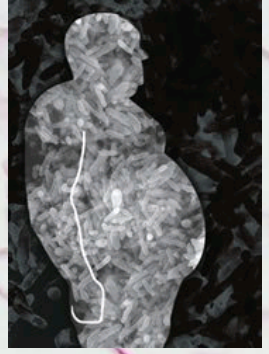

Adaptation des posologies des antibiotiques chez les patients obèses

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Université catholique de Louvain

Louvain Drug Research Institute et centre de pharmacie clinique

www.facm.ucl.ac.be

Est-ce un problème ?

Underdosing of common antibiotics for obese patients in the ED☆,☆☆

Jada L. Roe MD[a], Joseph M. Fuentes MD[b], Michael E. Mullins MD[b,*]

Table 1 Recommended antibiotic dosing for patients with BMI greater than 40 kg/m^2 and body mass more than 100 kg

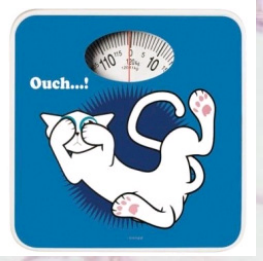
Cefazolin	CrCl ≥30, 2 g IV, every 8 h	CrCl 10-29 mL/min, 2 g, IV, every 12 h	CrCl <10, 2 g, IV, every 24 h
Cefepime	CrCl ≥60	CrCl 30-59 mL/min	CrCl <30
Serious infections[a]	2 g, IV, every 8 h	2 g, IV, every 12 h	2 g, IV, every 24 h
Other infections	2 g, IV, every 12 h	2 g, IV, every 24 h	2 g, IV, every 24 h
Ciprofloxacin	CrCl ≥30	CrCl <29	
IV	800 mg, IV, every 12 h	800 mg, IV, every 24 h[b]	
PO	750 mg, PO, every 12 h	750 mg, PO, every 24 h[c]	

Results: There were 1910 orders found to meet the study criteria: 775 orders for cefepime, 625 orders for cefazolin, and 510 orders for ciprofloxacin. Adherence rates for first dose of cefepime, cefazolin, and ciprofloxacin administered, respectively, were 8.0%, 3.0%, and 1.2%.

Conclusion: Emergency physicians frequently underdose cefepime, cefazolin, and ciprofloxacin in obese patients. Underdosing antimicrobials presents risk of treatment failure and may promote antimicrobial resistance. Education is necessary to improve early antibiotic administration to obese patients.

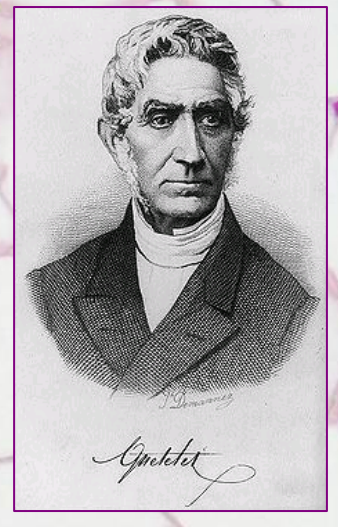
The American J. of Emergency Med., epub

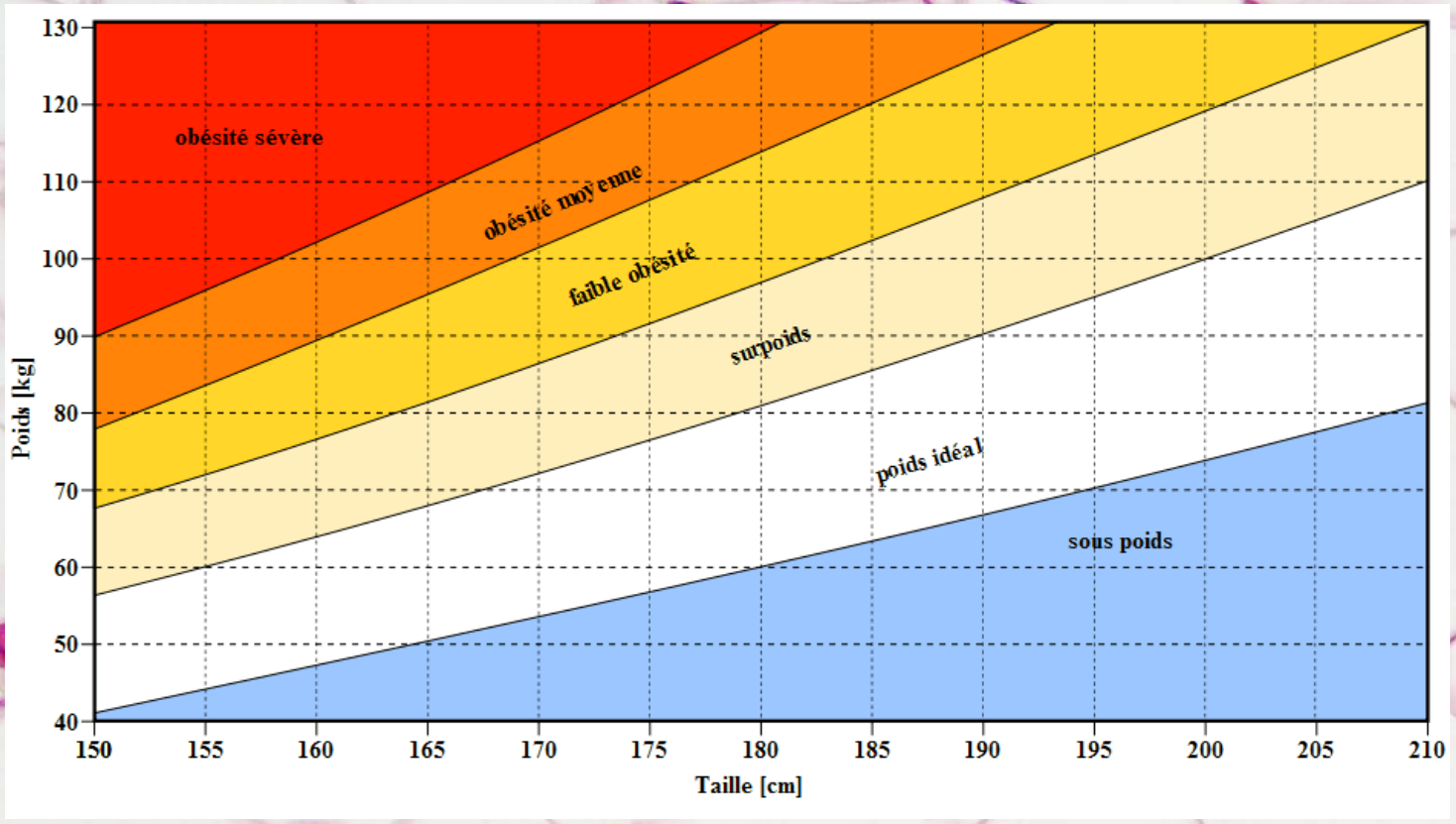
Mesures: il y a poids et poids …



Comment évaluer le poids ?

- BMI: Body Mass Index (Indice de Quetelet)





Comment évaluer le poids ?

- IBW: Ideal Body Weight

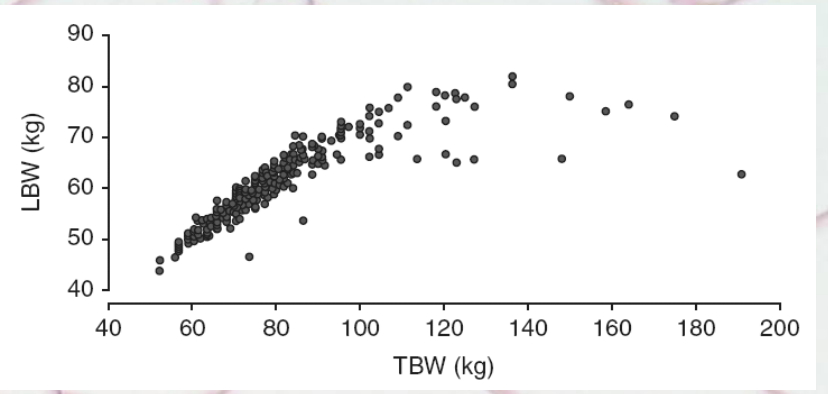
♀ IBW = 45.4 kg + 0.89 (height (cm) – 152.4)

♂ IBW = 49.9 kg + 0.89 (height (cm) – 152.4)

→ tient compte du sexe et de la taille,
MAIS pas de la composition corporelle

Devine, Drug Intell Clin Pharm (1974) 8: 650-656

Comment évaluer le poids ?



- LBW: Lean Body Weight

♀ LBW = 1.07 TBW* – 0.0148 x BMI x TBW

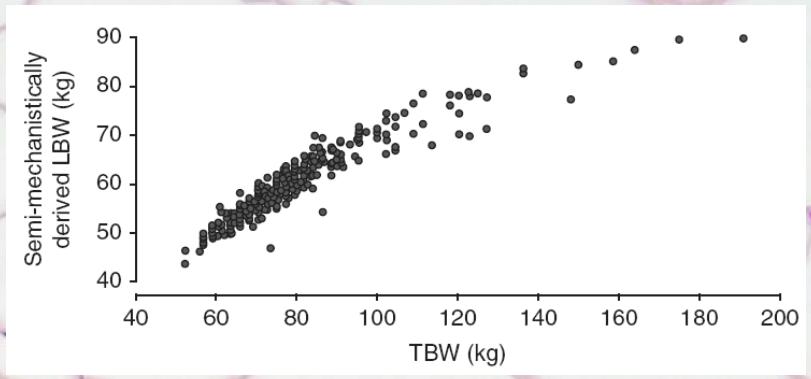
♂ LBW = 1.10 TBW* – 0.0128 x BMI x TBW

* TWB: Total Body Weight

→ représente le poids des fluides extracellulaires, muscles, os et organes vitaux
MAIS inexact pour poids /tailles extrêmes

Janmahasatian et al. Clin Pharmacokin. (2005) 44:1051-65

Comment évaluer le poids ?



- LBW: Lean Body Weight #

♀ LBW = 9270 TBW* / 8780 + 244 x BMI

♂ LBW = 9270 TBW* / 6680 + 216 x BMI

* TWB: Total Body Weight

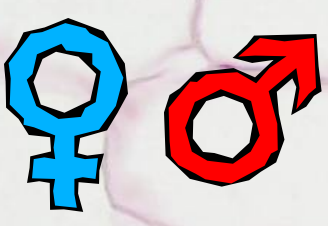
→ formule plus exacte pour poids /tailles extrêmes

Sur base d'un modèle basé sur des données d'impédence bioélectrique

Janmahasatian et al. Clin Pharmacokin. (2005) 44:1051-65

Comment évaluer le poids ?

- AjBW: Estimated Adjusted Body Weight



$$AjBW = IBW + DWCF^{*} \times (TBW - IBW)$$

Variable selon l'AB

excès de poids

* Dosing Weight Correction Factor

→ aussi appelé « Dosing Weight », car développé pour caractériser le profil PK de médicaments en « enlevant » la masse superflue

Dufful et al. Clin Pharmacokin. (2004) 43:1167-78

Comment évaluer le poids ?

