Population Pharmacokinetics of Imipenem on Burn Patients

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Physiopathology of Burns

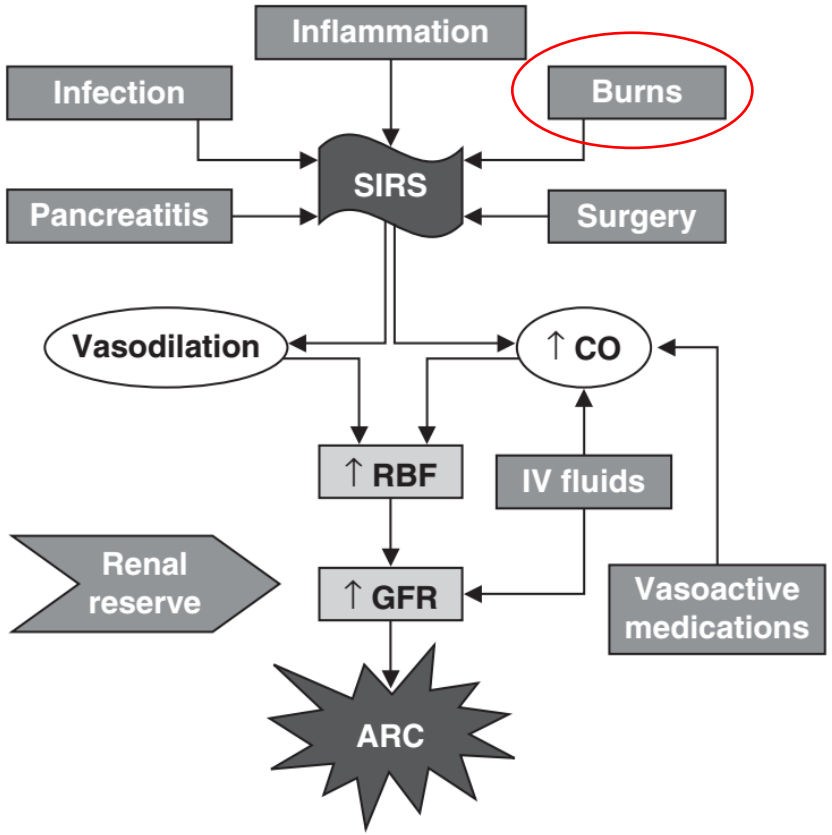
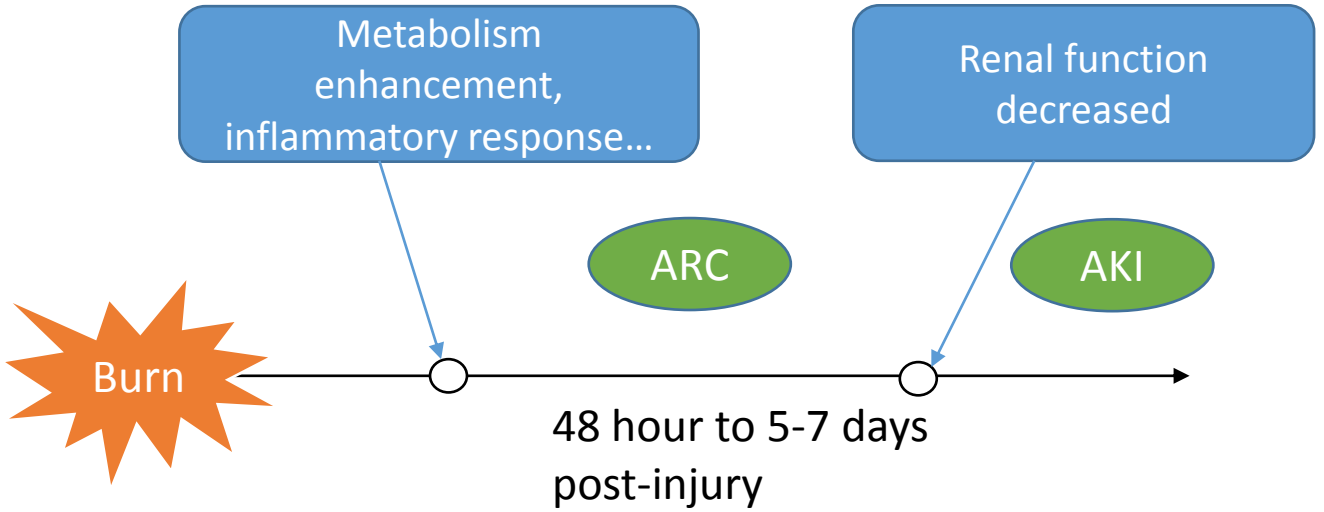


Fig. 2. Mechanisms underlying augmented renal clearance (ARC) in the critically ill. **CO** = cardiac output; **GFR** = glomerular filtration rate; **IV** = intravenous; **RBF** = renal blood flow; **SIRS** = systemic inflammatory response syndrome; ↑ indicates increase.

