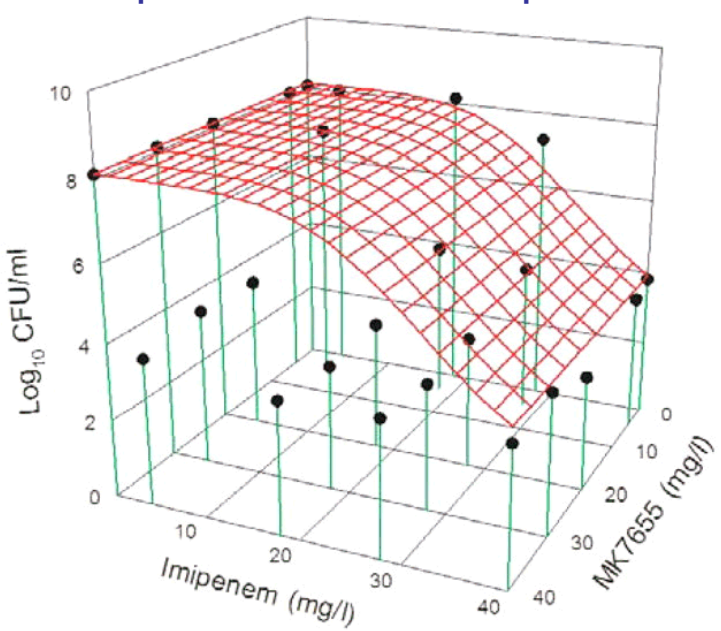
MK7655/imipenem combination

KPC-2

OrpD mutation + AmpC

calculated effect





experimental effect

KP6339

PA24226

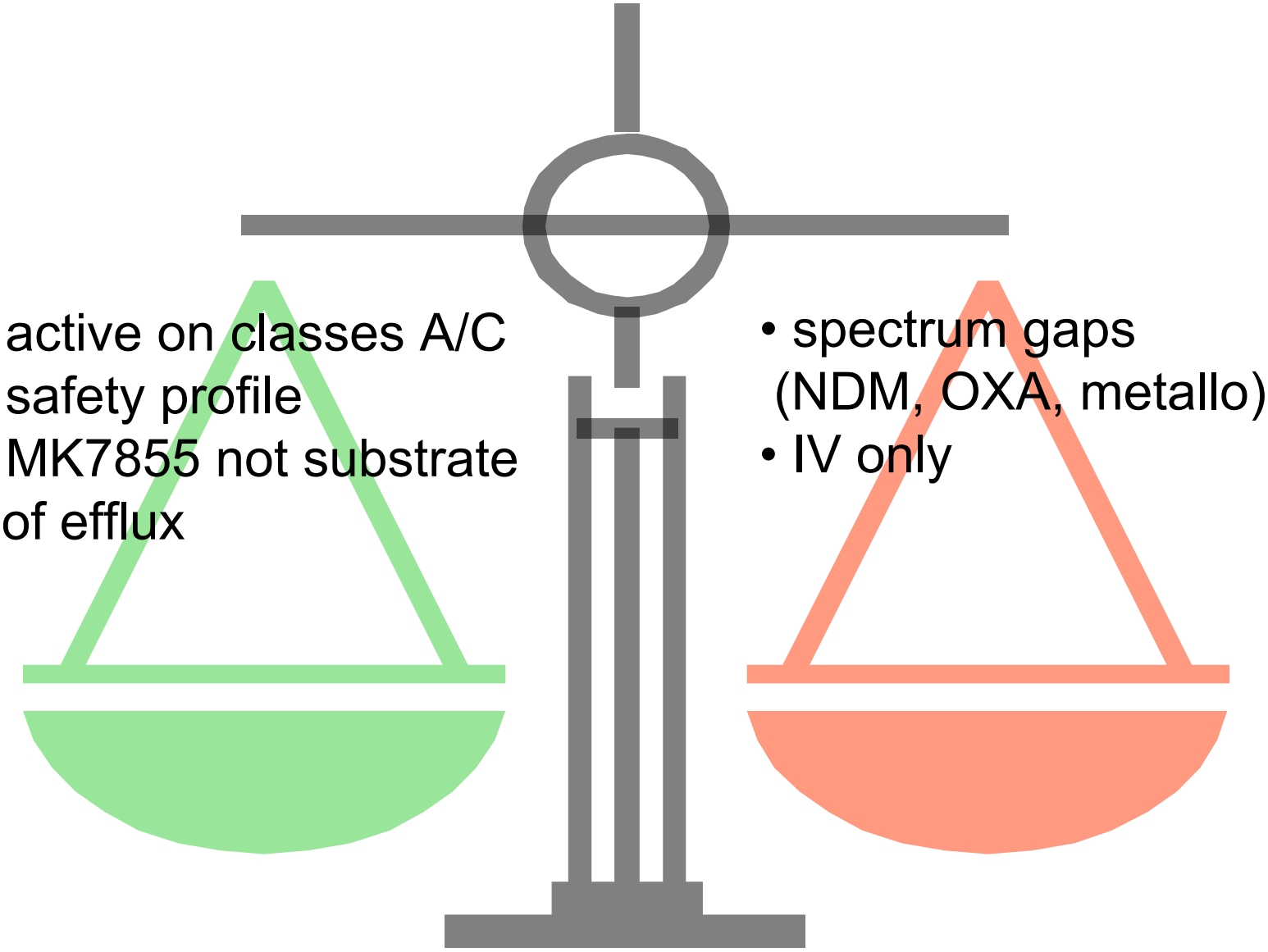
TABLE 1 Susceptibility testing results and assessment of combined killing activity of imipenem (IPM) plus MK-7655 (MK)[a]

Isolate	MIC (mg/liter) IPM	IPM with MK (4 mg/liter)	Interactive index (95% CI)
KP6339	128	2	0.50 (0.42–0.58)
PA24226	32	2	0.60 (0.58–0.62)

[a] In all cases, the interaction of IPM with MK was interpreted as synergistic.

Hirsh et al, AAC (2012) 56, 3753-7

Avibactam/MK7855 combinations : pros and cons



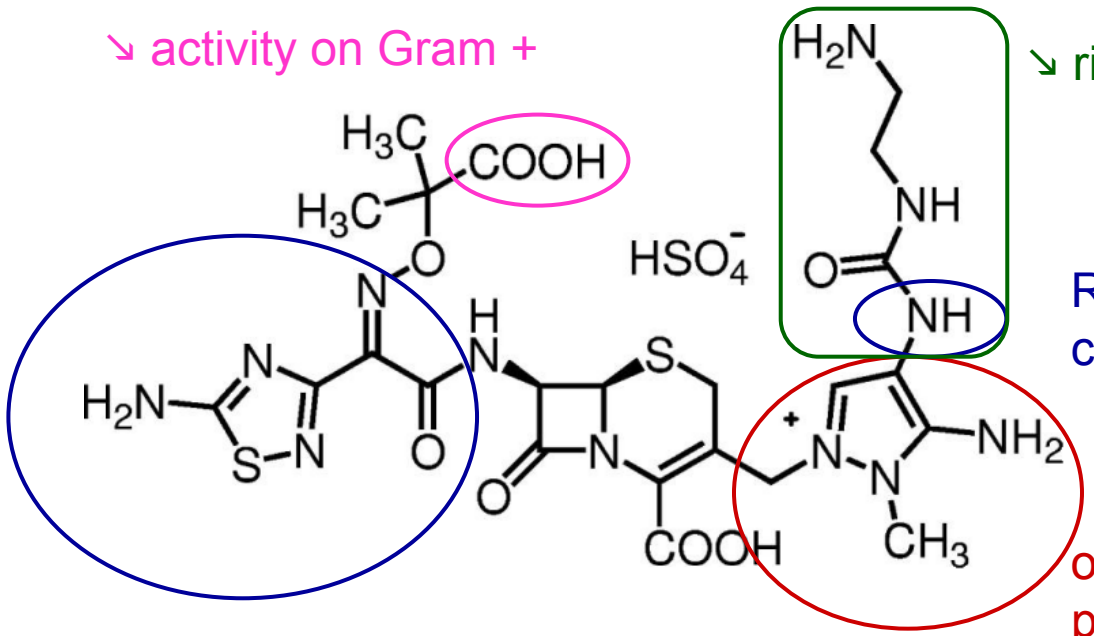
- active on classes A/C
- safety profile
- MK7855 not substrate of efflux

- spectrum gaps (NDM, OXA, metallo)
- IV only

CEFTOLOZANE

↘ activity on Gram +

↘ risk of convulsion



Resistance to β-lactamases

Resistance to class C β-lactamase

outer membrane permeability

- stable to AmpC β-lactamase
- associated with tazobactam to cover class A ESBL

Toda et al, Bioorg. Med. Chem. Lett. (2008) 18:4849–4852
Takeda et al, IJAA (2007) 30: 443–5

In vitro activity on *P. aeruginosa*

Activity of ceftolozane (CXA-101) and comparable antibiotics against *Pseudomonas aeruginosa* isolates expressing varying mechanisms of β-lactam resistance[2]

	All isolates ($n = 190$)			Isolates hyper-producing AmpC ($n = 45$)			Isolates hyper-producing MexAB ($n = 24$)			Isolates hyper-producing MexXY ($n = 25$)		
Antibiotic	%S	MIC_{50}	MIC_{90}	%S	MIC_{50}	MIC_{90}	%S	MIC_{50}	MIC_{90}	%S	MIC_{50}	MIC_{90}
CXA-101	98.9	0.5	1	100	1	2	100	1	1	100	1	2
CAZ	76.3	4	32	17.8	32	128	58.7	8	64	68.0	8	32
FEP	61.6	8	32	17.8	32	64	25.0	16	32	16.0	16	32
ATM	67.4	8	32	22.2	16	64	33.3	16	32	40.0	16	16
PIP	80.5	8	128	28.9	128	128	79.2	32	128	68.0	16	128
PIP/Tz	86.3	8	128	44.4	128	256	79.2	16	256	80.0	16	128
IMP	67.9	2	32	37.8	16	32	41.7	8	32	32.0	16	32
MER	77.4	1	16	44.4	8	16	41.7	8	32	44.0	8	16
CIP	71.6	0.25	32	40.0	32	32	45.8	2	32	24.0	32	32
LEV	68.4	1	32	35.6	32	32	33.3	8	32	16.0	32	32
GEN	78.9	2	64	46.7	32	64	66.7	2	64	40.0	32	64
TOB	81.6	0.5	64	51.1	4	64	66.7	1	64	48.0	8	64
AMK	98.4	4	8	100	4	8	100	4	8	100	4	16
COL	96.8	0.5	1	93.3	0.5	1	95.8	0.5	1	100	0.5	1

