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Grand Nancy Congrès & Événements

Temocilline, une nouvelle perspective dans la lutte contre les BGN résistants ?

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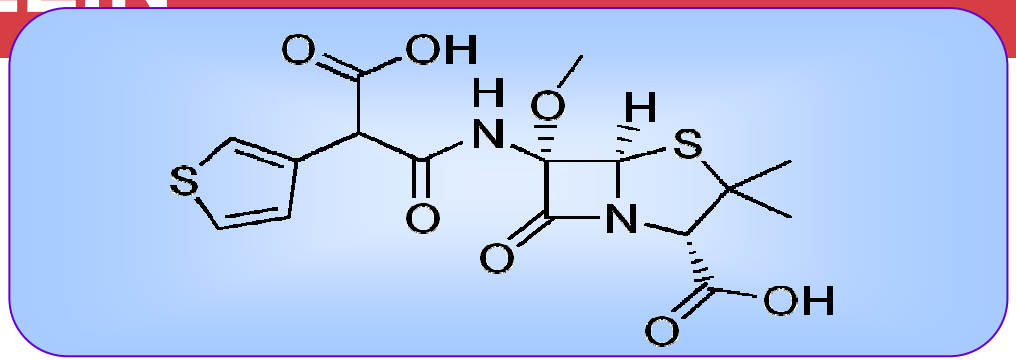
Brussels

Conflicts of interest

- **Advisory board**
  - Ferring, Aridis, Lascco, Inotrem
  - Eumedica

TEMOCILLIN



- **6-α-methoxy-ticarcillin**
- **Spectrum directed only against gram negative bacteria without non-fermenters (*Pseudomonas aeruginosa*, *Acinetobacter* spp.)**
- **active against all β-lactamases including ESBL and AmpC**
- **Indications**
  - urinary tract infections
  - gram negative nosocomial infections (LRTI, IAI, bacteremia, …)

Temocillin

- **Approved by Ministry of Health**
- **Marketing 1988**

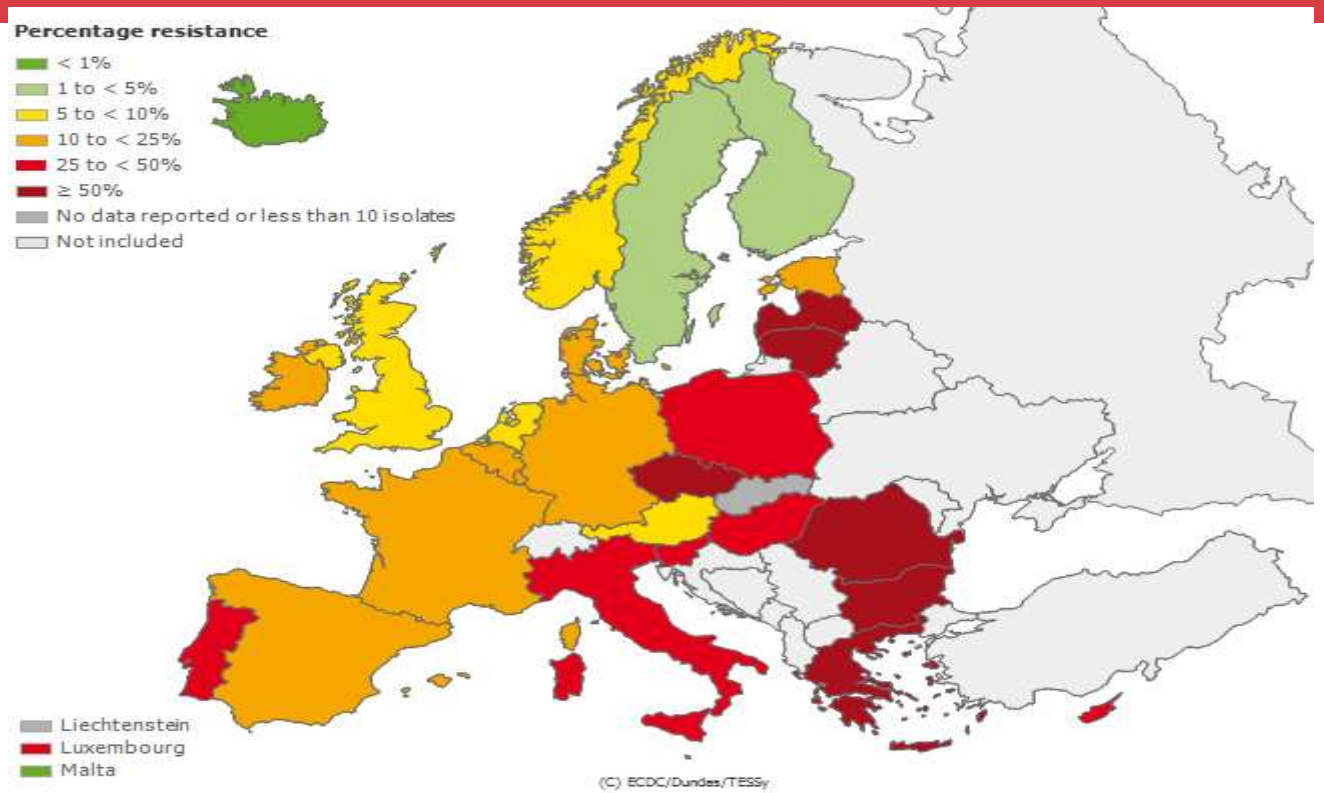
- **Narrow spectrum**
  - No impact on anaerobes
  - Context SDD

- **Late 90's ….ESBL**

Temocillin clinical studies ?

