JNI 21es Journées Nationales d'Infectiologie
Poitiers
et la région Nouvelle Aquitaine
Palais des Congrès du Futuroscope
du mercredi 9 septembre 2020
au vendredi 11 septembre 2020

PK/PD : comment adapter la posologie des antibiotiques chez l'enfant

Mehdi Oualha

Réanimation et Surveillance Continue Pédiatrique

EA7323 : Pharmacologie et Evaluation des thérapeutiques chez l'enfant et la femme enceinte

AP-HP. Centre Université de Paris

Necker Enfants Malades Hôpital Universitaire

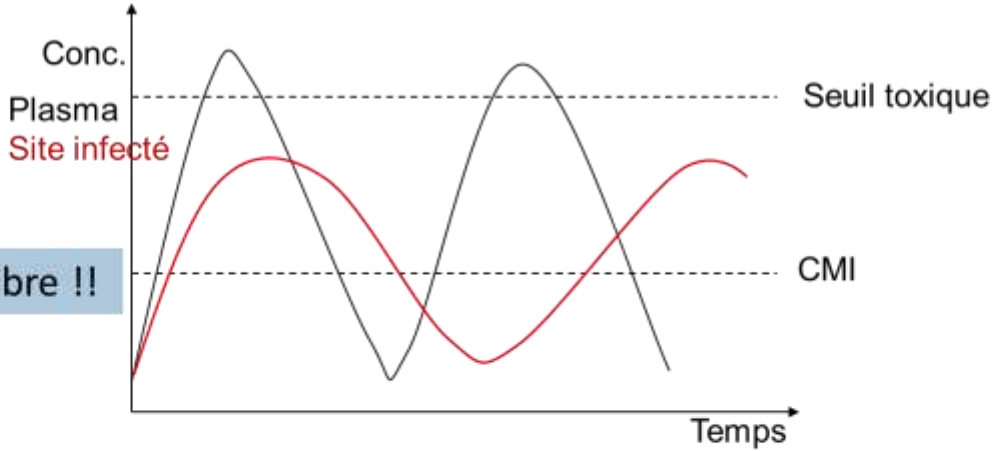
Université Paris Descartes

Université de Paris

La question

En quoi l'enfant est différent de l'adulte ? (PK/PD)

Bonne posologie = exposition optimale, pour TOUS



Concentration libre !!

- C_{max}/CMI
- $f(t)_{C>CMI}$
- AUC/CMI

→ **Efficacité clinique et bactériologique**

→ **Diminuer le risque d'émergence de germes résistants**

Effet optimal non observable / d'observation retardée
Risque de pérenniser une posologie inadéquate

Cible PK/PD : efficacité, émergence BMR

Guilhaumou et al. Critical Care (2019) 23:104
https://doi.org/10.1186/s13054-019-2378-9

Critical Care

REVIEW Open Access

Optimization of the treatment with beta-lactam antibiotics in critically ill patients—guidelines from the French Society of Pharmacology and Therapeutics (Société Française de Pharmacologie et Thérapeutique—SFPT) and the French Society of Anaesthesia and Intensive Care Medicine (Société Française d'Anesthésie et Réanimation—SFAR)

Romain Guilhaumou[1], Sihem Benaboud[2], Youssef Bennis[3], Sylvain Goutelle[7], Sandrine Lefeuvre[8], Nicolas Mongardon[9], Florian Lemaitre[12] and Marc Gainier[13*]

100 % *f*(t) > 4-8 X CM
Entérobactéries
Sepsis
Gravité

Clinical Pharmacokinetics
https://doi.org/10.1007/s40262-019-00791-z

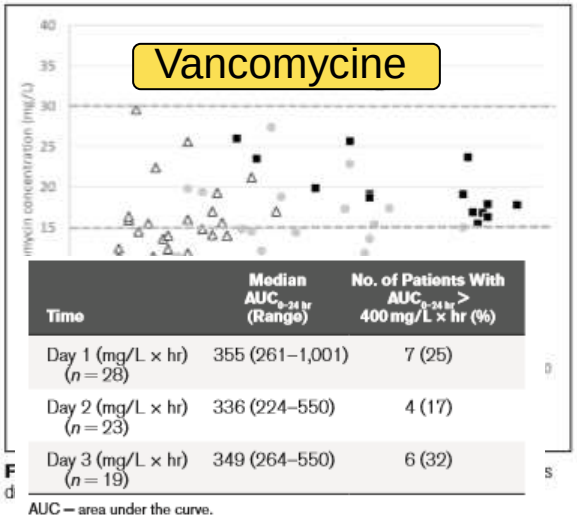
SYSTEMATIC REVIEW

What Antibiotic Exposures Are Required to Suppress the Emergence of Resistance for Gram-Negative Bacteria? A Systematic Review 2019

Chandra Datta Sumi[1] · Aaron J. Heffernan[1,2] · Jeffrey Lipman[4] · Jason A. Roberts[1,3,4,5] · Fekade B. Sime[1]

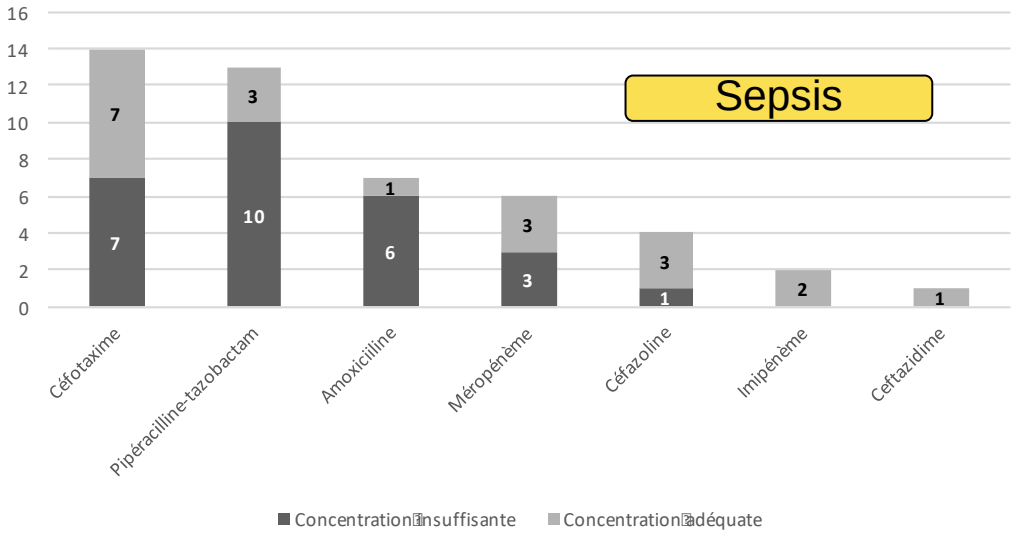
B lactamines : $C_{min}/CMI > 4$
Aminosides : $C_{max}/CMI > 20$
FQ : $AUC_{24}/MPC > 35$

Sous exposition fréquente !