- PNW: Predicted Normal Weight

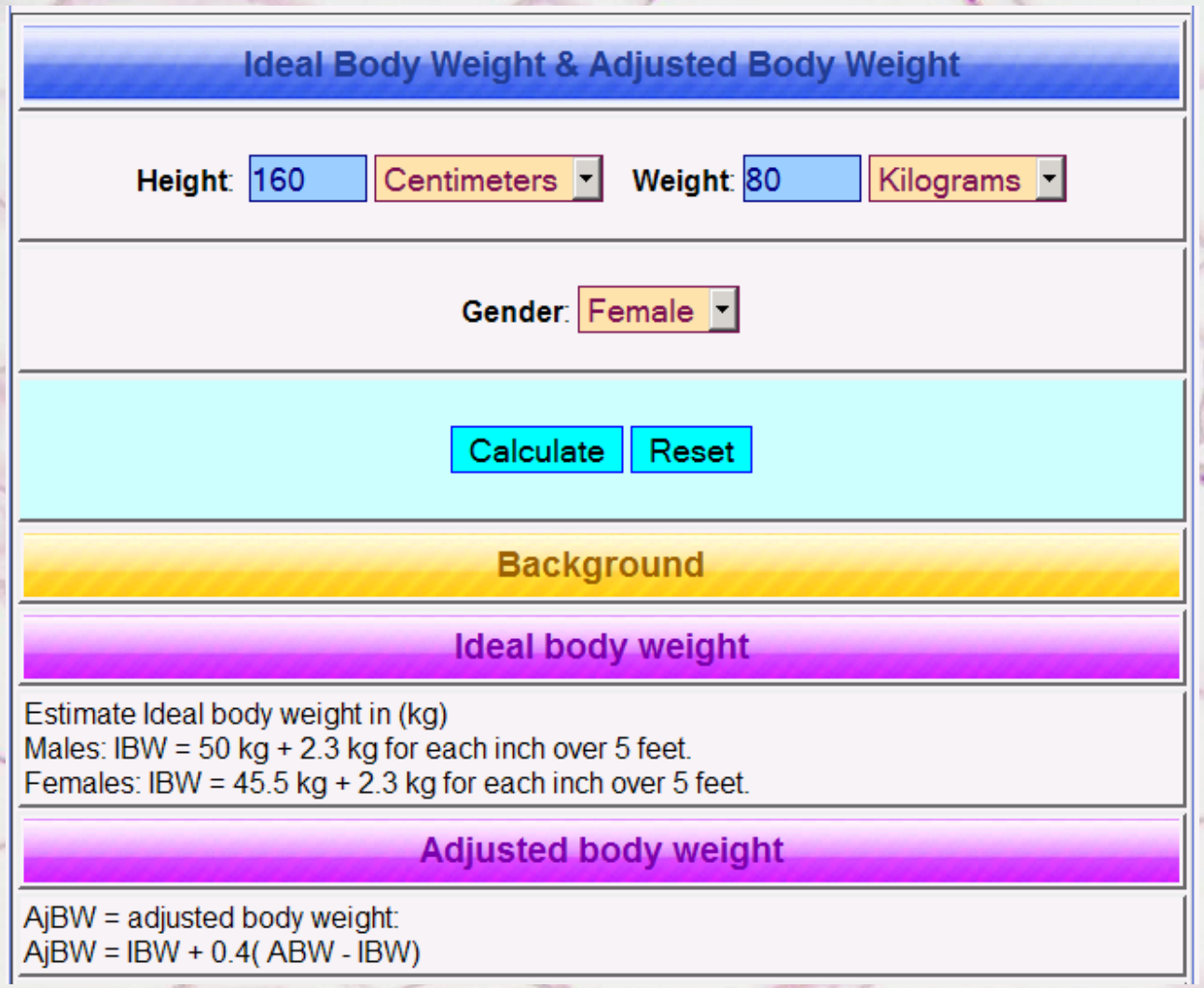
♀ PNW = 1.75 TBW – (0.0242 x BMI x TBW) – 12.6

♂ PNW = 1.57 TBW – (0.0183 x BMI x TBW) – 10.5

→ développé pour caractériser le profil PK de médicaments inclus la masse grasse « normale »

Dufful et al. Clin Pharmacokin. (2004) 43:1167-78

Brouillé avec les maths ?



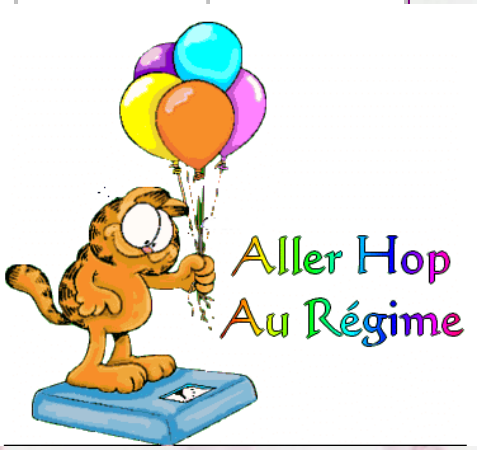
http://www.globalrph.com/ibw_calc.htm

Brouillé avec les maths ?

Weight calculator

sexe	size (cm)	size (m)	TBW (kg)	BMI	IBW	LBW	AJBW	PNW
F	160	1.6	52	20.3	52.2	40.0	52.1	52.8
	160	1.6	80	31.3	52.2	48.6	63.3	66.9
M	175	1.75	71	23.2	70.0	57.0	70.4	70.8
	175	1.75	100	32.7	70.0	68.2	82.0	86.7

BMI	Body Mass Index
IBW	Ideal Body Weight
LBW	Lean Body weight
AJBW	Adjusted Body Weight
PNW	Predicted Normal Weight



http://www.facm.ucl.ac.be/conferences

Brouillé avec les maths ?

Weight calculator

sexe	size (cm)	size (m)	TBW (kg)	BMI	IBW	LBW	AJBW	PNW
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	160	1.6	80	31.3	52.2	48.6	63.3	66.9
M	175	1.75	71	23.2	70.0	57.0	70.4	70.8
	175	1.75	100	32.7	70.0	68.2	82.0	86.7

BMI	Body Mass Index
IBW	Ideal Body Weight
LBW	Lean Body weight
AJBW	Adjusted Body Weight
PNW	Predicted Normal Weight

IBW indépendant du TBW

Brouillé avec les maths ?

Weight calculator

sexe	size (cm)	size (m)	TBW (kg)	BMI	IBW	LBW	AJBW	PNW
F	160	1.6	52	20.3	52.2	40.0	52.1	52.8
	160	1.6	80	31.3	52.2	48.6	63.3	66.9
M	175	1.75	71	23.2	70.0	57.0	70.4	70.8
	175	1.75	100	32.7	70.0	68.2	82.0	86.7

BMI	Body Mass Index
IBW	Ideal Body Weight
LBW	Lean Body weight
AJBW	Adjusted Body Weight
PNW	Predicted Normal Weight

LBW ↗ avec TBW

20-40 % excès de poids ~ masse maigre

Brouillé avec les maths ?

Weight calculator

sexe	size (cm)	size (m)	TBW (kg)	BMI	IBW	LBW	AJBW	PNW
F	160	1.6	52	20.3	52.2	40.0	52.1	52.8
	160	1.6	80	31.3	52.2	48.6	63.3	66.9
M	175	1.75	71	23.2	70.0	57.0	70.4	70.8
	175	1.75	100	32.7	70.0	68.2	82.0	86.7

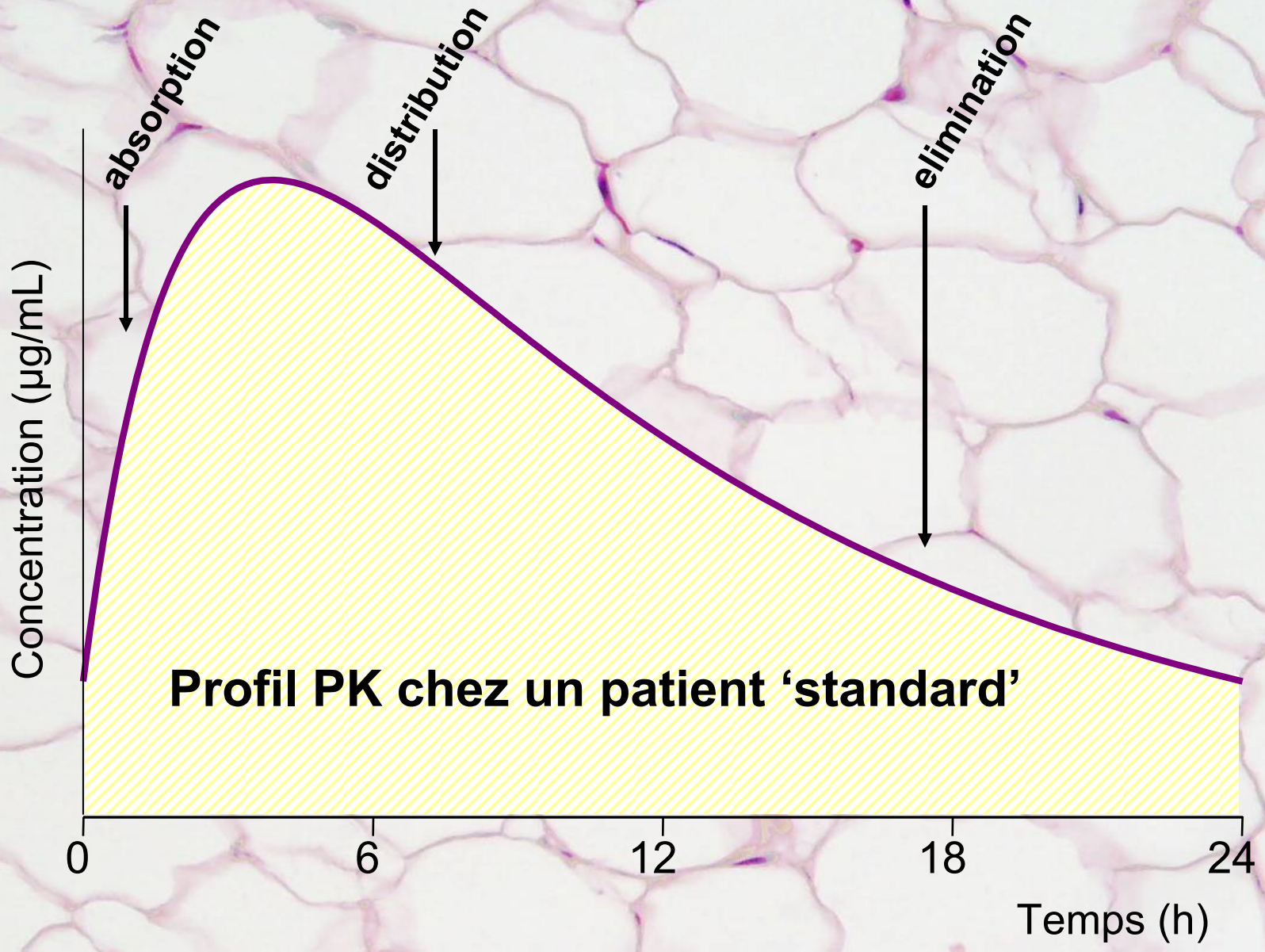
BMI	Body Mass Index
IBW	Ideal Body Weight
LBW	Lean Body weight
AJBW	Adjusted Body Weight
PNW	Predicted Normal Weight

AjBW et PNW
↗
avec TBW

utiles pour les ajustements PK

Poids et pharmacocinétique

Poids et paramètres PK



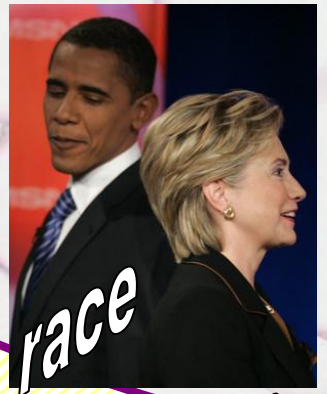
Mais qu'est-ce qu'un patient 'standard' ?