Shlaes, NYAS (2013) 1277:105-14

In vitro activity on *P. aeruginosa*

MIC profile of CXA-101 and comparators[a]

Isolates	Antimicrobial agent	MIC (μg/ml)			
		Range	Modal	MIC_{50}	MIC_{90}
All isolates	CXA-101	0.5–>64	1	2	2
	CXA-101/T	0.5–>64	1	1	8
	IMP	0.25–128	16	8	32
	MER	0.064–128	16	8	32
	TZP	0.5–256	256	64	256
	FEM	1–256	16	16	64
	TAZ	2–256	16	16	128
	CIP	0.032–128	32	4	64
	LEV	0.064–128	64	8	64
	TOB	0.125–256	1	2	128
MDR isolates	CXA-101	0.5–>64	2	2	>64
	CXA-101/T	0.5–>64	1	2	>64
	IMP	0.5–128	16	16	128
	MER	0.125–128	16	16	128
	TZP	2–256	256	256	256
	FEM	8–256	16	16	64
	TAZ	4–256	64	64	256
	CIP	1–128	32	32	64
	LEV	1–128	64	32	128
	TOB	8–256	128	128	256

Bulik, AAC (2010) 54: 557–9

Ceftolozane: pharmacokinetics

Mean PK values for ceftolozane alone and in combination with tazobactam after single (day 1) and multiple doses

	Mean (% CV) PK value at[a]:					
	1,000 mg (C) ($n = 5$)		1,000/500 mg (C/T, q8h) ($n = 10$)		1,500 mg (C, q12h) ($n = 5$)	
Parameter	Day 1	Day 10	Day 1[b]	Day 10	Day 1	Day 10
C_{max} (μg/ml)	68.8 (17.0)	73.4 (15.2)	69.1 (11.3)	74.4 (13.6)	110 (11.2)	110 (13.1)
t_{max} (h)[c]	1.03 (1.02–1.09)	1.00 (1.00–1.04)	1.02 (1.01–1.1)	1.07 (1.0–1.1)	1.01 (1.0–1.09)	1.01 (1.0–1.03)
$AUC_{0\text{-last}}$ (μg·h/ml)	168 (17.0)	195 (15.2)	172 (13.8)	197 (16.6)	259 (12.7)	266 (20.3)
$t_{1/2}$ (h)	2.30 (17.1)	2.73 (24.2)	2.77 (30.0)	3.12 (21.9)	2.52 (9.4)	2.48 (29.5)
CL (liters/h)	6.01 (14.0)	5.54 (13.3)	5.86 (13.7)	5.58 (12.6)	5.85 (11.5)	5.88 (17.4)
CL_R (liters/h)	6.42 (3.1)[d]	5.28 (17.4)[d]	5.58 (24.0)[e]	6.80 (49.4)	5.89 (16.8)[f]	4.55 (35.8)
V_{ss} (liters)	14.1 (18.1)	13.4 (18.1)	14.6 (16.0)	14.2 (16.6)	12.9 (11.4)	13.0 (9.3)
AI	NA	1.15 (2.0)	NA	1.14 (5.7)	NA	1.02 (7.6)

Dose used for cIAI : 1g q8h

Dose used for HAP : 3g q8h

Miller et al, AAC (2012) 56: 3086-91

Ceftolozane: pharmacokinetics

plasma

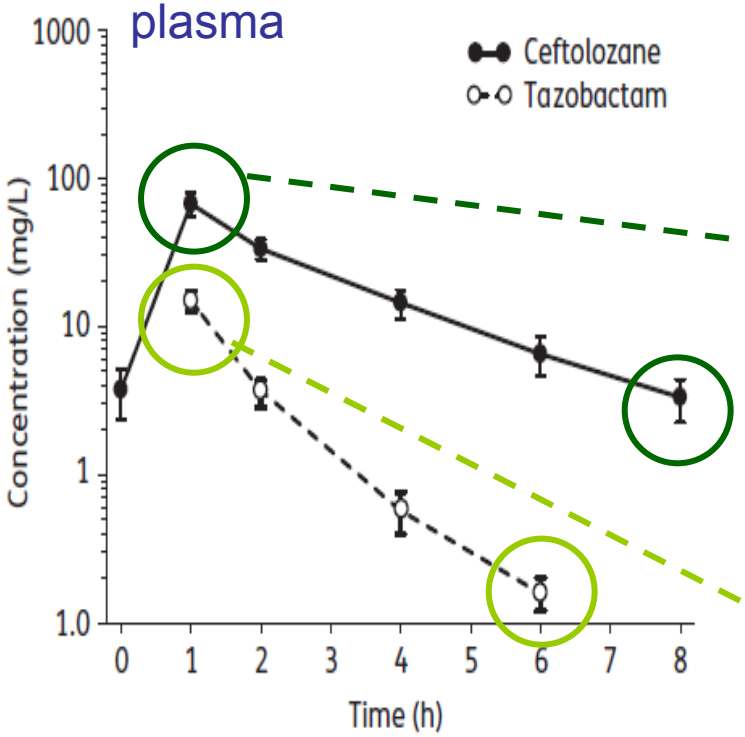


Figure 1. Mean (±SD) plasma concentration-versus-time profiles of 1000 mg ceftolozane and 500 mg tazobactam dosage regimens following the third antibiotic dose.

ELF

peak 2 x lower

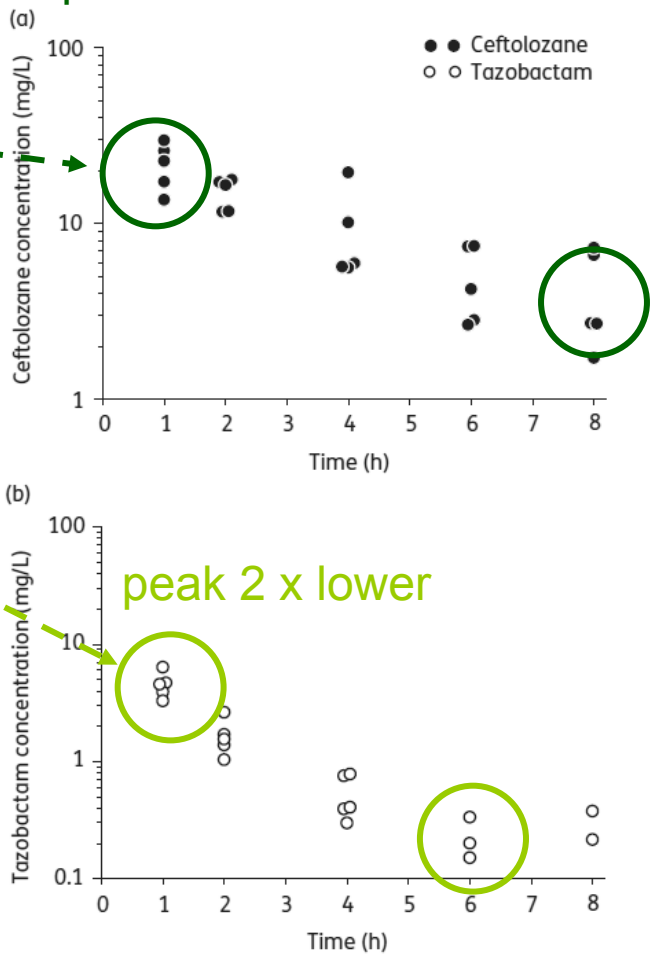
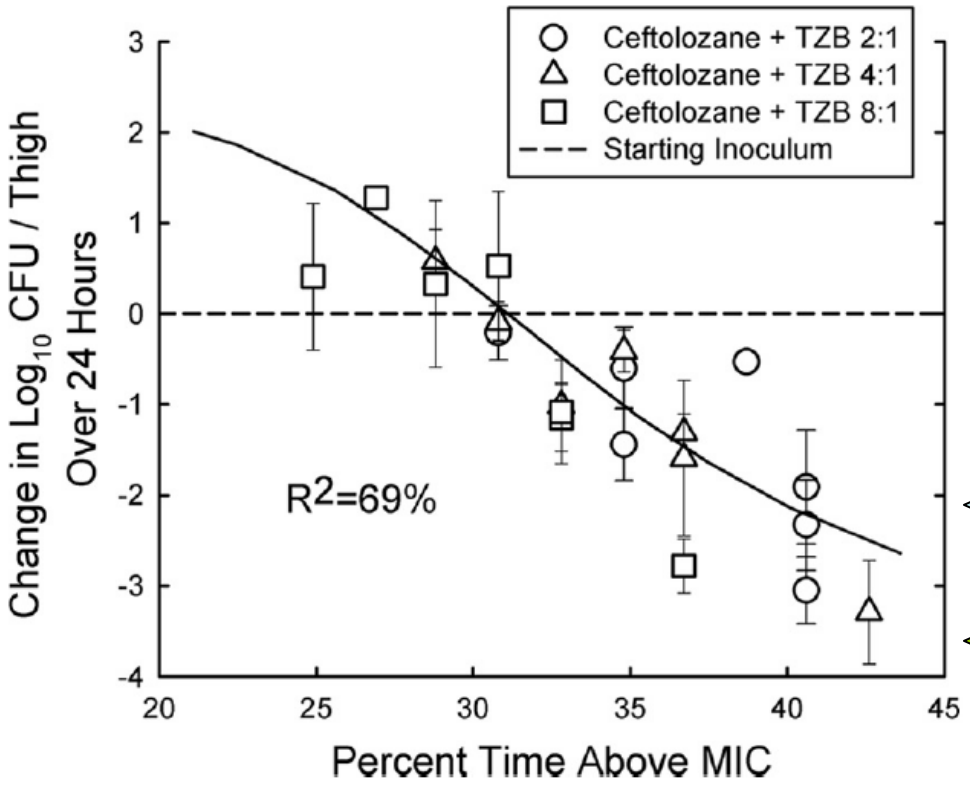


Figure 3. Individual concentrations of ceftolozane (a) and tazobactam (b) in ELF at 1, 2, 4, 6 and 8 h after the start of the last antibiotic infusion.