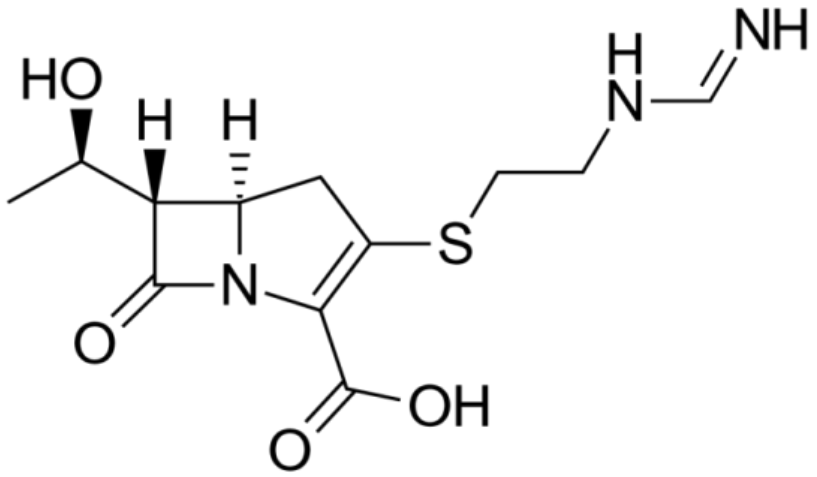
Udy et. al., Clin. Pharmacokinetics (2010)



Pharmacokinetic parameters changed (Vd, CL,…)

Drug blood level altered

Imipenem for infection on burn patients

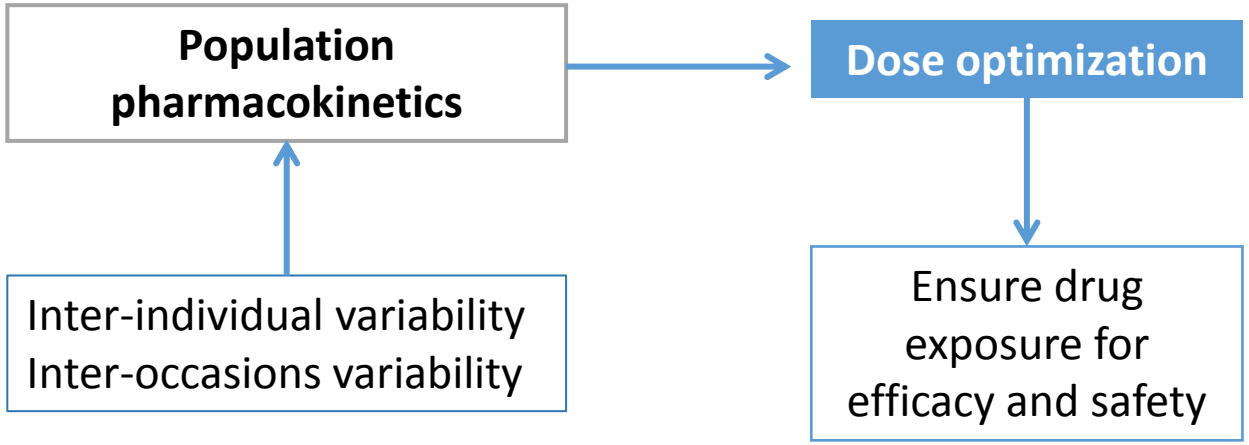


Imipenem

Renal elimination 70% [1]

In ICU, National Institute of Burns

- Carbapenems was most consumed antibiotics
- Imipenem was first choice among carbapenems for servere infection in burn patients.
- The resistance of hospital infectious pathogens was emerging [2]



1. *AHFS Drug information* (2011), imipenem-clilastatin
2. Luong QA (2016), Journal of disaster medicine and burns injuries [Vietnamese]

Pharmacokinetic variabilities on burned patients

Baseline **Occasion 1** **Occasion 2**

Inter Individual variation (IIV)

Patient 1

Patient 2

Patient n

ARC

AKI

Renal failure

Inter occasion variation (IOV)

Should empirical dose fit all?