poids

âge

condition physique

Kim Clijsters pose avec sa fille Jada. Photo AFP



race

taille

maladie

fonctions d'élimination

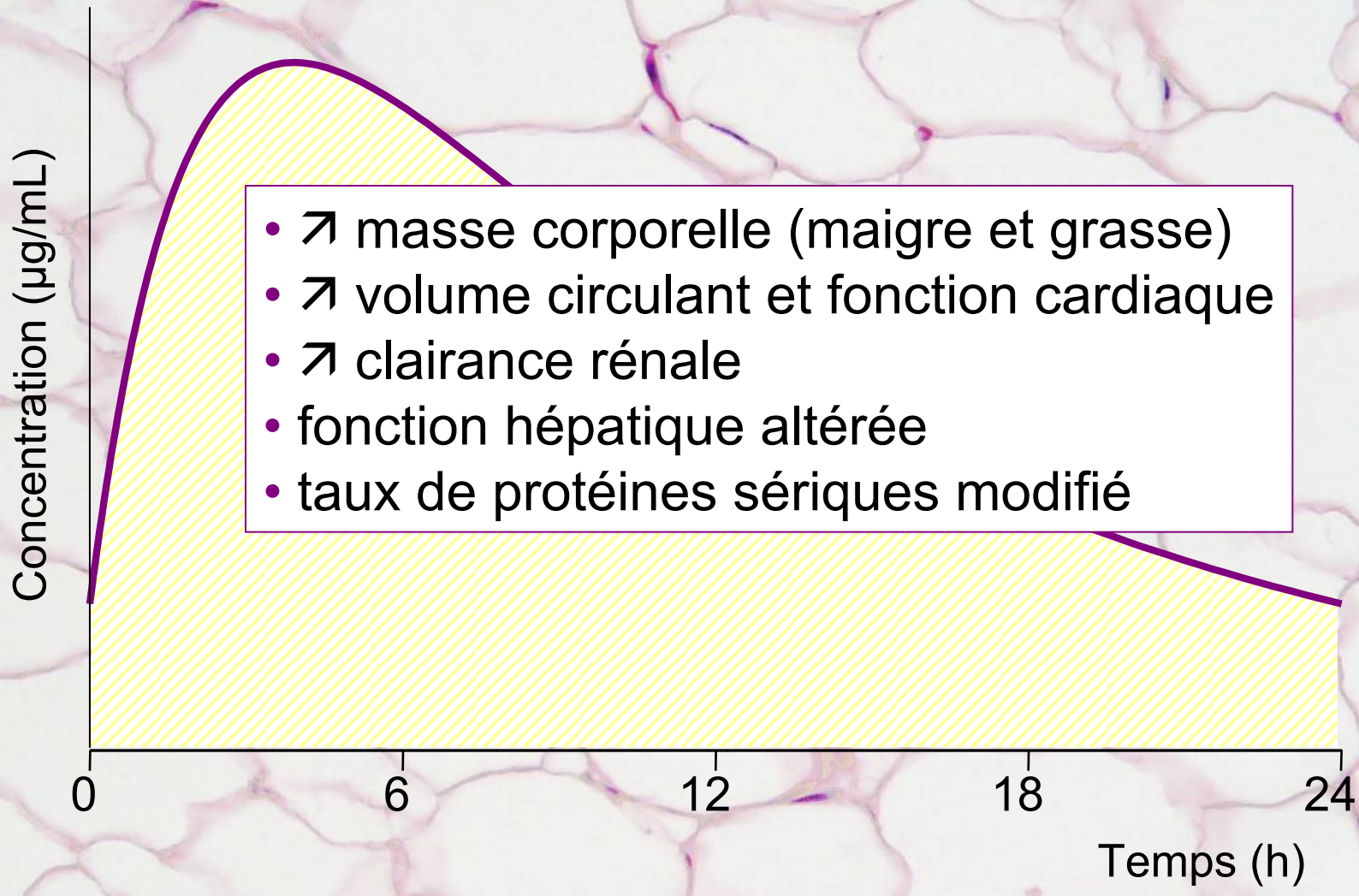
0

12

24

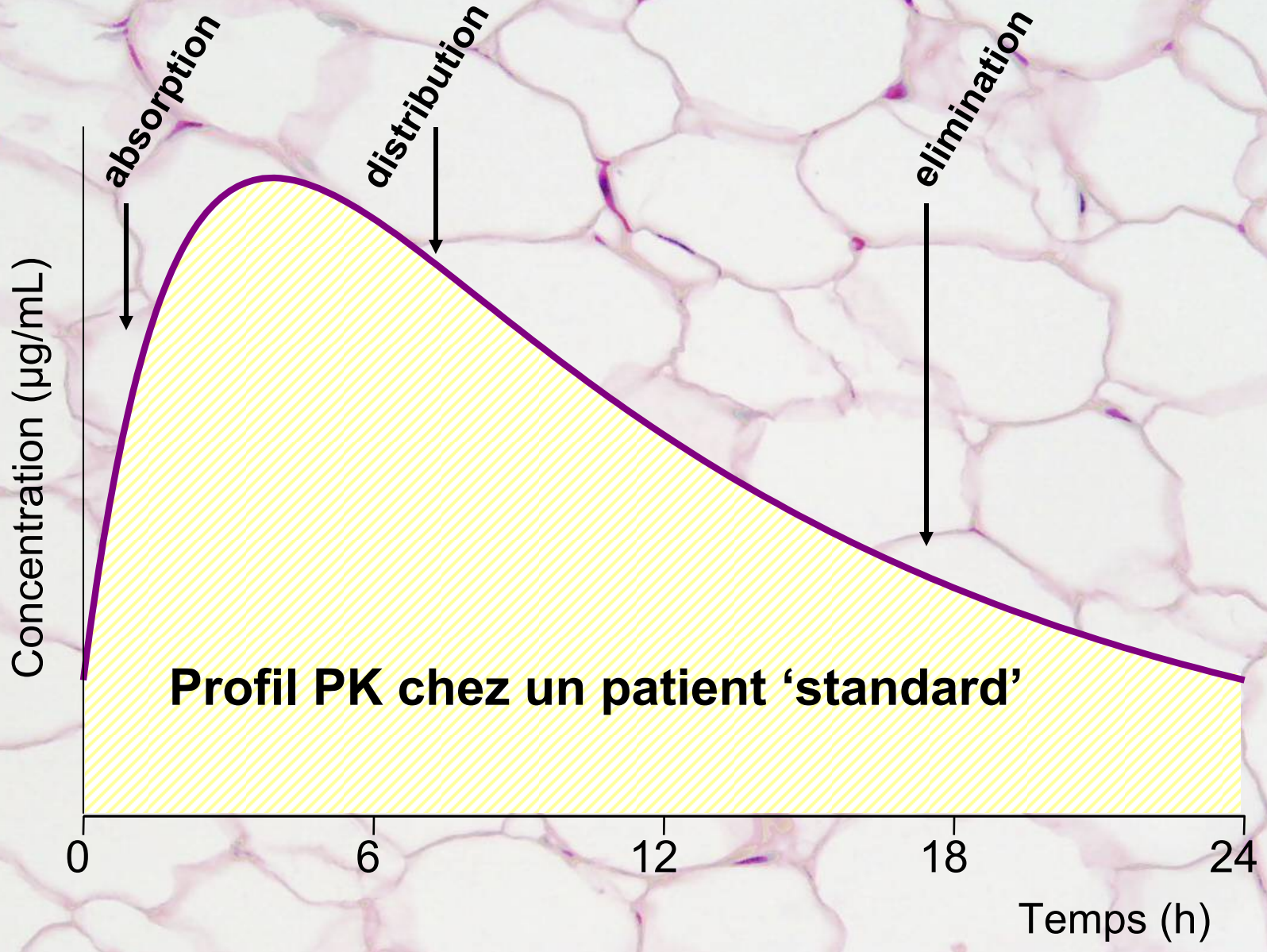
Temps (h)

Poids, physiologie et paramètres PK

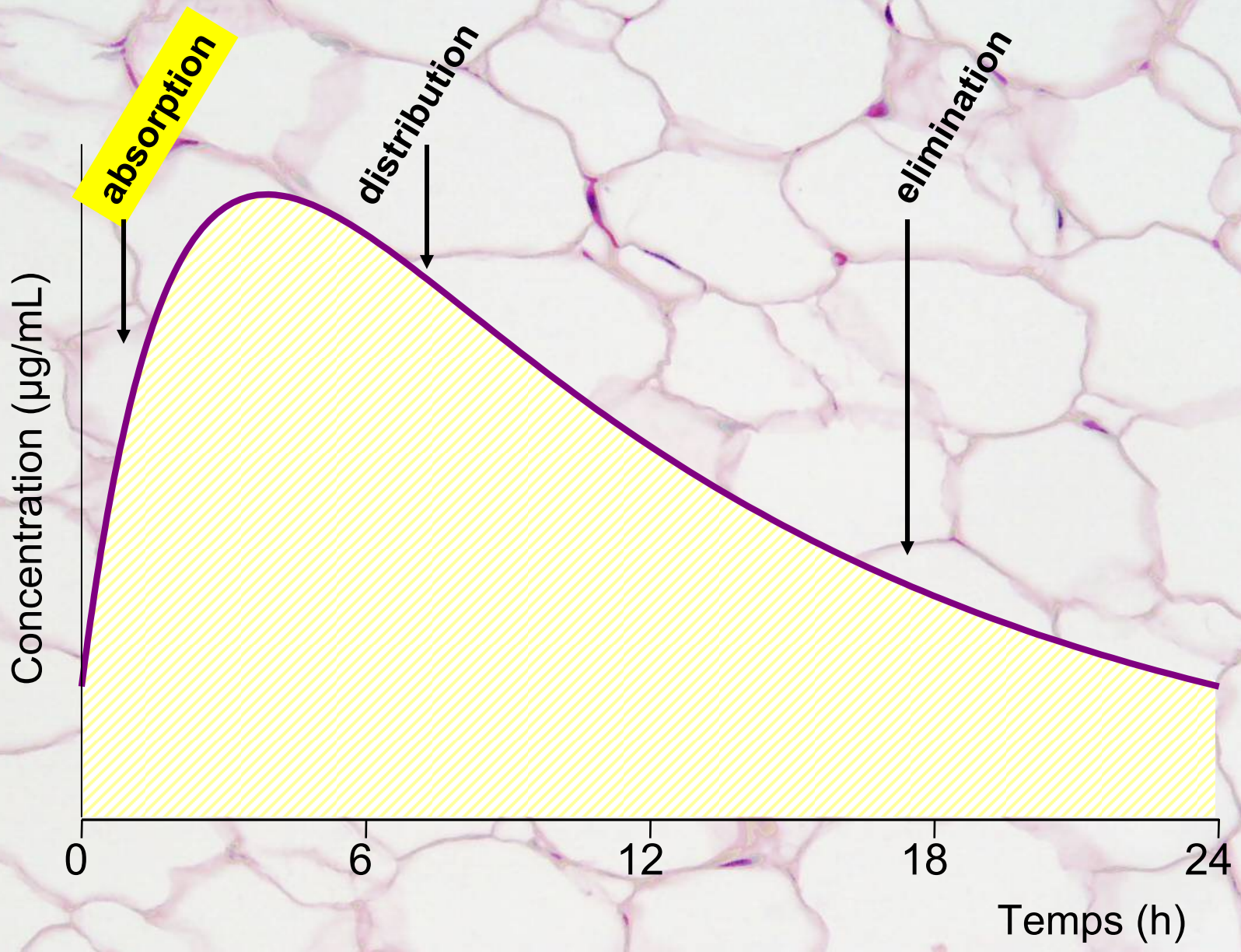


- ↗ masse corporelle (maigre et grasse)
- ↗ volume circulant et fonction cardiaque
- ↗ clairance rénale
- fonction hépatique altérée
- taux de protéines sériques modifié

Poids et paramètres PK



Poids et paramètres PK



Poids et absorption

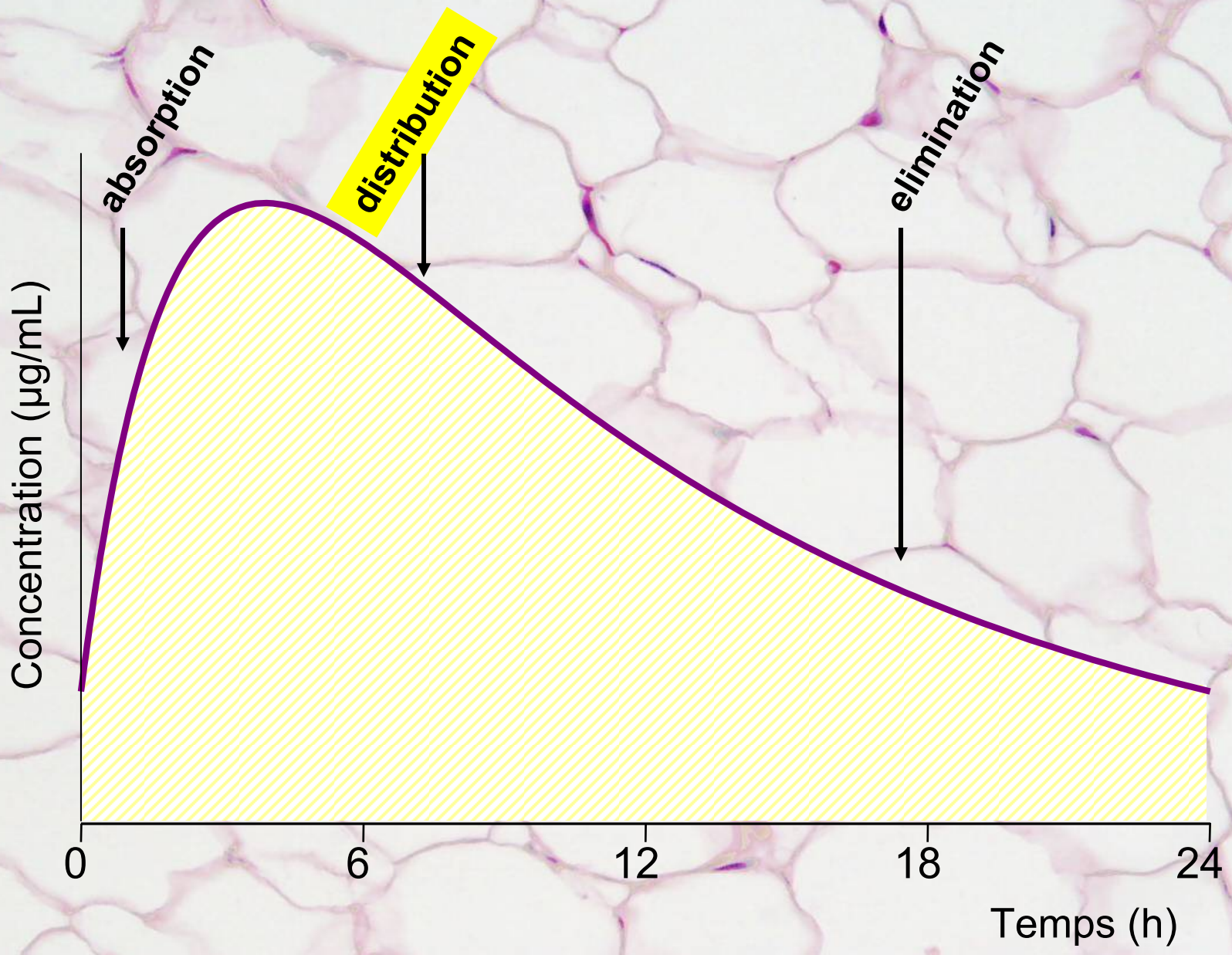
Mal connu !

