

Spécificités des poids et âges extrêmes

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Problématique

Obésité

Maigreur

Musclé

Agé

Jeune

Conclusion

Problématique

Obésité

Maigreur

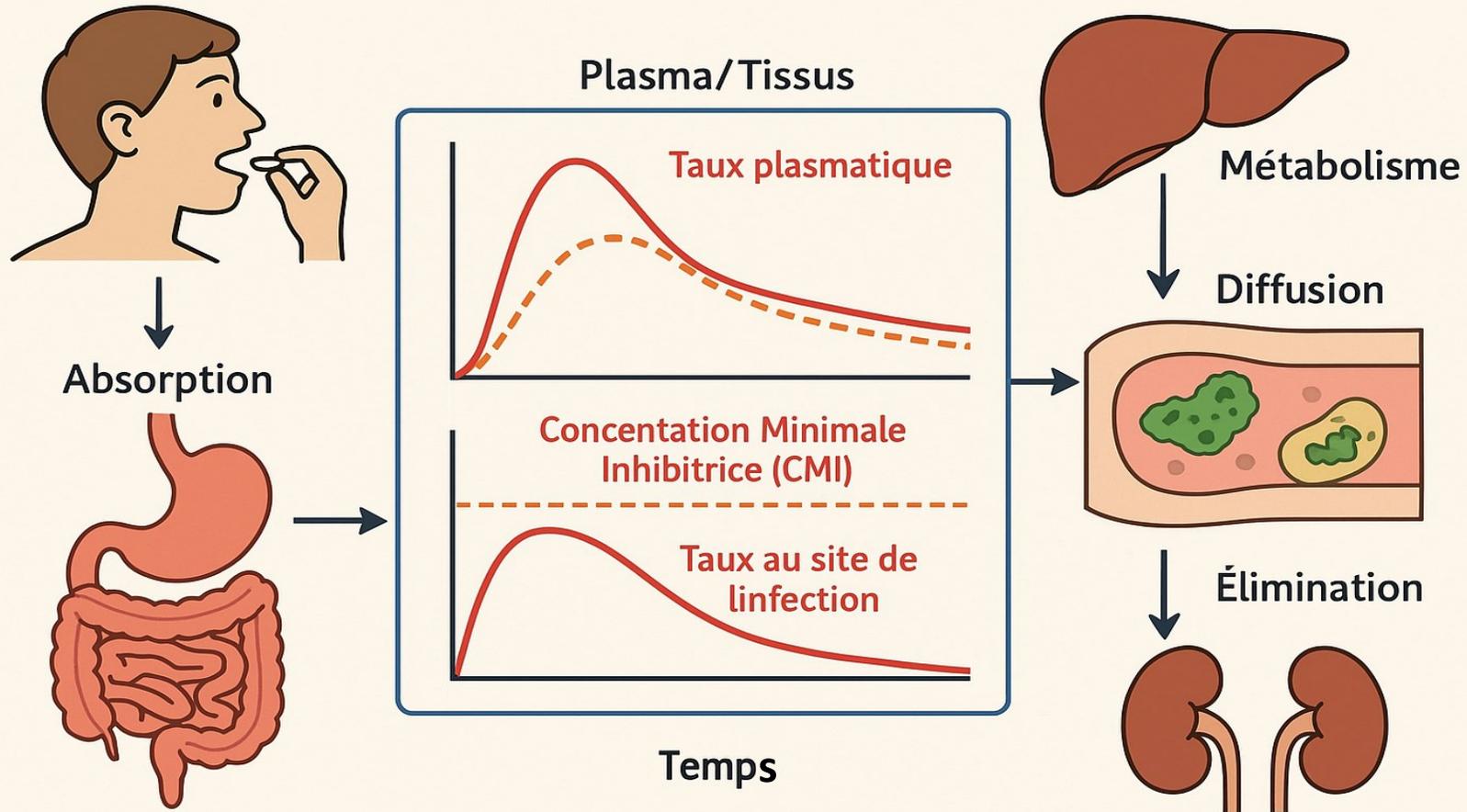
Musclé

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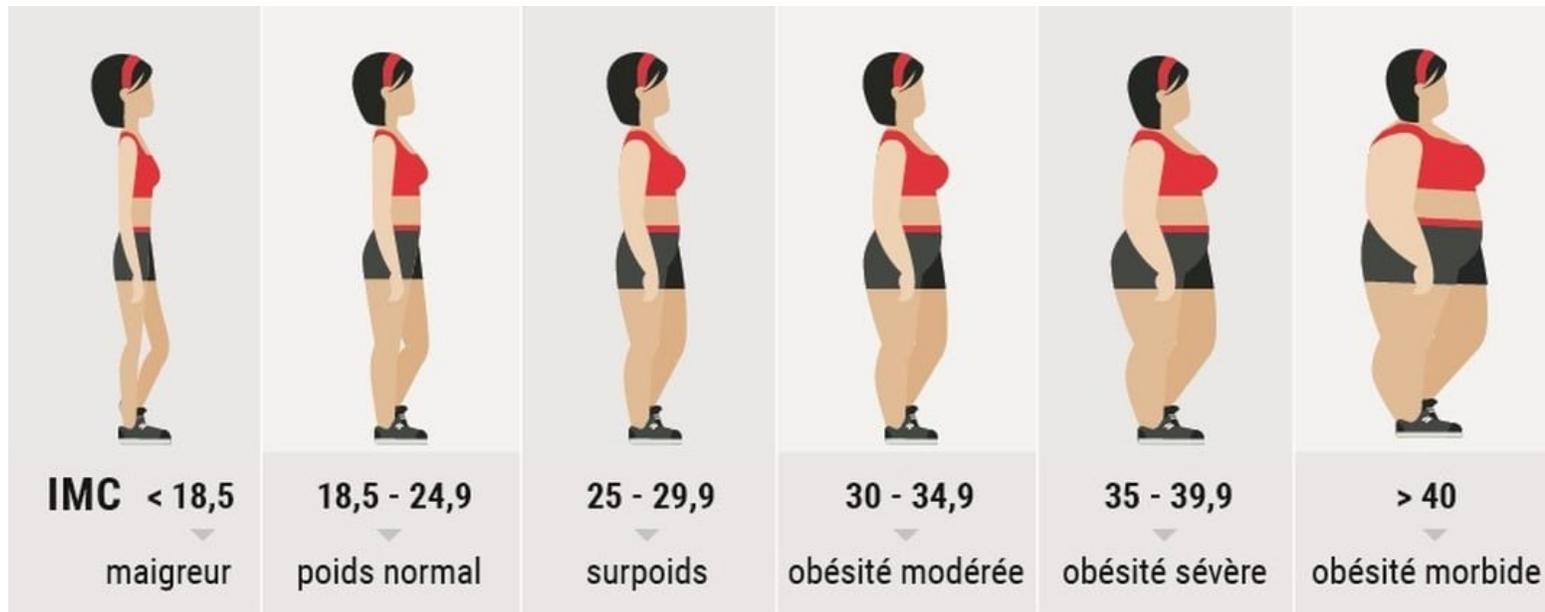