- Limited data and mostly in UTI
- Years : 80-90 and ecology differed ?
- Indication : UTI
- Dosing ? Limited PK/PD data
- No clinical data in other indications

Klebsiella Cephalosporins 3rd generation R/I 2009



In vitro activity of temocillin against prevalent extended-spectrum beta-lactamases producing *Enterobacteriaceae* from Belgian intensive care units

Y. Glupczynski · T.-D. Huang · C. Berhin · G. Claeys · M. Delmée · L. Ide · G. Ieven · D. Pierard · H. Rodriguez-Villalobos · M. Struelens · J. Vaneldere

Eur J Clin Microbiol Infect Dis (2007) 26:777–783
DOI 10.1007/s10096-007-0370-9

Table 1 Number and percentage of non-susceptible isolates to the tested antimicrobials, classified by species

	Number of non-susceptible isolates (%)				
Species[a] (No. isolates)	Ceftazidime	Meropenem	Temocillin	Amikacin	Ciprofloxacin
Escherichia coli (186)	10 (5.4)	0	4 (2.2)	2 (1.2)	32 (17.2)
Enterobacter cloacae (115)	38 (33)	0	7 (6.1)	3 (2.6)	5 (4.3)
K. pneumoniae (75)	24 (32.0)	0	9 (12)	11 (14.7)	16 (21.3)
Enterobacter aerogenes (72)	48 (66.7)	2 (2.8)	18 (25)	11 (15.3)	41 (57)
K. oxytoca (62)	3 (4.8)	0	3 (4.8)	1 (1.6)	18 (29)
S. marcescens (39)	1 (2.6)	0	10 (25.6)	2 (5.1)	8 (20.5)
Proteus mirabilis (35)	0	0	1 (2.9)	0	5 (14.3)
M. morganii (27)	5 (18.5)	0	0	0	2 (7.4)
Citrobacter freundii (15)	4 (26.7)	0	0	1 (6.7)	2 (13.3)
Total[a] (652)	134 (20.5)	2 (0.4)	53 (8.1)	31 (4.8)	131 (20.1)

[a] In addition to the species groups detailed, this total also includes: *Proteus vulgaris* (9); *Hafnia* spp. (6), *Citrobacter diversus* (5); *Providencia* spp (3); *Serratia liquefaciens* (2), *Proteus penneri* (1)
These isolates were all susceptible to the tested agents with the single exception of one ESBL-producing *Providencia rettgeri* (resistant to ceftazidime (MIC≥32 μg/ml) and to ciprofloxacin (MIC≥256 μg/ml)

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Table 2 MIC distribution of temocillin for *Enterobacteriaceae* isolates with characterized resistance mechanisms

	MIC (μg/ml)[b]							
	1	2	4	8	16	32	64	≥128
All species combined[c]								
Hyperproduced AmpC (80)			12	22	35[a]	8	2	1
Non-CTX-M ESBL (64)		1	8	4	26[a]	23	2	
CTX-M (13)			2	6[a]	4	1		
Hyperproduced K1 enzyme (16)				10[a]	5	1		
Escherichia coli								
Hyperproduced AmpC (8)			3	3[a]	2			
Non-CTX-M ESBL (6)			1		4[a]		1	
CTX-M (6)				5[a]	1			
Klebsiella[d]								
Non-CTX-M ESBL (23)			3	1	11[a]	8		
CTX-M (4)					3[a]	1		
Hyperproduced K1 enzyme (16)				10[a]	5	1		
Enterobacter aerogenes								
Hyperproduced AmpC (24)			3	6	12[a]	3		
Non-CTX-M ESBL (26)			2	2	7	14[a]	1	
Enterobacter cloacae								
Hyperproduced AmpC (31)			1	6	18[a]	5	1	
Non CTX-M ESBL (6)			1	1	4[a]			
CTX-M (3)			1	2[a]				
Morganella morganii								
Hyperproduced AmpC (6)			1	1	2[a]	1		1
Citrobacter freundii								
Hyperproduced AmpC (5)			2		1[a]	1	1	
S. marcescens								
Hyperproduced AmpC (4)				1	1[a]	1	1	

[a] Modal values
[b] E-test MICs falling within two dilutions in a log2 base scale were rounded up to the highest value
[c] In addition to the species groups detailed, this total also includes three ESBL-positive isolates (two *Proteus mirabilis* and one *Providencia stuartii*)
[d] Includes 23 *K. pneumoniae* isolates all ESBL producing and 20 *K. oxytoca* isolates (16 K1 enzyme hyperproducers and 4 ESBL producers)

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	1	2	4	8	16	32	64	≥128
All species combined[c]								
Hyperproduced AmpC (24)			3	6	12[a]	3		
Non-CTX-M ESBL (26)			2	2	7	14[a]	1	
Enterobacter cloacae								
Hyperproduced AmpC (31)			1	6	18[a]	5	1	
Non CTX-M ESBL (6)			1	1	4[a]			
CTX-M (3)			1	2[a]				
Morganella morganii								
Hyperproduced AmpC (6)			1	1	2[a]	1		1
Citrobacter freundii								
Hyperproduced AmpC (5)			2		1[a]	1	1	
S. marcescens								
Hyperproduced AmpC (4)				1	1[a]	1	1	

and ESBL-producing isolates. These data indicate the well preserved activity of temocillin over the years against *Enterobacteriaceae* and show the wide variation in prevalence of ESBL-producing *Enterobacteriaceae* isolates in Belgian intensive care units. Prospective clinical studies are,

[a] Modal values
[b] E-test MICs falling within two dilutions in a log2 base scale were rounded up to the highest value
[c] In addition to the species groups detailed, this total also includes three ESBL-positive isolates (two *Proteus mirabilis* and one *Providencia stuartii*)
Includes 23 *K. pneumoniae* isolates all ESBL producing and 20 *K. oxytoca* isolates (16 K1 enzyme hyperproducers and 4 ESBL producers)

Activity of temocillin against prevalent ESBL- and AmpC-producing Enterobacteriaceae from south-east England

David M. Livermore[1]*, Russell Hope[1], Elizabeth J. Fagan[1], Marina Warner[1], Neil Woodford[1] and Nicola Potz[2]

Journal of Antimicrobial Chemotherapy
doi:10.1093/jac/dkl043
Advance Access publication 10 March 2006

N = 846

Table 1. MIC distributions of temocillin for β-lactamase-producing Enterobacteriaceae[a]