- voie orale : ↗ flux sanguin splanchnique
- injections intramusculaires ~ injections intralipomateuses

MAIS conséquences sur l'absorption non caractérisées

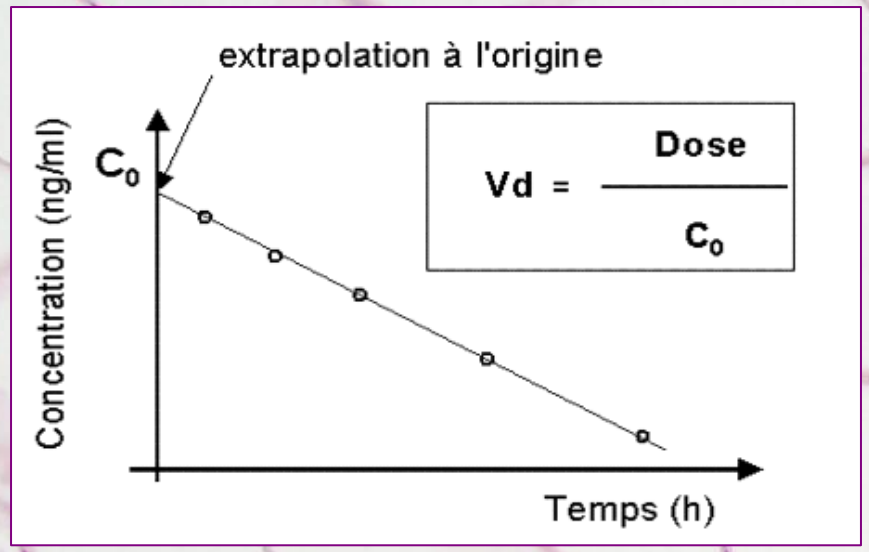
Alexander et al. Cardiovasc. Res. Center Bull. (1962-63) 1:39-44; Cockshott et al. N Engl J Med. (1982) 307:356-8.

Poids et paramètres PK



Distribution des médicaments

Volume de distribution



Compartiment central (sang) (3 L plasma) → **Vd 0.05 L/kg**

↓

liquides extracellulaires (8 L) → **Vd 0.2 L/kg**

↓

tissus

↓

compartiments intracellulaires (25 L eau) → **Vd 0.6 L/kg**

↓

Accumulation tissulaire → **> 1 L/kg**

Volume de distribution des antibiotiques

macrolides

fluoroquinolones

rifampicine

tetracyclines

→ accumulation cellulaire

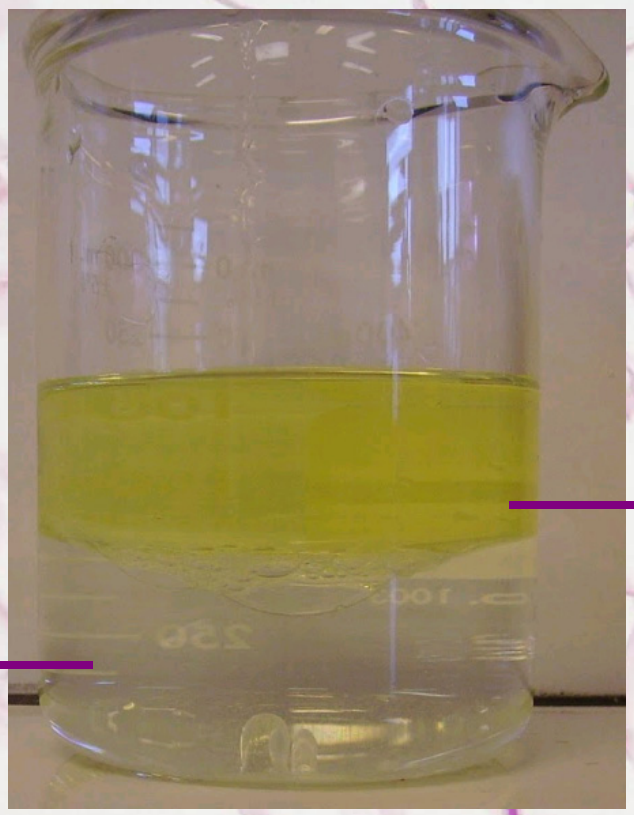
β-lactames

glycopeptides

aminoglycosides

→ distribution extracellulaire

Solubilité des antibiotiques



« hydro »

- β-lactames
- glycopeptides
- aminoglycosides
- polymyxines
- fosfomycine

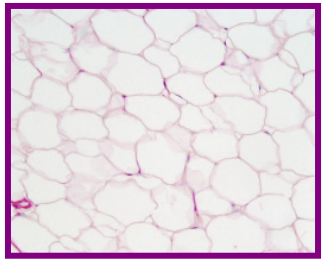
« lipo »

- fluoroquinolones
- macrolides
- lincosamides
- tetracyclines
- oxazolidinones
- co-trimoxazole
- rifampicine
- chloramphénicol

Falagas & Karageorgopoulos, Lancet (2010) 375: 248-51

Solubilité des antibiotiques et PK

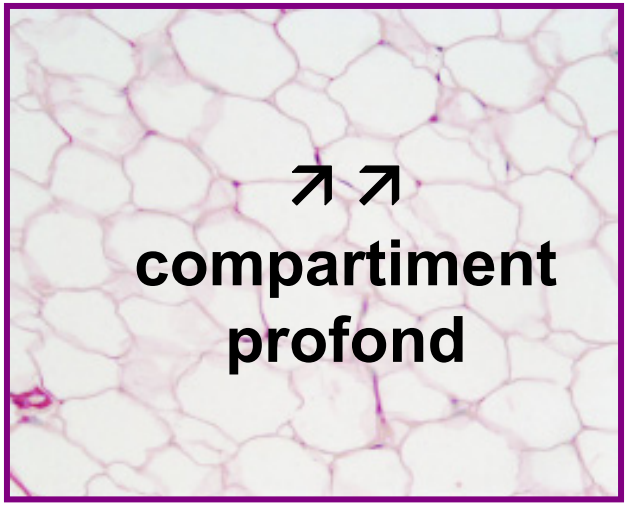
normal



« hydro »

- β-lactames
- glycopeptides
- aminoglycosides
- polymyxines
- fosfomycine

obèse

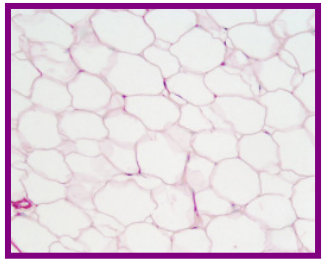


→ volume de distribution faiblement ↗
(30 % eau dans tissu adipeux)

Hanley et al. Clin. Pharmacokin. (2010) 49: 71-87

Solubilité des antibiotiques et PK

normal



obèse

« lipo »

- fluoroquinolones
- macrolides
- lincosamides
- tetracyclines
- oxazolidinones
- co-trimoxazole
- rifampicine
- chloramphénicol

↗↗
compartiment profond

→ volume de distribution ↗↗ chez obèse
→ concentration circulante ↘

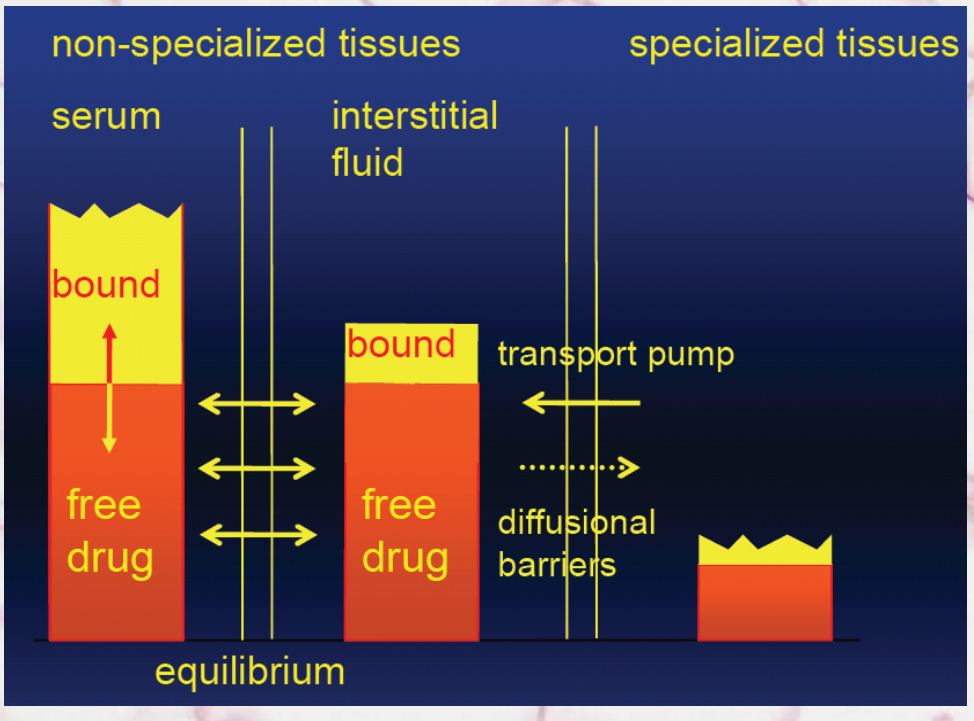
Hanley et al. Clin. Pharmacokin. (2010) 49: 71-87

Poids et liaison aux protéines

Chez les patients obèses:

- pas de modification de l'albumine
- ↗ α_1-glycoprotéine acide
- ↗ lipoprotéines
- ↗ triglycérides, cholestérol et acides gras

peuvent déplacer les médicaments de leur liaison à l'albumine !



U. Theuretzbacher, ISAP 2008

Antibiotiques et liaison aux protéines

>90%

Oxacillin, ceftriaxone, ertapenem, teicoplanin, daptomycin, dalbavancin, televancin, fusidic acid, rifapentine, iclaprim

>70%

Cefazolin, rifampicin, oritavancin, tigecycline temocillin

>30%

Penicillin G, cefixime, cefotaxime, moxifloxacin, erythromycin, clarithromycin, azithromycin, telithromycin vancomycin, linezolid

>10%

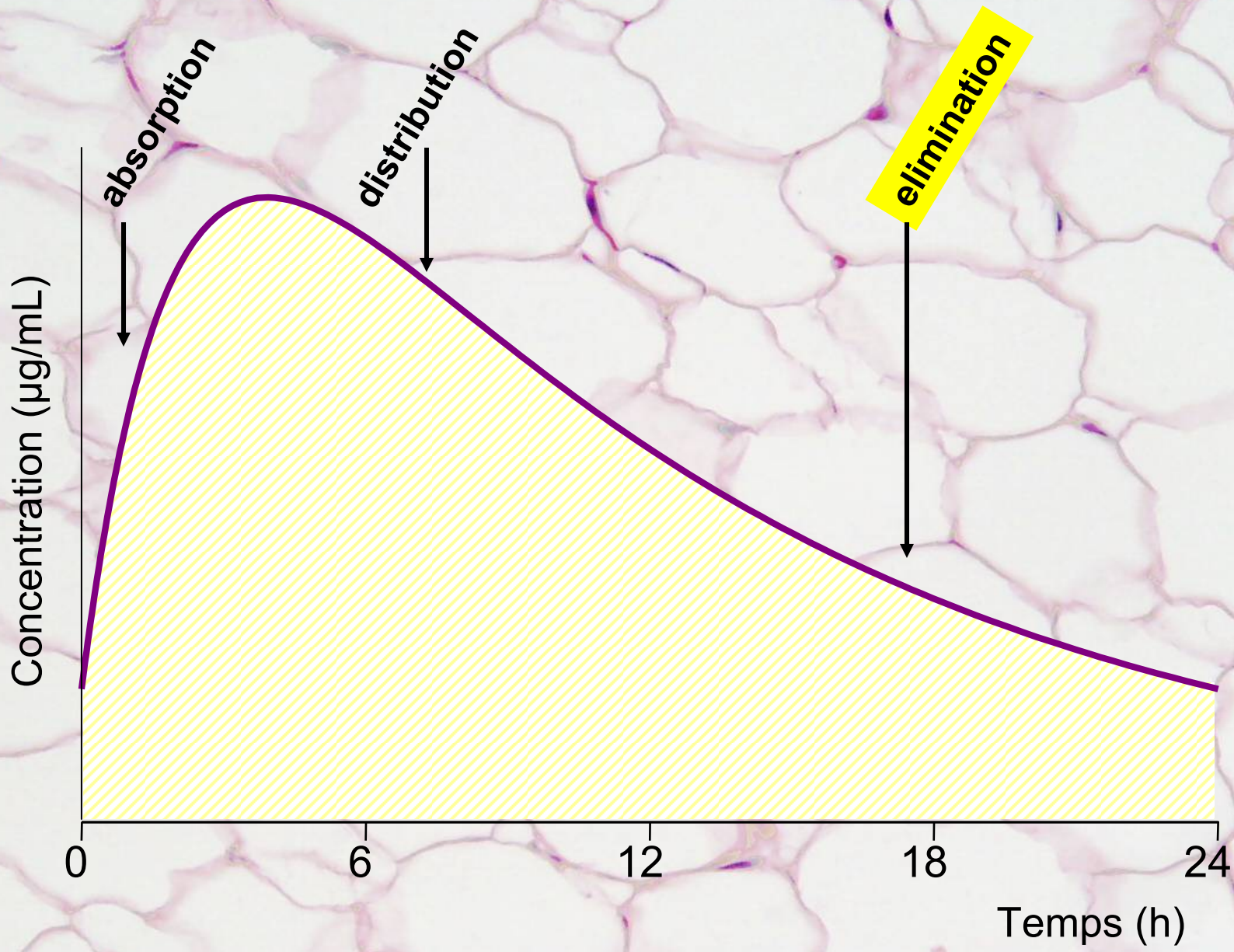
Amoxicillin, piperacillin cefpodoxime, cefuroxime, ceftazidime, imipenem ciprofloxacin, levofloxacin, gatifloxacin, metronidazole

<10%

Meropenem, doripenem, aminoglycosides, fosfomycin

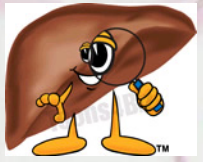
U. Theuretzbacher, ISAP 2008

Poids et paramètres PK



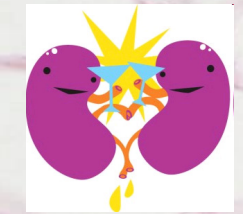
Poids et fonctions d'élimination

Chez les patients obèses:



- peu de modification des réactions de Phase I MAIS ↗ CYP2E1 et ↘ CYP3A4

- ↗ des réactions de Phase II (conjugaison)



- ↗ clairance à la créatinine

Pas de consensus sur le calcul des clairances chez les patients obèses !

