

Pharmacokinetics and PK/PD of temocillin in non-ICU urinary tract infection patients with various stages of renal insufficiency

Gert-Jan Wijnant¹, Perrin Ngougni Pokem¹, Marie Coessens²,
Eleonora Cottone², Lieven Goeman³, Steven Vervaeke², Françoise Van Bambeke¹

1. Pharmacologie Cellulaire et Moléculaire, Louvain Drug Research Institute, Université catholique de Louvain, Brussels, Belgium
2. Laboratory Medicine Department, AZ Delta Hospital, Roeselare, Belgium
3. Urology Department, AZ Delta Hospital, Roeselare, Belgium

Date: 24/04/2022

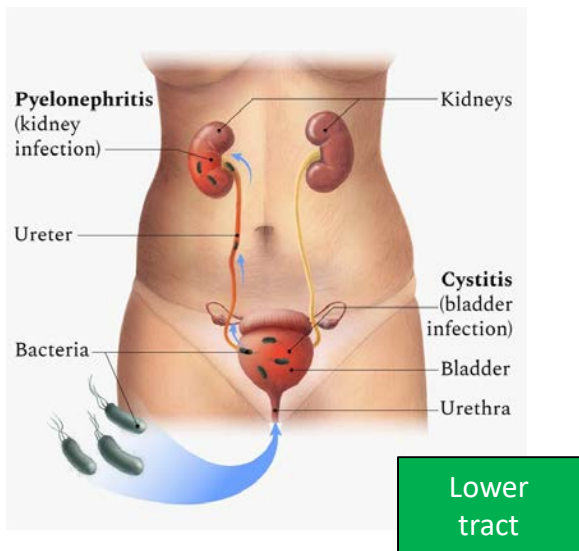
Abstract number: 02597

Session: Clinical PK/PD studies and TDM to improve dosing of anti-infectives

Treatment of urinary tract infection (UTI)