Time	Median $AUC_{0\text{-}24\ hr}$ (Range)	No. of Patients With $AUC_{0\text{-}24\ hr}$ > 400 mg/L × hr (%)
Day 1 (mg/L × hr) ($n = 28$)	355 (261–1,001)	7 (25)
Day 2 (mg/L × hr) ($n = 23$)	336 (224–550)	4 (17)
Day 3 (mg/L × hr) ($n = 19$)	349 (264–550)	6 (32)

AUC — area under the curve.



tic target

	50% $fT_{>MIC}$	50% $fT_{>4xMIC}$	100% $fT_{>MIC}$	100% $fT_{>4xMIC}$
Cohort [n = 50]	29 (58)	15 (30)	17 (34)	5 (10)
Patients with an identified pathogen and MIC [n = 18]	15 (83.3)	13 (72.2)	12 (66.7)	5 (27.8)

Data are expressed as n (%)

MIC minimum inhibitory concentration

Pipéracilline

Genuini PCCM 2018
Chosidow Therapies 2020
Béranger Clin PK 2019

Exposition variable selon les classes

58 enfants, 210 prélèvements

Posologies usuelles

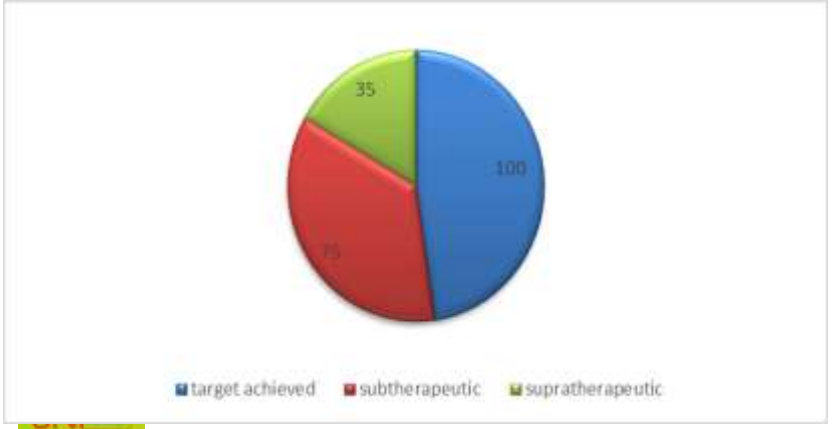
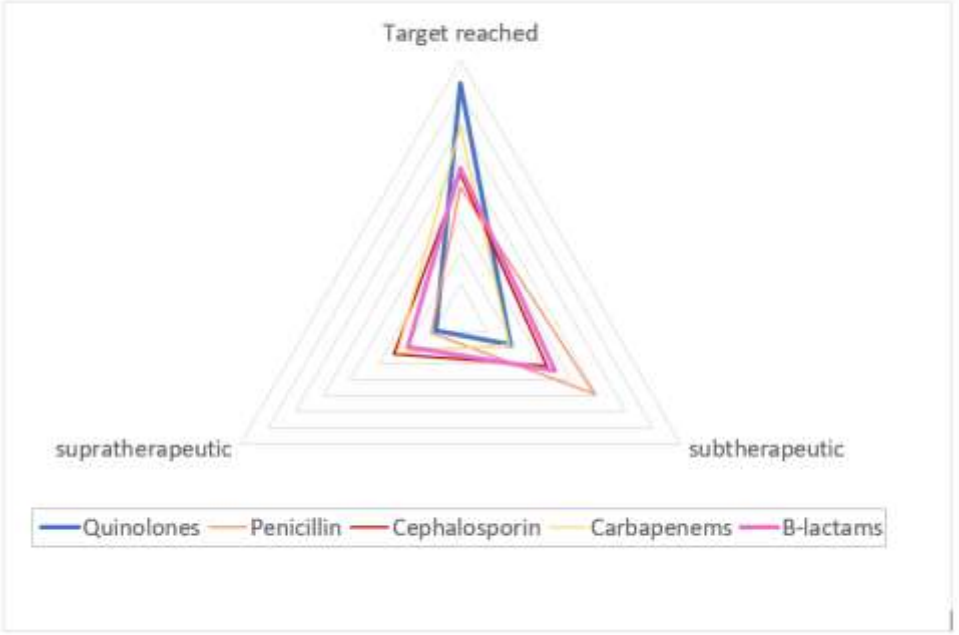
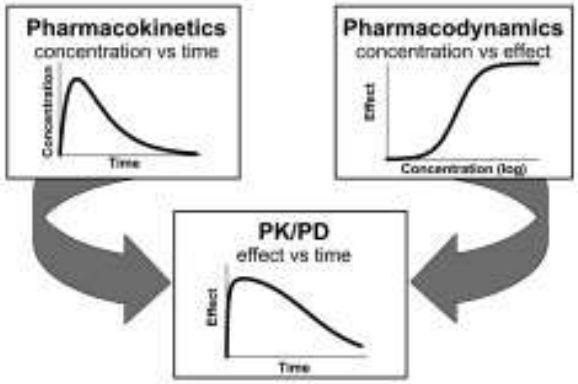
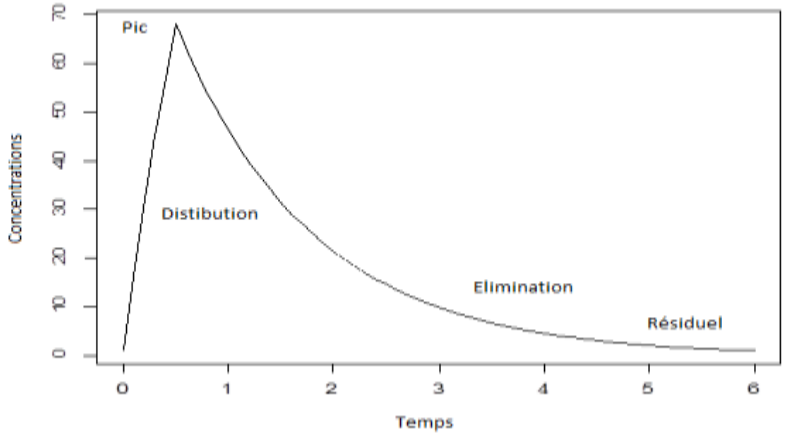


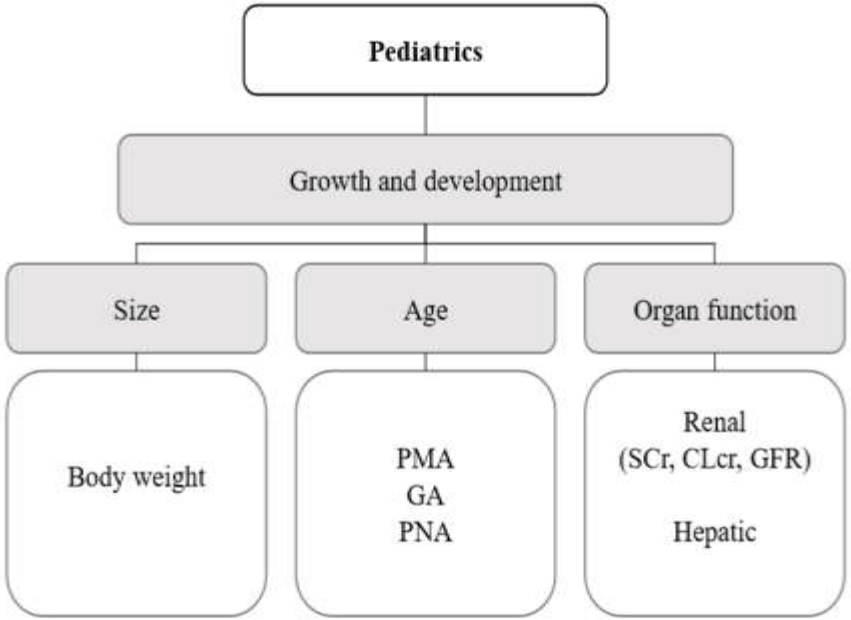
Figure 4. Results of Quinolones et B-Lactams measurements



PK/PD : l'enfant, un adulte en miniature ?