Conclusion

PHARMACOCINÉTIQUE DES ANTIBIOTIQUES





- Obésité = maladie
- Excès de masse grasse qui entraîne des conséquences néfastes pour la santé



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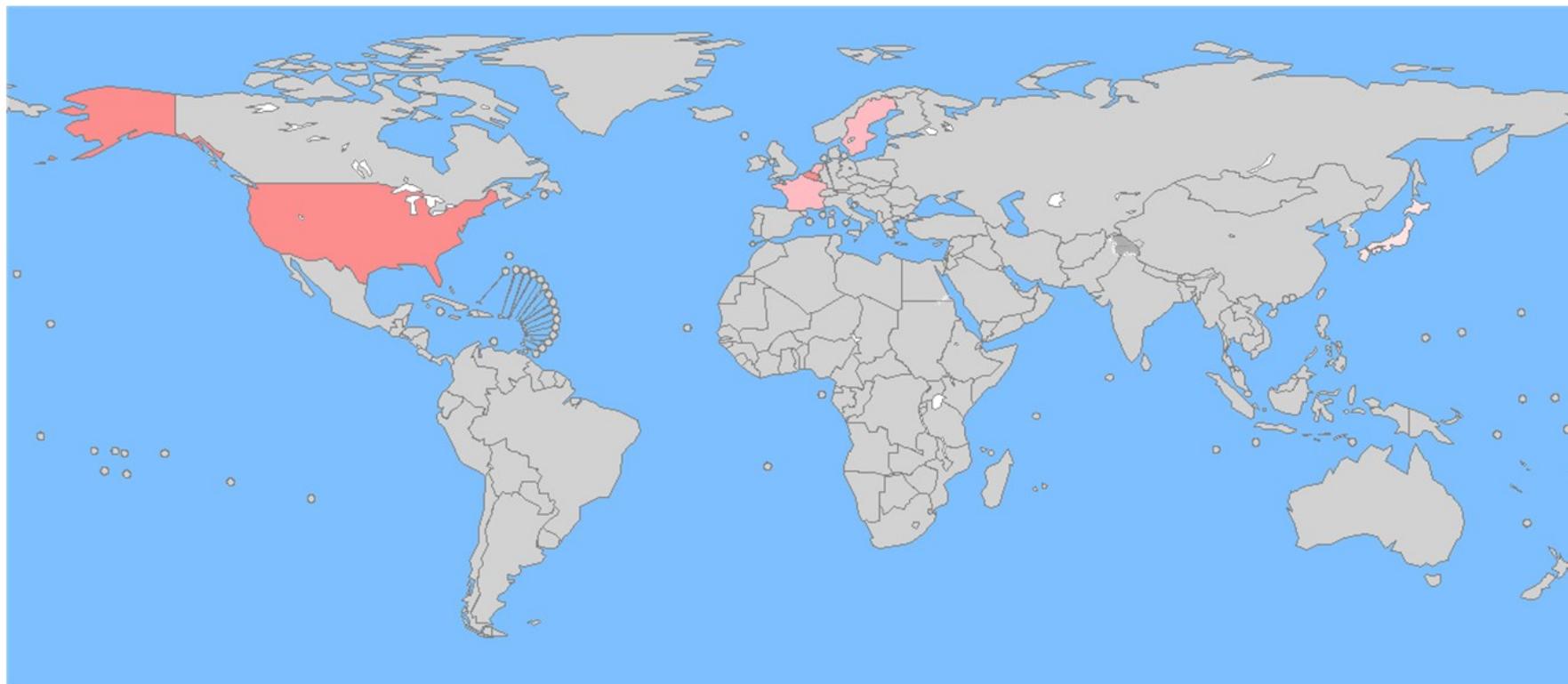
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Une population croissante ...