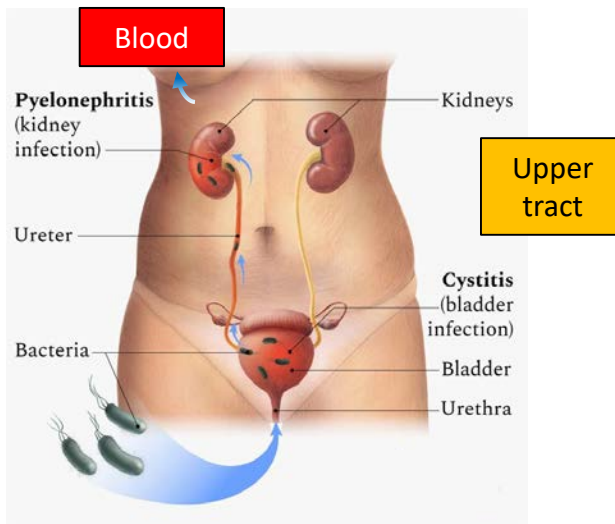
“Simple” UTI

- Short-course oral ABs at home



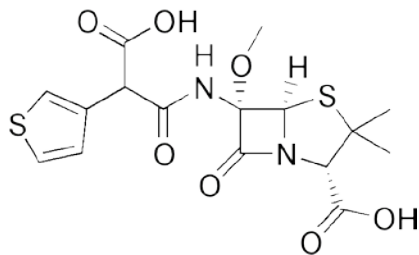
“Complicated” UTI ± urosepsis

- Longer-course IV ABs in hospital
- ESBL Enterobacterales: carbapenems



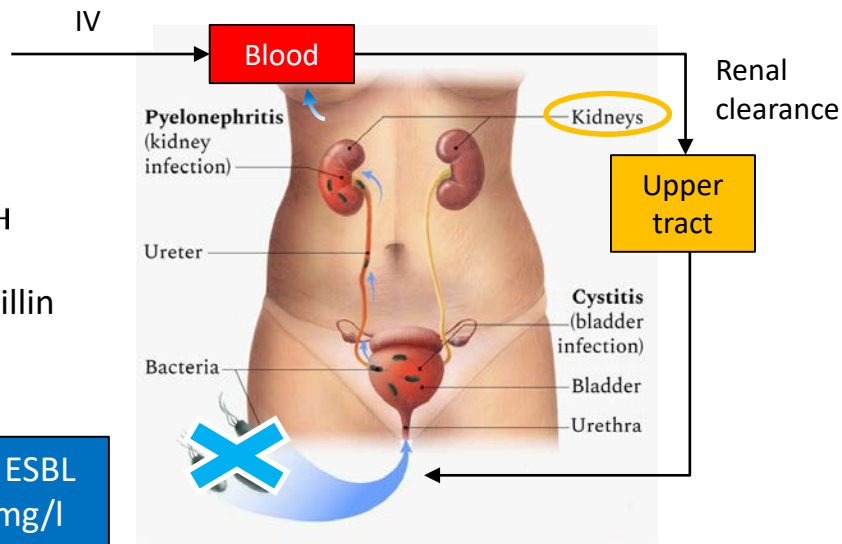
Alternative to carbapenems in cUTI: temocillin

- “Forgotten” narrow-spectrum penicillin AB (°1980s)
- Routinely used in Belgium & some other EU countries (Negaban®)
- Indications: infections caused by susceptible Gram (-), cUTI > pneumonia



Temocillin = 6- α -methoxy-ticarcellin

Active against Enterobacterales \pm ESBL
(β -lactamase stable): MIC = 1-16 mg/l



Temocillin dosing in cUTI: controversial



Negaban® Summary of Product Characteristics (SPC):

Population	Posologie par 24 heures	
	Dosage standard	Dosage élevé*
Adultes	4 g en 2 administrations (2 g/12 h) (injections I. M., I. V. ou perfusion)	6 g en 3 administrations (2 g/8 h) (injections I. V. ou perfusion) ou sous forme de perfusion continue (administrer une dose de charge de 2 g avant de commencer la perfusion continue)

4g/day = standard dose cUTI
 Dose ↓ renal insufficiency (RI)
 Dose ↑ critically ill (ICU)

Clairance de la créatinine (ml/min)	Posologie : dose standard	
	Dose par administration	Intervalle entre administrations
supérieure à 60	2 g	12 h
60 à 30	1 g	12 h
30 à 10	1 g	24 h

Temocillin dosing in cUTI: controversial



Negaban® Summary of Product Characteristics (SPC):

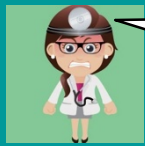
Population	Posologie par 24 heures	
	Dosage standard	Dosage élevé*
Adultes	<p>en 2 administrations de 2 g/12 h (injections I. M., I. V. ou perfusion)</p>	<p>6 g en 3 administrations (2 g/8 h) (injections I. V. ou perfusion) ou sous forme de perfusion continue (administrer une dose de charge de 2 g avant de commencer la perfusion continue)</p>

4g/day = standard dose cUTI
Dose ↓ renal insufficiency (RI)
Dose ↑ critically ill (ICU)

Clairance de la créatinine (ml/min)	Posologie : dose standard	
	Dose par administration	Intervalle entre administrations
supérieure à 60	2 g	12 h
60 à 30	1 g	12 h
30 à 10	1 g	24 h

EUCAST 2020 MIC breakpoint:

- “Susceptible, increased exposure” (I): $I \leq 16$ mg/l
- 6g/day = “new” standard dose for most cUTI