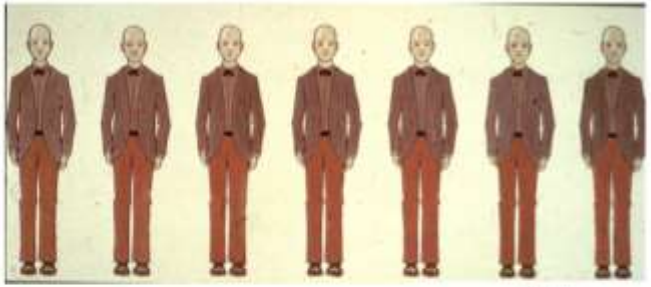




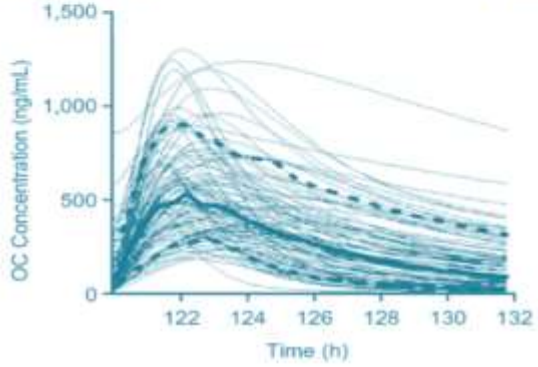
Muller CPT 2001
Thakkar Phar Res 2017

PK/PD : l'enfant, un adulte en miniature ?

« Dream »

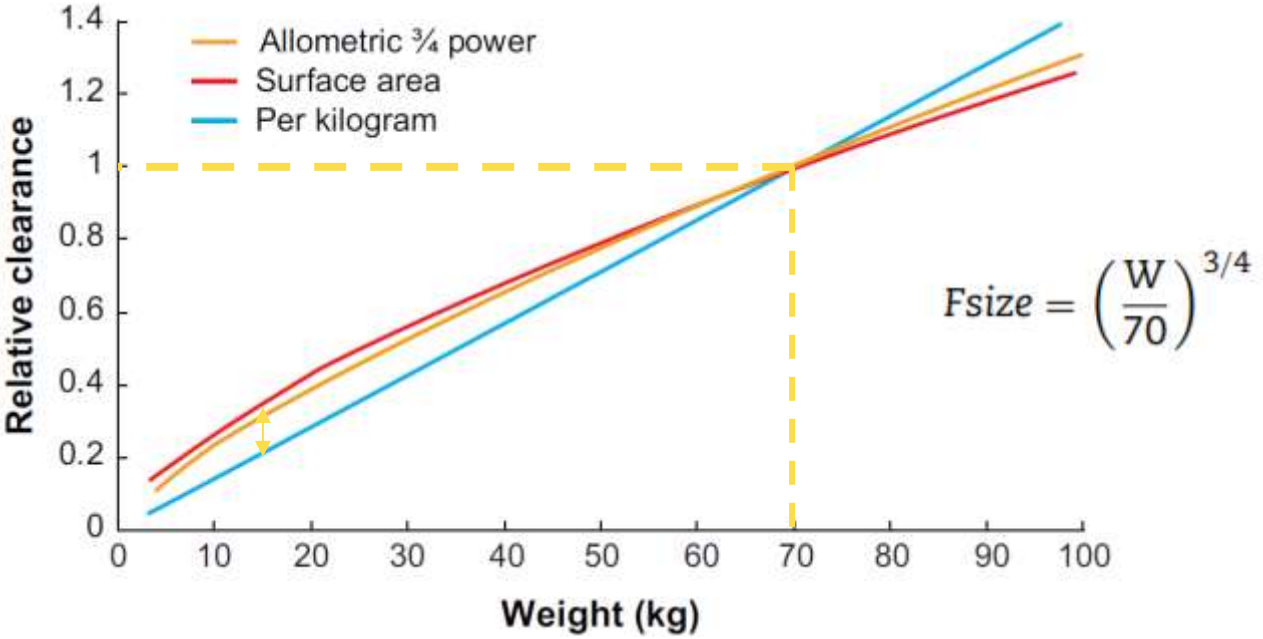


Reality



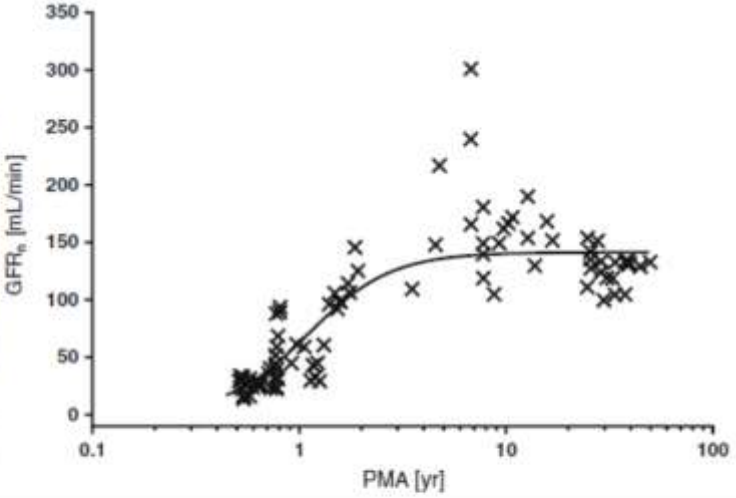
Forte variabilité PK (poids/âge)

Allométrie et clairance



Anderson Annu Rev Pharmacol Toxicol 2008

Maturation, exemple du rein



$$MF = \frac{PMA^{y}}{TM_{50}^{y} + PMA^{y}}$$

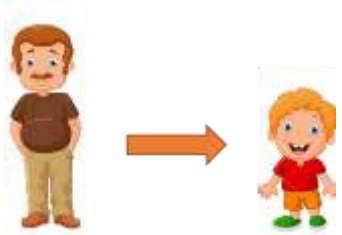
Anderson Annu Rev Pharmacol Toxicol 2008