1980



Problématique

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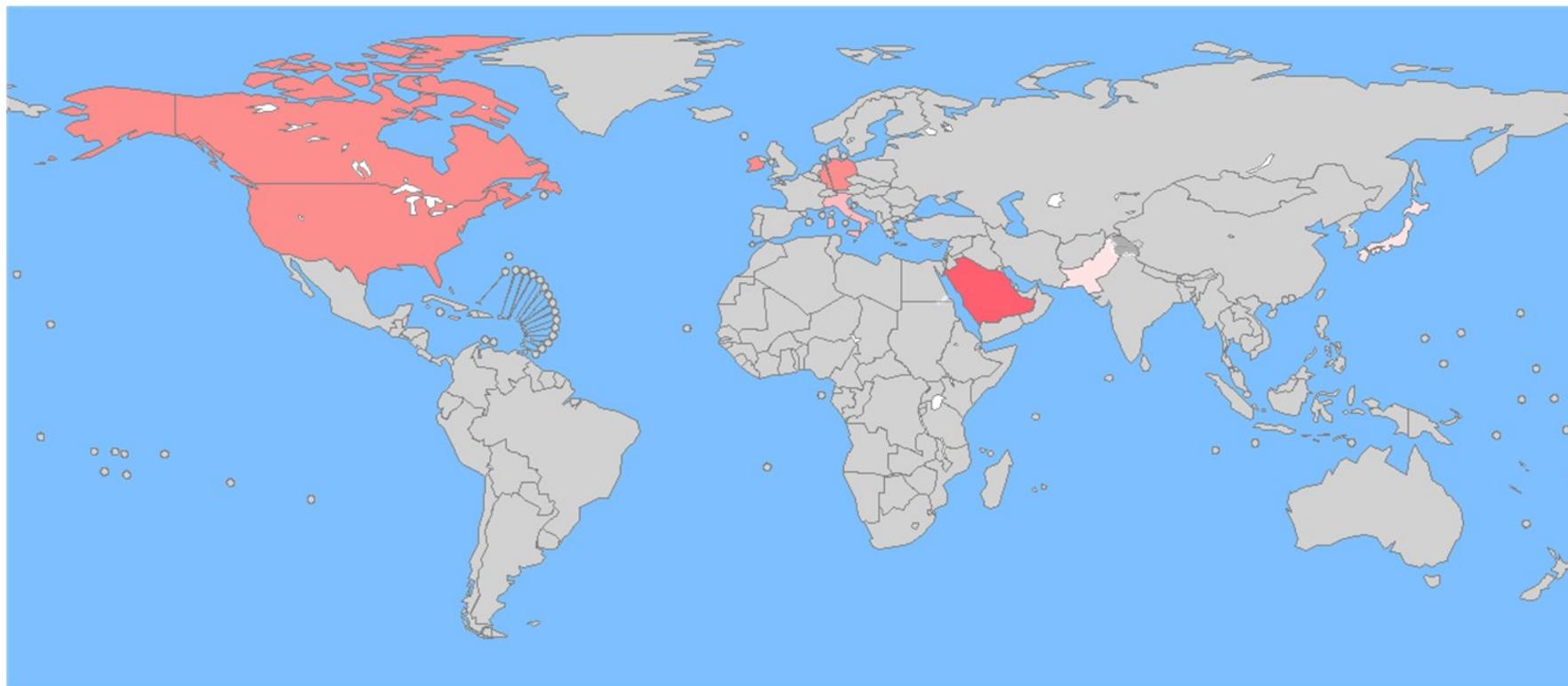
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Une population croissante ...