	MIC (mg/L)							
	1	2	4	8	16	32	64	>64
All species combined[b]								
Hyperproduced AmpC		14	34	**76**	43	16	2	
CTX-M		10	39	**248**	138	63	4	
Non-CTX-M ESBL	1	13	20	**77**	23	9		2
ESBL + hyperproduced AmpC			1	1	1	1		
Hyperproduced K1 enzyme			**5**	3	1			
E. coli								
Hyperproduced AmpC (40)[c]		1	3	**20**	13	2	1	
CTX-M (293)[d]		5	18	**165**	76	27	1	
Non-CTX-M ESBL (88)		3	10	**53**	16	5		1
Strain A only (79)			6	**61**	9	3		
Klebsiella spp.[e]								
CTX-M (199)		4	17	**80**	61	34	3	
Non-CTX-M ESBL (25)	1	4	3	**12**	1	4		
ESBL + hyperproduced AmpC (2)			1			1		
Hyperproduced K1 enzyme (9)		**5**	3	1				
Enterobacter spp.								
Hyperproduced AmpC (90)[f]		8	17	**33**	22	9	1	
CTX-M (8)			4	3		1		
Non-CTX-M ESBL (26)		4	6	**9**	6			1
ESBL + hyperproduced AmpC (2)				1	1			
Citrobacter spp.								
Hyperproduced AmpC (28)		3	8	**14**	2	1		
CTX-M (2)					1	1		
Non-CTX-M ESBL (3)		1	1	1				
Serratia spp.								
Hyperproduced AmpC (14)			2	**6**	4	2		
Non-CTX-M ESBL (2)				2				
Morganella morganii								
Hyperproduced AmpC (9)		1	**4**	2	1	1		
CTX-M (1)		1						

In vitro activity of temocillin against extended spectrum b-lactamase-producing Escherichia coli

Hector Rodriguez-Villalobos*, Vincent Malaviolle, Joëlle Frankard, Ricardo de Mendonça, Claire Nonhoff and Marc J. Struelens

Journal of Antimicrobial Chemotherapy (2006) 57, 771–774

Temocillin versus ESBL-producing *E. coli*

Table 2. MIC distribution of ESBL-producing *E. coli* for 12 antimicrobial drugs

Antimicrobial drug	Number of isolates (total n = 162) with MIC values (mg/L)													
	≤0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	128	>128	%S
Amikacin	0	0	0	20	44	32	33	16	10	0	0	0	7	86
Gentamicin	0	3	23	44	16	9	6	7	8	14	14	2	16	62
Tobramycin	0	5	19	28	8	3	8	23	36	18	5	0	9	44
Piperacillin/tazobactam	0	0	3	13	24	36	43	14	10	2	4	0	13	88
Cefotaxime	1	4	3	8	7	17	21	15	12	8	6	0	60	47
Ceftazidime	0	0	1	1	4	4	13	23	25	21	23	0	47	28
Cefepime	5	4	8	21	17	22	11	13	13	16	27	0	5	62
Meropenem	162	0	0	0	0	0	0	0	0	0	0	0	0	100
Cefoxitin	0	0	0	0	1	5	51	45	15	7	19	0	19	63
Temocillin	0	0	0	0	1	8	43	80	18	10	2	0	0	92
Ciprofloxacin	48	2	7	4	2	3	3	21	10	12	12	6	38	39
Trimethoprim/sulfamethoxazole	44	3	7	1	3	2	1	2	2	2	0	0	95	37

S, susceptible.

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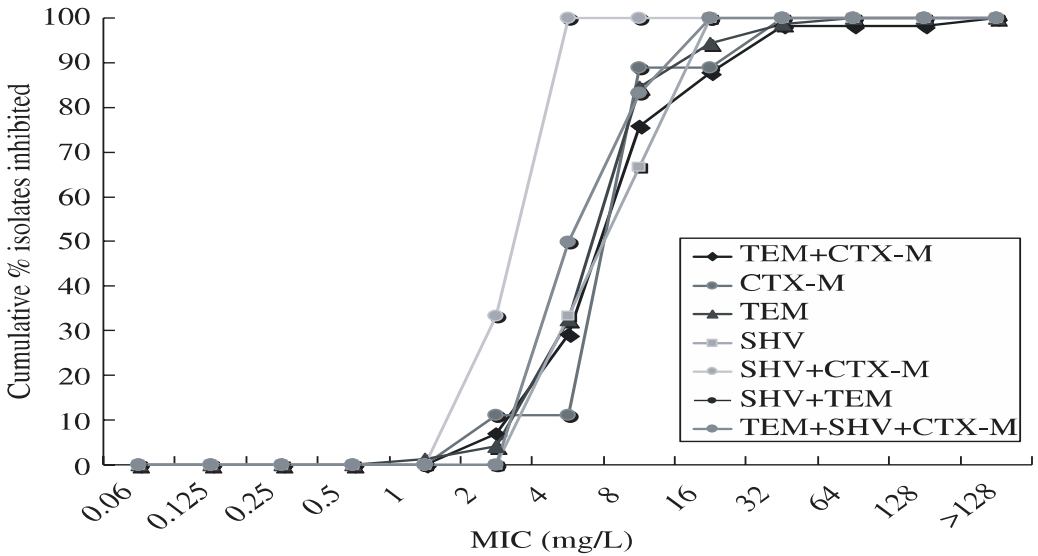


Figure 1. Distribution of temocillin MICs for ESBL-producing *E. coli* by ESBL family or combination.

Activity of temocillin in a murine model of urinary tract infection due to *Escherichia coli* producing or not producing the ESBL CTX-M-15

J. F. Soubirou[1,2], B. Rossi[1,2], C. Couffignal[1,2], E. Ruppé[1–3], F. Chau[2], L. Massias[1,4], R. Lepeule[5], F. Mentre[1,2] and B. Fantin[1,2,5*]

J Antimicrob Chemother
doi:10.1093/jac/dku542

2015

Table 2. Optimal dosing regimens used in mice for temocillin, imipenem and cefotaxime and their corresponding PK/PD parameters against susceptible and resistant *E. coli* strains

		PK/PD parameter			
	Optimal dosing regimen in mice	C_{max} (mg/L)	protein binding (%)	*f*T>MIC (%) for *E. coli* CFT073-RR (MIC)	*f*T>MIC (%) for *E. coli* CFT073-RR CTX-M-15 (MIC)
Temocillin	200 mg/kg every 2 h	199	16	82% (4 mg/L)	70% (8 mg/L)
Imipenem	100 mg/kg every 2 h	91	34	87% (0.5 mg/L)	87% (0.5 mg/L)
Cefotaxime	100 mg/kg every 2 h	128	12	100% (0.125 mg/L)	0% (>1024 mg/L)

C_{max}, peak value of total concentration at steady-state obtained from PK model for the three antibiotics; *f*T>MIC, percentage of time of the dosing interval during which free-drug concentrations remained above the MIC for the corresponding strain.

