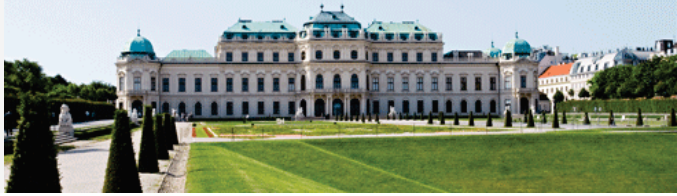


Optimisation of therapy in Gram-negative infections:

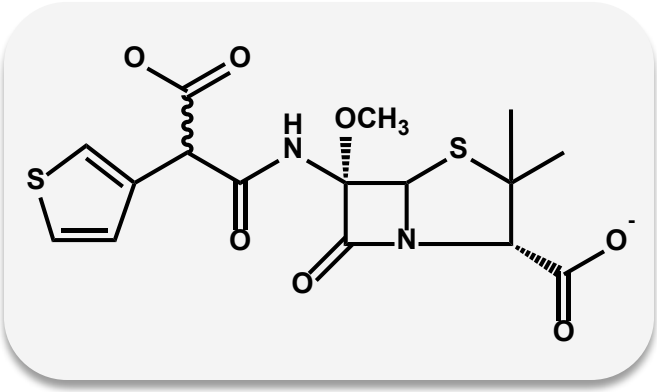
TEMOCILLIN

Françoise Van Bambeke, PharmD, PhD

Pharmacologie cellulaire et moléculaire
Louvain Drug Research Institute
Université catholique de Louvain,
Brussels, Belgium

<www.facm.ucl.ac.be>

In a nutshell … Temocillin identity card



- **Name:** temocillin ; 6-α-methoxy-ticarcillin
- **Passport number**: ATC code J01CA17
- **Birthdate:** 1984
- **Birthplace**: Beecham company, London, UK
- **Current address:** Eumedica, Manage, Belgium
- **VISA:** registered in Belgium; Luxembourg, UK

Current position: IV/IM – infections by Gram(-) bacteria

- empirical treatment:
  - ➲ complicated urinary tract infections
- documented treatment:
  - ➲ lower respiratory tract infections
  - ➲ wound infections
  - ➲ bacteraemia
- orphan drug designation:
  - ➲ *Burkholderia cepacia* infection in cystic fibrosis patients

SPC, last revision 2012

Spectrum of activity

Susceptible organisms

MIC < 1 mg/L	1 mg/L < MIC < 10 mg/L	10 mg/L < MIC < 100 mg/L
Moraxella catarrhalis	*Brucella abortus*	*Serratia marcescens*
Haemophilus influenzae	*Citrobacter spp.*	***Enterobacter spp***
Legionella pneumophila	*Escherichia coli*	
Neisseria gonorrhoeae	***Klebsiella pneumoniae***	
Neisseria meningitidis	*Pasteurella multocida*	
	Proteus mirabilis	
	Proteus spp (indole +)	
	Providencia stuartii	
	Salmonella Typhimurium	
	Shigella sonnei	
	Yersinia enterocolitica	

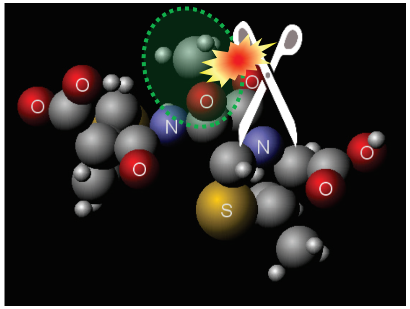
Intrinsically resistant organisms

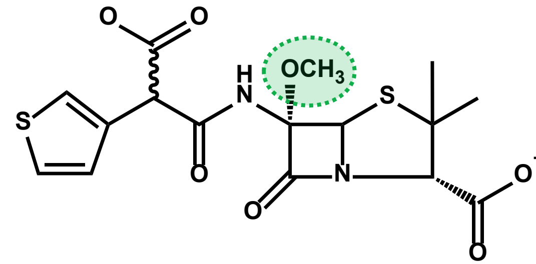
anaerobes
Gram(+) bacteria
Acinetobacter spp
Pseudomonas aeruginosa

ESKAPE pathogens

SPC, last revision 2012; Van Landuyt et al, AAC 1982; 22:535-40

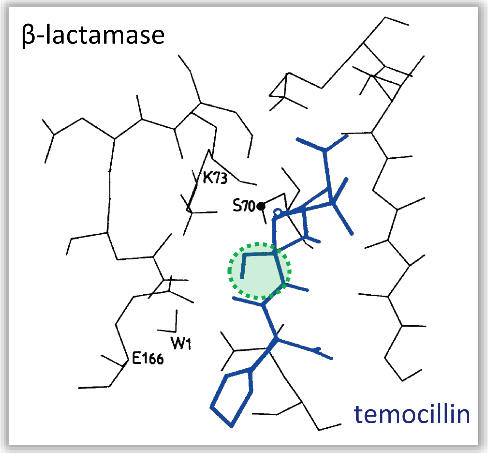
What about ESBL/carbapenemase producers ?