1990



Problématique

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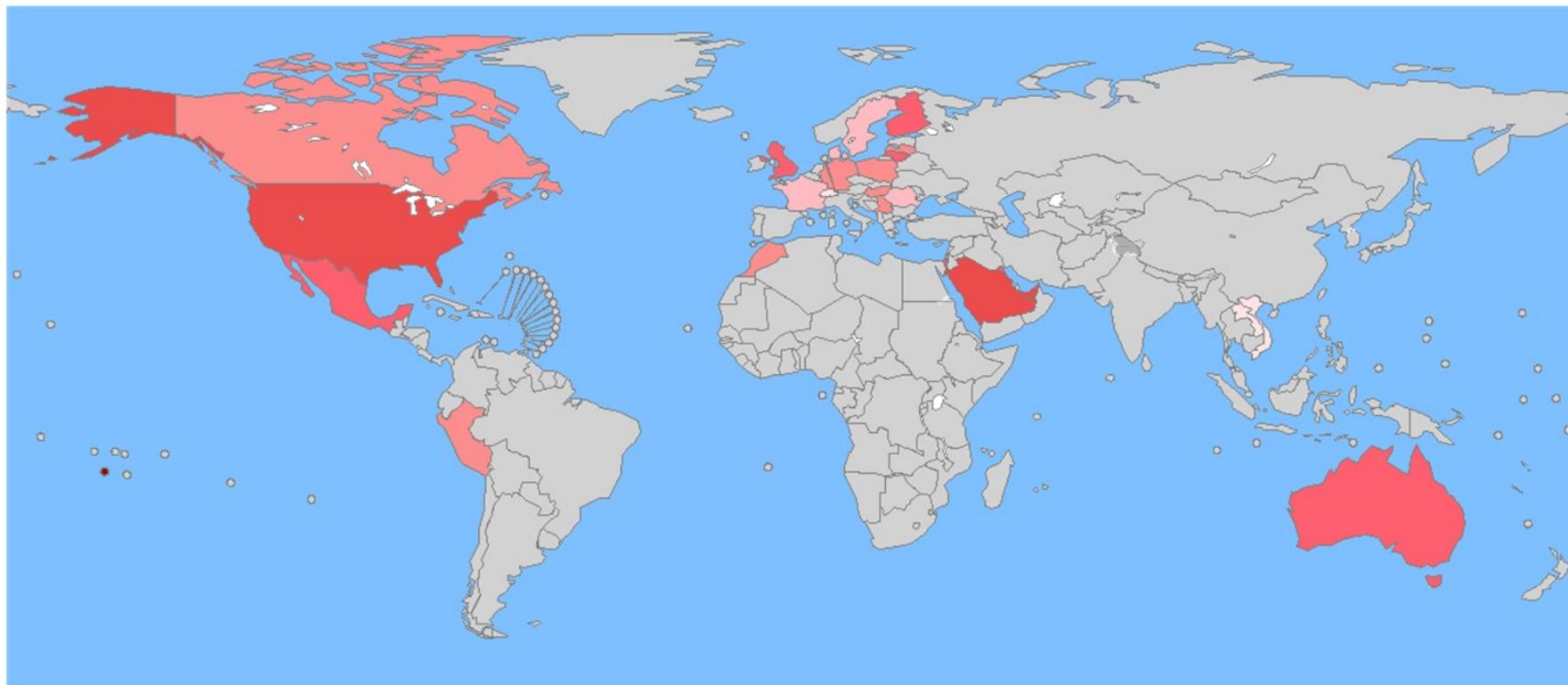
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Une population croissante ...

2000



Problématique

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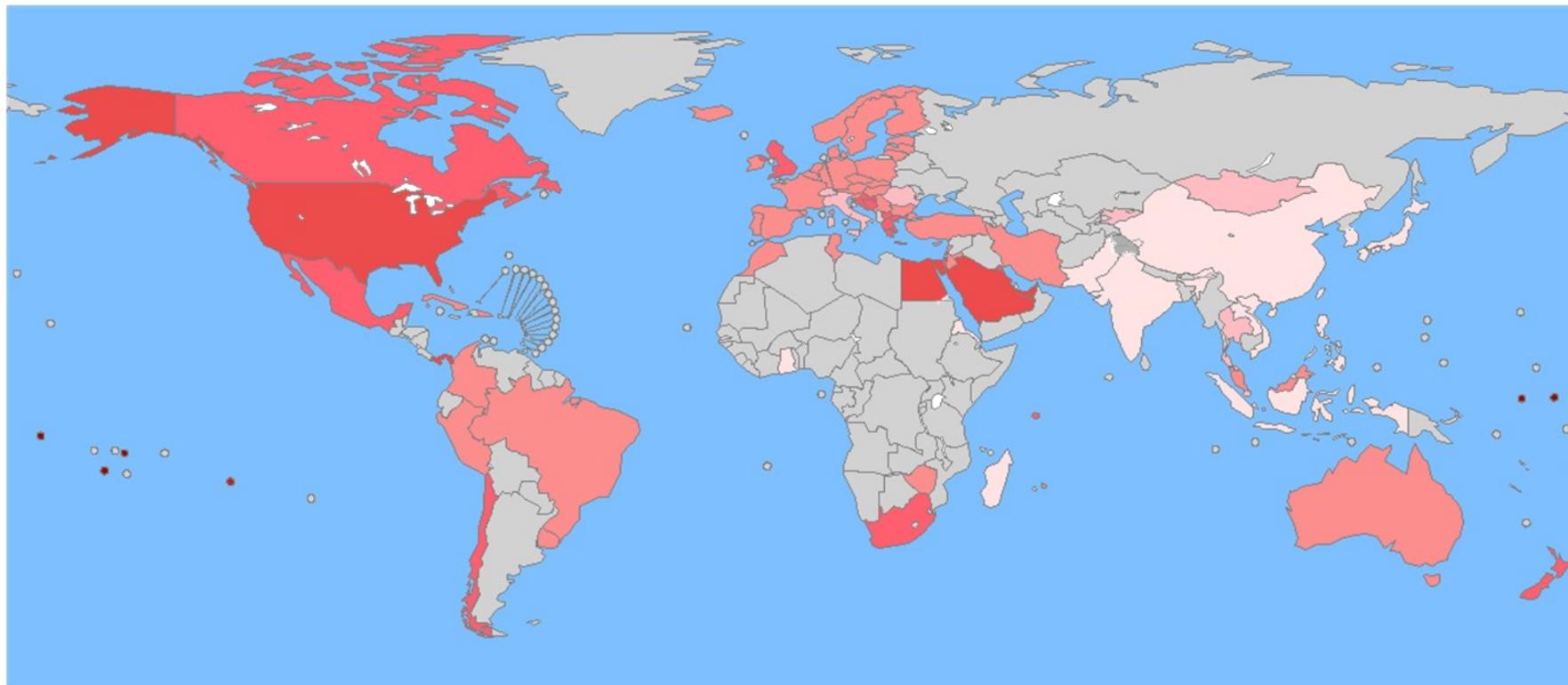
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Une population croissante ...