Poids et fonctions d'élimination

Estimation de la clairance à la créatinine chez les patients obèses

- Cockroft & Gault

$$\frac{(140-\text{âge}) \times \text{TBW}}{72 \times \text{Cr.}_{\text{Ser}}}$$

- Cockroft & Gault « modifié »

$$\frac{(140-\text{âge}) \times \text{IBW}}{72 \times \text{Cr.}_{\text{Ser}}} \text{ ou } \frac{(140-\text{âge}) \times \text{AjBW}}{72 \times \text{Cr.}_{\text{Ser}}}$$

- Salazar-Corcoran

$$\frac{(146-\text{âge}) \times [(0.287 \times \text{TBW}) + (9.75 \times \text{taille [m]}^2)]}{60 \times \text{Cr.}_{\text{Ser}}}$$

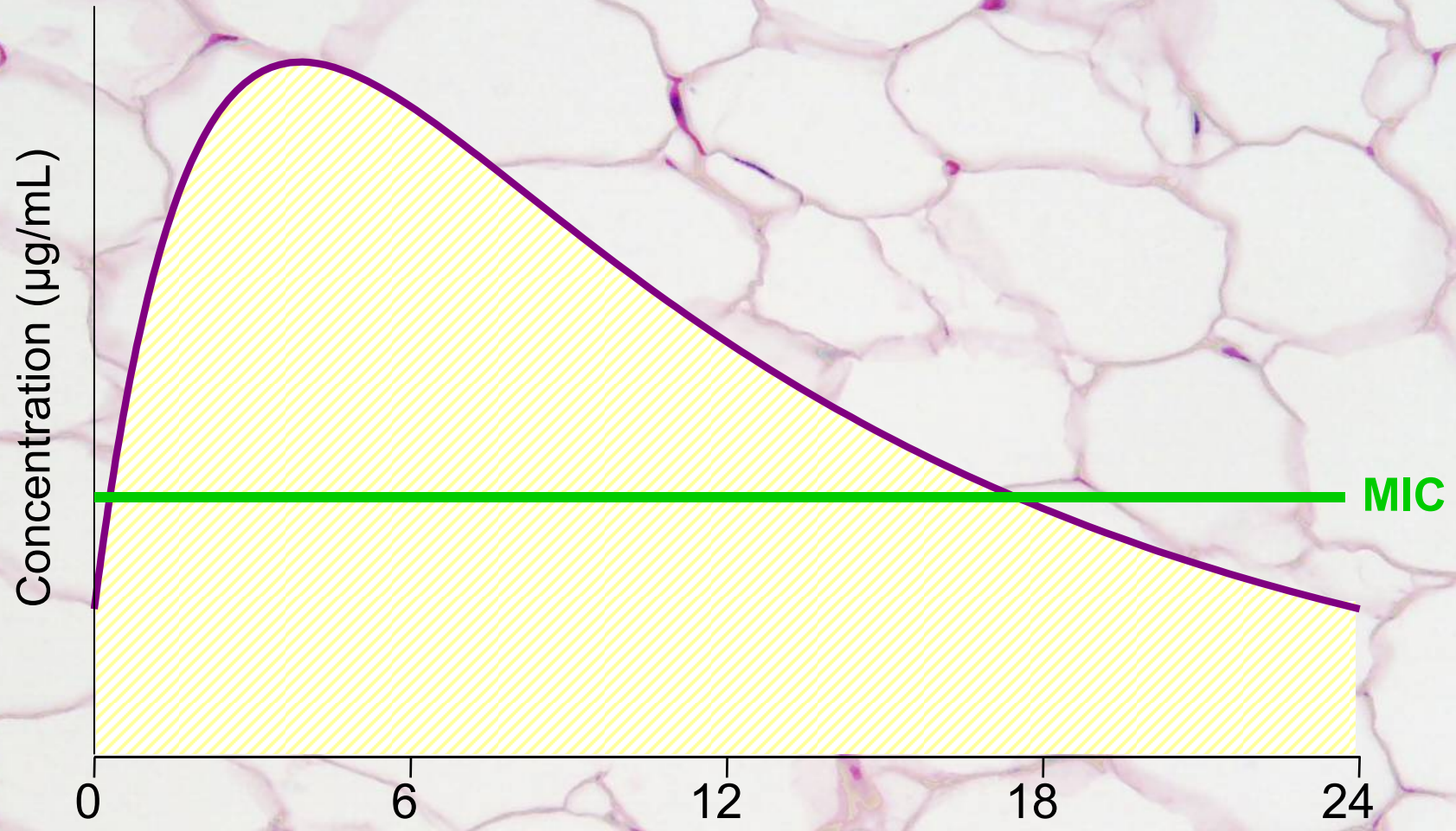
$$\frac{(137-\text{âge}) \times [(0.285 \times \text{TBW}) + (12.1 \times \text{taille [m]}^2)]}{51 \times \text{Cr.}_{\text{Ser}}}$$