Chandorkar et al, JAC (2012) 67:2463-9

Ceftolozane: pharmadynamics

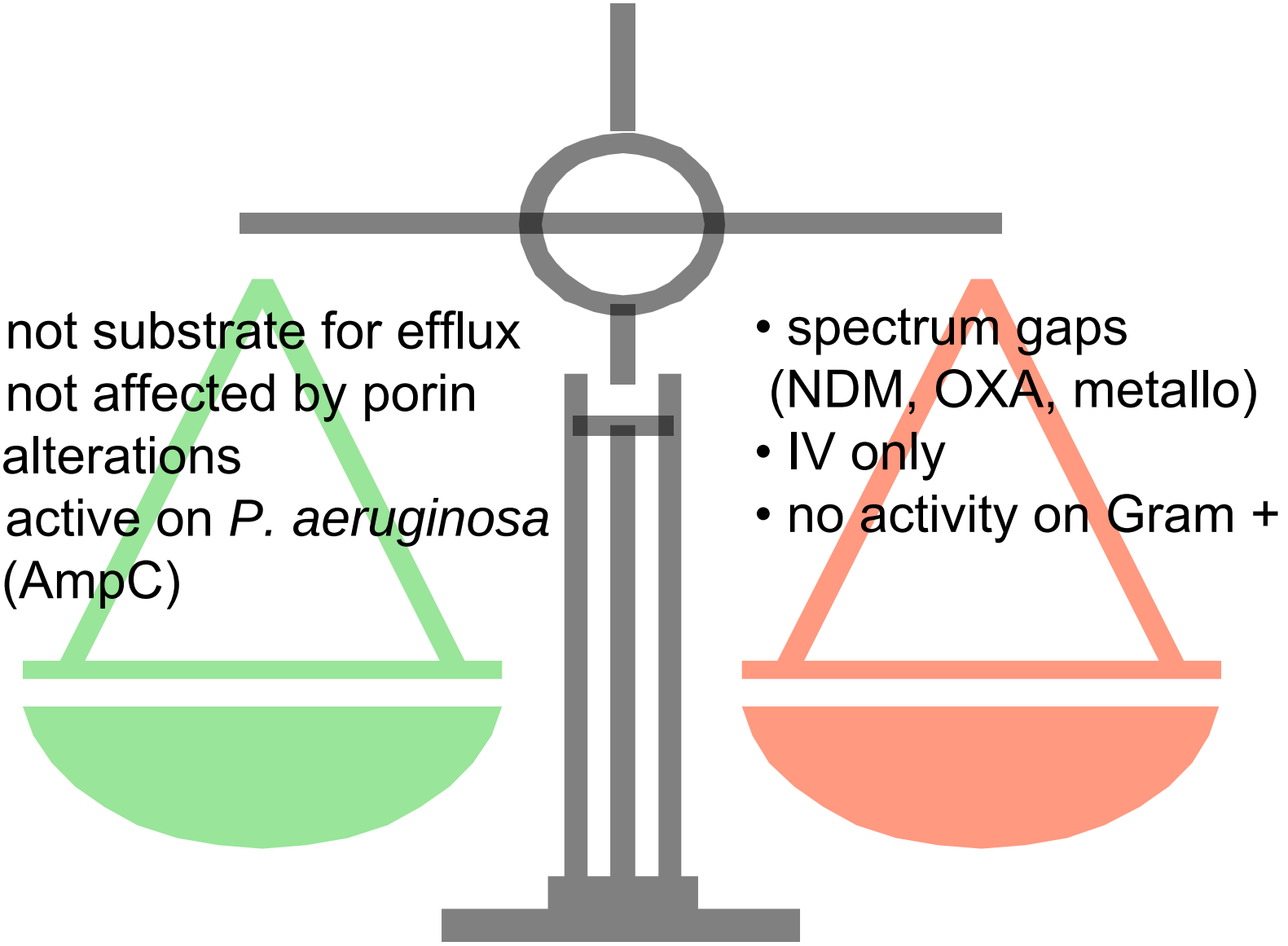


MIC < ~ 20 mg/L for 1 g

MIC < ~ 25 mg/L for 3 g in BAL

Craig & Andes, AAC (2012) 57: 1577-82

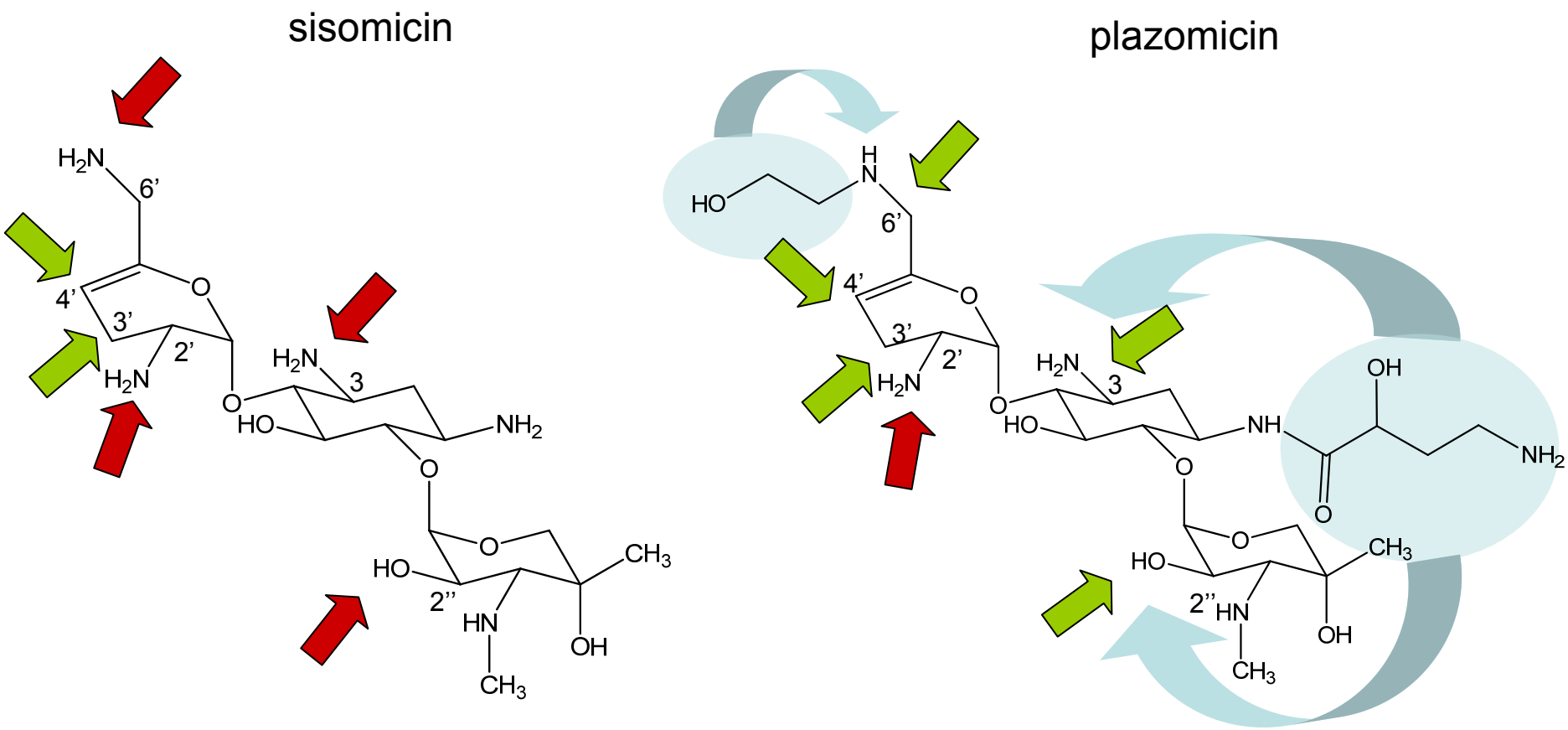
Ceftolozane : pros and cons



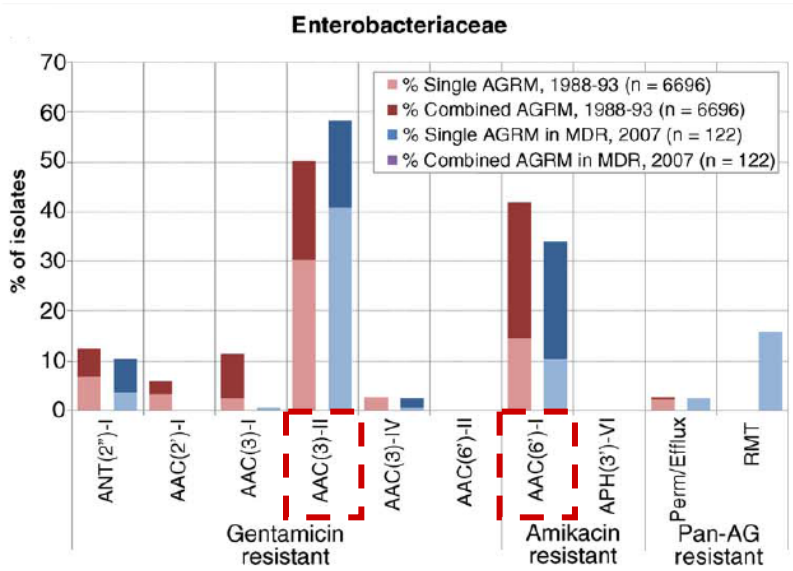
- not substrate for efflux
- not affected by porin alterations
- active on *P. aeruginosa* (AmpC)