2010





... devenue fréquente !

Données OMS 2016 (Adultes)

- Plus de 1,9 milliards de personnes en surpoids dont plus de 650 millions sont obèses.
 - 40 % de la population mondiale des adultes est en surpoids ou obèse
 - 13 % de la population mondiale adulte est obèse
- La prévalence mondiale de l'obésité a quasi triplé entre 1975 and 2016.



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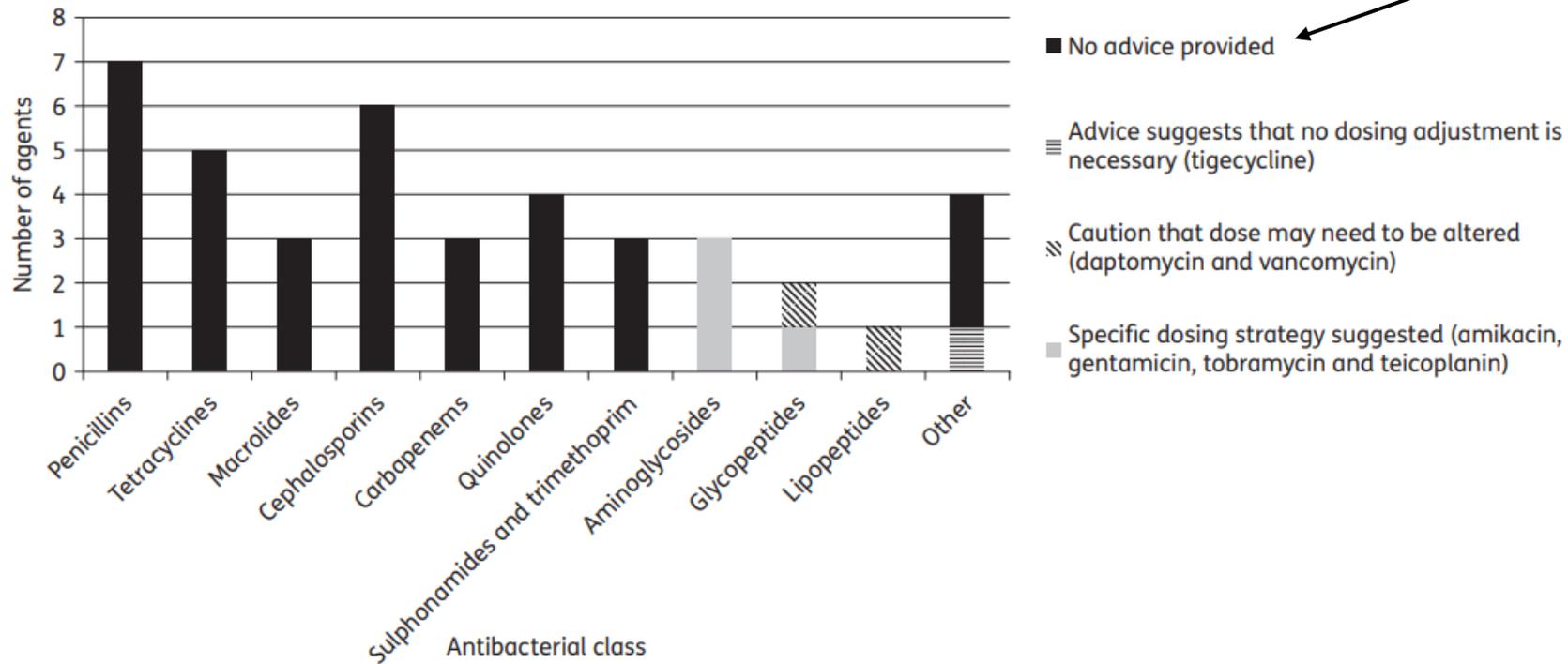
Pourtant exclue des études, en raison d'une physiologie modifiée

*“Physiologic alterations seen in obesity commonly impact the pharmacokinetics (PK) and pharmacodynamics (PD) of antibiotics and **may result in suboptimal dosing in this expanding but understudied population.** Much of the published clinical and PK evidence to date consists of small patient populations and are retrospective with, not infrequently, heterogeneous results that in some cases are contradictory.”*