hydrolysis

- ☒ NDM
- ☒ VIM
- ☒ IMP
- ☒ OXA-48



NO hydrolysis

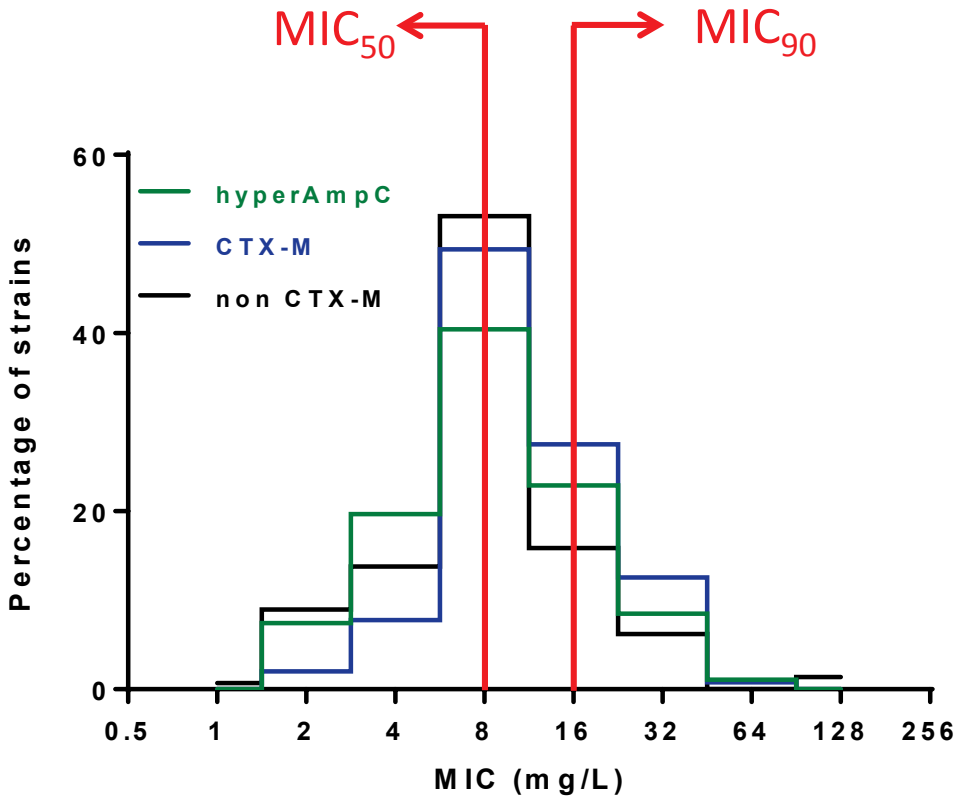
- ☑ TEM
- ☑ SHV
- ☑ CTX-M
- ☑ KPC
- ☑ most OXA

Know your local epidemiology !

Matagne et al, Biochem J 1993; 293:607-11; Livermore et al, Int J Antimicrob Agents. 2011; 37:415-9

What about ESBL/carbapenemases producers ?

Temocillin MIC distribution for ESBL and AmpC overproducers
(*E. coli, Klebiella spp, Enterobacter spp, Citrobacter spp, Serratia spp*)



Adapted from Livermore et al, JAC 2006; 57:1012-4

PK and dosage

Creat. Clearance	dose	Cmax (1 g)	$T_{1/2}$	Estimated Cmin (1 g)
Normal	1-2 g q12h	173 mg/L	**4.2 h**	~ 22 mg/L
> 60 ml/min	1-2 g q12h			
30-60 ml/min	1 g q12h	120 mg/L	20 h	~ 80 mg/L
10-30 ml/min	1 g q24h	118 mg/L	17 h	
< 10 ml/min	0.5-1 g q24-48h		28 h	
hemodialysis	1 g after dialysis 0.5 g if 24 h			

Protein binding ~ 85 %

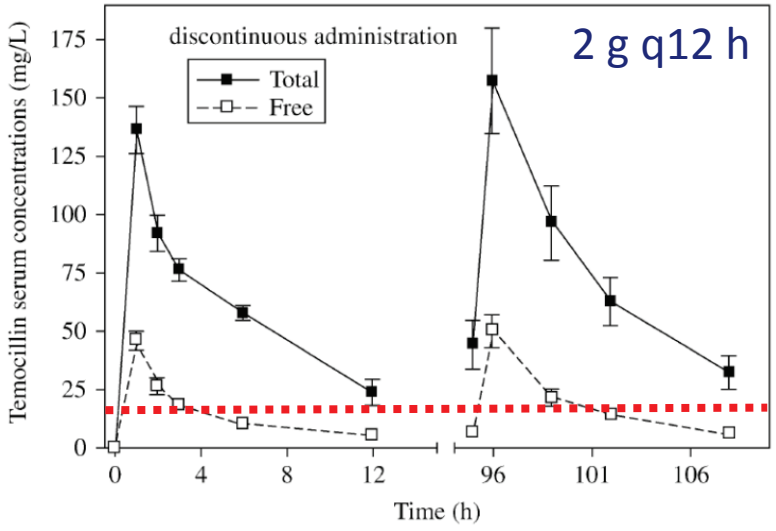
SPC, last revision 2012

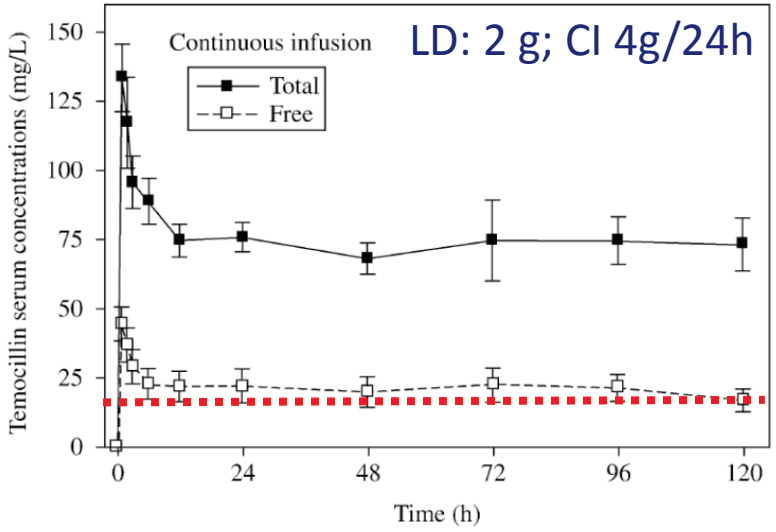
What does temocillin bring to the pharmacologist ?