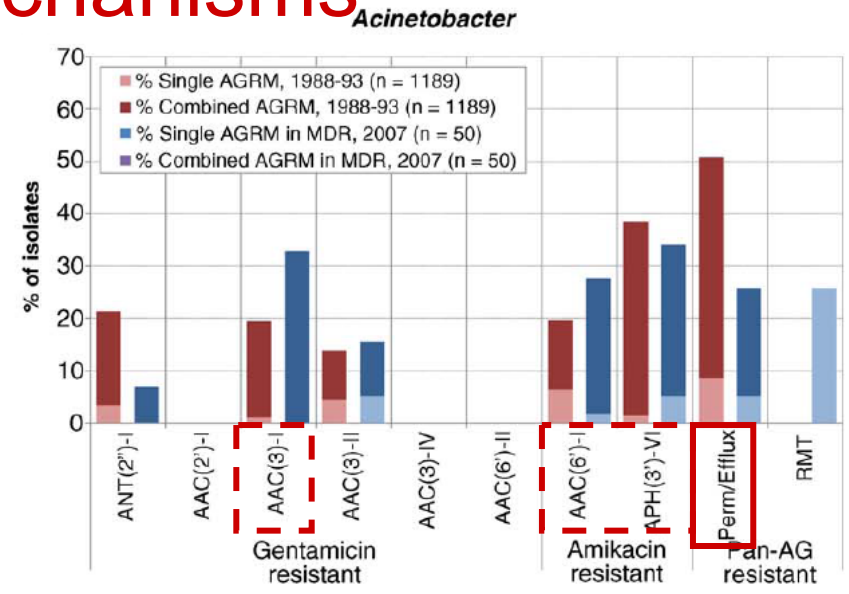
- spectrum gaps (NDM, OXA, metallo)
- IV only
- no activity on Gram +

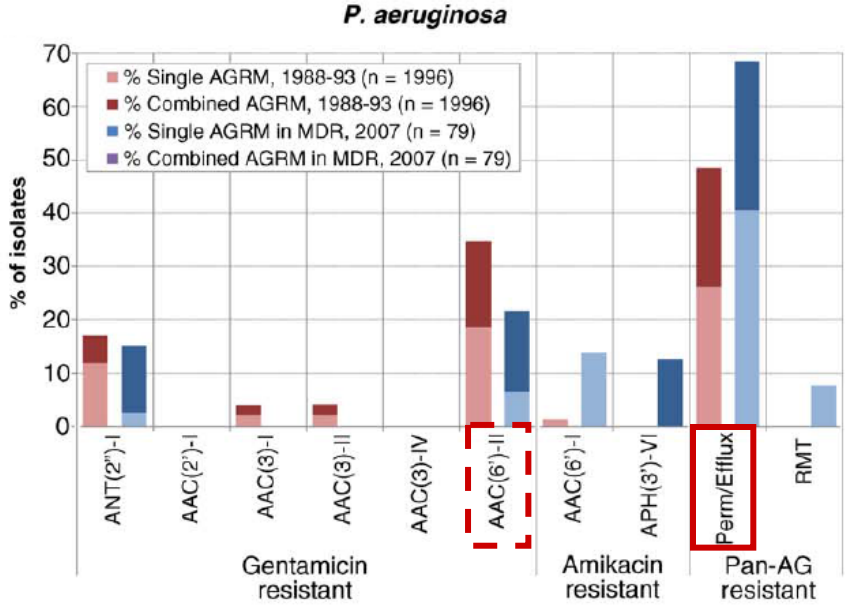
PLAZOMICIN


sisomicin
plazomicin
position susceptible to AME
position resistant to AME

Aminoglycoside resistance: frequent mechanisms

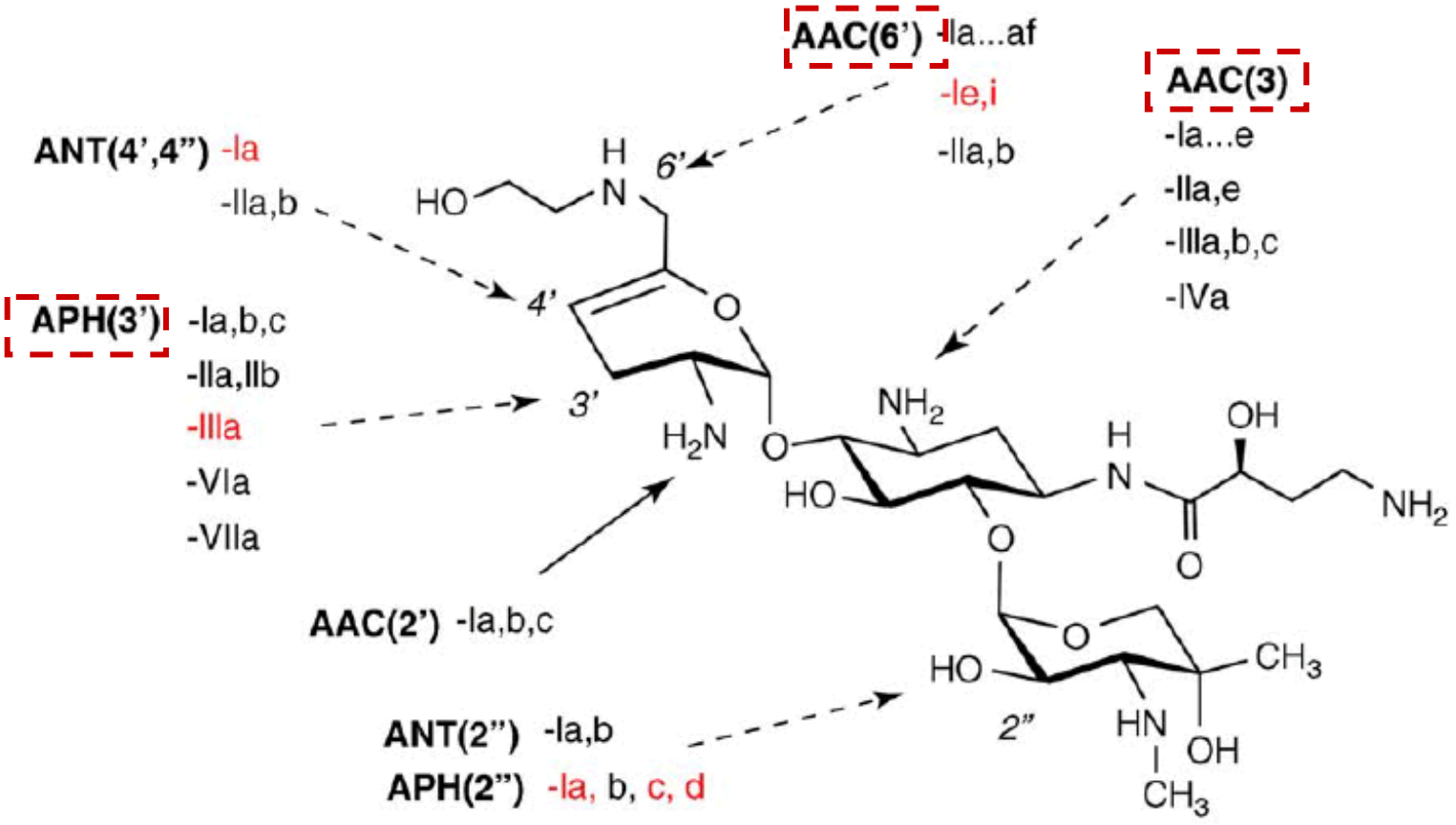






Armstrong & Miller, Curr Op Microbiol (2010) 13:565-73

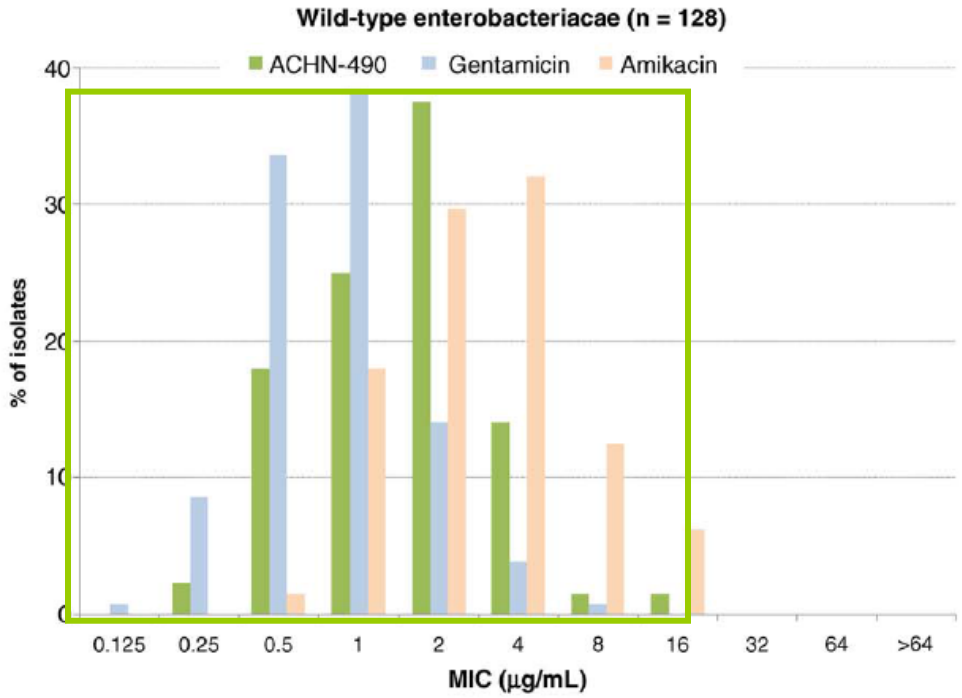
Plazomicin: how does it behave ?