Meng, Pharmacotherapy, 2017



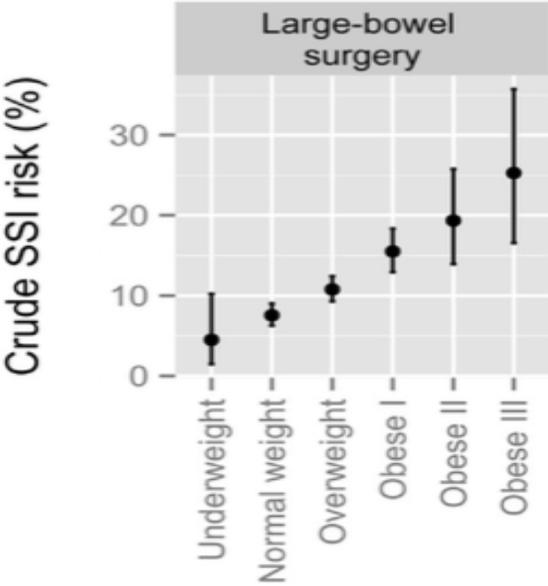
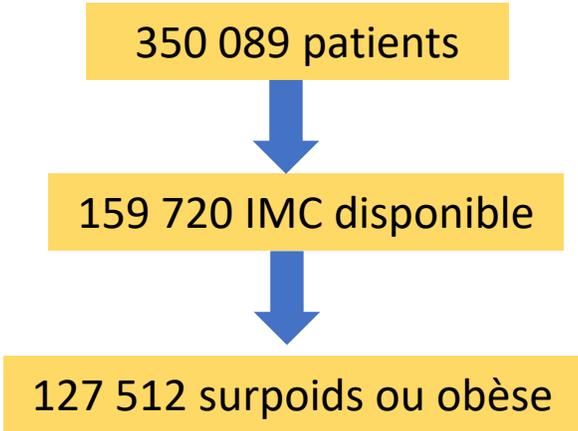
35 des 42 ATB les plus prescrits





Etude de cohorte
 206 centres au Royaume Uni
 De 2007 à 2011
 Chirurgies :

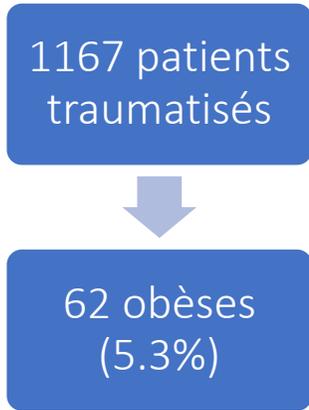
- Hystérectomie par voie haute
- Pontage aorto coronarien
- Prothèse de hanche
- Prothèse de genou
- Colectomie



| OR (95% CI) | |
|-------------|--------------------------|
| 0.59 | (0.23–1.52) |
| 1.00 | |
| 1.50 | (1.14–1.97) ^b |
| 2.02 | (1.48–2.76) ^a |
| 2.99 | (1.90–4.70) ^a |
| 2.71 | (1.46–5.01) ^b |



Etude prospective monocentrique sur 24 mois
Trauma center à Baltimore



| Variable | Odds ratio (95% CI) | p Value |
|------------------------------|---------------------|---------|
| HLOS (d) | 10.1 (6.8–13.4) | < 0.001 |
| ILOS (d) | 7.7 (5.1–10.4) | < 0.001 |
| Ventilator days | 8.2 (5.5–10.96) | < 0.001 |
| Foley catheter days | 10.9 (8.14–13.5) | < 0.001 |
| Central venous catheter days | 11.1 (9.2–13.9) | < 0.001 |

| Outcomes variable | Odds ratio for obesity (95% CI) | p Value |
|-------------------------|---------------------------------|---------|
| ICU admission | 2.9 (1.05–8.2) | 0.04 |
| Urinary tract infection | 2.0 (1.06–3.4) | 0.029 |
| Line infection | 2.1 (1.3–3.2) | 0.002 |
| Pneumonia | 2.0 (1.02–3.76) | 0.01 |

| Outcomes variable | BMI 30–49 (n = 49) Odds ratio (95% CI) | p Value | BMI ≥ 49 (n = 13) Odds ratio (95% CI) | p Value |
|-------------------|---|---------|--|---------|
| Mortality | 4.2 (2.5–7.1) | < 0.01 | 8.8 (4.6–11.1) | < 0.001 |



Pharmacocinétique : Étude du devenir des médicaments dans l'organisme

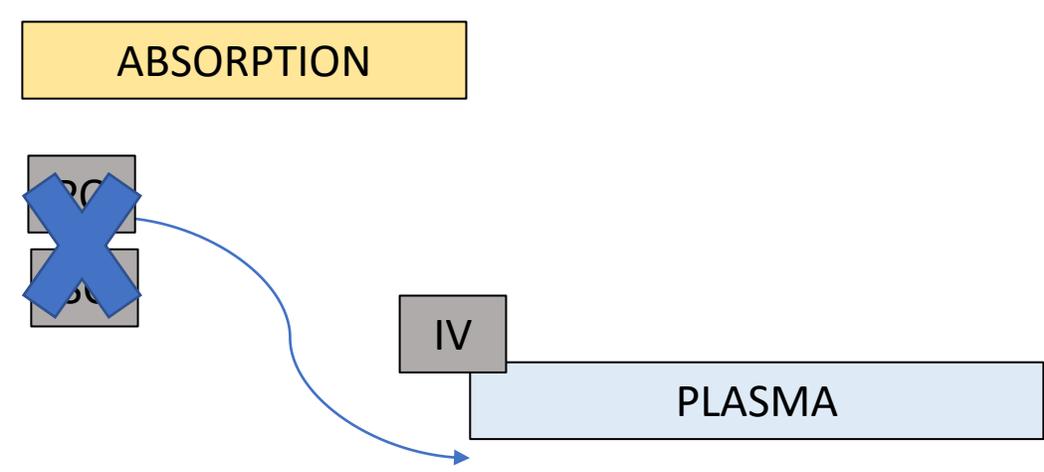
ADEM :