Pharmacy
Barmherzige Brüder Vienna

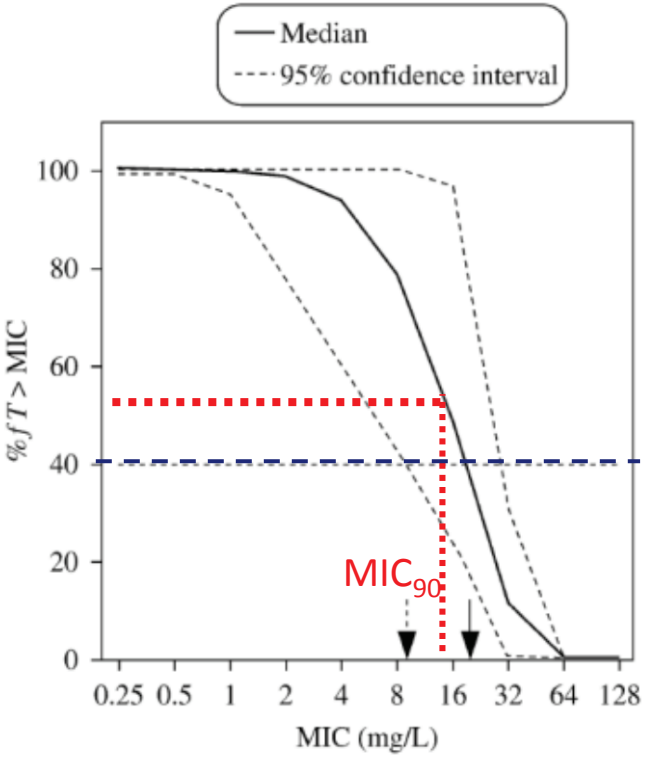
Dosage: PK/PD to the rescue

ICU patients





Monte Carlo simulation



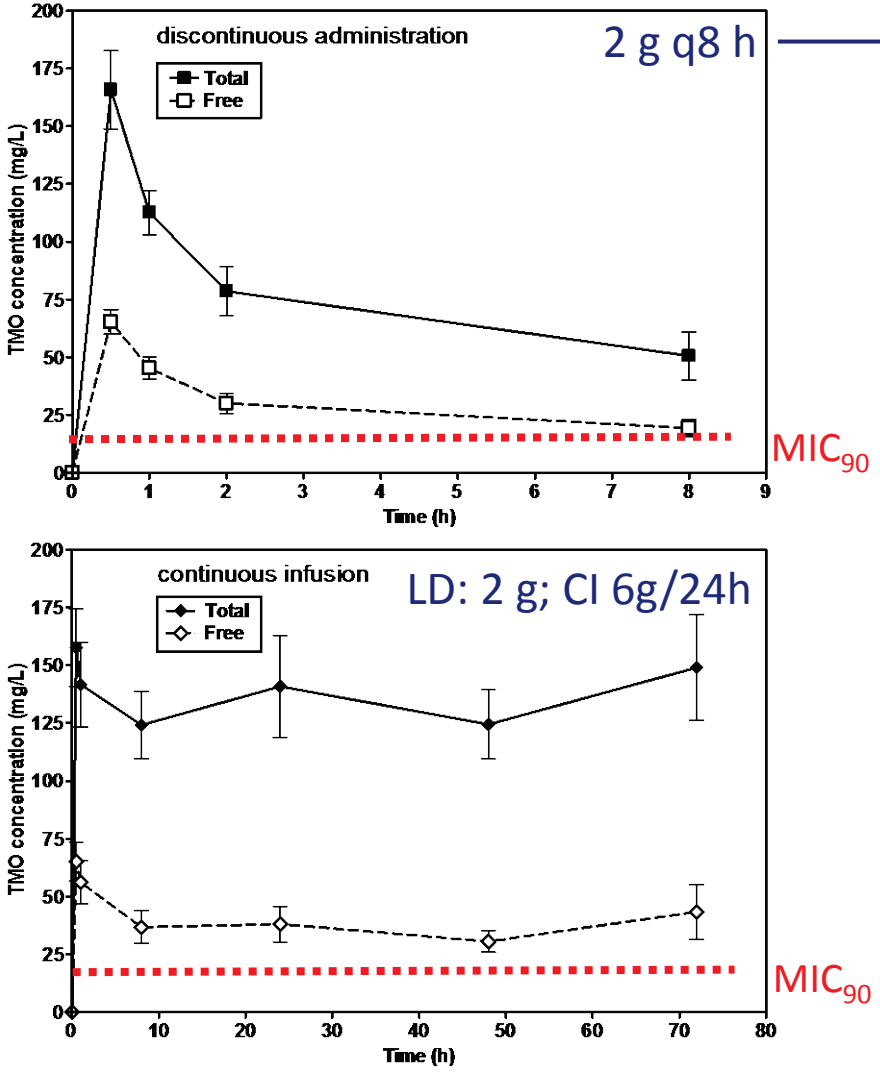
PK/PD Bkpt 8-16 mg/L

BSAC Bkpt: ≤ 8 mg/L (systemic)
≤ 32 mg/L (urinary)