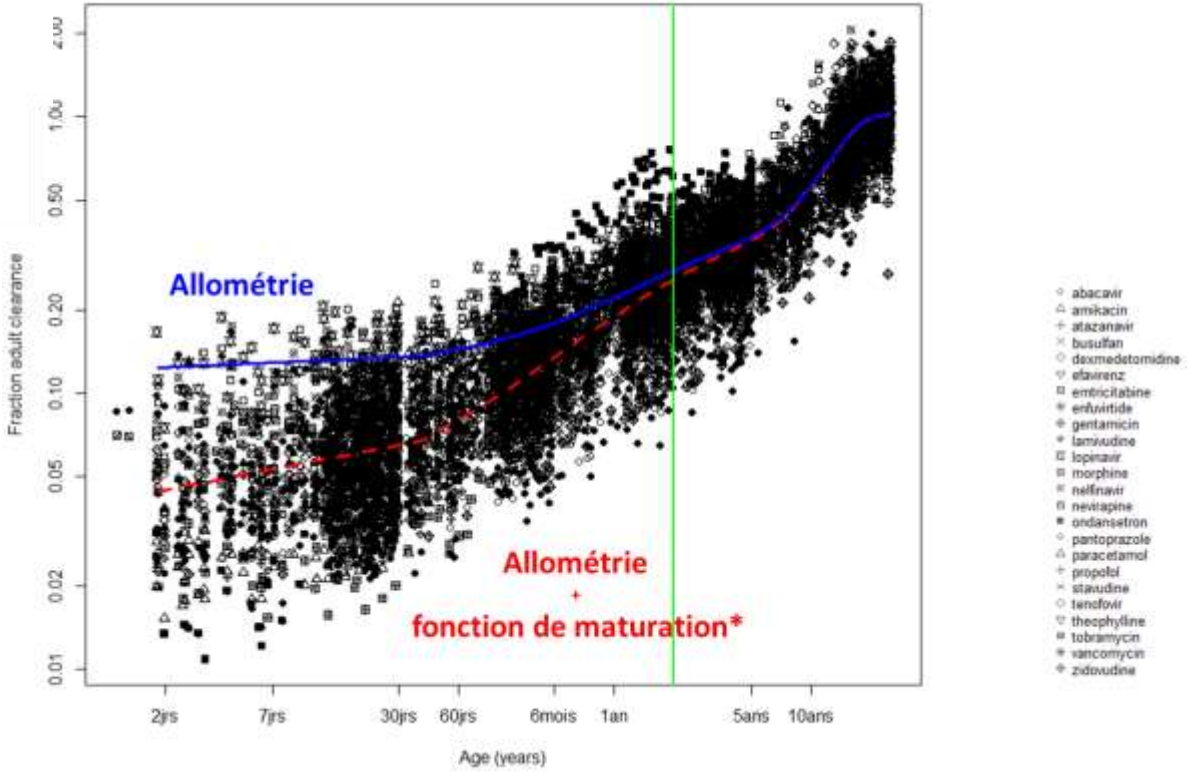
Maturation et allométrie

Pediatric Pharmacology

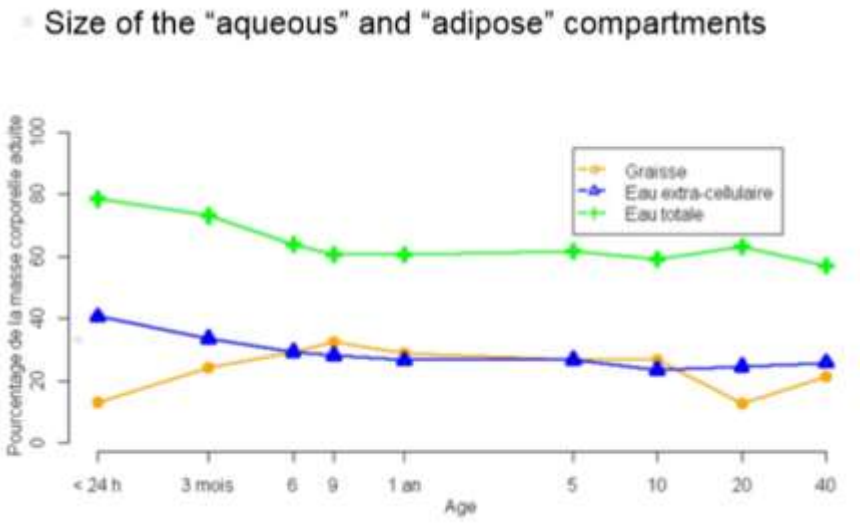
Prediction of Drug Clearance in Children

Frantz Foissac, PhD[1–3], Naim Bouazza, PhD[1–3], Elodie Valade, PharmD[1–3], Mailys De Sousa Mendes, PharmD[1–3], Floris Fauchet, PharmD, PhD[1–3], Sihem Benaboud, PharmD, PhD[1–4], Déborah Hirt, PharmD, PhD[1–4], Jean-Marc Tréluyer, MD, PhD[1–4], and Saik Urien, MD, PhD[1–3]





Eau et graisse

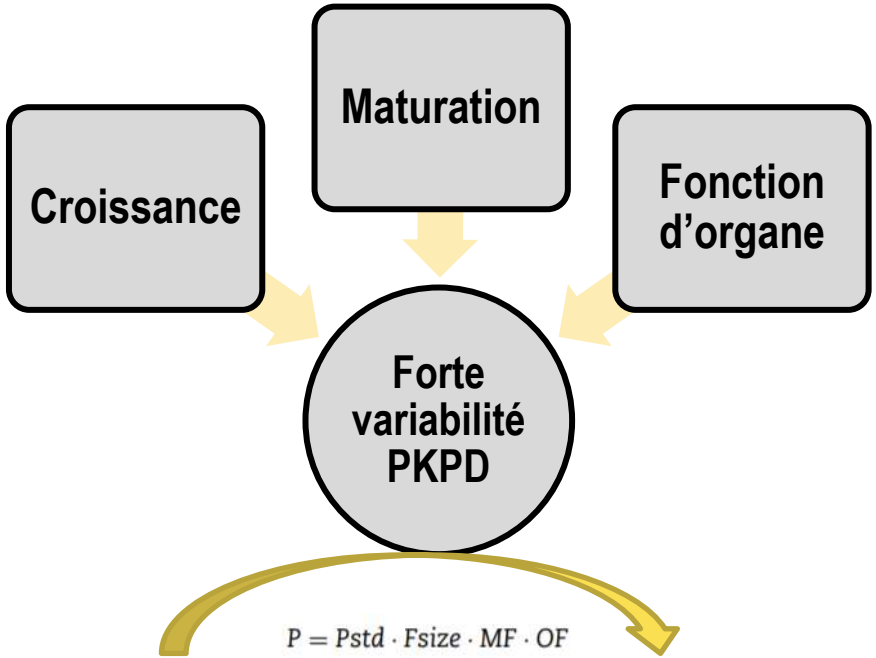


Body Compartment	Premature Infant (1.5 kg)	Full-Term Infant (3.5 kg)	Adult (70 kg)
Total body water (% body weight)	83	73	60
Extracellular fluid (% body weight)	62	44	20
Blood volume (mL/kg)	60	85-105	70
Intracellular water (% body weight)	25	33	40
Muscle mass (% body weight)	15	20	50
Fat (% body weight)	3	12	18

From Cook DR, Marcy JH: *Neonatal anesthesia*, Pasadena, Calif, 1988, Appleton Davies.