Absorption

Distribution

Élimination

Métabolisme



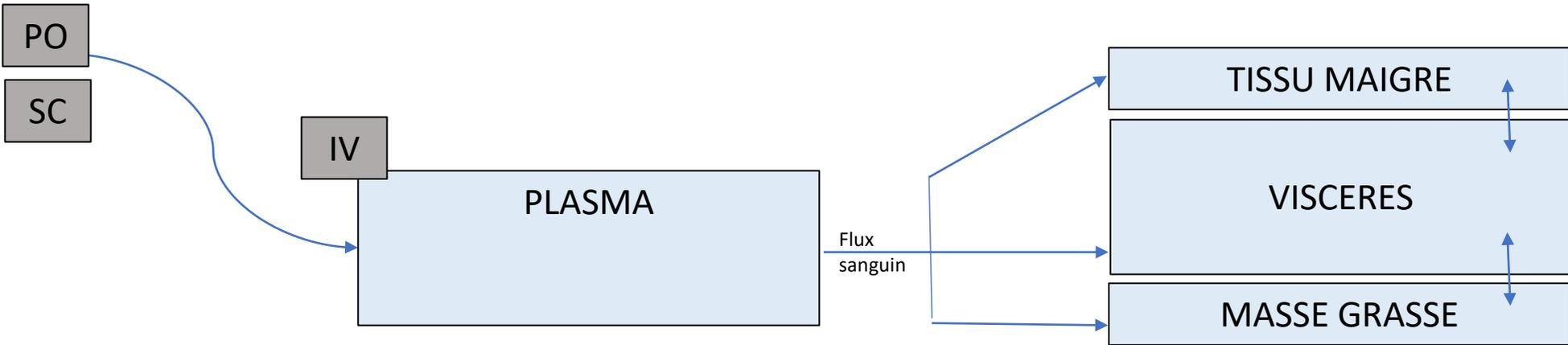


Volume de distribution : dose administrée / concentration plasmatique

- Vd élevé : forte affinité pour les tissus, diffusion importante
- Vd faible : molécule qui reste concentrée dans le plasma et diffuse peu dans les tissus

ABSORPTION

DISTRIBUTION





Volume de distribution : dose administrée / concentration plasmatique

- Vd élevé : forte affinité pour les tissus, diffusion importante
- Vd faible : molécule qui reste concentrée dans le plasma et diffuse peu dans les tissus