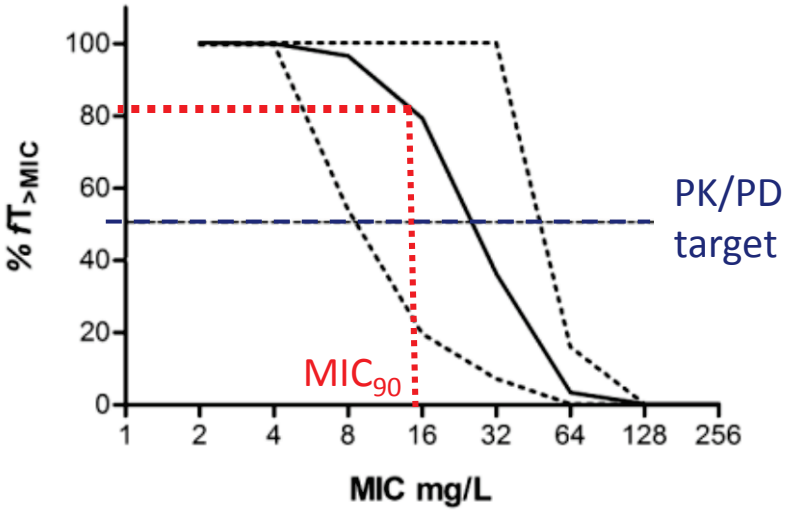
De Jongh et al, JAC 2008; 61:382-8

Dosage: PK/PD to the rescue

ICU patients



Monte Carlo simulation



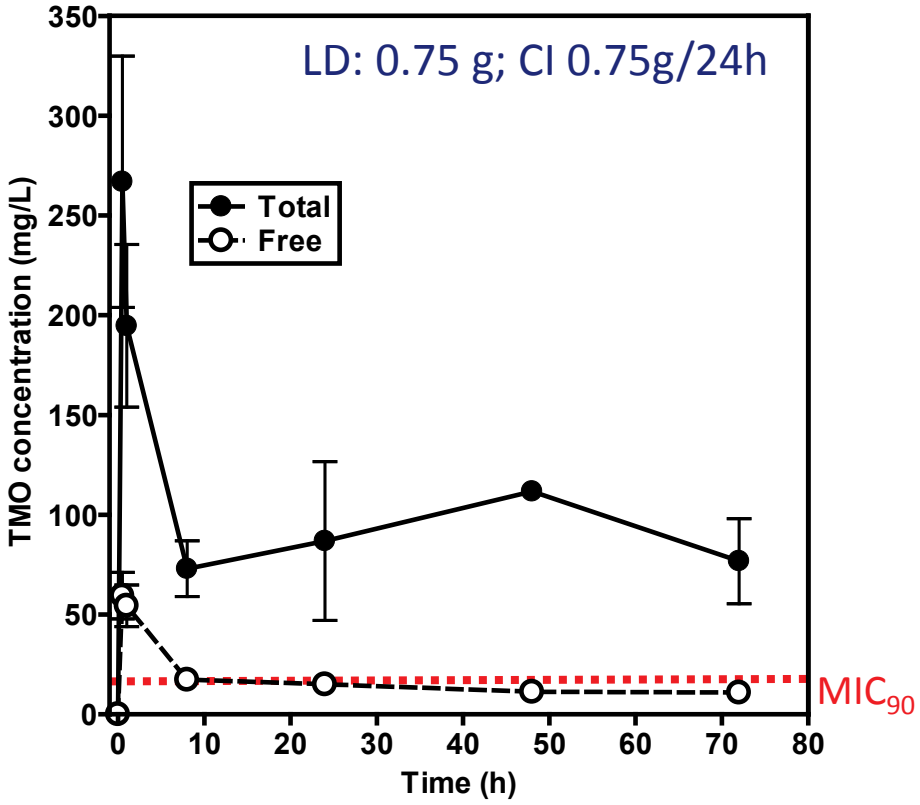
PK/PD Bkpt 8-32 mg/L

BSAC Bkpt: ≤ 8 mg/L (systemic)
≤ 32 mg/L (urinary)

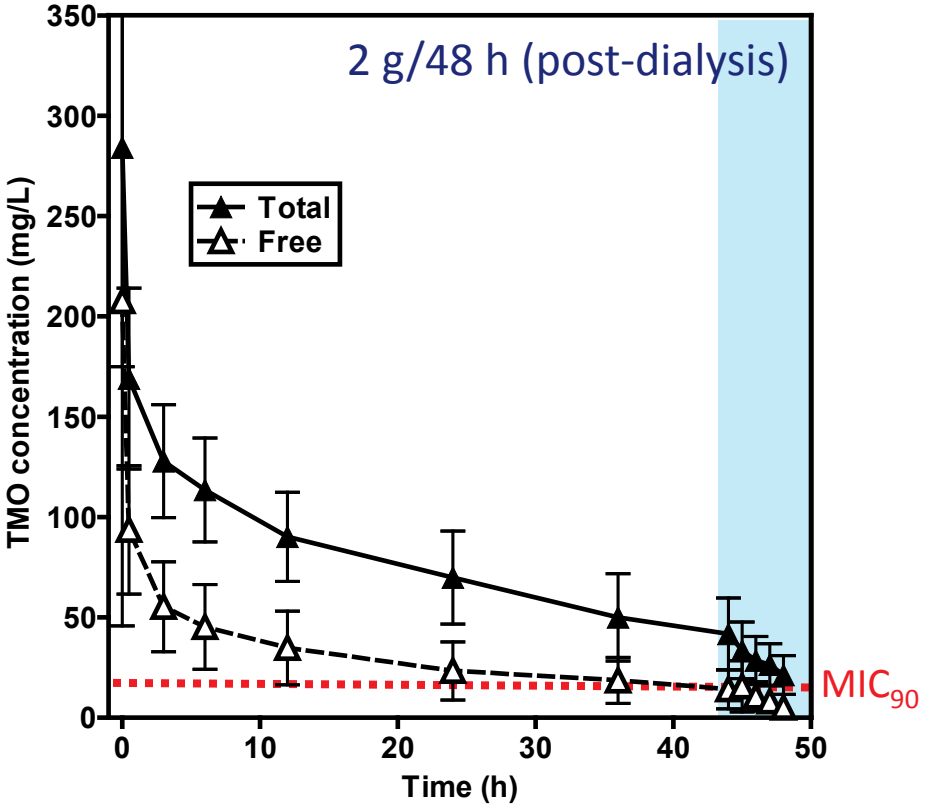
Laterre et al, JAC [accepted]