Calculateur: http://www.globalrph.com/salazar.cgi

Cockroft & Gault. Nephron (1976) 16:31-41
Lake. Pharmacotherapy (1985) 5:340-4

Dosage des antibiotiques et BMI

PK/PD pour l'optimisation des doses



PK/PD pour l'optimisation des doses

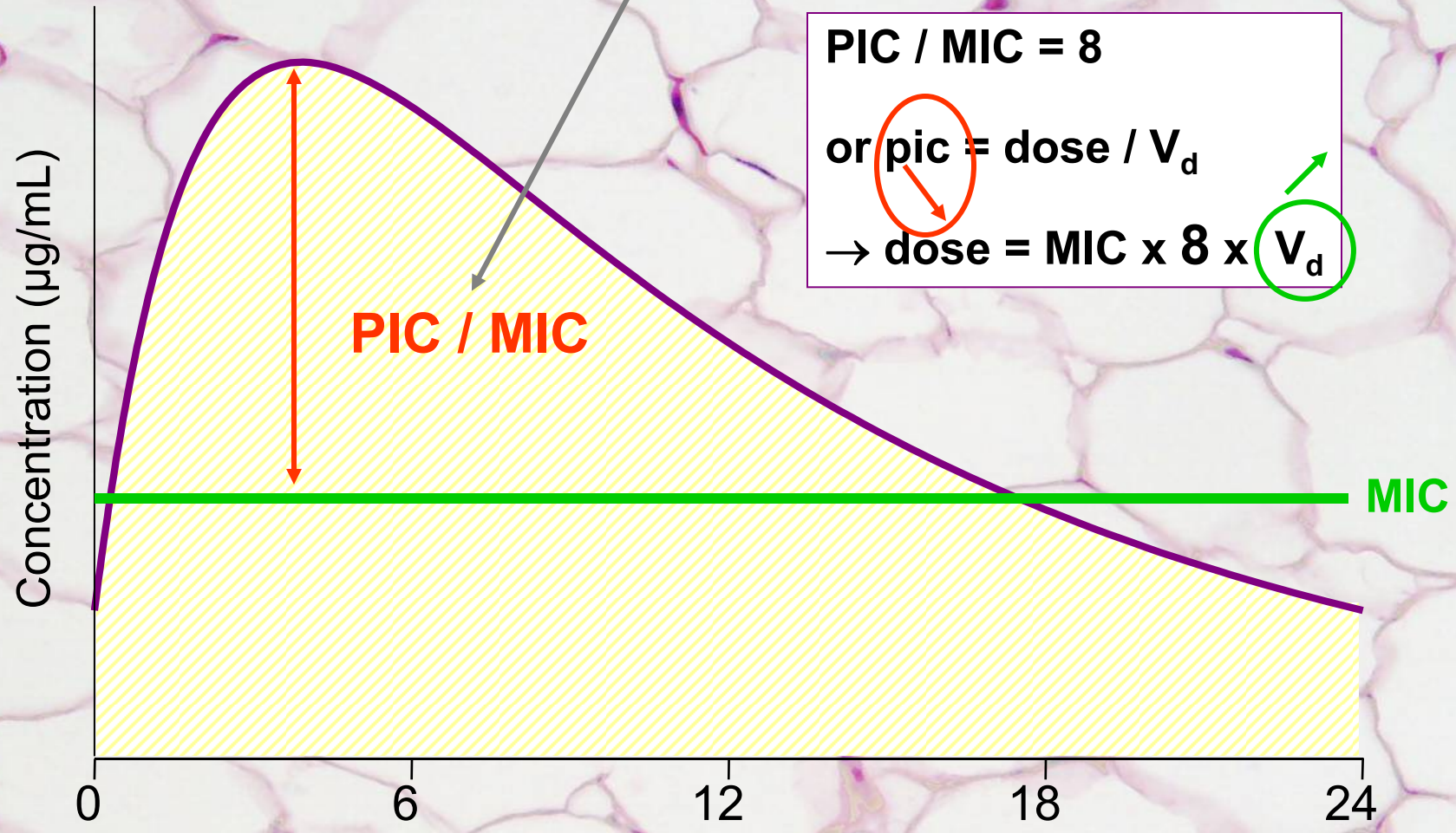
Efficacité

aminoglycosides

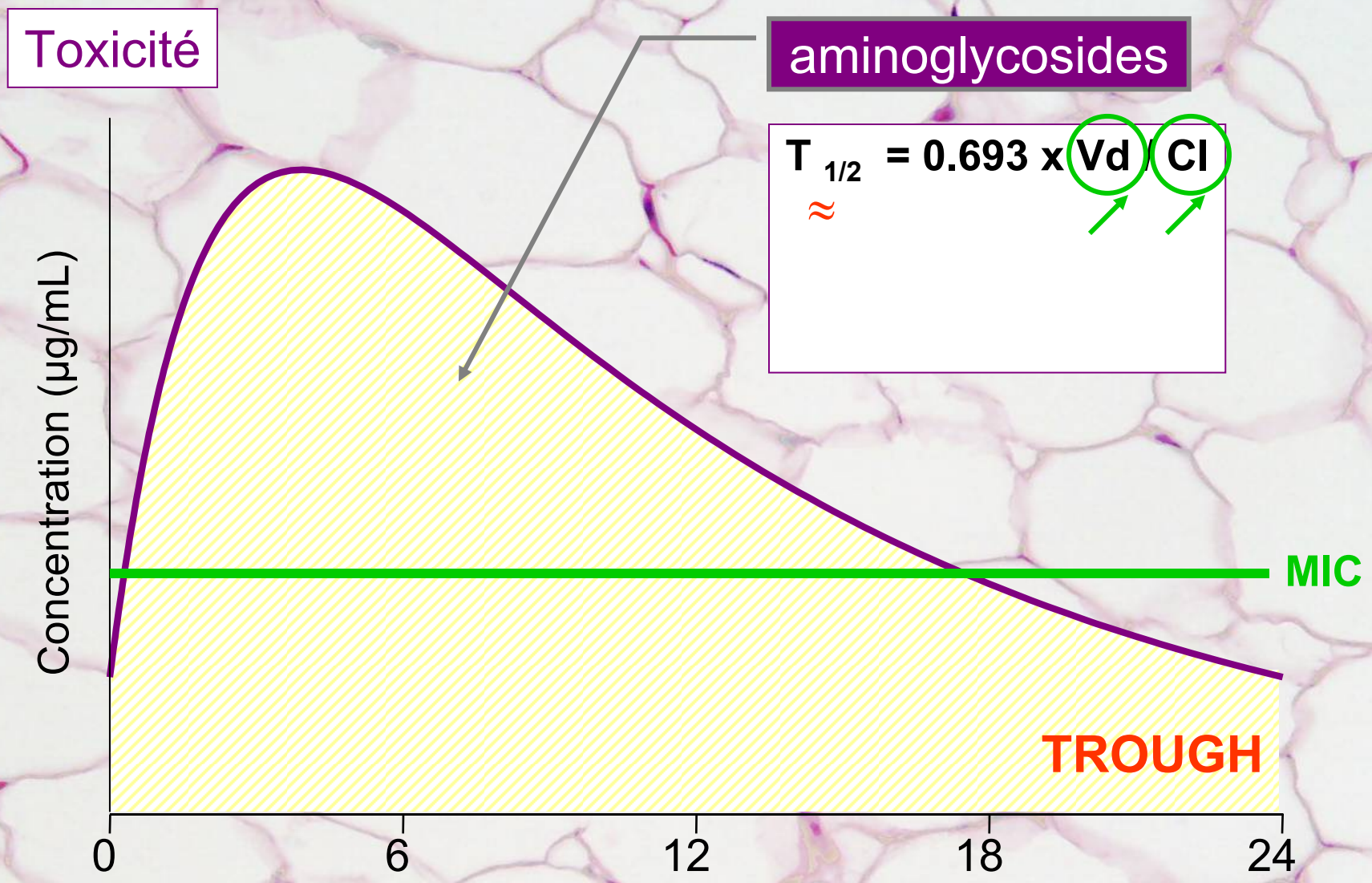
PIC / MIC = 8

or pic = dose / V_d

→ dose = MIC x 8 x V_d



PK/PD pour l'optimisation des doses



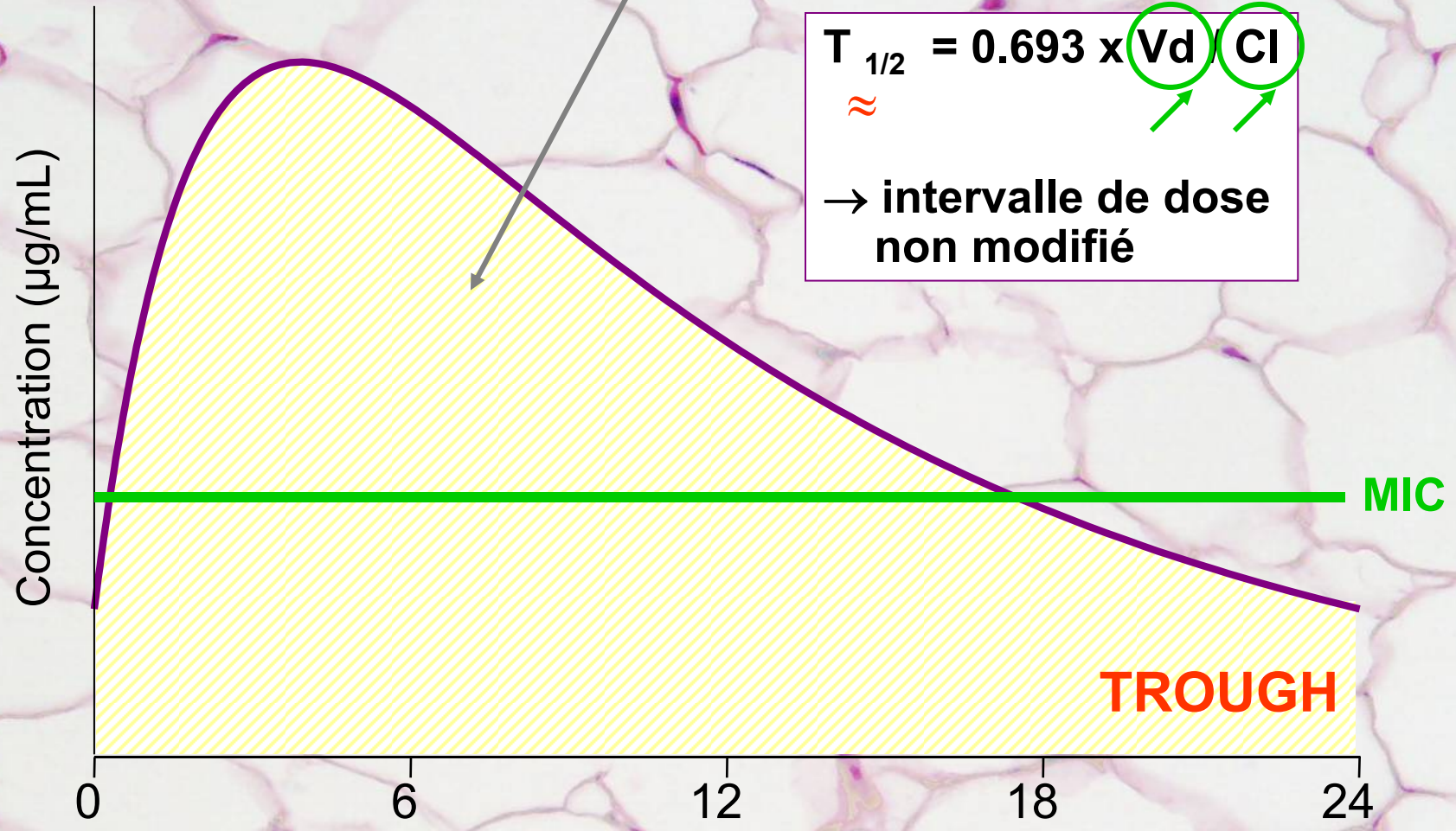
PK/PD pour l'optimisation des doses

Toxicité

aminoglycosides

$T_{1/2} \approx 0.693 \times \frac{Vd}{Cl}$

→ intervalle de dose non modifié



Aminoglycosides: ajustement de dose

AjBW = IBW + 0.4 x (TBW-IBW)

Clairance à la créatinine: formule de Cockroft & Gault modifiée

$Cl_{cr} = \frac{(140\text{-âge}) \times AjBW}{(72 \times \text{creat. ser.})}$

→ Calculateurs de dose

http://www.globalrph.com/aminoglycosides.htm

http://prodruginfo.com/Formulary/PharmacokineticDrugDosing/TradDosingAV.asp

…

Wurtz et al. CID (1997) 25:112-8

Aminoglycosides: ajustement de dose

paramètre		Gentamicine		Amikacine	
		normal	obese	normal	obese
Poids (kg)	TBW	73	138	72	147
	IBW	68	69	72	72
Vd (L/kg)	TBW	0.25	0.17	0.26	0.18
	IBW	0.26	0.41	0.26	0.44
$T_{½}$ (h)		2.2	2.2	2.2	2.0
CL_{cr} (ml/min)		119	153	109	165
Cmax (mg/L)		[6.5]*	6.8#	[25]*	25#