Pharmacokinetic of imipenem on burned patients

The study aimed:

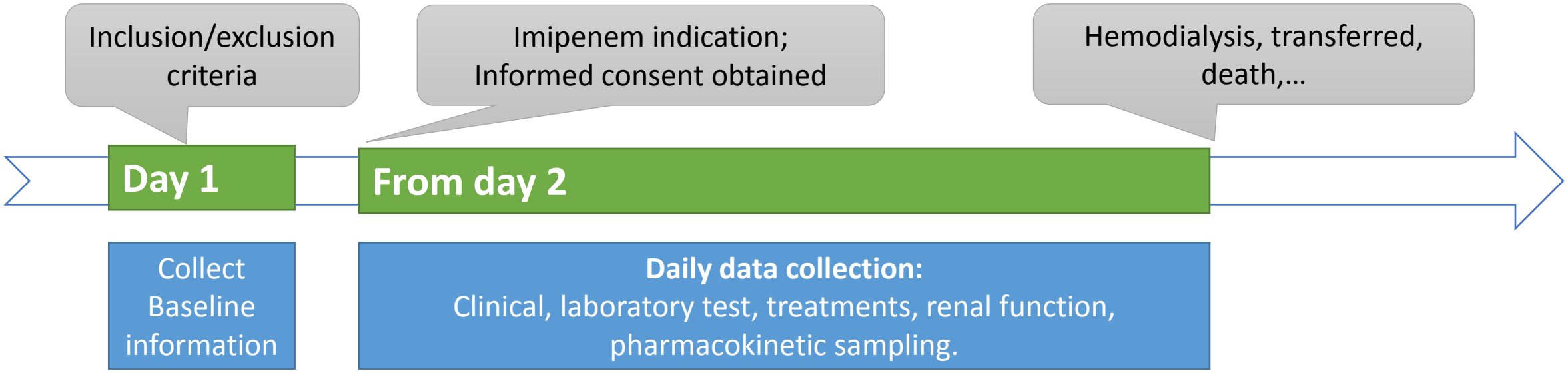
- To estimate population PK paramenters (including IIV and IOV)

- To explore potential covariates influencing PK properties of imipenem on burn patients.

Methods – Patients and data collection

Burned patients in Intensive Care Unit, National Institute of Burns of Vietnam;

Inclusion	Exclusion
✓ Age ≥ 18 ✓ Hospitalized within 72 hours after injury ✓ Injure ≥ 20% body surface area ✓ Imipenem indication	× Renal failure or other serious conditions before injury. × Refuse to participate into the study