Dosage: PK/PD to the rescue

continuous veno-venous hemofiltration



hemodialysis



Laterre et al, JAC [in revision]; Miranda Bastos et al, ESCMID old antibiotics 2014; P26

What does temocillin bring to the microbiologist?

Tree of life
by Gustav Klimt in 1909.

Rapid screening test for carbapenemase

Carbapenemase distribution according to different inhibition diameters cut-offs and their performance for the detection of CPE among isolates referred to the NRLs in France and in Belgium in 2012 ($n = 1354$)

			Number of isolates per carbapenemase enzyme					Performance of the detection of CPE			
	Zone diameter cut-offs (mm)	Total, 1354	OXA-48, 323	KPC, 60	VIM, 32	NDM, 20	negative, 919	sensitivity (%)	specificity (%)	PPV (%)	NPV (%)
Susceptibility breakpoints[a]	MEM <23	452	125	59	23	19	226	**52.0**	75.4	49.9	76.8
	TZP <21	1083	322	60	32	20	649	99.8	29.4	40.0	99.6
	TMO <19	952	323	54	32	18	525	98.2	42.9	44.8	98.0
Modified cut-offs	MEM <29	929	322	60	32	20	495	**99.8**	46.1	46.6	99.8
	TZP <16	790	319	59	30	19	363	**98.2**	60.5	54.0	98.6
	TMO <12	457	317	8	28	12	92	83.9	**90.0**	79.9	92.2
Combination of cut-offs	TZP <16 and TMO <12	426	315	8	26	12	65	83.0	92.9[b]	**84.7**	
	TZP ≥16 and TMO ≥12	533	2	1		1	**529**				**99.2**

MEM, meropenem 10 μg disc; TZP, piperacillin/tazobactam 100/10 μg disc; TMO, temocillin 30 μg disc; PPV, positive predictive value; NPV, negative predictive value. The results shown in bold are discussed further in the text.

[a]According to 2013 CLSI guidelines (for meropenem and piperacillin/tazobactam) and to Fuchs *et al.*[11] (for temocillin).

[b]The specificity of combined cut-offs was calculated for carbapenemase-negative isolates when at least one of the two criteria was not fulfilled.

Huang et al, JAC 2014; 69:445-50

What does temocillin bring to the clinician ?

Hygeia - detail from "Medicine,"
the second of the University of Vienna's three commissioned works
by Gustav Klimt from 1900-1907.

What does temocillin bring in our arsenal ?

(1) Targeted spectrum ⇨ sparing of broad spectrum drugs

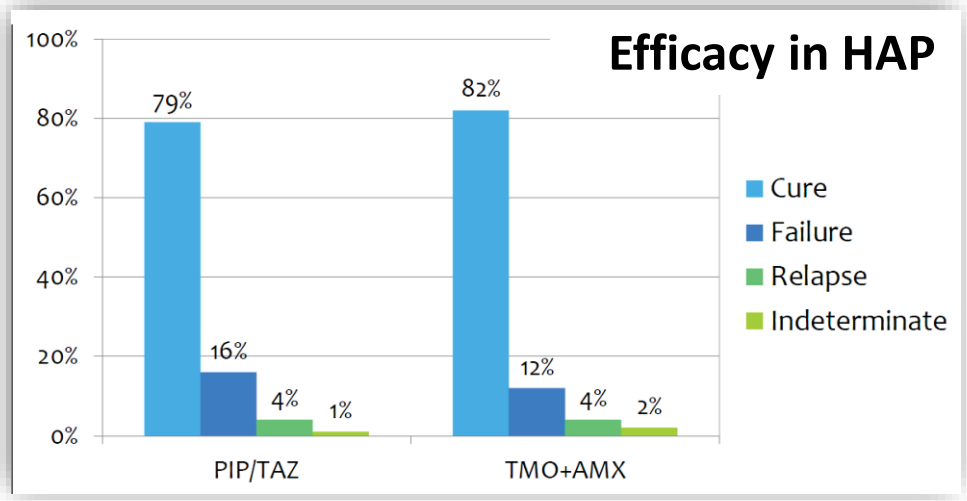
Comparative activity of the tested antibiotics against ESBL-positive and ESBL-negative *Enterobacteriaceae* isolates