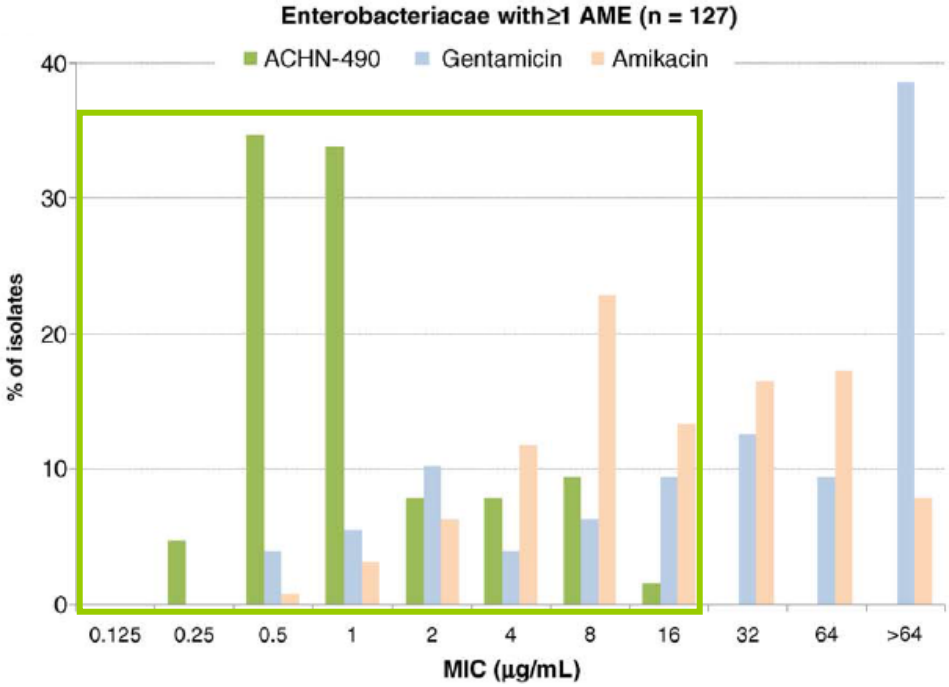
Plazomicin is not a substrate anymore !

Armstrong & Miller, Curr Op Microbiol (2010) 13:565-73

In vitro activity: enterobacteriaceae

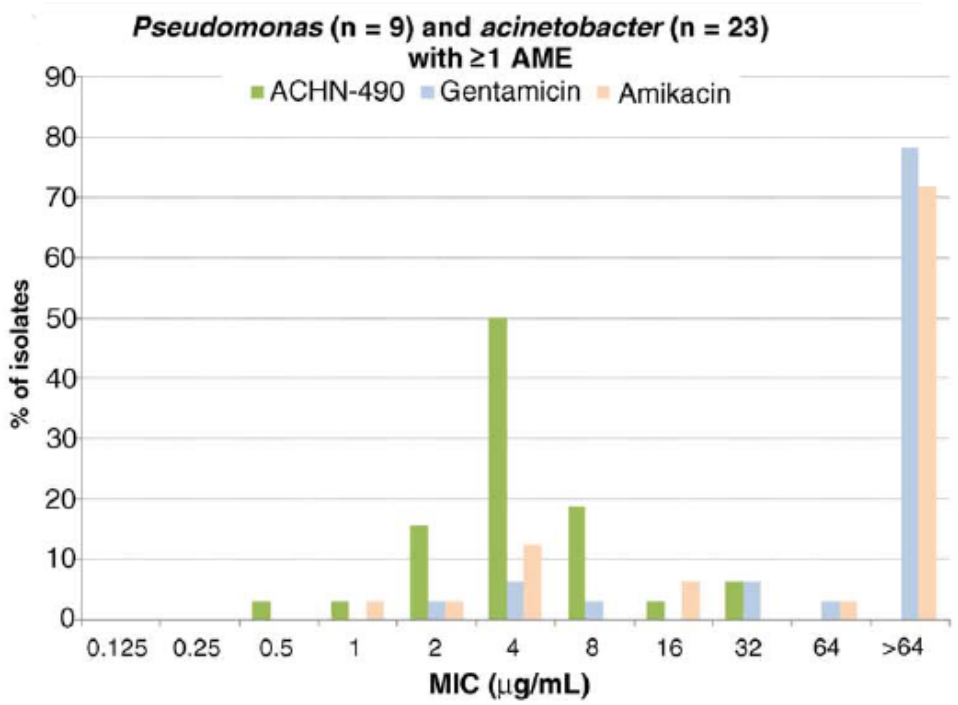


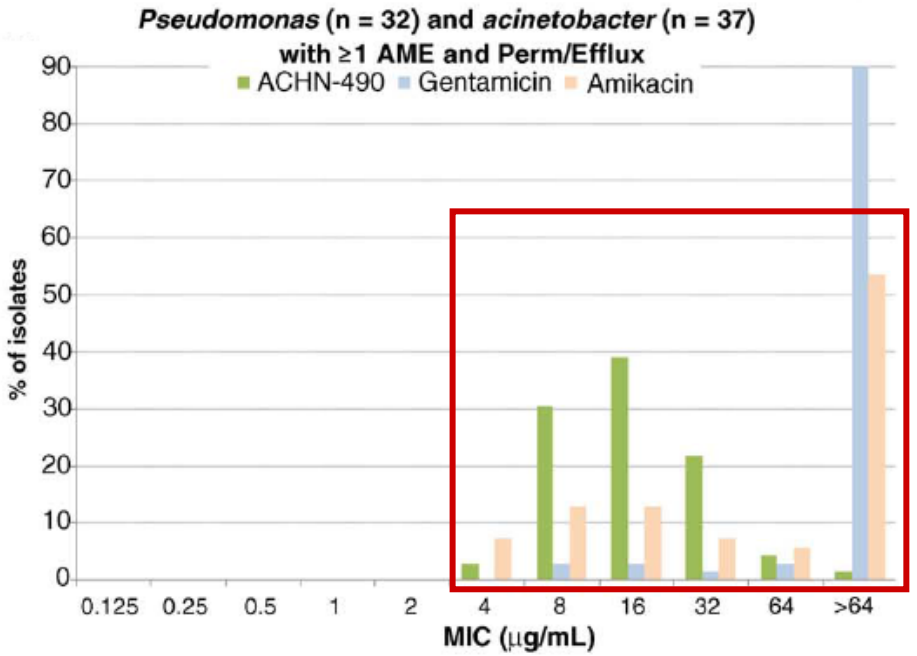
Same MIC distribution for strains producing or not AME



Armstrong & Miller, Curr Op Microbiol (2010) 13:565-73

In vitro activity: Pseudomonas/Acinetobacter





Efflux / (Arm) remain unsolved …

Armstrong & Miller, Curr Op Microbiol (2010) 13:565-73

Plazomicin pharmacokinetics

Mean (SD) Plasma Plazomicin Plasma and ELF Parameters in Healthy Subjects following a Single 15 mg/kg 10-Minute IV Infusion, and Calculated Percent Penetration into ELF

	C_{max} (µg/mL)	C_{10hr} (µg/mL)	T_{max} (hr)	$AUC_{0\text{-}inf}$ (hr*µg/mL)	$AUC_{0\text{-}10hr}$ (hr*µg/mL)	$T_{1/2}$ (hr)
Plasma	161 (31)	5.3 (2.5)	0.21 (0.1)	309 (45)	286 (32)	2.8 (0.6)
ELF*	5.9	1.7 (1.2)	2	39.5	28.8	4.3
% penetration**	3.7	32	NA	12.8	10.1	NA

* ELF PK Parameters derived from composite mean ELF concentration-time profile with 2-3 subjects per scheduled time point.

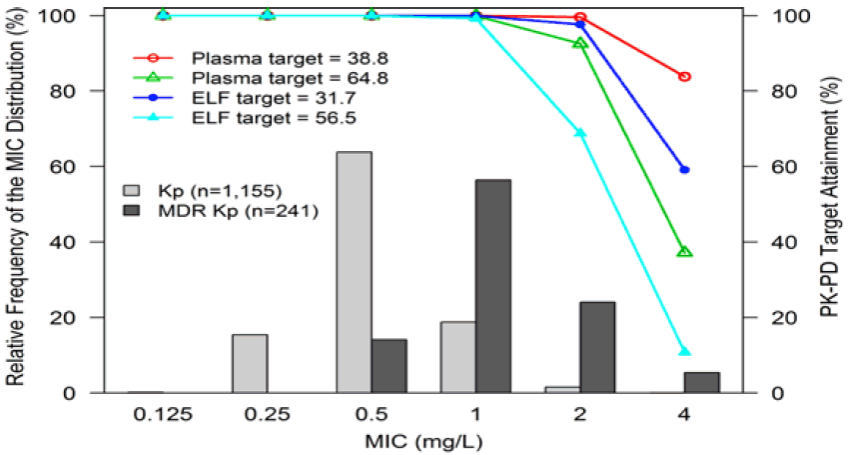
** ELF/Plasma PK Parameter Ratio was calculated as the ELF PK Parameter / Mean Plasma PK Parameter

ELF = epithelial lining fluid, NA = not applicable

Cass et al, ECCMID 2013, P-1637

Plazomicin pharmacodynamics

%PTA by MIC among simulated patients with normal renal function based on plasma and ELF AUC_{0-24}:MIC ratio targets