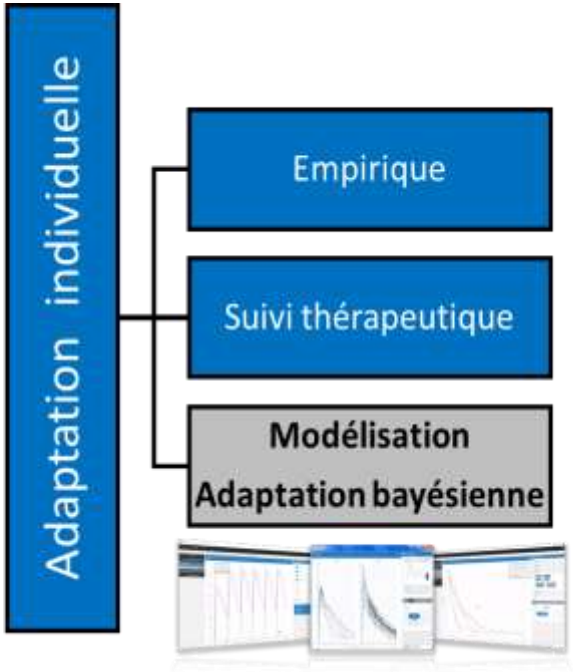
Kearns NEJM 2003

Variabilité non linéaire, quelles solutions ?

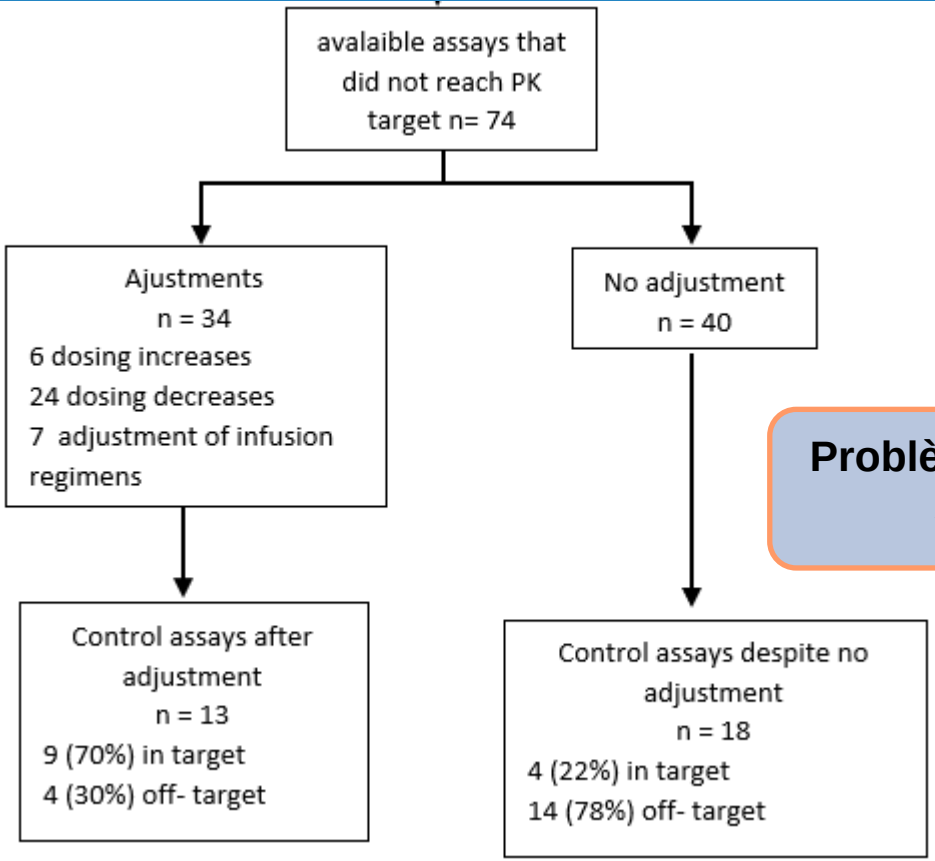


Posologie unitaire mg/kg

Exposition **suboptimale**
Impact clinique



Le STP, utile chez l'enfant ?



Problème : délai > 24 h, utile en situation critique ??

De Caqueray (thèse)

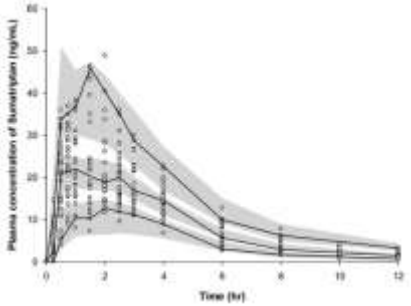
La modélisation

Approche Bottom-up

Paramètres molécule-dépendant + Paramètres population-dépendant (pédiatrique)