Results: MICs of temocillin and imipenem were 4/8 and 0.5/0.5 mg/L, for CFT073-RR and CFT073-RR Tc, respectively. *In vivo*, when given every 2 h (*f*T>MIC = 82% and 70%), temocillin was bactericidal and as effective as imipenem in kidneys against both strains without selecting resistant mutants. Temocillin remained active even when given every 4 h, generating an *f*T>MIC of 41% and 35%, which corresponded to a breakpoint of 16 mg/L in humans with the standard regimen.

Conclusions: Our observations support the consideration of a standard regimen of temocillin as an alternative to carbapenems for the treatment of UTI due to CTX-M-producing *E. coli* strains with an MIC of 16 mg/L or less.

Continuous versus intermittent infusion of temocillin, a directed spectrum penicillin for intensive care patients with nosocomial pneumonia: stability, compatibility, population pharmacokinetic studies and breakpoint selection

Raf De Jongh[1], Ria Hens[1], Violetta Basma[2], Johan W. Mouton[3], Paul M. Tulkens[2]* and Stéphane Carryn[2]

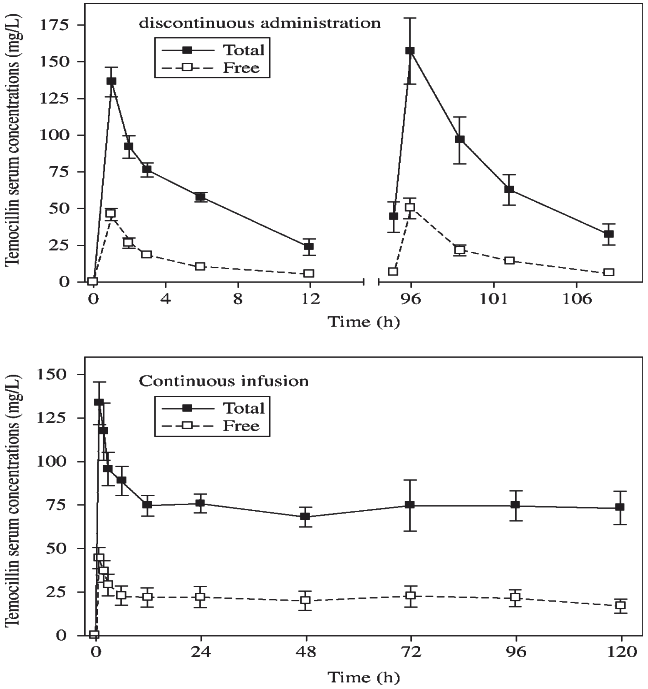


Figure 1. Serum concentrations (total and free) of temocillin in patients receiving temocillin. Upper panel: patients received 2 g every 12 h (discontinuous administration) with samples taken after the first administration (0–12 h) and 1 h before and after the ninth administration (95–108 h). Lower panel: patients received a loading dose of 2 g followed by CI at a rate of 4 g per 24 h (CI). All values are means + SD (n ¼ 6 for each treatment group).