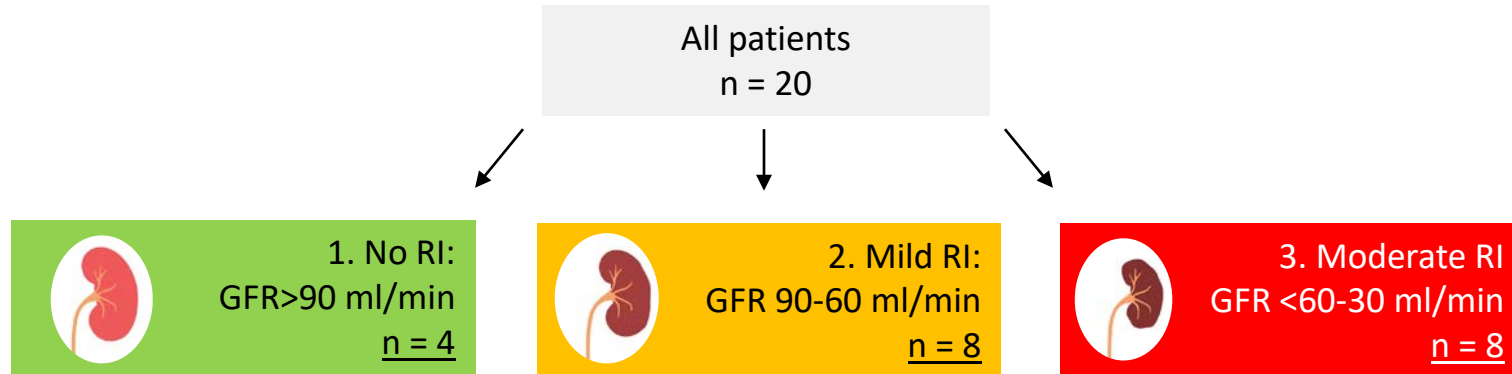


... based on 6g/day PK/PD in ICU pneumonia!

Study aim

Evaluate the PK and PK/PD of temocillin in non-ICU cUTI patients to support optimal dose selection based on renal function (GFR)

1. All patients: 4g/day (2g/12h, IV) regardless of GFR → blood (≥ 4 doses)
2. Analyze total & protein-free drug levels in plasma (LC-MS/MS)
3. Retrospectively divided patients into 3 groups \neq stage of RI:



Patient characteristics for the 3 groups

Parameters	Demographic			Clinical & microbiological			Biological	
	N	GFR (ml/min)	Age (years)	Urosepsis (%)	Temocillin MIC (mg/l)	CRP (mg/l)	Plasma Protein (mg/l)	Plasma albumin (mg/l)
1. None	4	> 90	46.5 (35-72)	75% (3/4)	8 (8-8)	88.3 (57-118)	69.2 (60-78)	41.8 (32.9-50.6)
2. Mild	8	72 (61-89)	75.5 (40-90)	50% (4/8)	8 (4-32)	104 (9-385)	65.9 (53-78)	41.5 (27-50.6)
3. Moderate	8	43.5 (34-55)	80 (65-91)	87.5% (7/8)	8 (4-32)	54.5 (26-328)	70.4 (62- 72.7)	30.7 (29.4 – 32)
Significant ≠? (Kruskal-Wallis)		* (P < 0.05)	ns	ns	ns	ns	ns	ns

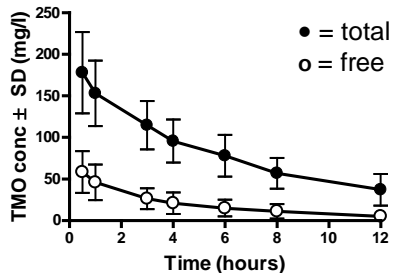


Trend GFR ↓ ~ age ↑, severe illness ↑, albumin ↓

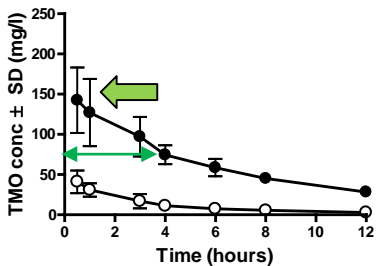
Plasma PK for 2g/12h temocillin (IV)