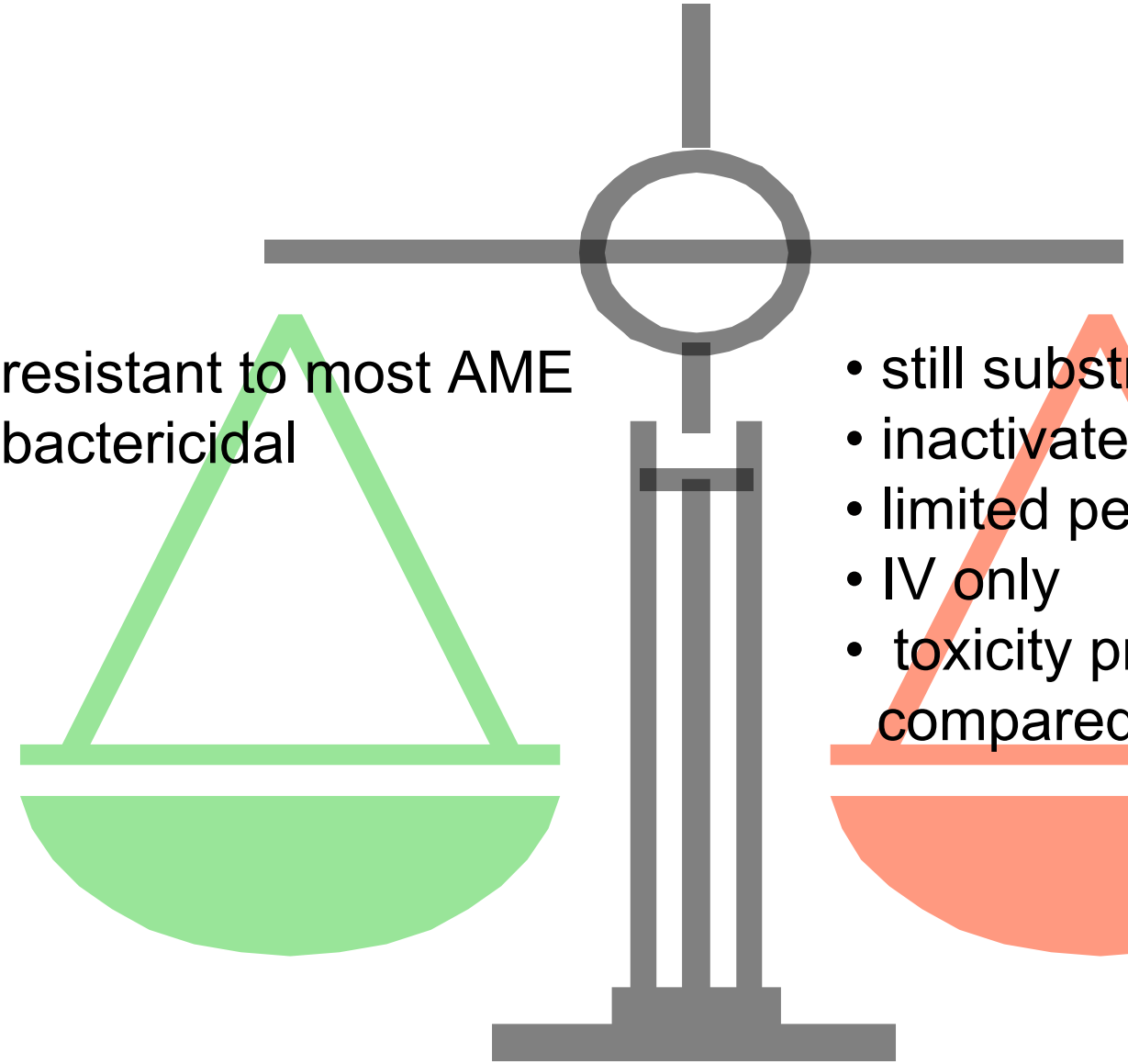
%PTA across renal function groups based on plasma and ELF AUC_{0-24}:MIC ratio targets for MIC=2 mg/L and over a MIC distribution for plazomicin against MDR Kp

Renal function group (CLcr range, in mL/min/1.73 m²)	%PTA based on plasma or ELF AUC_{0-24}:MIC ratio targets associated with a 2-log_{10} CFU reduction from baseline in Kp			
	Plasma AUC_{0-24}:MIC target=39[a]		ELF AUC_{0-24}:MIC target=32[b]	
	MIC=2	Overall[c]	MIC=2	Overall[c]
Normal (90 to 150)	99.6	99.0	97.7	97.2
Mild impairment (60 to <90)	99.9	99.5	99.2	98.1
Moderate impairment (30 to <60)	99.9	99.4	99.4	98.5
Severe impairment (15 to <30)	100	99.6	99.2	98.5

a. %PTA results based on Day 1 plasma AUC_{0-24} values and median plasma AUC:MIC target of 39.
b. %PTA results based on Day 2 ELF AUC_{0-24} values (which assumed ELF to plasma equilibration by this time point) and the median ELF AUC_{0-24}:MIC target of 32.
c. Based on %PTA by MIC results over the MIC distribution for MDR Kp.

Riddle et al & Van Wart et al,ECCMID 2013, P-914 & 918

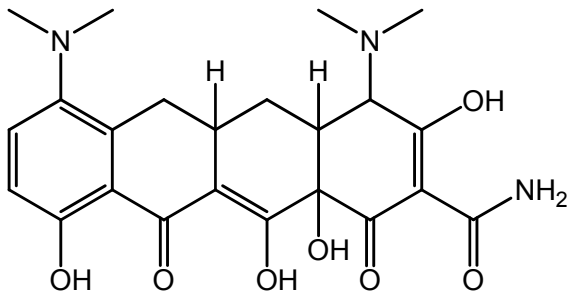
Plazomicin : pros and cons



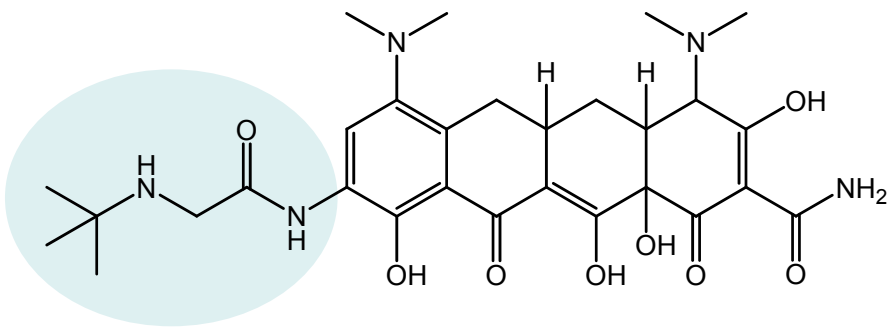
- resistant to most AME
- bactericidal

- still substrate for efflux
- inactivated by methylases
- limited penetration in ELF
- IV only
- toxicity profile to be compared with other AG

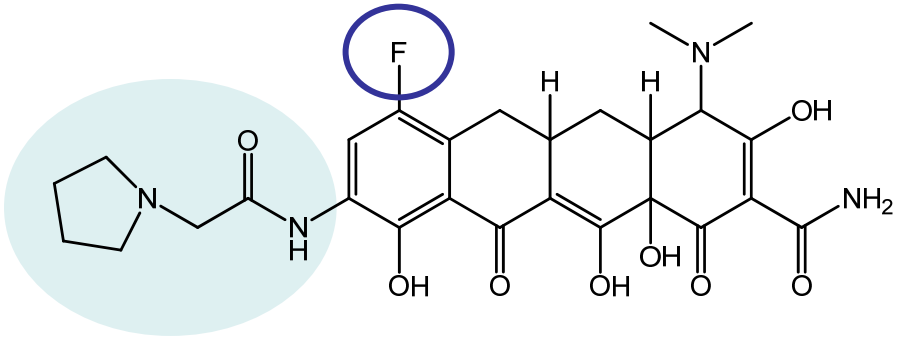
ERAVACYCLINE



minocycline

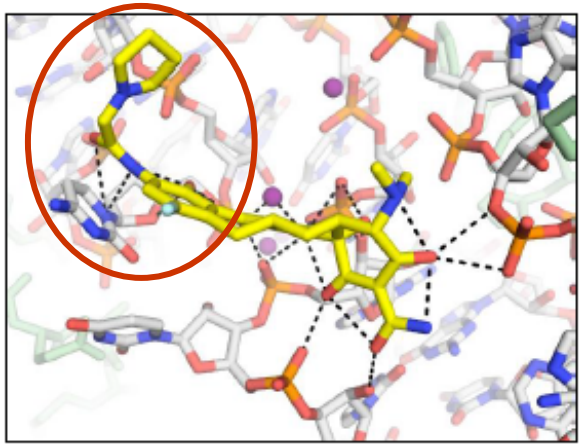


tigecycline

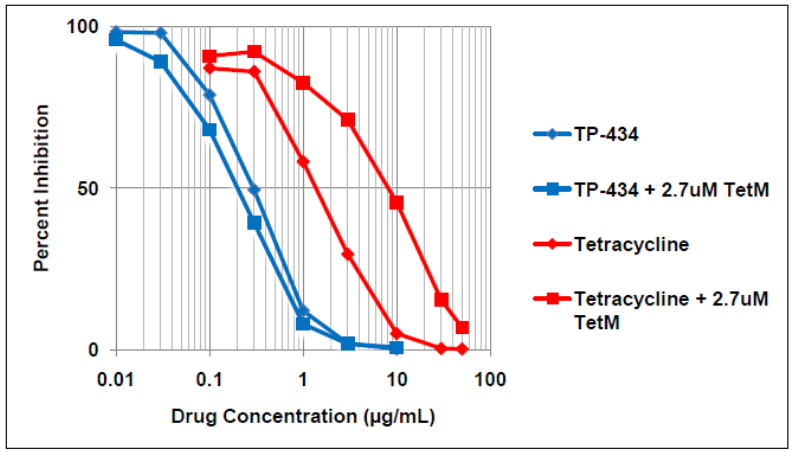


eravacycline

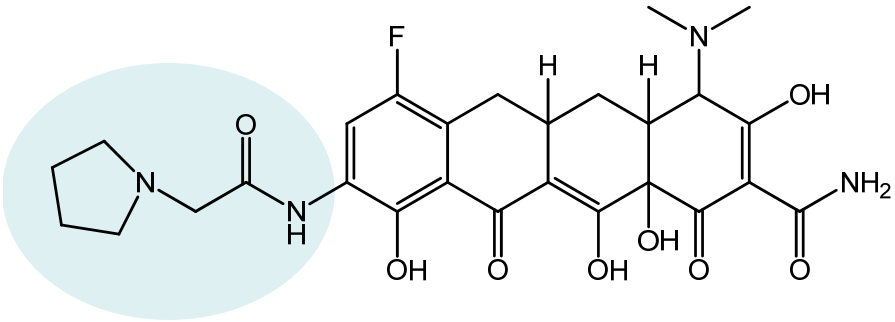
Eravacyline: mode of action



TP-434 Inhibits Protein Synthesis in the Presence of Tet(M)