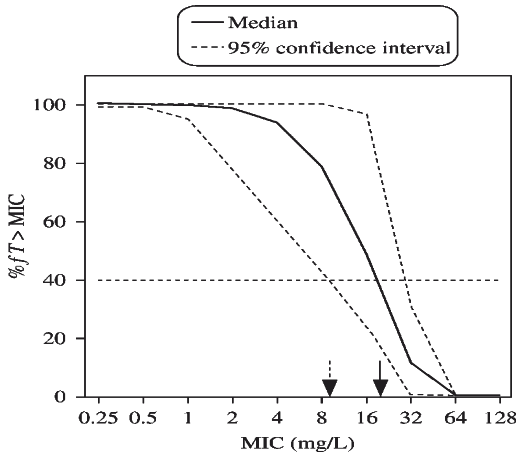


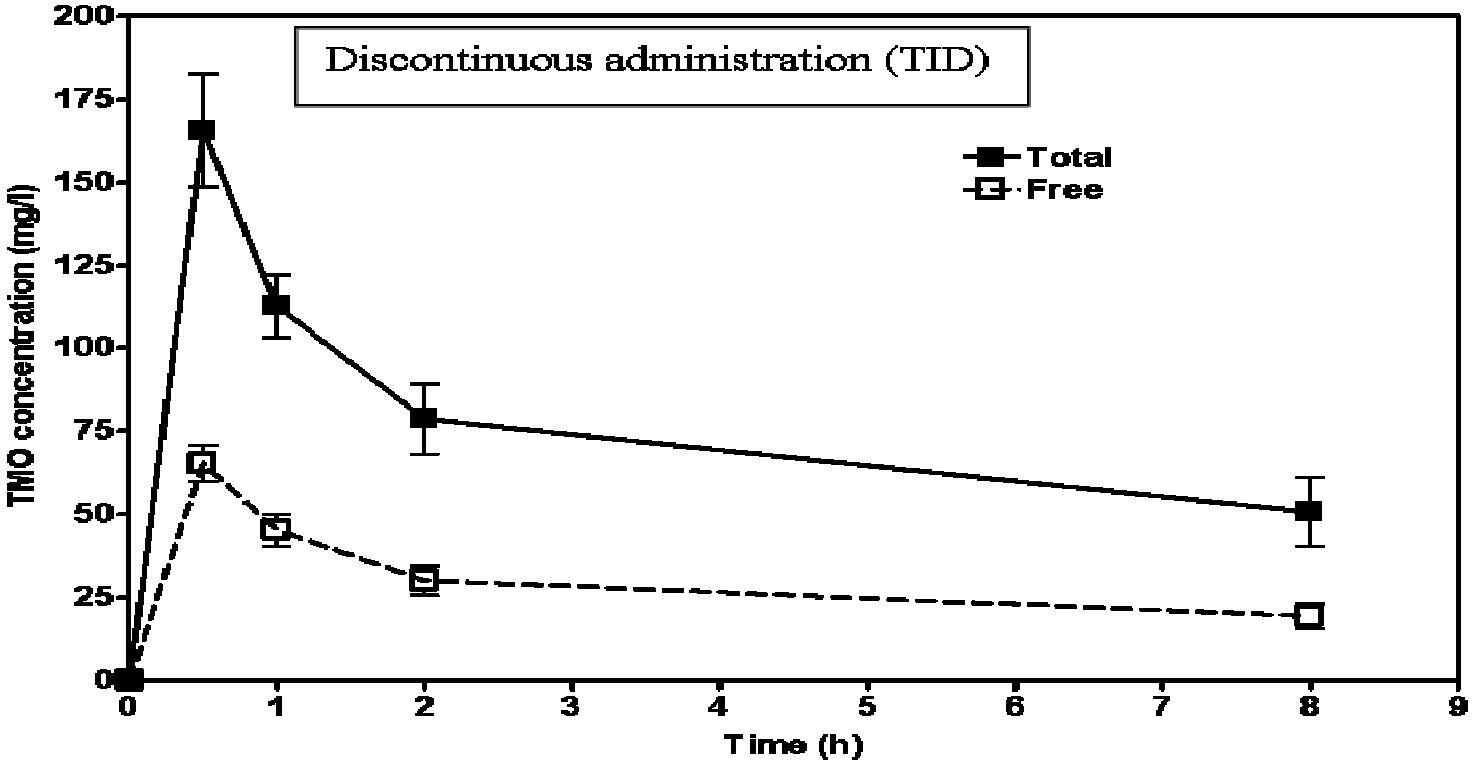
Figure 2. Probabilities of target attainment of temocillin (as obtained with the Monte Carlo simulation: solid line, median value; dotted lines, 95% confidence interval) for the currently registered treatment (2 g every 12 h), using the pharmacokinetic data of the six patients treated according to this dosage and schedule in this study (twice daily group). The abscissa shows the MIC range used for the simulations and the ordinate the fraction of time (as a percentage) during which free serum levels remain above the corresponding MIC. The horizontal dotted line indicates the 40% fT . MIC limit achieving a bacteriostatic effect and survival for penicillins in animal models with Gram-negative bacteria.[1] The highest MIC at which this target will be obtained is shown by the vertical arrows (arrow with solid line, median; arrow with dotted line, 95% probability).

Aim of the study

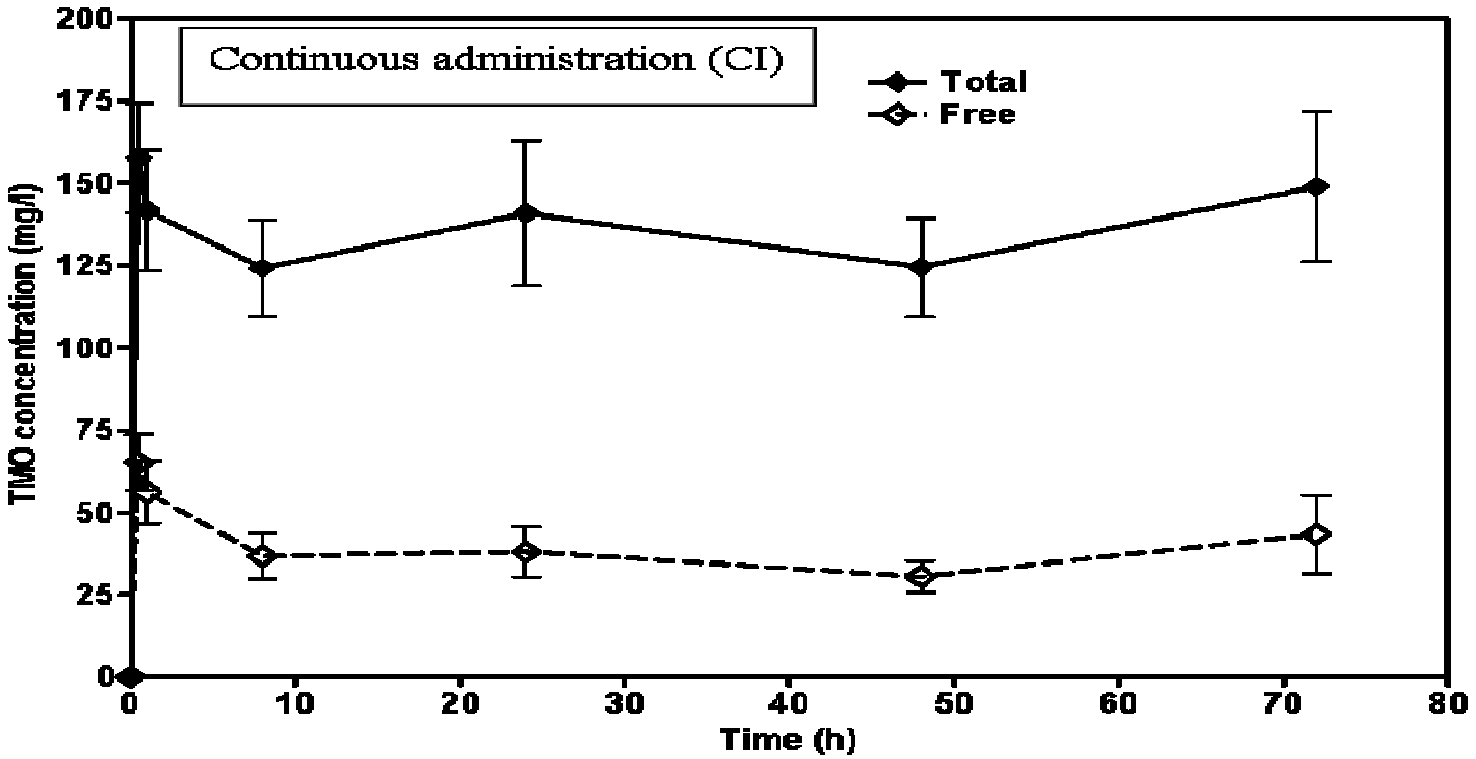
- Pharmacokinetics and safety of 6g daily of Temocillin
- Comparison of conventional administration (2g q8h – TID) vs. 6g/24h in continuous infusion (CI)
- PK/PD analysis