GFR ↓ ~ C_{max} ↑ T_{1/2} ↑

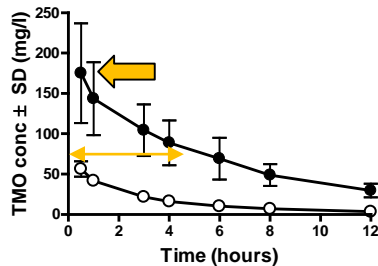
All patients (n=20)



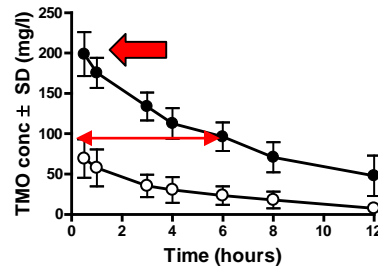
No renal insufficiency (n=4)
GFR >90 ml/min



Mild renal insufficiency (n=8)
GFR 90-60 ml/min

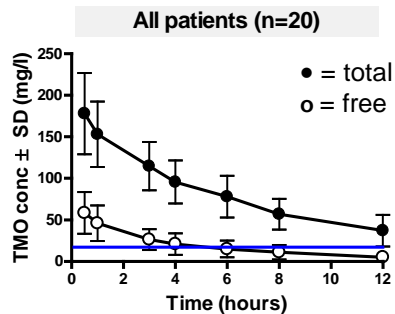


Moderate renal insufficiency (n=8)
GFR <60-30 ml/min



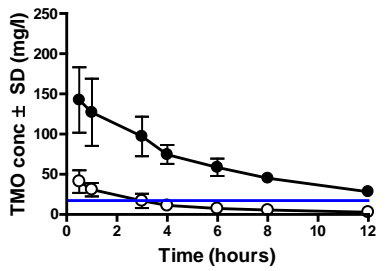
Plasma PK/PD for 2g/12h temocillin (IV)

Penicillins = time-dependent
Dosing ~ max %fT > MIC

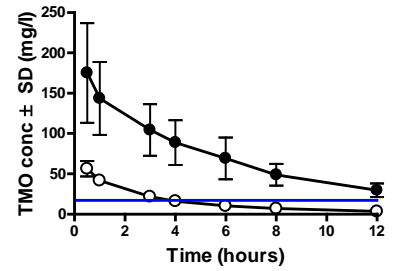


MIC = 16 mg/l

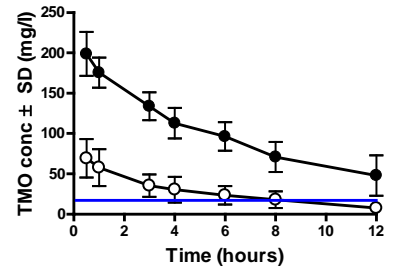
No renal insufficiency (n=4)
GFR >90 ml/min



Mild renal insufficiency (n=8)
GFR 90-60 ml/min



Moderate renal insufficiency (n=8)
GFR <60-30 ml/min

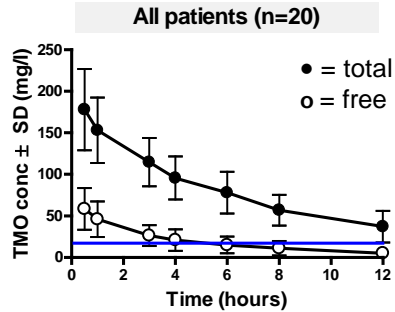


Plasma PK/PD for 2g/12h temocillin (IV)

EUCAST

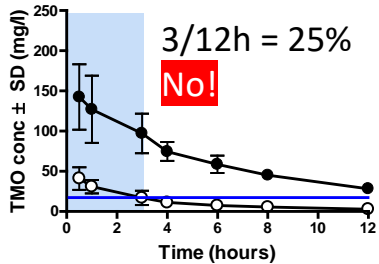
3/8h = 37.5%
Yes!

Common PK/PD target
≥ 35% $fT > MIC$:
is 2g/12h high enough?