Methods - Pharmacokinetic sampling

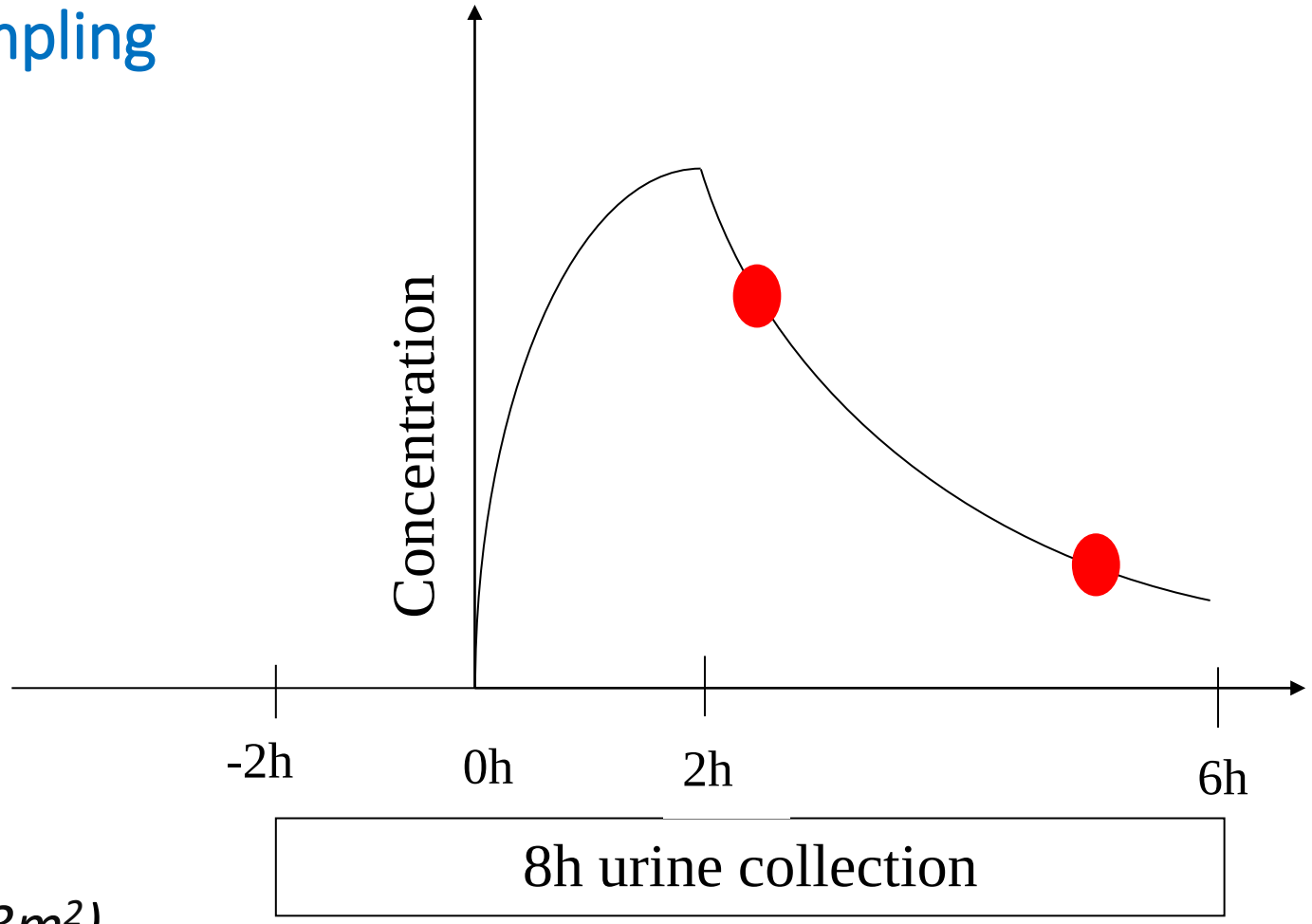
Sampling occasions:

+ At steady state (After 12 h)
+ 5-7 days after hospitalization
+ Optional: AKI (AKIN 2 or higher)

Sample set of one occassion:

+ 2 plasma samples (HPLC analysis)
+ A 8h urine sample
+ A plasma creatinine sample

(ARC: 8h-urine Clcr > 130 ml/min/1,73m²)