TETRAPHASE PHARMACEUTICALS



eravacycline

Hunt et al, ICAAC 2010, F1-2157

Eravacyline: in vitro activity

In vitro Activity of TP-434 and Comparators against *ESKAPE* Pathogens

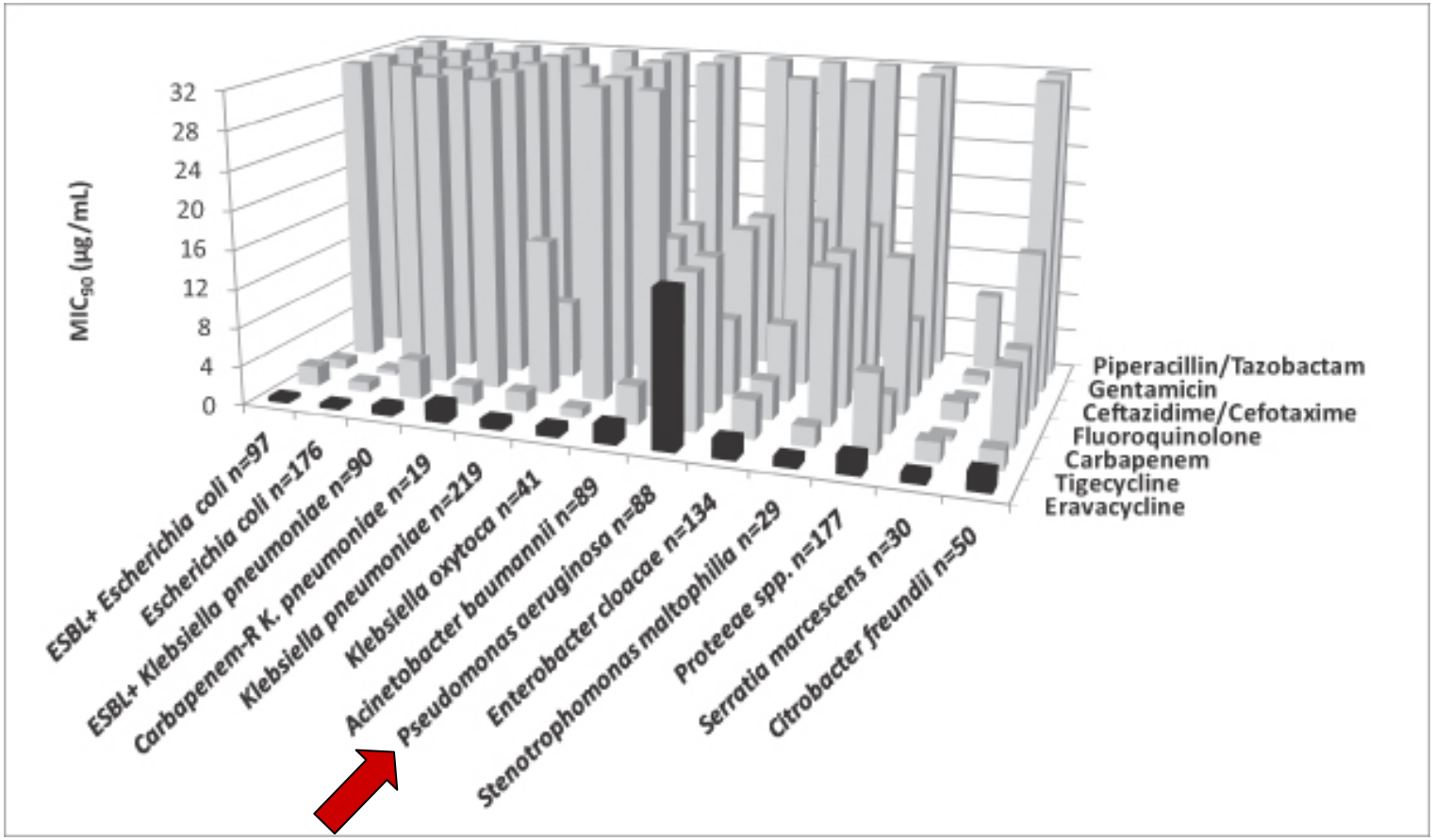
Organism	N	MIC range (µg/mL) MIC_{50}/MIC_{90} (µg/mL)						
		TP-434	Carbapenem[a]	Fluoroquinolone[b]	3rd Gen Ceph[c]	Gentamicin	Piperacillin/ Tazobactam	Tigecycline
Klebsiella pneumoniae	208	0.13-16 0.5/2	0.063->32 0.5/16	≤0.016->32 1/>32	≤0.016->64 32/>32	≤0.25->32 4/>32	1->128 8/>128	0.13-16 0.5/4
ESβL+ *Klebsiella pneumoniae*	91	0.13-8 0.5/1	0.03->32 0.5/>32	0.03->32 8/>32	0.13->64 >32/>64	≤0.25->32 >8/>32	2->128 >64/>128	0.13-8 1/4
Carbapenem-resistant *K. pneumoniae*	19	0.13-16 0.5/1	4->32 32/>32	4->32 >32/>32	32->32 >32/>32	2->32 16/>32	>128->128 >128/>128	0.25-16 1/1
Acinetobacter baumannii	89	≤0.016-4 0.5/2	0.12->32 1/>32	0.02->32 8/>16	0.12->16 >16/>16	0.5->32 32/>32	1->128 >128/>128	≤0.016-8 1/4
Pseudomonas aeruginosa	88	1->64 8/16	0.12->32 1/16	0.06->2 025/>2	1->16 >16/>16	0.12->32 2/16	1->128 8/>128	1->16 16/>16
Enterobacter cloacae	134	0.03-4 0.5/2	0.06-32 0.5/4	0.008->32 0.25/>4	0.03->64 >16/>64	≤0.25->32 0.5/>8	0.5->128 >64/>128	0.06-8 0.5/4
Enterobacter aerogenes	30	0.25-2 0.25/0.25	≤1-2 ≤1/≤1	≤0.25-0.5 ≤0.25/≤0.25	≤0.5->64 ≤0.5/16	≤0.25-1 ≤0.25/0.5	≤0.5->64 2/16	0.25-4 0.5/0.5

Green boxes indicate that the MIC_{90} of TP-434 < MIC_{90} of tigecycline

[a]meropenem, ertapenem, imipenem; [b]levofloxacin, ciprofloxacin; [c]cetazidime, ceftriaxone; ESβL+ = extended spectrum β-lactamase producing isolates

Hunt et al, ICAAC 2010, F1-2157

Eravacycline: in vitro activity



http://www.sec.gov/Archives/edgar/data/1373707/000119312513048887/d441172ds1.htm

Eravacycline: pharmacokinetics

AUC and C_{max} are listed below; $T_{1/2}$ was 14-21 hours on Day 1 and 17-36 hours on Day 7

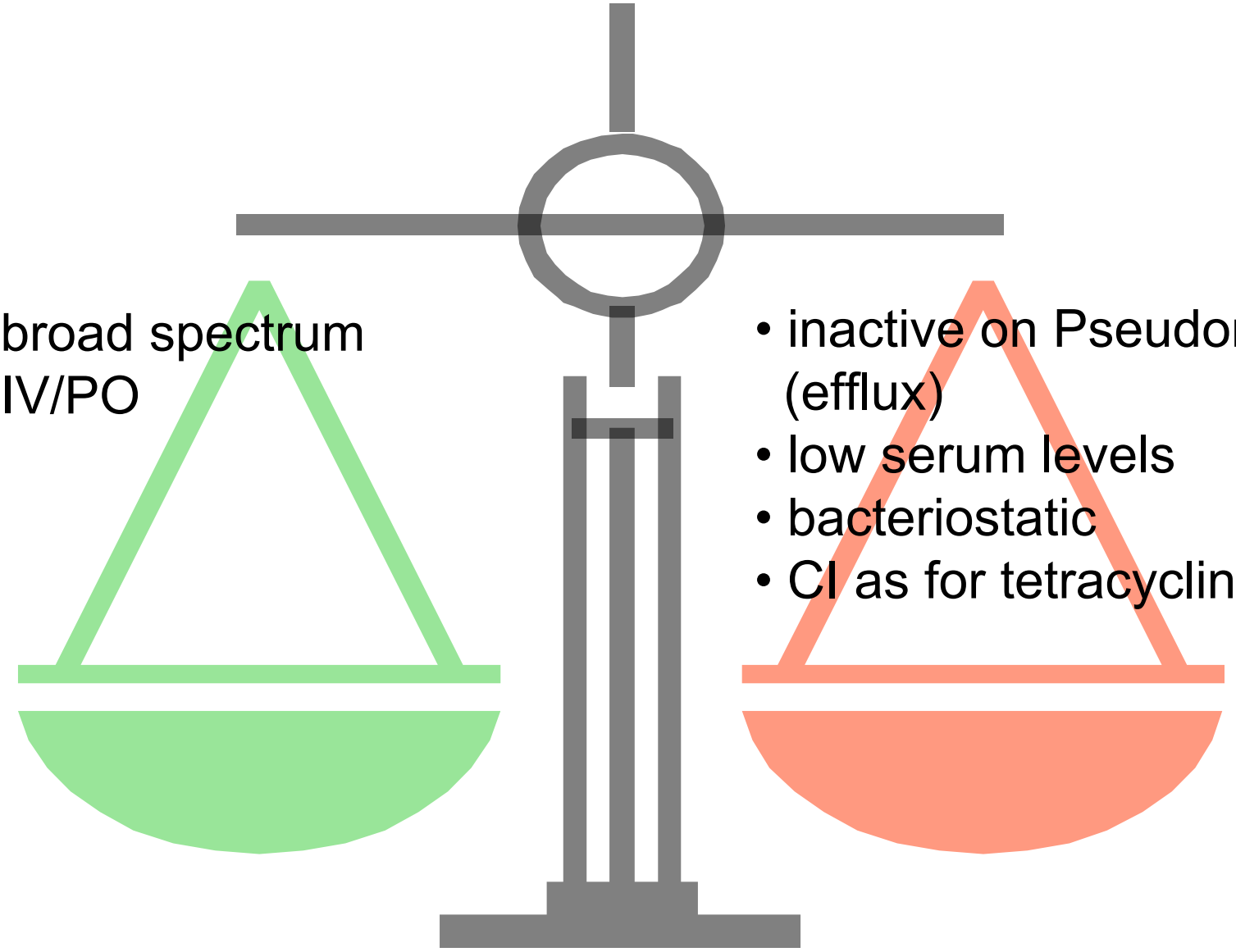
Dose (mg)		Day 1		Day7	
		C_{max} (ng/mL)	AUC (ng*hr/mL)	C_{max} (ng/mL)	AUC(ng*hr/mL)
100	fast (n=8)	117	1924		
	fed (n=8)	41	724		
	light (n=6)	43	496	48	902
300	fast (n=6)	206	3154	342	9511

light = light breakfast, fed = FDA specified breakfast, fast = minimum 8 hour fast

Lower than MICs ???