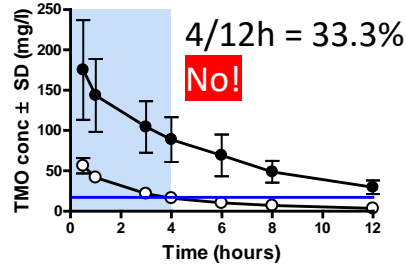


MIC = 16 mg/l

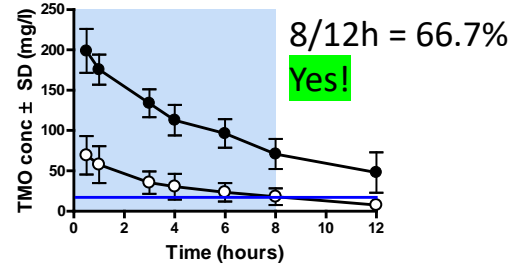
No renal insufficiency (n=4)
GFR >90 ml/min



Mild renal insufficiency (n=8)
GFR 90-60 ml/min



Moderate renal insufficiency (n=8)
GFR <60-30 ml/min



Conclusion

- 1st study PK/PD temocillin standard dose (4g/day) in the most common patient population (non-ICU cUTI)
- Based on our results, the current daily doses in SPC for cUTI might be too low:

GFR (ml/min)	SPC	Proposed
>90	4g	6g
60-30	4g	4/6g? PTA!
<60-30	2g	4g

- But: 100% cure at 4g/day!
 - MIC = 8 mg/l vs 16 mg/l?
 - Drug exposure plasma vs urine?

Thanks



Nurses & patients
Marie Coessens
Eleonora Cottone
Dr Lieven Goeman
Dr Steven Vervaeke



Perrin Ngougni Pokem
Virginie Mohymont
Ambre Freyberg
Alix Mangin
Romain Tricot
Prof Françoise Van Bambeke

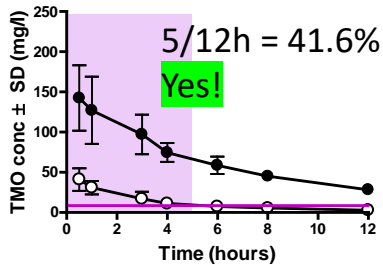
Back-up slides

Plasma PK/PD for 2g/12h temocillin (IV)

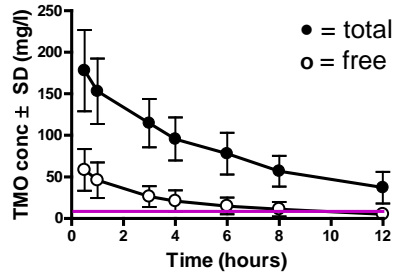
EUCAST

5/8h = 62.5%
Yes!

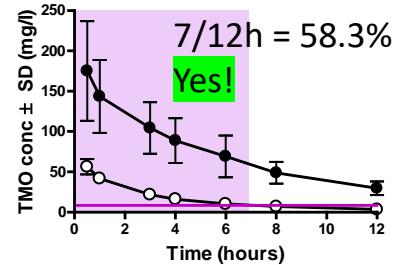
No renal insufficiency (n=4)
GFR >90 ml/min



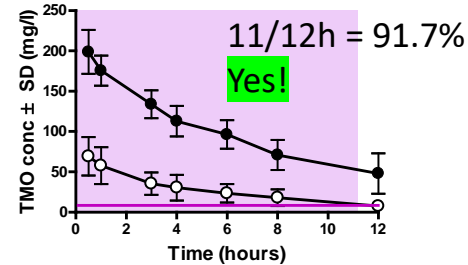
All patients (n=20)



Mild renal insufficiency (n=8)
GFR 90-60 ml/min



Moderate renal insufficiency (n=8)
GFR <60-30 ml/min



Common PK/PD target
 $\geq 35\% fT > MIC$:
is 2g/12h high enough?

MIC = 8 mg/l = "old" BE breakpoint