- Population : Critically ill patients with documented infection due to a Gram negative bacteria susceptible to Temocillin
- Setting : 2 Intensive care Unit (1 teaching hospital, and 1 general hospital)

PK/PD – Pharmacokinetic profile with discontinuous administration



PK/PD – Pharmacokinetic profile with continuous administration



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Journal of Antimicrobial Chemotherapy

Temocillin (6 g daily) in critically ill patients: continuous infusion versus three times daily administration

2014

Pierre-François Laterre[1], Xavier Wittebole[1], Sebastien Van de Velde[2]†, Anouk E. Muller[3], Johan W. Mouton[4], Stéphane Carryn[2]‡, Paul M. Tulkens[2]* and Thierry Dugernier[1,5]

	Group		
	three times daily[a]	continuous infusion[b]	CWH[c]
Recruitment			
patients enrolled, *n*	14	14	4
pharmacokinetic population, *n*	13	12	4
Demography			
male/female, *n*/*n*	6/8	11/3	0/4
age (years), mean ± SD	65 ± 15	68 ± 11	60 ± 16
weight (kg), mean ± SD	68 ± 12	71 ± 15	58 ± 7
BMI (kg/m^2), mean ± SD	24 ± 4	24 ± 5	23 ± 2
CL_{CR} (mL/min), mean ± SD	82 ± 48	56 ± 34	NA
severity score on admission			
APACHE II,[25] median	16	17	20.5
SOFA,[19] median	7	8.5	16[d]
Infection type			
LRTI (positive blood culture), *n*	6	4 (1)	1
IAI (positive blood culture), *n*	6 (2)	8 (3)	3 (2)
UTI (positive blood culture), *n*	1 (1)	1	0
BSI of unknown origin, *n*	1	1	0
Treatment parameters and outcomes			
treatment duration (days), mean ± SD	6 ± 2	7 ± 5	5 ± 3
dosage adjustment for CL_{CR}			
50–31 mL/min, *n*	3	1	0
30–10 mL/min, *n*	2	4	0
clinical cure, % (*n*/*n*)	79 (11/14)	93 (13/14)	75 (3/4)
overall ICU mortality, % (*n*/*n*)	36 (5/14)	14 (2/14)	50 (2/4)

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Table 1. Temocillin dose adjustment for CL_{CR}

	Daily dose	
CL_{CR} (mL/min) or condition	three times daily[a]	continuous infusion[b]
>50	3×2 g	6 g/24 h
50–31	3×1 g	3 g/24 h
30–10	1×1.5 g	1.5 g/24 h
<10	1×750 mg	750 mg/24 h
CVVH	NA	750 mg/24 h

NA, not applicable.
[a]Administration as 30 min infusions at 8 h intervals.
[b]Administration by continuous infusion over 24 h. Each patient received a 2 g loading dose.

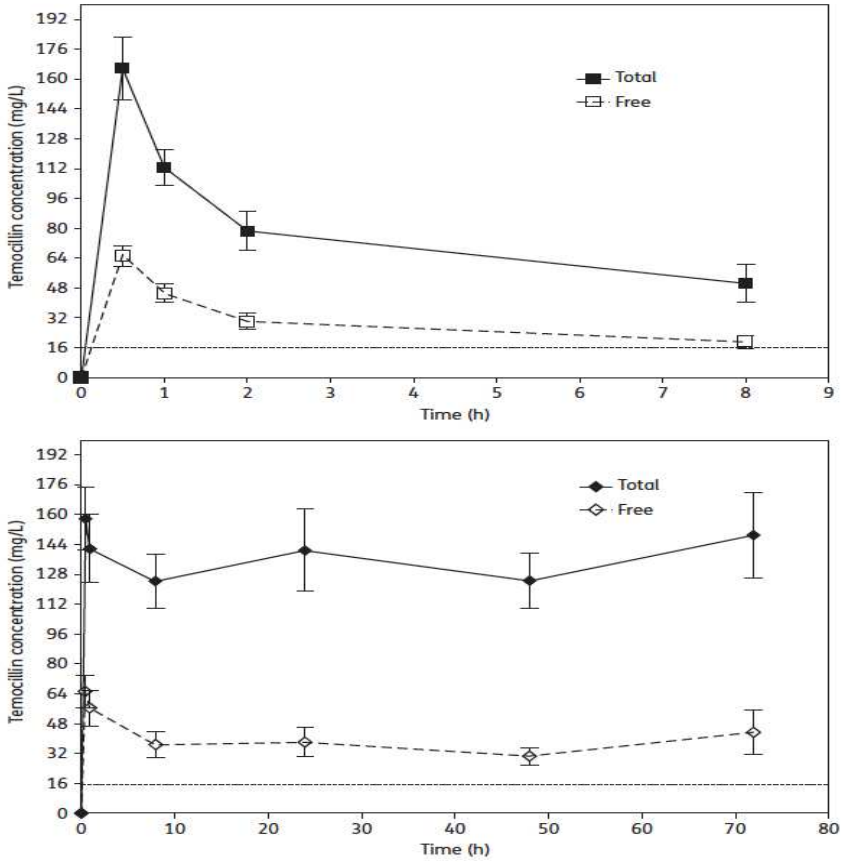

Figure 1. Total and free temocillin serum concentrations. Upper panel: patients ($n=13$) in the three times daily group (daily dose of 6 g divided into three administrations at 8 h intervals). Lower panel: patients ($n=11$) in the continuous infusion group (2 g loading dose followed by a 6 g/24 h continuous infusion). All values are means ± SEM. The horizontal broken line is drawn at a serum concentration value of 16 mg/L (potential susceptibility breakpoint).