* conc. prédites

\# dose ajustée sur base du AjBW

Bauer et al. Eur. J. Clin. Pharmacol (1983) 24:643-47

PK/PD pour l'optimisation des doses

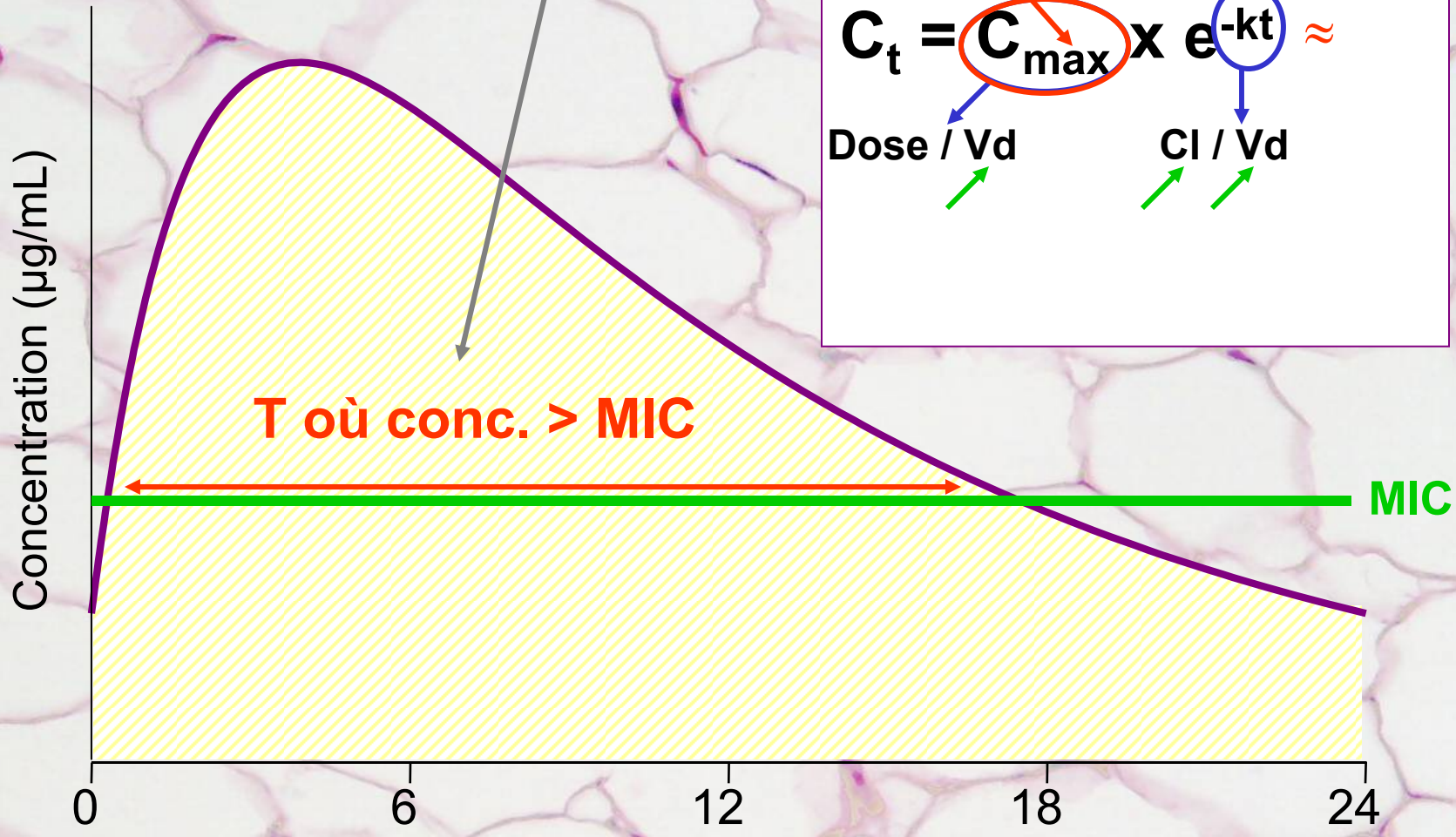
Efficacité

β-lactames

$C_t = C_{max} \times e^{-kt} \approx$

Dose / Vd

Cl / Vd



PK/PD pour l'optimisation des doses

Efficacité

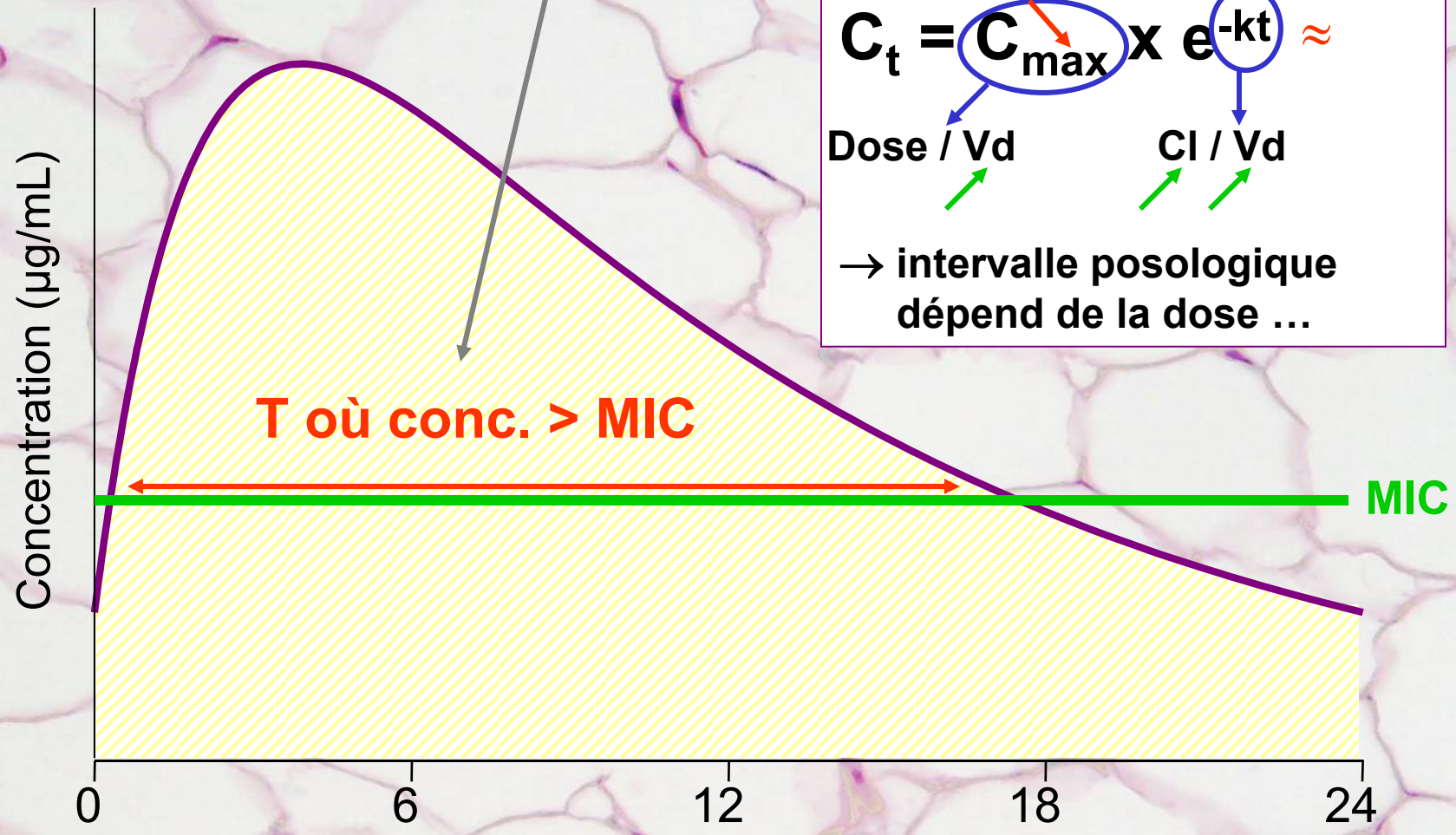
β-lactames

$C_t = C_{max} \times e^{-kt} \approx$

Dose / Vd

Cl / Vd

→ intervalle posologique dépend de la dose …



β-Lactames: Cefuroxime

cefuroxime, 1.5 g
à 6 patients obèses

Patient demographics.

Patient	Age (years)	Weight (kg)	Height (cm)	BMI (kg/m^2)	Serum creatinine (mg/dL)
1	54	138	170	48	0.79
2	60	140	178	44	1.15
3	63	109	152	47	0.82
4	49	132	163	50	0.67
5	76	131	160	51	0.67
6	19	140	163	53	0.76

Pharmacokinetic parameters of cefuroxime in plasma and the interstitial space fluid of muscle and subcutaneous (s.c.) adipose tissue.

Pharmacokinetic parameter	Plasma ($n=5$)		Skeletal muscle ($n=5$)	s.c. adipose ($n=6$)
C_{max} (μg/mL)	66.8 ± 18.9	←→ 100 normal !	60.1 ± 15.2	39.2 ± 26.4
T_{max} (h)	0.60 ± 0.22		1.03 ± 0.38	1.00 ± 0.28
$t_{1/2}$ (h)	2.37 ± 0.69	←→ 1.3h normal !	1.98 ± 0.98	1.65 ± 0.58
AUC_{0-last} (h μg/mL)	158.7 ± 54.6[a]	= 140 normal !	150.0 ± 65.5[b]	88.8 ± 65.3[b]
$AUC_{0-\infty}$ (h μg/mL)	201.9 ± 80.3[a]		189.4 ± 98.7[b]	104.2 ± 78.9[b]
CL (L/h)	8.39 ± 3.07		–	–
V_z (L)	26.6 ± 7.35		–	–
V_{ss} (L)	25.3 ± 5.95		–	–
CL_{Cr} (L/h)	6.79 ± 2.06		–	–
$fAUC_{ISF\ tissue}/AUC_{plasma}$			1.03 ± 0.24	0.63 ± 0.52
$fAUC_{ISF\ tissue}/fAUC_{plasma}$[c]	–		1.53 ± 0.36	0.94 ± 0.78

C_{max}, peak drug concentration; T_{max}, time to C_{max}; $t_{1/2}$, half-life; AUC_{0-last}, area under the concentration–time curve from 0 to the last measured value; $AUC_{0-\infty}$, AUC from 0 to infinity; CL, clearance; V_z, volume of distribution based on the terminal phase; V_{ss}, volume of distribution at steady state; CL_{Cr}, creatinine clearance; $fAUC_{ISF\ tissue}/AUC_{plasma}$, free concentration–time curve ratio of ISF tissue/total plasma; $fAUC_{ISF\ tissue}/fAUC_{plasma}$, free concentration–time curve ratio of ISF tissue/free plasma.

[a] Based on total concentrations.
[b] Based on free concentrations.
[c] Based on a protein binding of 33%

Foord et al. (1976) 9:741-47
Bardour et al. IJAA (2009) 34:231-5

β-Lactames: Meropenem

Table 1: Patient Demographics	
Age (yr)	46.1 ± 7.5
Weight (kg)	154.6 ± 28.9
BMI (kg/m^2)	56.9 ± 11.2
IBW (kg)	56.4 ± 6.4

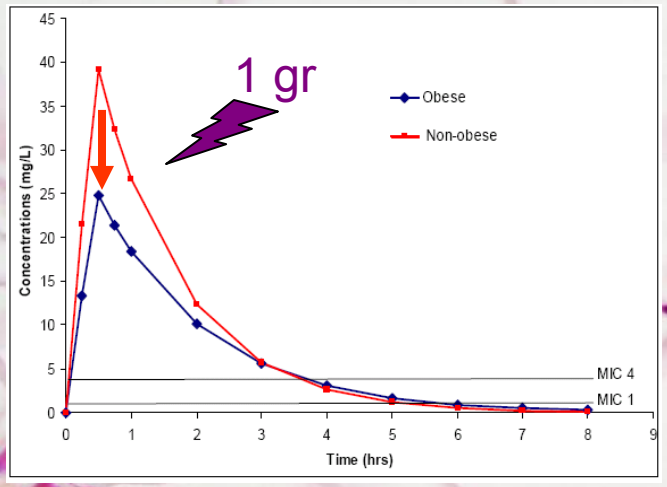


Table 2: Mean Pharmacokinetic and Pharmacodynamic Results		
	Obese (n = 9)	Non-obese*
CL (L/hr)	20.8 ± 3.9	16.3 ± 4.08
Vss (L)	28.8 ± 5.8	20.9 ± 4.6
t½ (hr)	1.16 ± 0.3	0.9 ± 0.09
AUC (mg·hr/L)	49.7 ± 9.9	56.7 ± 3.9
%T>MIC (MIC_{90} = 1 mg/L)	65.8	66.6
%T>MIC (MIC_{90} = 4 mg/L)	41.8	44.3

*Nakashima M, Uematsu T, Kanamaru M. Clinical, phase I study of meropenem. Chemotherapy (Tokyo) 1992;40 Suppl.1: 258-75.

Bearden et al. ICAAC (2005) A10

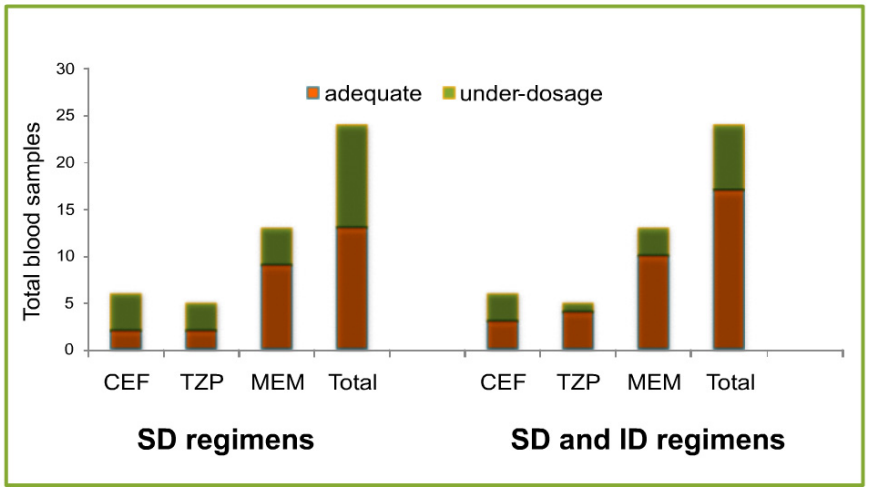
β-lactames: ajustement de dose

Base de l'ajustement	β-lactames
Pas d'ajustement	cefotetan meropenem
AjBW = IBW + 0.3 x (TBW-IBW)	cefepime cefotaxime ceftriaxone
Clairance à la créatinine	cefuroxime ceftazidime imipenem

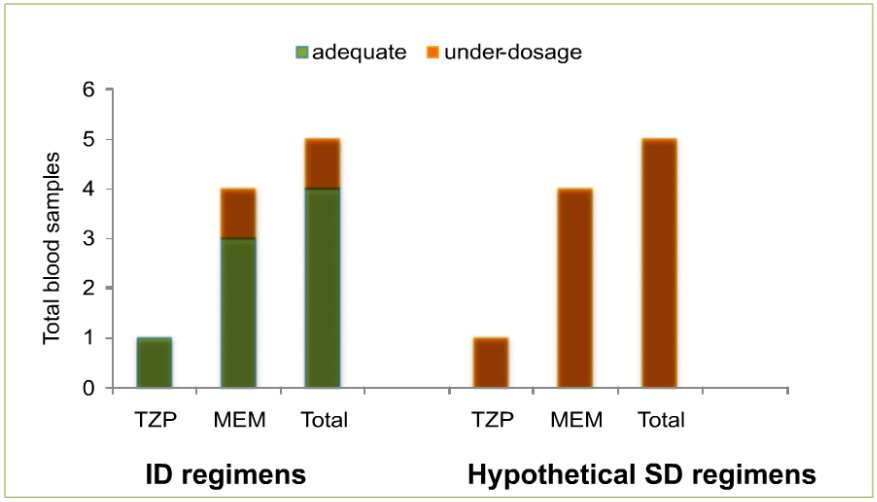
Siu. Drug Therapy Topics (2006) 35:9-12

β-lactames: quid des patients obèses à l'USI ?

Graph 1. Adequacy of drug serum concentrations when SD regimens were administered and when hypothetical ID regimens are considered.



Graph 2: Adequacy of drug serum concentrations when ID regimens were administered and when hypothetical SD regimens are considered.

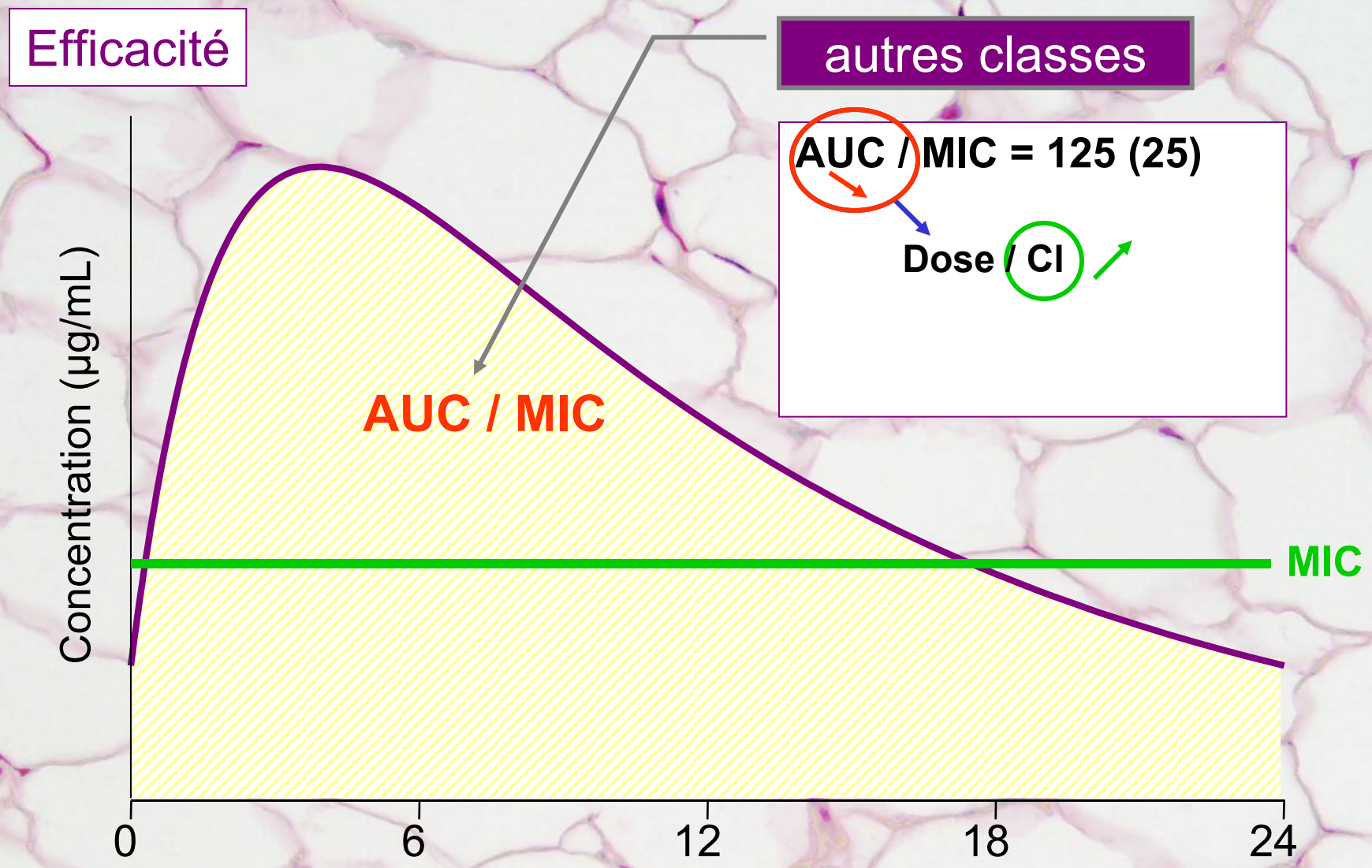


- **Interpretation of drug serum levels:**
  - Adequate therapy was defined as:
    - drug serum levels **> 4 times the MIC** for « difficult to treat » Gram-negative bacteria