Data analysis

+ Nonlinear mixed effect model
+ Monolix 2016R1

Results – Baseline and follow up monitoring

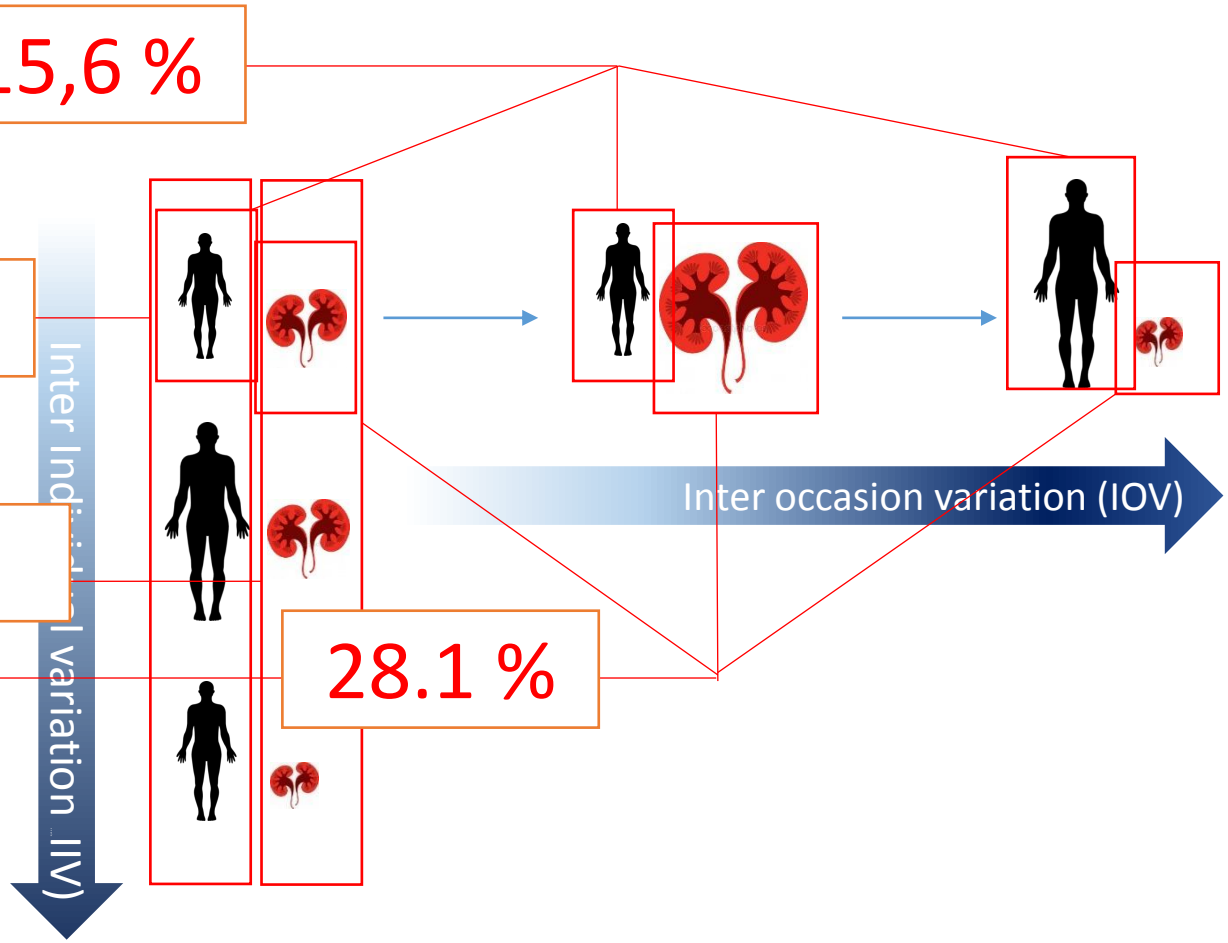
Parameters	n	(%)
Gender (Male)	15	(62.5)
Age (yearrs) (#)	38.9	(17.5)
SOFA score ($)	5	(4 - 6)
APACHE II score ($)	14	(11 – 18)
eGFR (ml/min/1,73m^2)	85.9	(29.4)
Burned surface (m^2) (#)	50.8	(17.3)
To hospitalization (hrs) ($)	4.5	(3 - 9.5)
To imipenem use (days)($)	5	(3-7)

($) mean (interquartile range);
(#) mean (standard deviation)

Parameters	n	(%)
Imipenem dosage (n=47)		
1g q.i.d.	38	(80.9)
1g t.i.d.	7	(14.9)
0,5g q.i.d.	1	(2.1)
0,5g t.i.d.	1	(2.1)
Imipenem courses (days) (#)	7.5	(6 – 10)
Patients with ARC (N=24)	13	(54.2)
Occations with ARC (N = 47)	18	(38.3)
Occation(s) per patient		
1	6	
2	30	
3	3	
4	8	

Results – Basic pharmacokinetic model

	Estimation (95% CI)
Pop. Vd (L)	33.5 (28.2-38.8)
IIV (CV%)	18.2
IOV (CV%)	15.6
Pop. Cl (L/h)	18.8 (15.9-21.7)
IIV (CV%)	27.0
IOV (CV%)	28.1
Residual (CV%)	27.2



IIV: inter individual variation
IOV: Inter occasion variation
CV%: Coefficient of variation

From Pop PK modelling: one compartment with proportional error showed best fit.

Results – Covariate model

	Estimation (95% CI)	p
Vd (L)		
Non-ARC	32.6 (26.7-38.5)	
ARC	33.6 (26.5-40.7)	0.83
Age (10 years) (*)	0.874 (0.802-0.952)	0.002
Cl (L/h)		
Non-ARC	16.4 (14.24-18.56)	
ARC	24.9 (20.6-29.2)	<0.001
Age (10 years) (*)	0.872 (0.816-0.932)	<0.001