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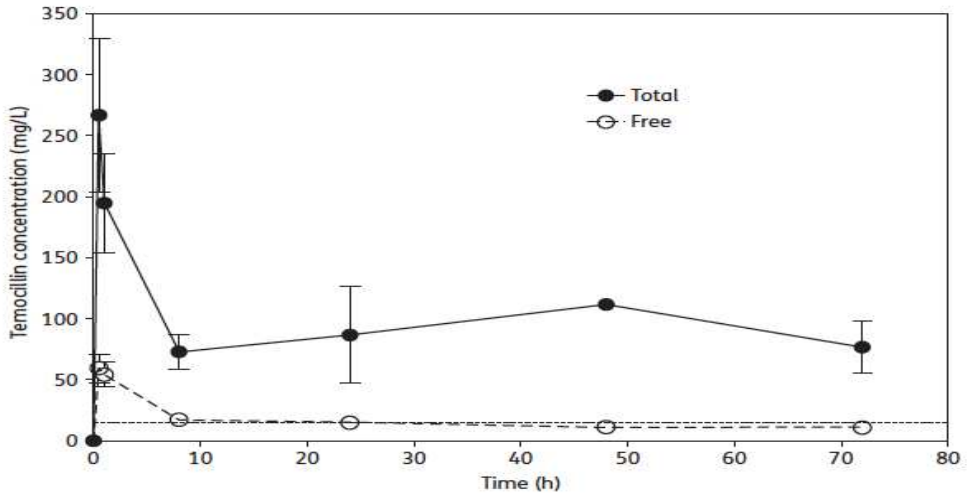

Figure 2. Total and free temocillin serum concentrations in patients ($n=4$) undergoing CVVH (750 mg loading dose followed by 750 mg/24 h by continuous infusion). All values are means ± SEM. The horizontal broken line is drawn at a serum concentration value of 16 mg/L (potential susceptibility breakpoint).

PK/PD - *f*T>MIC

- **Fraction of time (%) during which the free serum concentration (median values) remains above a given MIC (*f*T>MIC) after administration of 2g of temocillin every 12h (q12h; BID), every 8h (q8h; TID) or 6g of temocillin per day by continuous infusion.**

	*f*T>MIC (in %) of free temocillin		
MIC (mg/L)	4g/24h – BID[1]	6g/24h – TID[2]	6g/24h – CI[2]
4	100.0	100.0	100.0
8	79.7	99.3	100.0
16	**45.1**	**98.5**	**100.0**
32	9.5	20.4	59.6

1Data from De Jongh et al., 2007
2Data from the present study

Retrospective:Material and Methods

- **Hundred and nine infection episodes developing in 101 patients and treated with TEM were reviewed.** For all patients, age, severity score (APACHE II and SOFA), source of infection, type of microorganism, susceptibility, underlying conditions and outcome were collected and analysed.

- **For bloodstream infections, the observed outcome was compared to the predicted outcome using APACHE II score.**

Material and Methods (2)

- For the treatment of bloodstream infections, TEM was given as a first line therapy in 8/45 episodes (17.7 %) or after microbiological documentation to narrow the antibiotic spectrum in 37/45 episodes (82.2 %).

- TEM daily dose was 6 gr. given as a continuous infusion and adjusted according to creatinine clearance.

Results (1)

- Forty three patients developed 45 episodes of bacteremia.
- Forty nine patients had documented infections without positive blood culture.

- Nine patients were excluded because of no documentation, antibiotic therapy < 48 h or care limitation.

Table 1 : Baseline characteristics of patients with and without positive blood culture

	Positive Blood Culture	Negative Blood Culture
N	43	49
Age (mean ± SD)	61.3 ± 14	58.8 ± 15
APACHE II (mean ± SD)	23.4 ± 9.4	16.3 ± 6.4
SOFA (mean ± SD)	8 ± 3.9	7.8 ± 32
COMORBIDITIES ▪ Cirrhosis (child C) ▪ Cancer (active) ▪ Immunosuppression (active) ▪ Chronic dialysis	 8/43 (18.6 %) 12/43 (27.9 %) 11/43 (25.6 %) 3/43 (6.9 %)	
Outcome (Hospital mortality)	14/43 (32.5 %)	10/49 (20.4 %)

Table 2 : Source of infection for all patients

	Positive Blood Culture (n = 45)	Negative Blood Culture (n = 49)
Source of infection		
➢ Intraabdominal	13/45 (29 %)	12/49 (24.5 %)
➢ LRTI	7/45 (15.5)	26/49 (53 %)
➢ UTI	9/45 (20 %)	10/49 (20.4 %)
▪ Catheter-related sepsis	4/45 (9 %)	
➢ Primary bloodstream infection	3/45 (6.7 %)	
➢ Other	9/45 (20 %)	1/49 (2 %)

Table 3 : Type of microorganisms for all patients and infection episodes

	Positive Blood Culture	Negative Blood Culture
➢ *E. coli*	23 (53.3 %)	18 (29.5 %)
➢ *E. cloacae*	1 (15.5 %)	15 (24.5 %)
➢ *E. aerogenes*	3 (6.7 %)	4 (6.5 %)
▪ *Klebsiella spp*	3 (6.7 %)	11 (18 %)
➢ *Citrobacter spp*	2 (4.4 %)	2 (3 %)
➢ *Other Enterobacteriaceae*	6 (13.3 %)	11 (18 %)
➢ *ESBL*	6 (13.3 %)	ND /

Temocillin use in England: clinical and microbiological efficacies in infections caused by extended-spectrum and/or derepressed AmpC β-lactamase-producing Enterobacteriaceae

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Table 1. Clinical and microbiological efficacies stratified by ESBL/dAmpC status and type of infection (UTI, BSI, HAP)

Variable	UTI	BSI	HAP	Total
Clinical cure[a]				
ESBL/dAmpC negative	6/7 (86%)	15/18 (83%)	4/5 (80%)	25/30 (83%)
ESBL/dAmpC positive	26/28 (93%)	19/23 (83%)	2/2 (100%)	47/53 (89%)
Total[b]	38/42 (90%)	35/42 (83%)	6/8 (75%)	79/92 (86%)
Microbiological cure[a]				
ESBL/dAmpC negative	6/7 (86%)	9/11 (82%)	4/5 (80%)	19/23 (83%)
ESBL/dAmpC positive	23/27 (85%)	18/22 (82%)	no data	41/49 (84%)
Total[b]	34/39 (87%)	28/34 (82%)	4/6 (67%)	66/79 (84%)

[a]Clinical and microbiological cure rates were not statistically different between patients infected with ESBL/dAmpC-positive and -negative strains ($P > 0.05$).
[b]Numbers include patients infected with strains of undefined ESBL/dAmpC status.