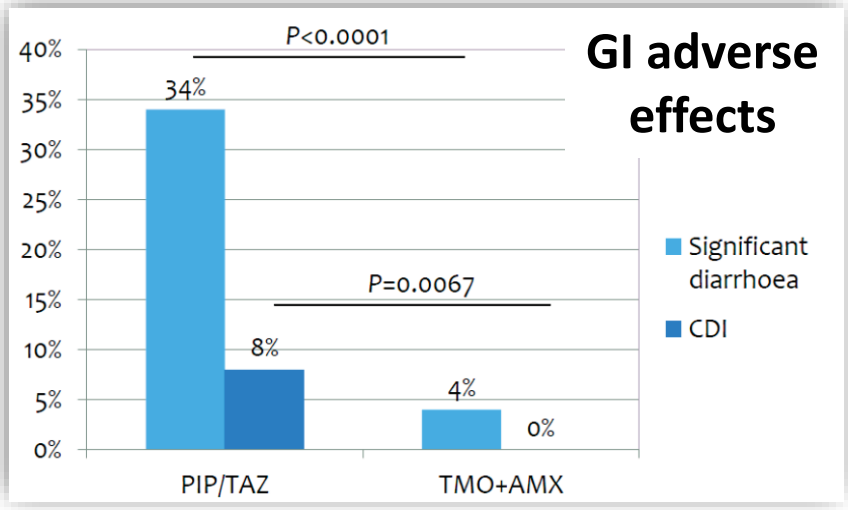
	Number of resistant isolates (%)					
No. isolates	Piperacillin-tazobactam	Ceftazidime	Meropenem	Temocillin	Amikacin	Ciprofloxacin
ESBL producing isolates (77)	34 (44.2%)	67 (87.0%)	1 (1.3%)	26 (33.8%)	14 (18.2%)	54 (70.1%)
ESBL non-producing isolates (575)	Not tested	62 (10.8%)	1 (0.2%)	27 (4.7%)	17 (3.0%)	77 (13.4%)
Fisher exact test	–	$P<0.00001$	$P=0.22$	$P<0.00001$	$P<0.00001$	$P<0.00001$

Glupczynski et al, Eur J Clin Microbiol Infect Dis 2007; 26:777–83

What does temocillin bring in our arsenal ?

(1) Targeted spectrum ⇨ sparing of broad spectrum drugs

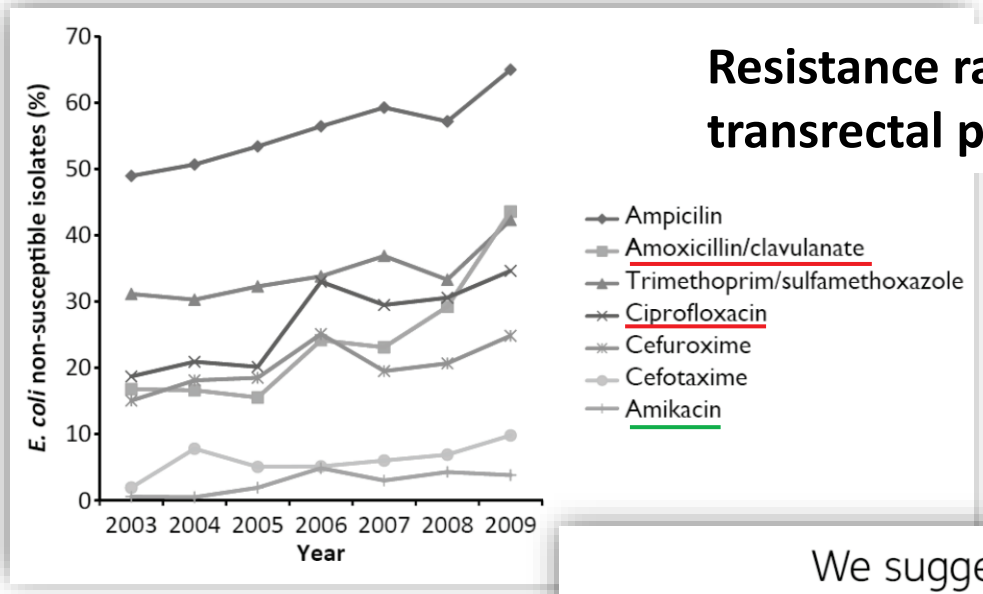




Habayeb, FIS 2013 and ECCMID 2013; O273

What does temocillin bring in our arsenal ?

(2) Targeted spectrum ⇨ sparing of broad spectrum drugs lack of cross resistance



Resistance rates in *E. coli* from transrectal prostate biopsy

Clinical interest

We suggest that the targeted spectrum of temocillin makes it a more appropriate option for transrectal ultrasound-guided needle biopsy prophylaxis than amikacin. We therefore preferentially supplement ciprofloxacin with temocillin using amikacin only in patients who give a history of penicillin allergy.

Steensels et al, CMI 2012; 18: 575–81

Balakrishnan & Smith; JAC 2013;68:2418-9

What does temocillin bring in our arsenal ?