Horn et al, IDSA et al (2011) P603

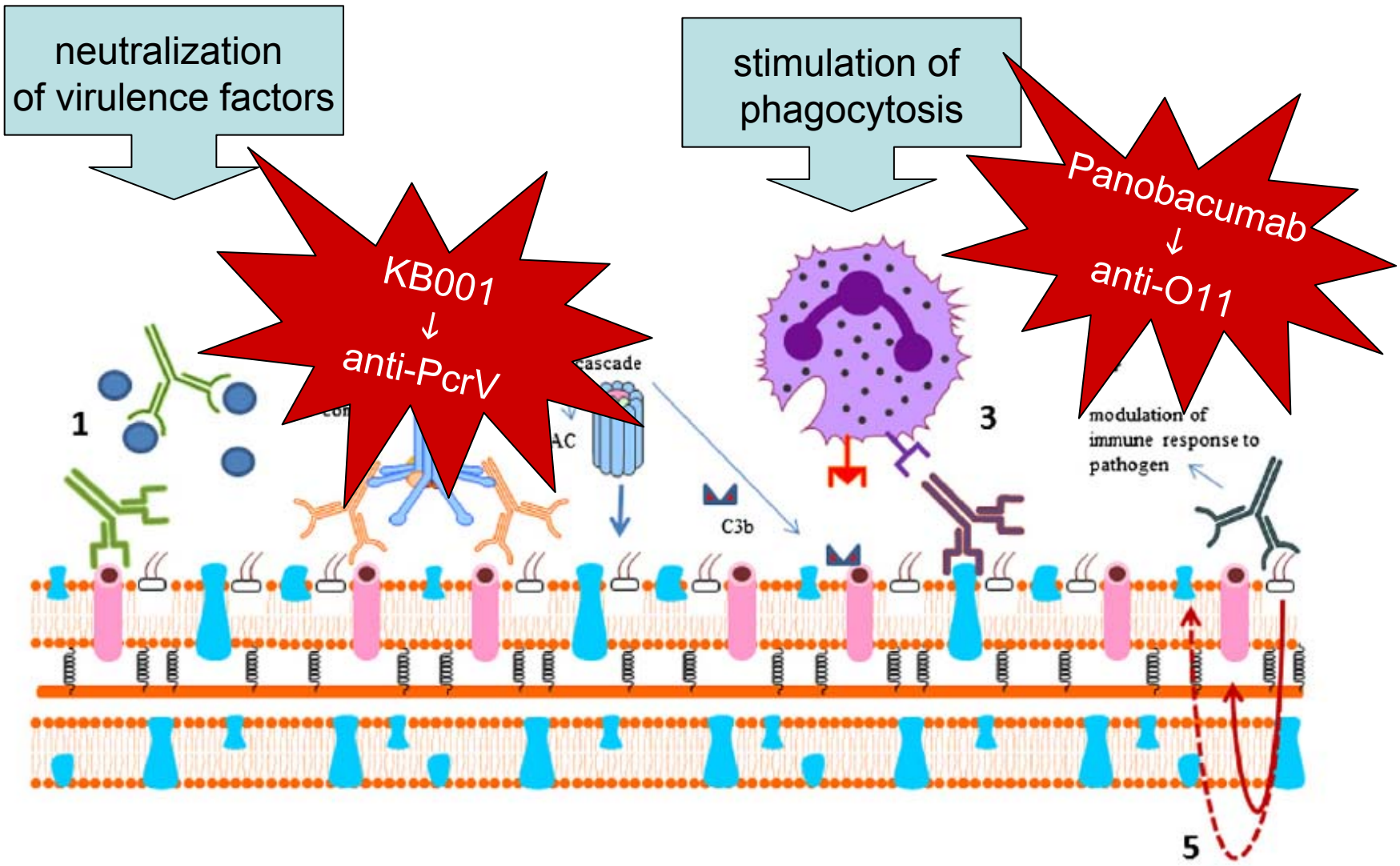
Eravacycline : pros and cons



- broad spectrum
- IV/PO

- inactive on Pseudomonas (efflux)
- low serum levels
- bacteriostatic
- CI as for tetracyclines

MONOCLONAL ANTIBODIES

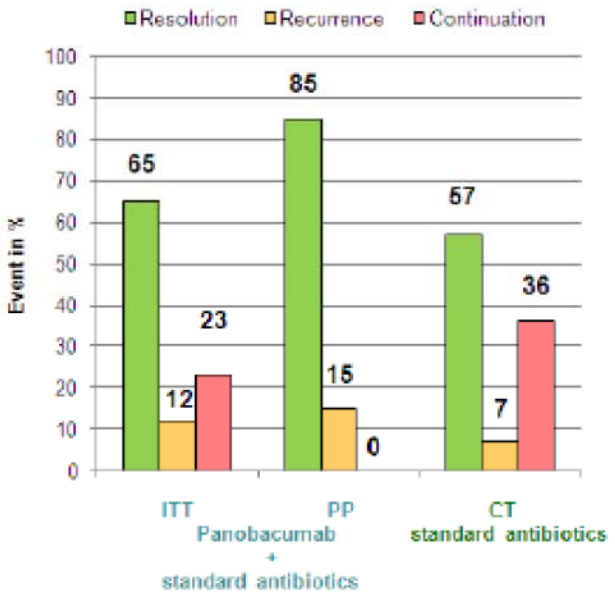


Oleksiewicz et al, Ach Biochim Biophys (2012) 256: 124-31

PANOBACUMAB

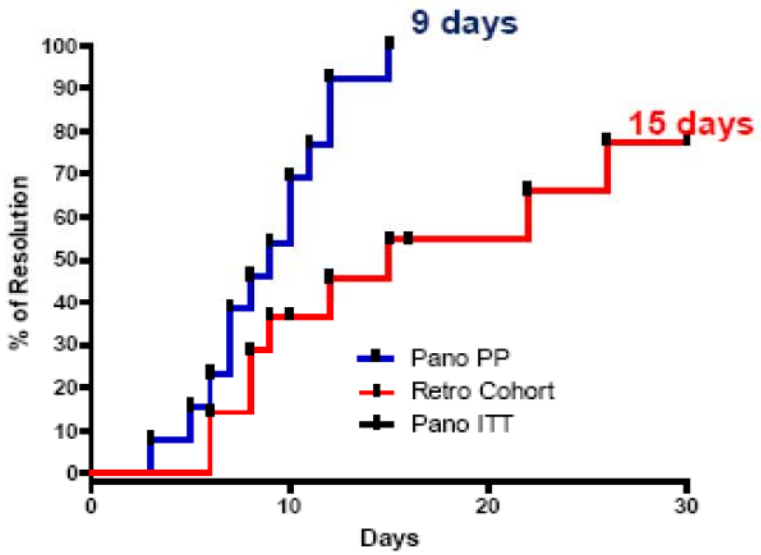
Panobacumab: retrospective cohort trial

Final Clinical Outcome



Populations	ITT	PP	CT
Initial Clin Res	76%	100%	64%
Final Clin Res	65%	85%	57%

Time to resolution



Log-rank (Mantel-Cox) Test	
Chi square	6.922
df	1
P value	0.0085

kenta BIOTECH

Page 30

Gafner. ECCMID 2010

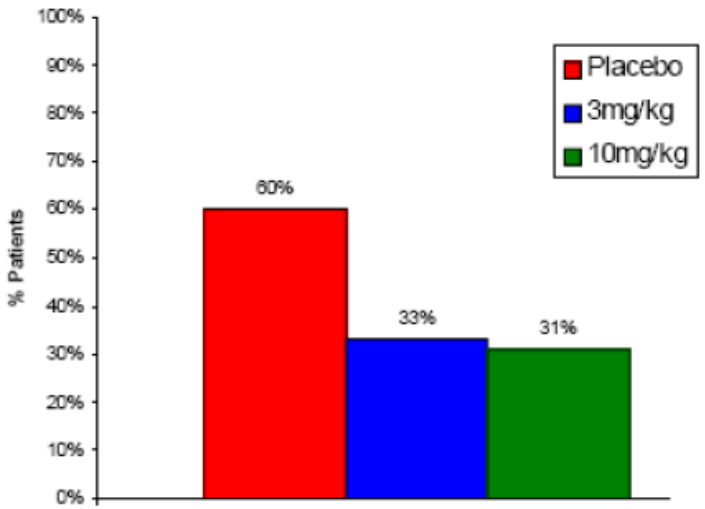
KB-001

KaloBios mAb for all P. aeruginosa in VAP

KB001 MVP Trial: Day 28 Clinical Outcomes

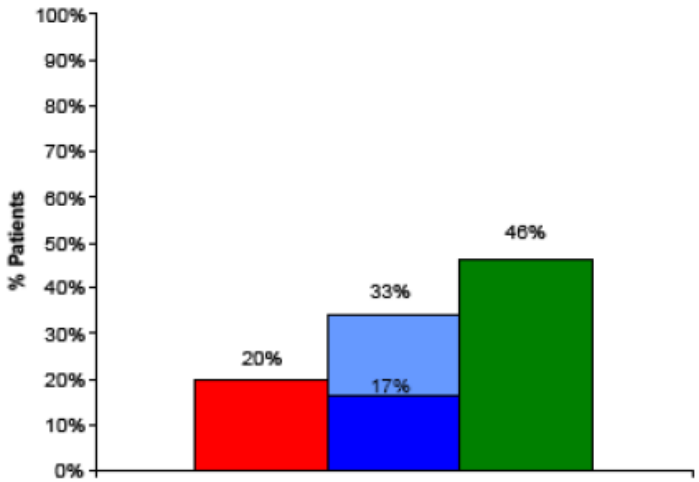
Improved clinical outcomes observed in 10mg/kg cohort

Decreased *Pa* VAP events



Patients with *Pa* Pneumonia Events

Increased *Pa* Event Free Survival



***Pa* Event Free Survival**

KaloBios 5

Summary for new molecules
Not yet the miracle drug …

Anti Gram-negative agents

New beta-lactam combinations all cover ESBLs

Remaining problems:
- *Acinetobacter* carbapenemases
- MDR *Pseudomonas*

Plazomicin: no cross resistance with beta-lactams but efflux and Arm unsolved
Arm and carbapenemase on the same plasmid!

Eravacycline: inactive on Pseudomonas
broad range of MIC in multiresistant organisms

→ combinations ? Colistin ?

Let’s hope in mankind !