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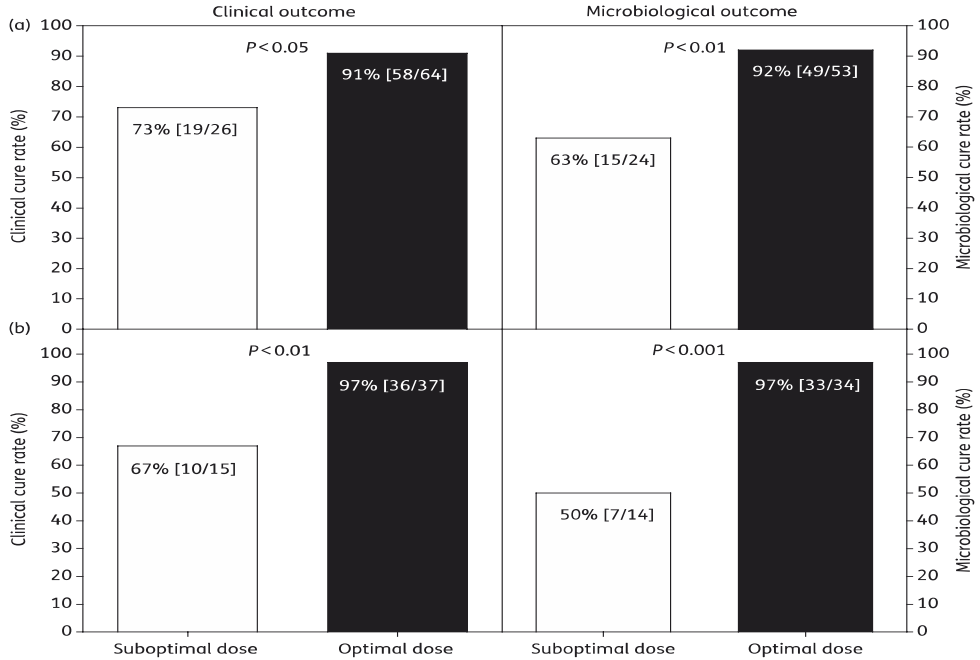

Figure 1. Effect of temocillin dosage regimen on efficacy. Clinical (left panel) and microbiological (right panel) efficacies of temocillin in patients treated by suboptimal (1 g twice daily or renally adjusted equivalent) and optimal (2 g twice daily or renally adjusted equivalent) dosage regimens. (a) All patients (two patients receiving 2 g twice daily were excluded because of a lack of information about their renal function). (b) Patients infected with ESBL/dAmpC-positive strains (one patient receiving 2 g twice daily was excluded because of a lack of information about his renal function).

Temocillin in ESBL infections

Period : 2009-2014 **Temocillin** in 202 pts **ESBL N=40**

Critically Ill treated by Temocillin (2gr bolus, 6gr daily continuous infusion)

N = 40				
Infection			**ESBL**	
IAI	16/40			
HAP/VAP	16/40		E coli 16	(40%)
UTI+BSI	2/40		N E coli 24	(60%)
BSI	6/40			
Severity				
AII	20,4	(8-35)		CVVH 5
SOFA	7,47	(4-14)		
Conc AB	Ampi 5	Vanco 10	Oxa 1	
Clin Cure	35/40	Mortality	9/40	

Pending questions

- **Controlled trials**
  - LRTI, IAI
  - Documented infections/Empiric +/- combination ?
- **Tissue concentration**
  - Lung
  - Intra-abdominal

Temocillin tissue concentration : SAP

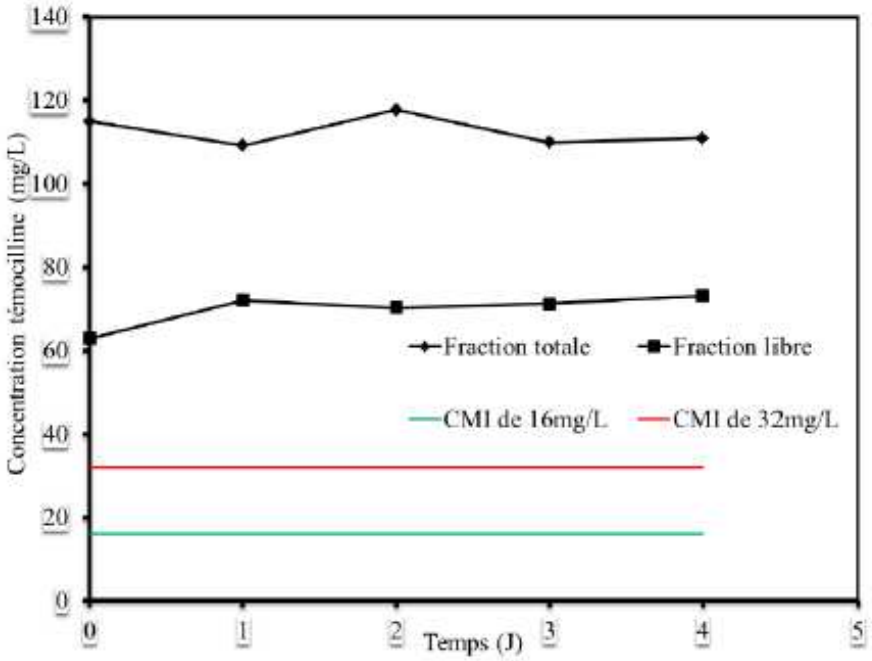

Figure 2 : Profil de la concentration sérique de témocilline en fonction du temps pour une patiente en soins intensifs après administration d'une dose de 6 g par jour en infusion continue.

Pancreas necrosis concentration :

186 mg/Kg , (>150% serum)

Conclusions

- Prolonged clinical experience
- Cure rate seems acceptable
- Alternative to Carbapenems in ESBL
- Continuous infusion offers free-drug levels > MIC and breakpoint
- Higher dosage well tolerated and indicated

Urgent need for larger, controlled studies in patients with non-UTI infections

Conclusions