(2) Targeted spectrum ⇨ sparing of broad spectrum drugs lack of cross resistance

Therapeutic results of the study at the Centre of Dermatology and Venereal Diseases of the University of Frankfurt

Dose	No. of patients		Success	Failure
	male	female		
0.5g (Group I)	11	2	11	2
1.0g (Group II)	54	8	57	5
Total (%)	65	10	68 (91)	7 (9)

Clinical efficacy against *N. gonorrheae*

Reimer et al, Drugs 1985; 29S5:210-2

Susceptibility of recent isolates (n=76)

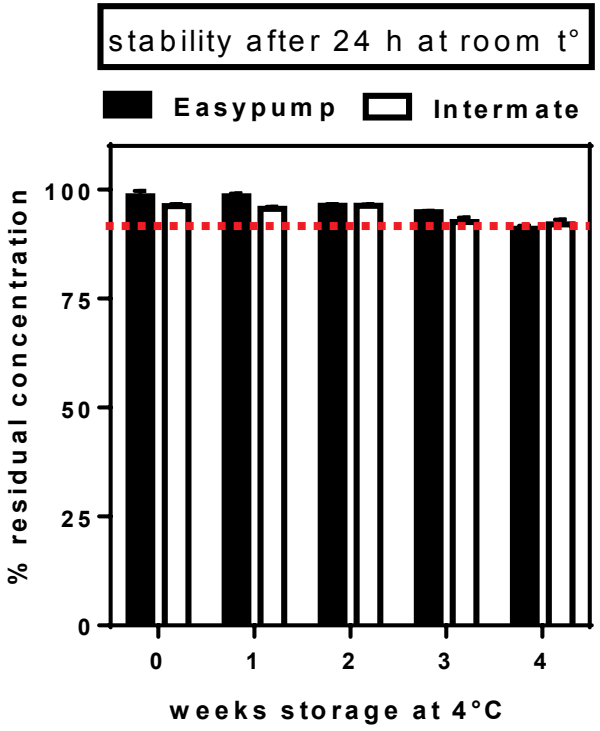
- CIP R : 49 %
- Pen I+R : 71 %
- CRO R: 0 %

median TEM MIC: 0.75 mg/L
(10-90%: 0.125-3 mg/L)

Ghathian et al, ECCMID 2013; O314

What does temocillin bring in our arsenal ?

(3) Chemical stability ⇨ Outpatient Parenteral Antibiotic Therapy



***B. cepacia* infections in CF patients**

Resistant urinary tract infections

Dube & Iqbal, FIS 2013

adapted from *Carryn et al, JAC 2010; 65:2045-6*

What does temocillin bring in our arsenal ?

(4) Salvage therapy for MDR *Burkholderia spp*

Successful Use of Temocillin as Salvage Therapy for Cervical Osteomyelitis Secondary to Multidrug-Resistant *Burkholderia cepacia*

Marcela Rodriguez,[1] Miranda Nelson,[2] James E. Kelly,[3] Alexis Elward,[2] and Sharon Celeste Morley[2]
[1]Department of Pediatrics, Southern Illinois University School of Medicine, Springfield; and Departments of [2]Pediatrics, and [3]Radiology, Washington University School of Medicine, St Louis, Missouri

Journal of the Pediatric Infectious Diseases Society pp. 1–4, 2013. DOI:10.1093/jpids/pis110

Journal of Cystic Fibrosis 5 (2006) 121 – 124
Journal of Cystic Fibrosis
www.elsevier.com/locate/jcf

Temocillin in the treatment of *Burkholderia cepacia* infection in cystic fibrosis

Anastasios Lekkas, Khin M. Gyi, Margaret E. Hodson *

Monday , 06 October 2008

ERS SOCIETY
every breath counts

London 3 Session 298 14:45-16:45
ECS E-Communication Session : Cystic fibrosis: new mechanisms, monitoring and treatment tools

A UK experience of temocillin in the treatment of adult cystic fibrosis patients

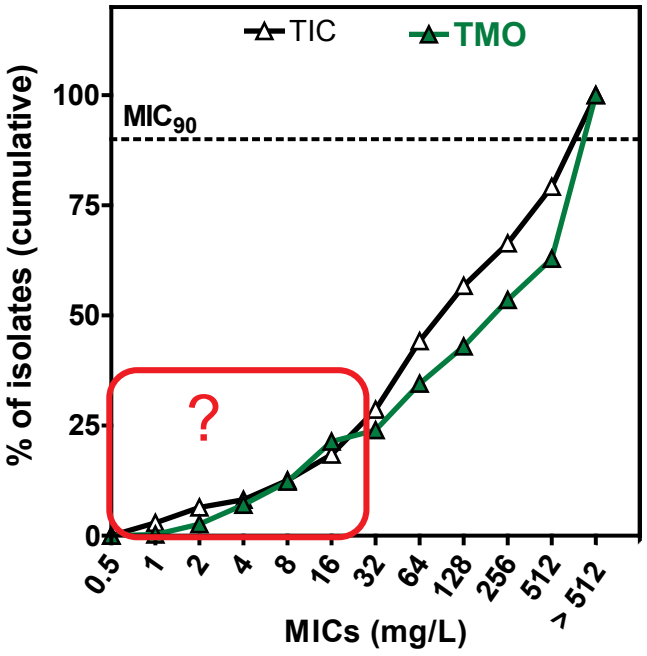
K. Nimako, K. McNulty, J. Hull, T. Ho (Camberley, United Kingdom)

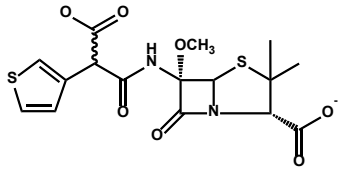
Conclusions

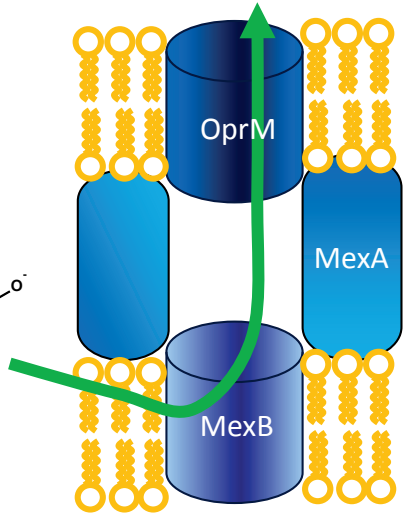
Our findings suggest that temocillin administration is well tolerated in CF and in this cohort was associated with a significant improvement in BMI and WCC. This improvement was seen in patients with *P. aeruginosa* infection as well as those with proven *B. cepacia*. Further studies are needed to further evaluate the role of temocillin in CF.