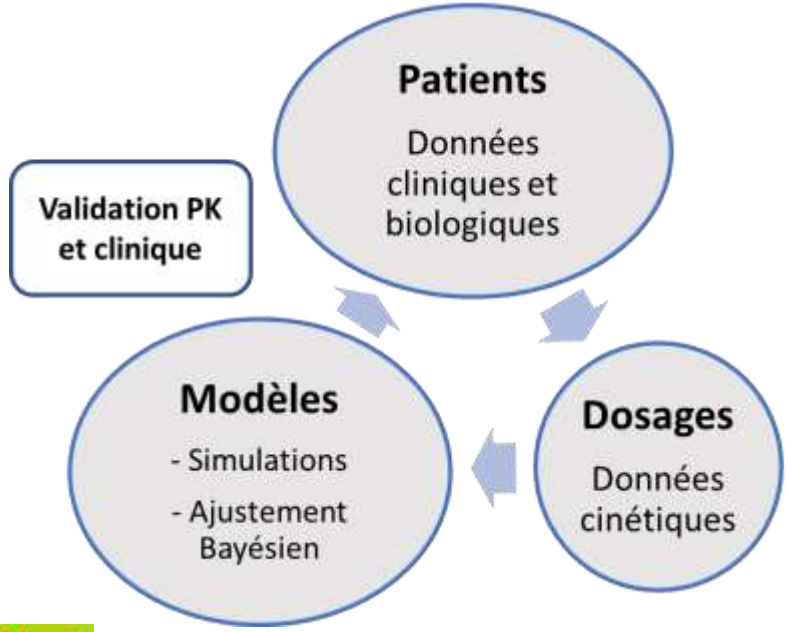
Modèle PBPK enfant

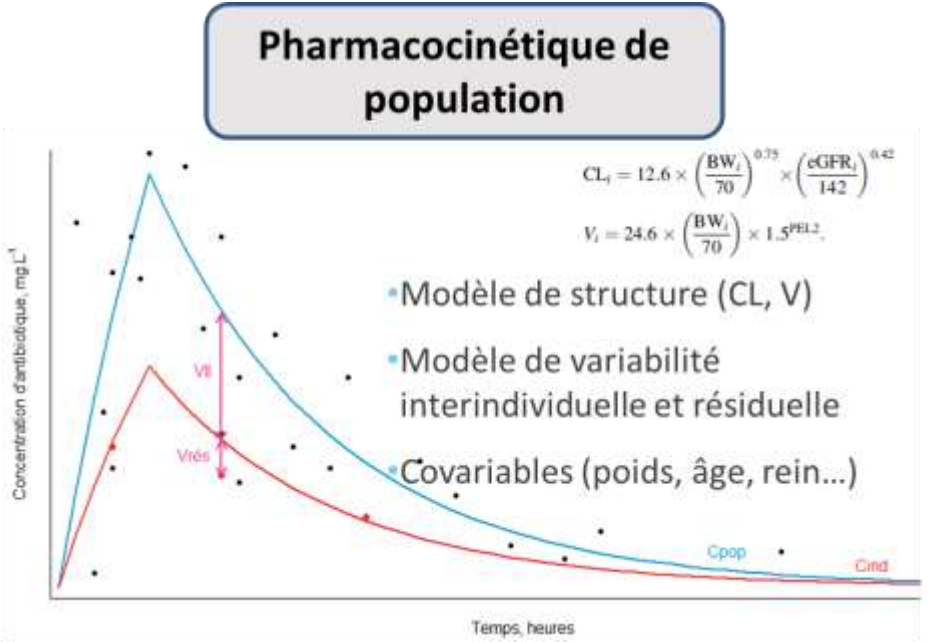
Approche Top-down



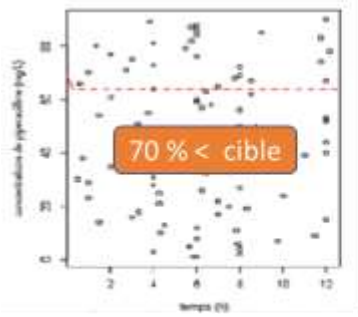
Modèle PKPOP enfant

Population Pharmacokinetics : PKPOP



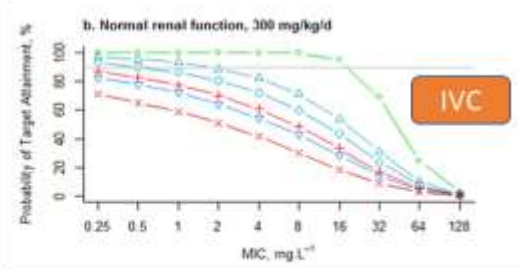


PKPOP: pipéracilline, céfazoline



$$CL_i = 12.6 \times \left(\frac{BW_i}{70}\right)^{0.75} \times \left(\frac{eGFR_i}{142}\right)^{0.42}$$

$$V_i = 24.6 \times \left(\frac{BW_i}{70}\right) \times 1.5^{PEL2}.$$



Posologies usuelles inadéquates → Création du modèle PK de population → Simulation de posologies (selon cible)

BW (kg)		< 10		10-30		> 30	
eGFR (mL/min/1.73m²)		60-200	> 200	60-200	> 200	60-200	> 200
MIC (mg/L)	0.064	100 mg/kg/d CI				100 mg/kg/d CI or q6h	
	0.125						
	0.25						
	0.5						
	1						
	2	150 mg/kg/d CI			150 mg/kg/d CI		150 mg/kg/d CI

Béranger Clin PK 2019
Salvador CMI 2020

Adaptation bayesiènne, mieux que le STP ?

Meropénème

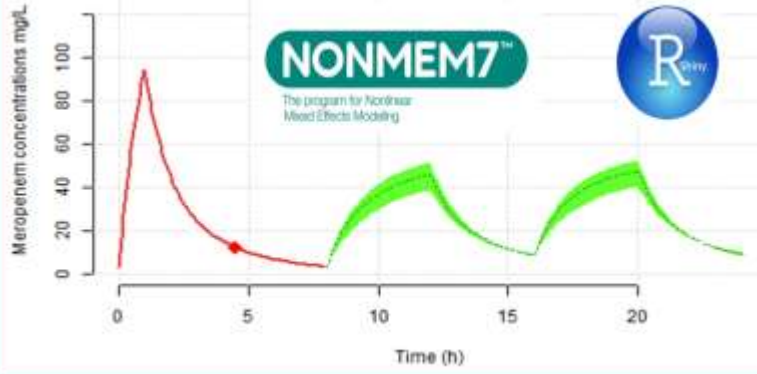
Interpretation

- **The predicted meropenem residual concentration is : 3.1 mg/L**

- *Efficacy target 4 x ECOFF, i.e. 8 mg/L for Pseudomonas aeruginosa*

- **Suboptimal level, the infusion time should be increased to 4 hours**

Dose suggestion graph



Vancomycine

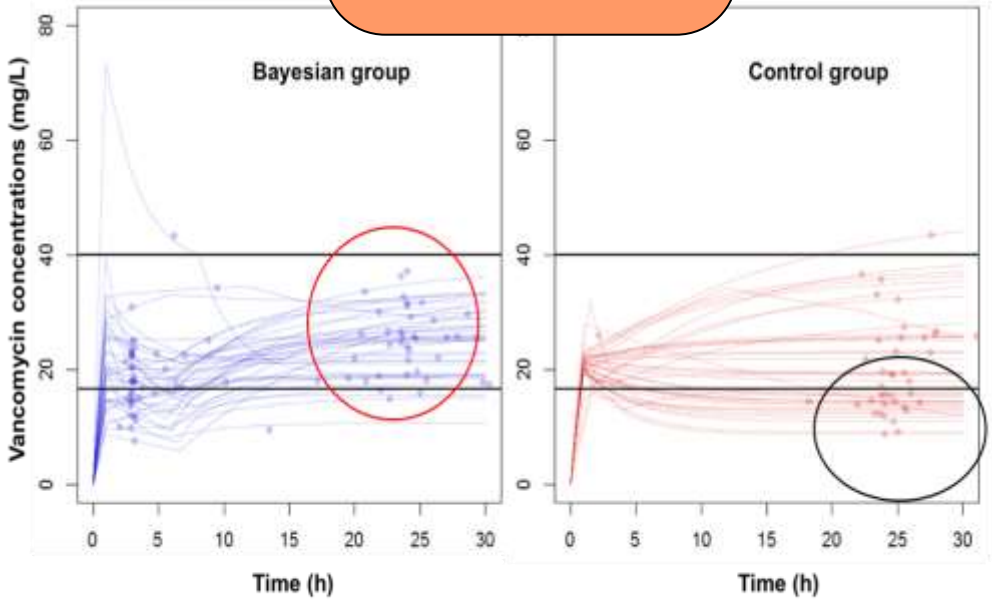


Figure 4 Evolution of vancomycin plasma concentration over time for each patient of each group. Blue and red points symbolise vancomycin plasma concentration measurements.

Berthaud AAC 2019

Mon logiciel au lit du patient !

Demographics

Age [yrs.] | Weight [kg] | Height [cm]

6 | 20 | 130

Sex

male

Dose [mg] | Infusion dur. [h]

Time	Dose	Duration
02/02/2020/06:00	1500	0.5
02/02/2020/12:00	1500	0.5
02/02/2020/18:00	1500	0.5
03/02/2020/00:00	1500	0.5

\+ -

Dosing interval (for next dose) [h]