    (ex: *Pseudomonas aeruginosa*) during optimal periods of time for each drug:
      - **CEF:** 4 x MIC > 70% of time
      - **TZP:** 4 x MIC > 50% of time
      - **MEM:** 4 x MIC > 40% of time

Hites, Taccone, Cotton, Wolff, Surin, Layeux, Vincent, Jacobs – Erasme - 2011 – Eur. Soc. IC Medicine

PK/PD pour l'optimisation des doses



PK/PD pour l'optimisation des doses

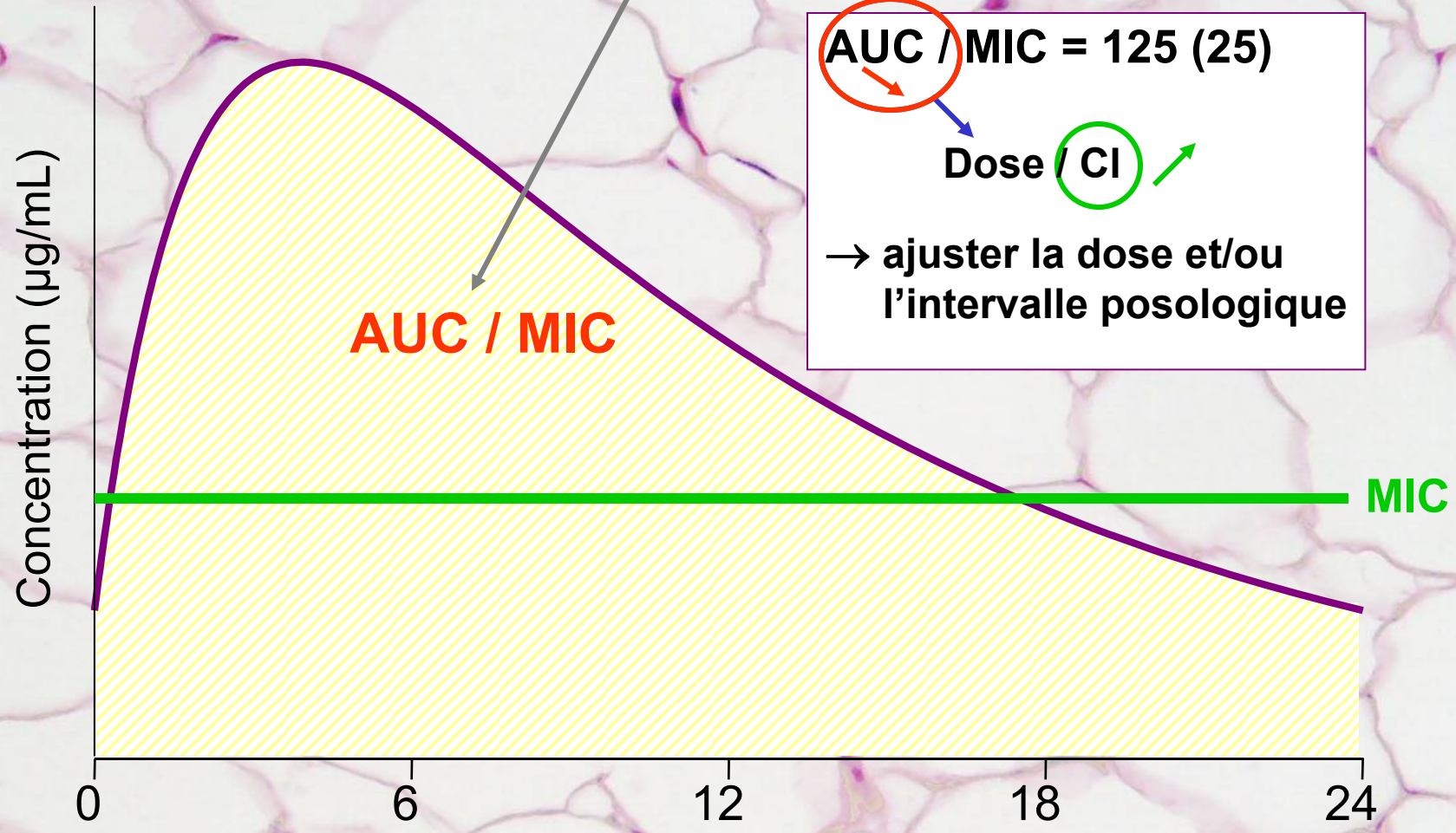
Efficacité

autres classes

AUC / MIC = 125 (25)

Dose / Cl

→ ajuster la dose et/ou l'intervalle posologique



Antibiotiques AUC-dependants: ajustements de dose

Base de l'ajustement	antibiotiques
Pas d'ajustement	moxifloxacine linezolid tigecycline
AjBW = IBW + 0.45 x (TBW-IBW)	ciprofloxacine
IBW	erythromycine
TBW	vancomycine (20-30 mg/kg) daptomycine synercid
Pas d'information	azithromycine clindamycine sulfamides metronidazole

Siu. Drug Therapy Topics (2006) 35:9-12

Antibiotiques AUC-dependants: ajustements de dose

Base de l'ajustement	antibiotiques
Pas d'ajustement	moxifloxacine **linezolid** tigecycline
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Pas d'information	azithromycine clindamycine sulfamides metronidazole

Siu. Drug Therapy Topics (2006) 35:9-12

Linezolid

1 dose de 600 mg (iv/oral)

Parameter	Value			
	ICU patients (n = 94)	Obese patients[b] (n = 95)	Elderly patients (n = 74)[d]	All patients (n = 318)
V_c (liters/65 kg)	39.8 (25)	43.9 (18)	38.2 (21)	39.6 (23)
V_{ss} (liters/65 kg)	67.7 (24)	69.7 (18)	64.2 (22)	65.8 (23)
CL_{ratio}	0.288 (32)	0.298 (28)	0.269 (32)	0.269 (34)
K_m (μg/ml)	1.38 (42)	1.53 (62)	1.53 (56)	1.46 (68)
CL_i (liters/65 kg)	46.8 (59)	43.8 (45)	40.7 (37)	43.5 (53)
V_{max} (mg/h/65 kg)	55.8 (28)	57.4 (26)	53.8 (25)	53.3 (26)
AUC (μg/ml · 24 h)	206 (60)	210 (56)	269 (54)	228 (58)
CL_{tavg} (liters/h/65 kg)	7.65 (50)	7.27 (49)	5.68 (52)	6.85 (50)

[a] Patients may be represented in more than one category. The CV (percent) is shown in parentheses.
[b] Patients were categorized as obese if total body weight was >30% above the calculated IBW.
[c] Patients were either started on oral linezolid or switched to oral therapy following initiation of i.v. linezolid.
[d] Patients >70 years of age were considered to be elderly.

Meagher et al., AAC (2003) 47, 548-53

Linezolid

1 dose de 600 mg (oral)

Table 1. Pharmacokinetic Parameters of Linezolid in Obese Patients

Patient	Gender	TBW (kg)	IBW[a] (kg)	Serum Concentration (µg/mL) 1 h	6 h	12 h	AUC_{0-12} (µg•h/mL)	$t_{1/2}$ (h)
1	M	101	63	9.2	4.4	1.5	57	4.3
2	M	102	65	13.6	6.6	3.6	90	5.7
3	F	195	56	7.0	6.8	3.0	69	5.1
4	F	164	58	18.6	11.2	7.9	145	8.9
5	F	125	61	16.5	10.2	7.1	131	9.1
6	M	160	71	6.9	2.4	1.1	38	4.1
7	F	175	61	14.1	8.9	5.5	111	8.1
Mean		146	62	12.3	7.2	4.2	92	6.5
SD		37	5	4.6	3.2	2.7	33	2.2

IBW = ideal body weight; $t_{1/2}$ = half-life; TBW = total body weight.
[a]Males, 50 kg + 1.9 kg/in for height over 5 ft; females, 49 kg + 1.7 kg/in for height over 5 ft.

16-24 mg/L chez normal

138 mg.h/L chez normal

5 h chez normal

Stein et al., Annals Pharmacother. (2005) 39:427-32

Antibiotiques AUC-dependants: ajustements de dose

Base de l'ajustement	antibiotiques
Pas d'ajustement	moxifloxacine linezolid tigecycline
AjBW = IBW + 0.45 x (TBW-IBW)	**ciprofloxacine**
IBW	erythromycine
TBW	vancomycine (20-30 mg/kg) daptomycine synercid
Pas d'information	azithromycine clindamycine sulfamides metronidazole

Siu. Drug Therapy Topics (2006) 35:9-12

Ciprofloxacine

Table 1 Pharmacokinetic parameters for the plasma compartment after intravenous administration of 2.85 mg/kg of ciprofloxacin in obese ($n = 12$) and normal-weight subjects ($n = 12$)

TBW !

Pharmacokinetic parameter	*Obese subjects*	*Lean subjects*
$C_{max\text{-}calc}$ (mg/l)	9.97 ± 5.64*	2.59 ± 1.06
AUC (mg · h/l)	6.18 ± 1.70*	3.02 ± 0.95
MRT (h)	3.26 ± 0.64	3.15 ± 0.69
$T_{1/2}\ \beta$ (h)	2.74 ± 0.42	2.56 ± 0.55
V_{ss} (l)	144.26 ± 28.39	150.71 ± 33.36
Cl (l/min)	0.76 ± 0.16	0.83 ± 0.21

*$P < 0.05$ compared with control.

$C_{max\text{-}calc}$, calculated C_{max}; AUC, area under the concentration – time curve; MRT, I mean resident time; $T_{1/2}\alpha$, half life of the α phase; $T_{1/2}\ \beta$, half life of the β phase; V_{ss}, volume of distribution at steady state; Cl, clearance.

Hollenstein et al., International Journal of Obesity (2001) 25, 354-8

Antibiotiques AUC-dependants: ajustements de dose

Base de l'ajustement	antibiotiques
Pas d'ajustement	moxifloxacine linezolid tigecycline
AjBW = IBW + 0.45 x (TBW-IBW)	ciprofloxacine
IBW	erythromycine
TBW	**vancomycine** (20-30 mg/kg/j) daptomycine synercid
Pas d'information	azithromycine clindamycine sulfamides metronidazole

Siu. Drug Therapy Topics (2006) 35:9-12

Vancomycine

paramètres	Normaux (24)	obèses (24)
TBW (kg)	68	165
CL_{cr} (ml/min)	77	197
Vd (L)	46	52
Vd (L/kg TBW)	68	32
Vd (L/kg IBW)	0.64	0.83
Dose (mg/24 h)	954 x 2	1938 x 3 (20) 1250 x 2 (4)
Cmax (mg/L)	26	29
Cmin (mg/L)	9	7

↗ dose
↗ fréquence

30 mg/kg TBW

Bauer et al., Eur J Clin Pharmacol. (1998) 54:621-5.

Conclusions et perspectives

Quelle dose pour quel patient ?

- calculer « les » poids de chaque patient
- calculer la clairance rénale de chaque patient
- adapter la dose si nécessaire

MAIS peu de données …et mauvaise prédictabilité !

- faire un suivi thérapeutique des conc. pic et vallée
- mesurer les CMI !
- réadapter la dose si nécessaire pour optimiser l'index PK/PD

Questions non résolues

Pharmacocinétique:
- fraction libre ?
- concentrations tissulaires ?
- interactions médicamenteuses ?

Pharmacodynamie:
- indice PK/PD chez les patients obèses ? et comorbidités ?

Facteurs propres au patient:
- patients en surpoids très important ?
- comorbidités ?

Bon appétit !