What about *Pseudomonas aeruginosa* ?

Temocillin vs ticarcillin MIC distribution for *P. aeruginosa* collected from CF patients (n= 335)







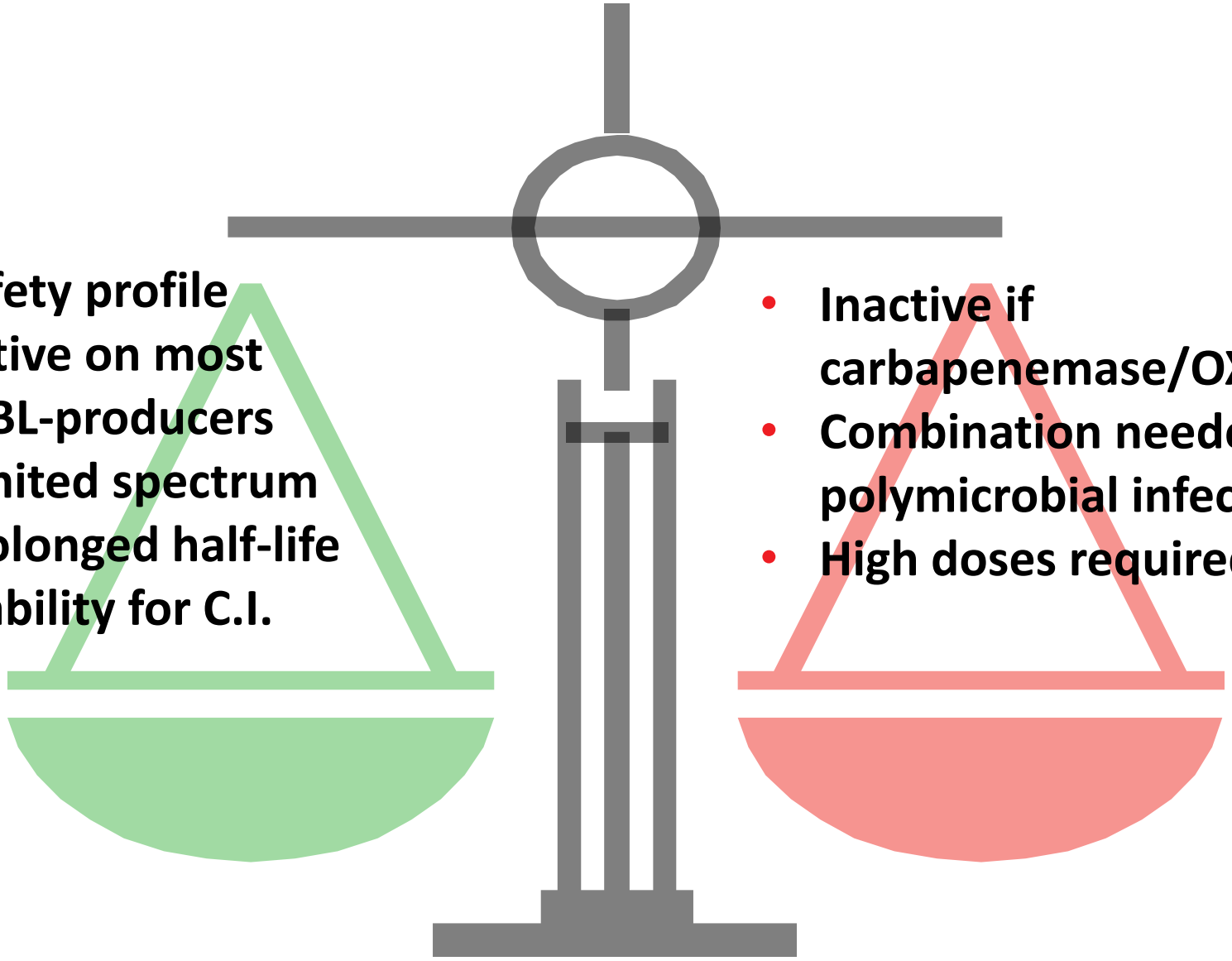
Strain/genotype	MIC (mg/L)
PAO1	256
PAO1 ΔmexAB-oprM	4
CF strain; deletion in *mexB*	1
CF strain; deletion in *mexA*	2
CF strain; mutation in *mexA*	32

efflux non functional !

Buyck et al, JAC 2012; 67:771-5; Chalhoub et al, ESCMID old antibiotics 2014, P02

Take home message

Temocillin PROS and CONS



- Safety profile
- Active on most ESBL-producers
- Limited spectrum
- Prolonged half-life
- Stability for C.I.

- Inactive if carbapenemase/OXA-48
- Combination needed if polymicrobial infection
- High doses required

Perspective for future research

Perspective for future research

- **Definition of PK/PD breakpoint**
- **Any specific mechanism of resistance beside carbapenemases ?**
- **PK in specific populations (paediatrics, e.g.)**
- **Further documentation of clinical efficacy for currently off-label indications**