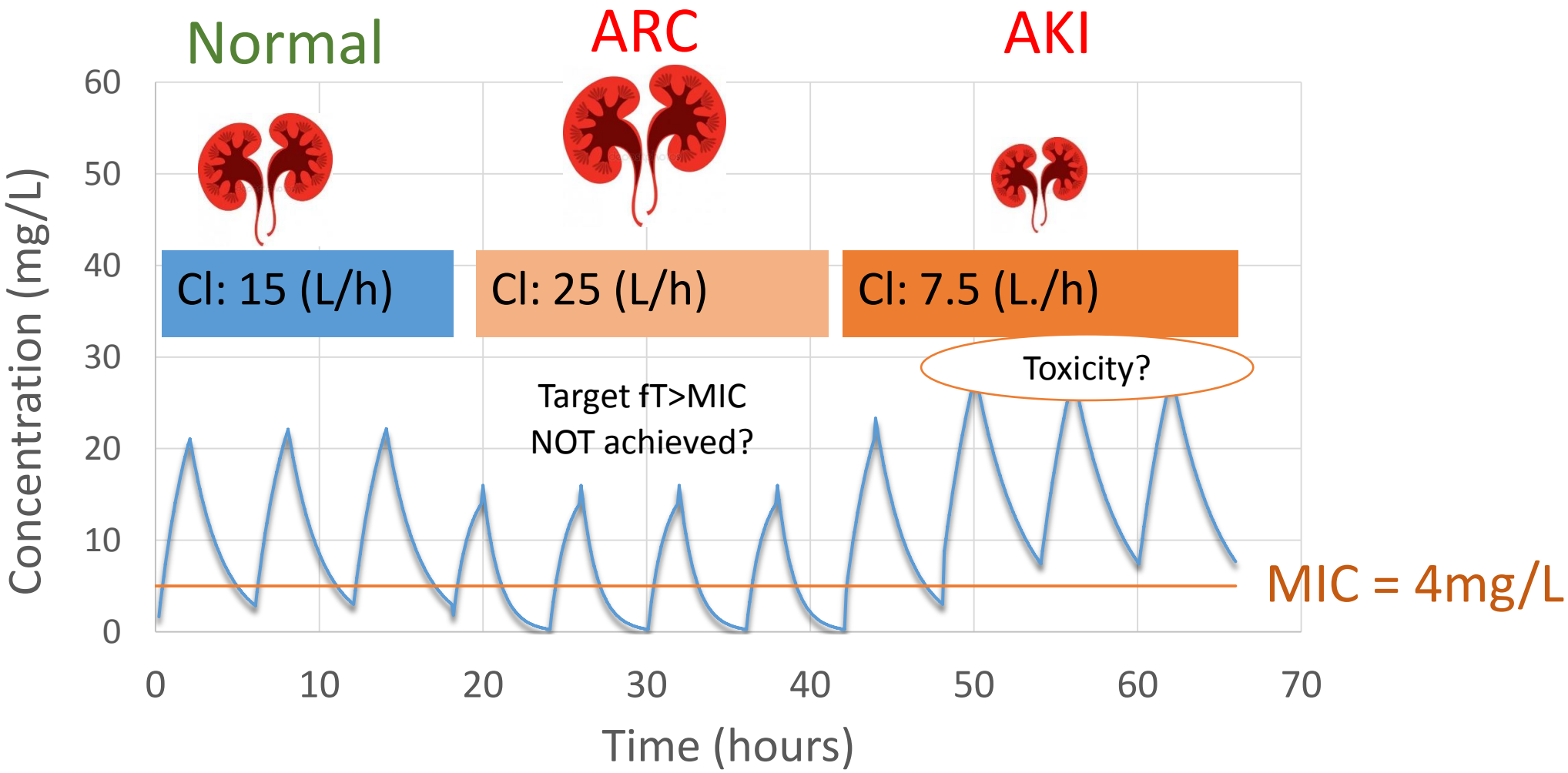
10 years older, ↓ 13% Vd

10 years older, ↓ 13% Cl

Age was centralized by mean value of 38.9;
(*) present relative reduction of parameters;

Elimination rate may be unchanged
Dose adjustment is not neccessary

Inter-occasions variability, The risk?



Simulated imipenem concentration in a burn patient (one compt.)

Fixed: Dose 1000mg IV infusion for 2 h; dose interval 6h; Vd 33 L

Conclussions

- Imipenem PK parameters (Cl, Vd) substantial varied between burned patients and between occasions.
- Age was significant covariate predicting Cl and Vd, ARC showed no effect on Vd but it did predict Cl.
- Target PK/PD may not be attained in ARC patients. Monitoring urine Clcr may be the solution for detecting ARC and then adjusting imipenem's dose to ensure the efficacy.

Thank
You