6

Laboratory

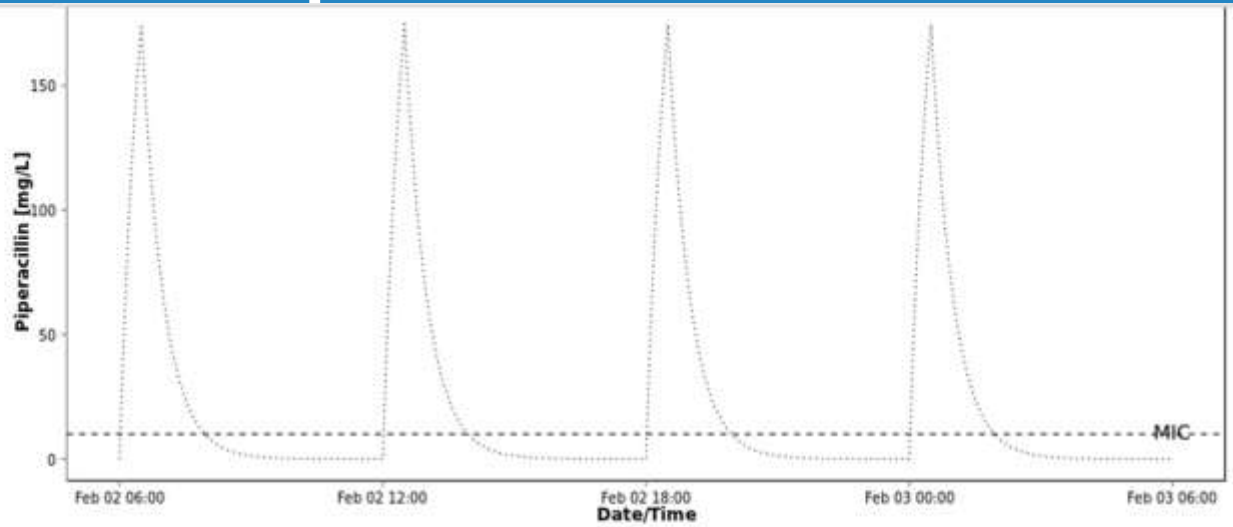
Serum creatinine [mg/dL]

Time	cCreatinine
02/02/2020/13:00	0.7

\+ -

MIC [mg/L]

10



http://www.tdmx.eu/Launch-TDMx/

PK/PD Target (%fT>MIC)

calculate

Select dosing regimens to be evaluated by probabilistic dosing:

BID scenarios

4 g / 0.5 h BID | 4 g / 6 h BID

TID scenarios

4 g / 0.5 h TID | 4 g / 4 h TID

QID scenarios

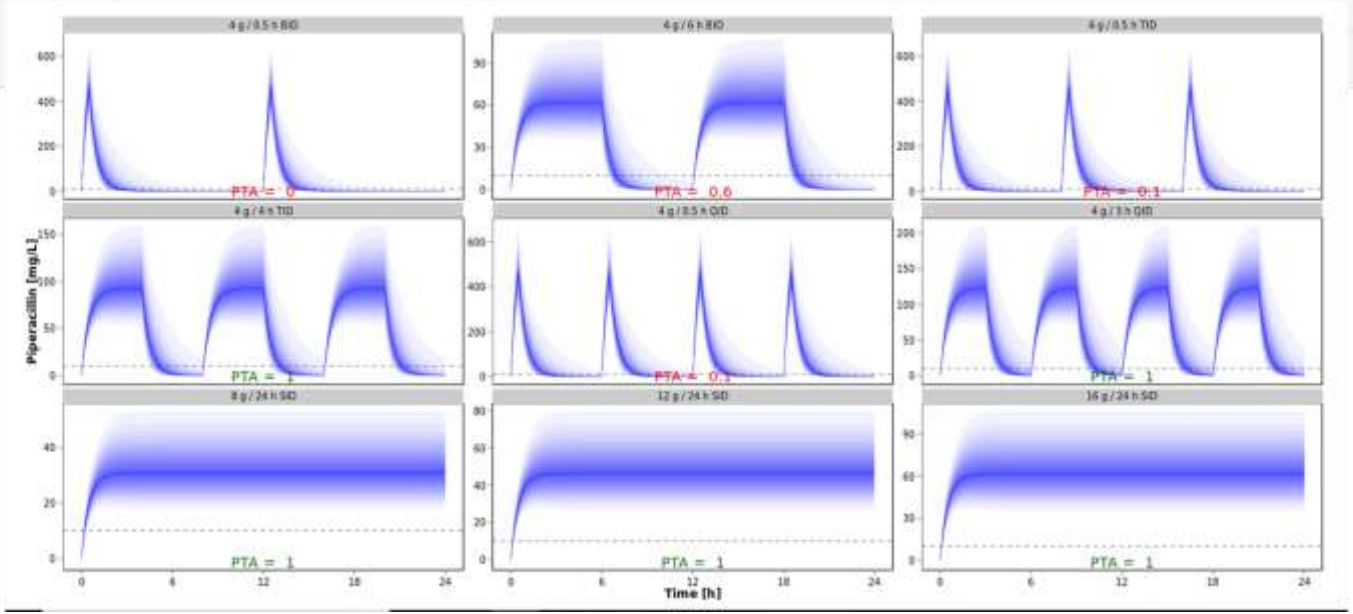
4 g / 0.5 h QID | 4 g / 3 h QID

Continuous scenarios

8 g / 24 h SID

12 g / 24 h SID

16 g / 24 h SID



PK/PD Target (%fT>MIC)

0 99

calculate

Select dosing regimens to be evaluated by probabilistic dosing:

BID scenarios

4 g / 0.5 h BID | 4 g / 6 h BID

TID scenarios

4 g / 0.5 h TID | 4 g / 4 h TID

QID scenarios

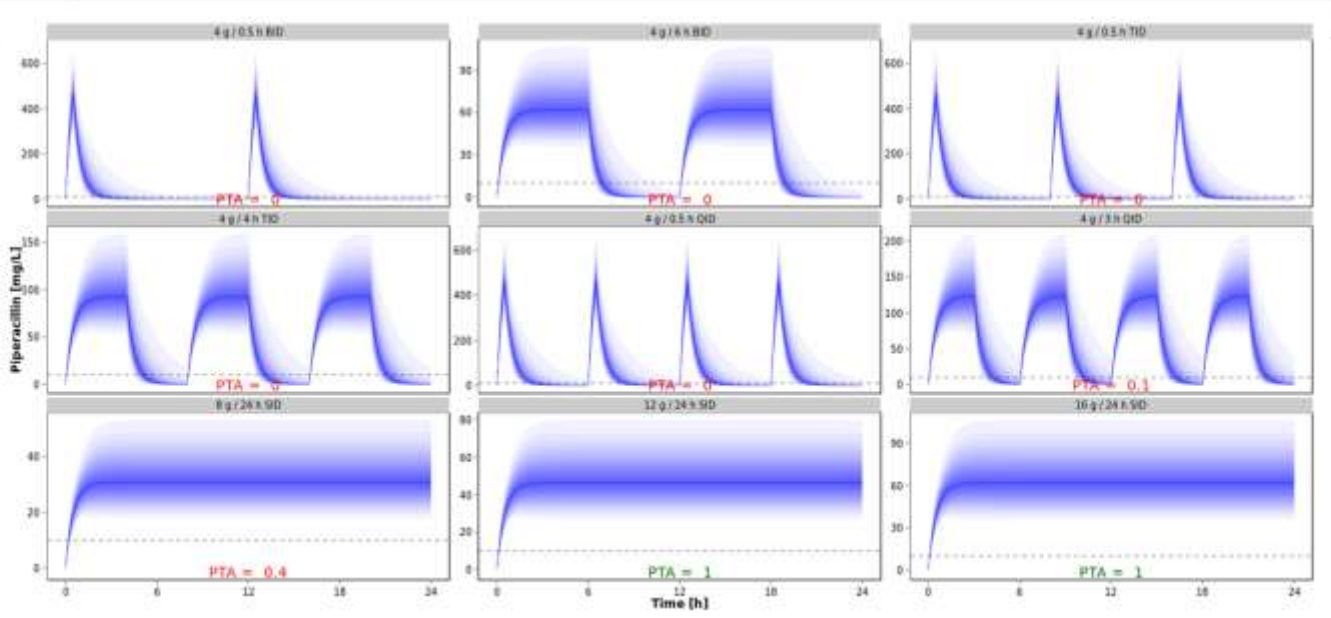
4 g / 0.5 h QID | 4 g / 3 h QID

Continuous scenarios

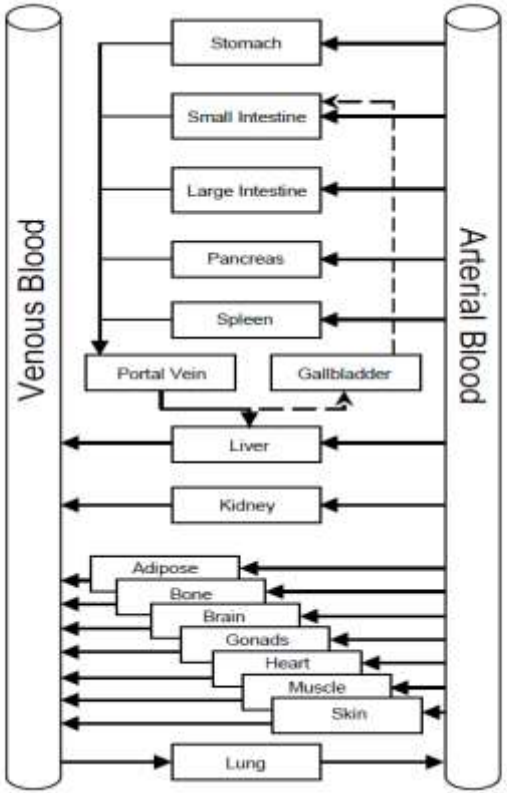
8 g / 24 h SID

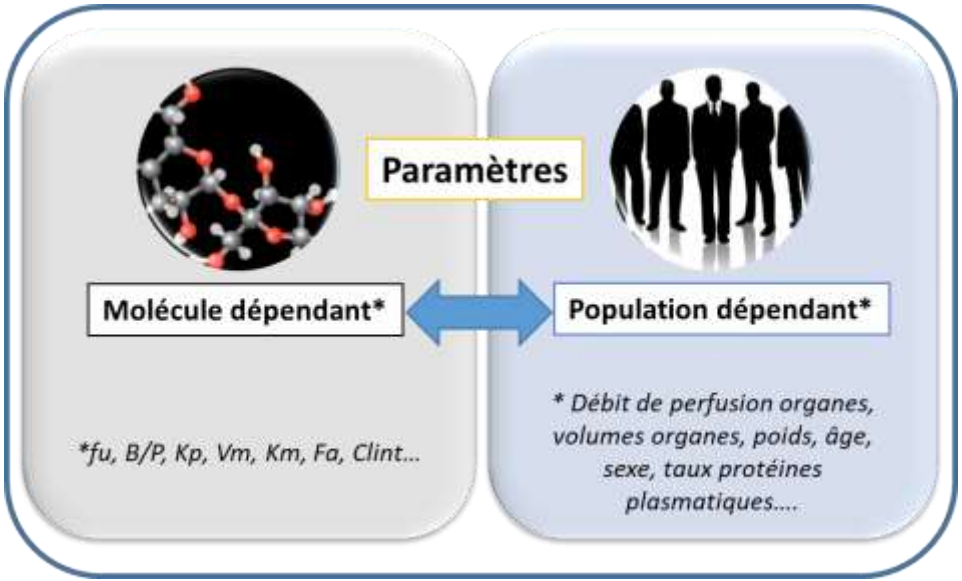
12 g / 24 h SID

16 g / 24 h SID



Physiologically Based Pharmacokinetic Modelling
PBPK

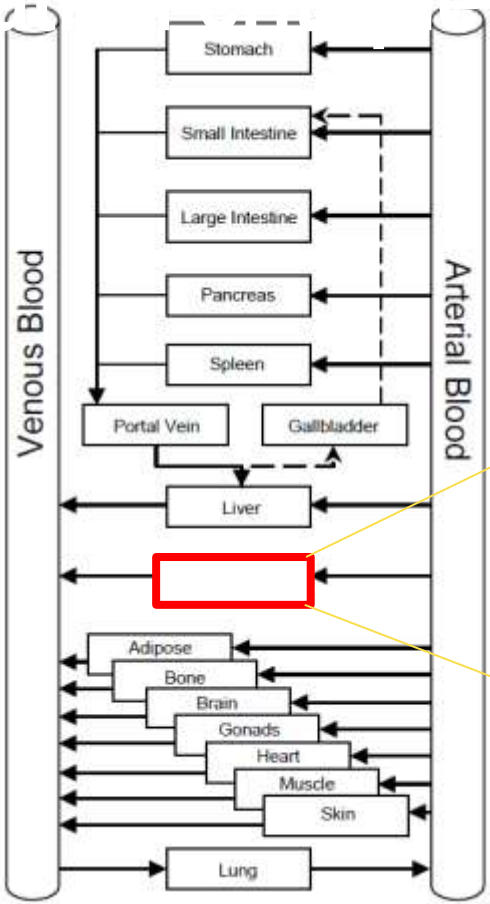




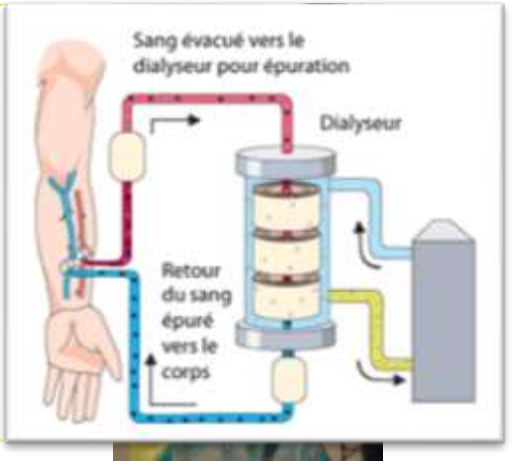
PBPK, en situation critique

Déb

15- 65% ARC in I



Débit sanguin



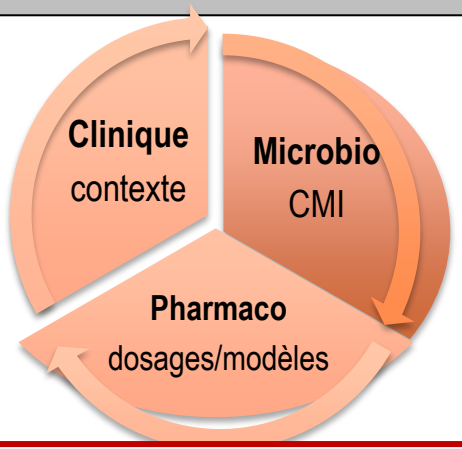
Adapter la posologie chez l'enfant

Posologie mg/kg

Variabilité PK non linéaire

Echec clinique
Émergence germes résistants

Exposition non optimale



Suivi thérapeutique

Adaptation empirique, délai

Posologie (mg ± x) /kg

Modélisation

Adaptation bayésienne

Posologie mg /kg[a] x âge x DFG

Particularités PK de l'enfant

IVC (B-lactamines)