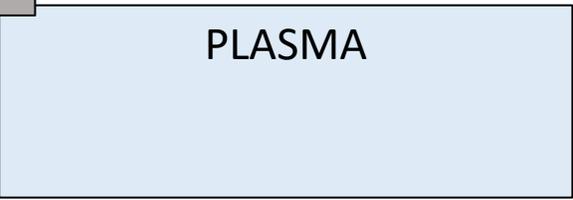
ABSORPTION

DISTRIBUTION

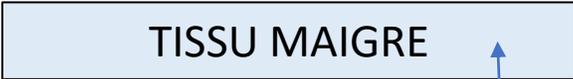
PO

SC

IV

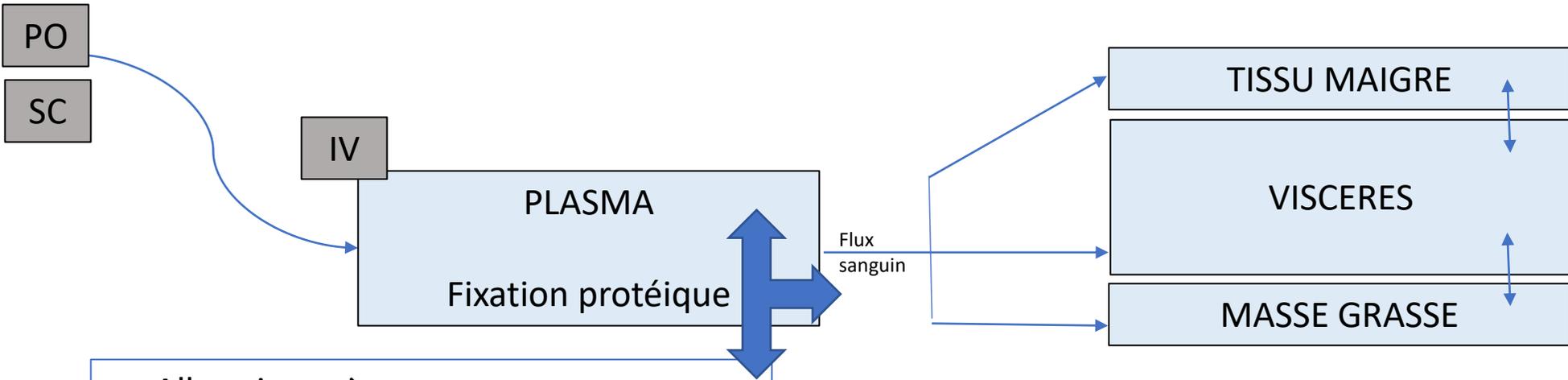


Flux sanguin



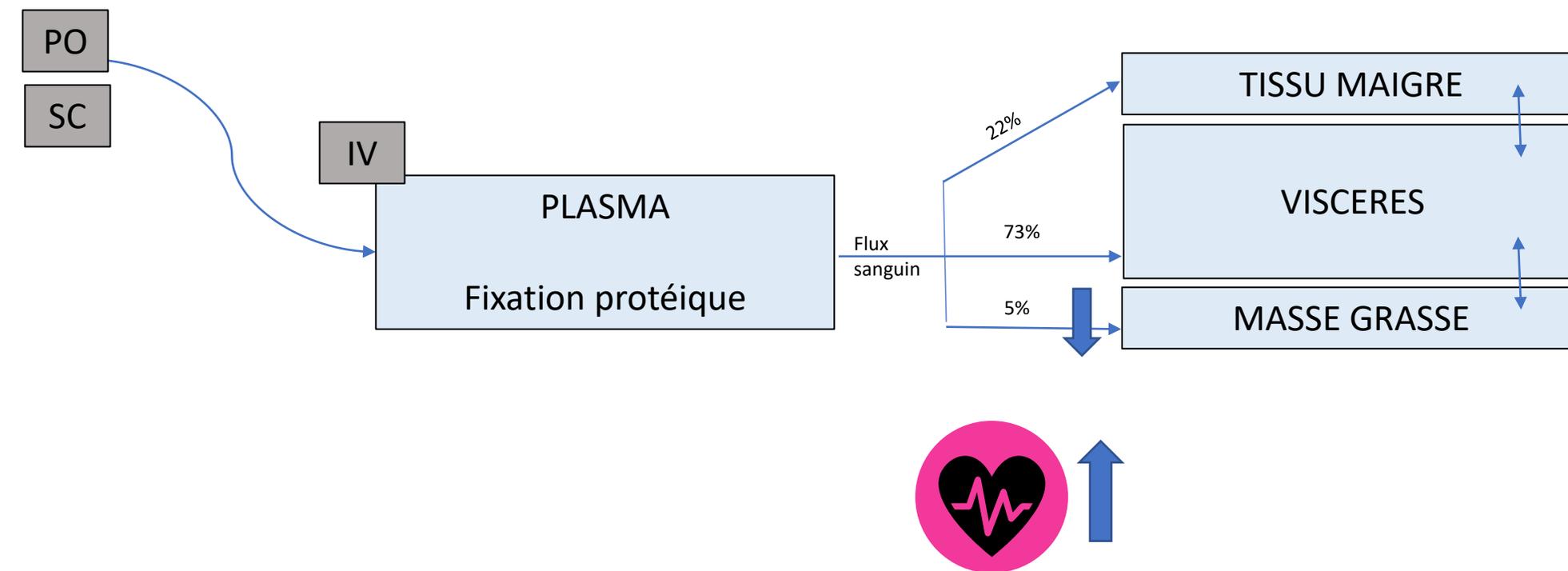
- Facteurs dépendant de la molécule
- Poids moléculaire
 - Degré d'ionisation
 - Capacité de liaison aux protéines
 - Capacité à traverser les membranes biologiques
 - Caractère hydrophile ou lipophile

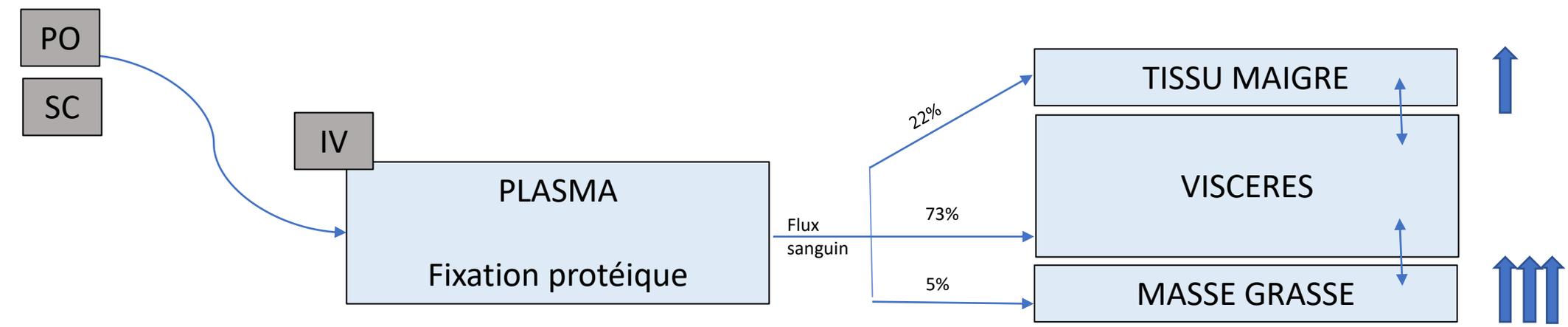




- Albumine : →
- α 1 glycoprotéine : ↑
- Lipo protéines : ↑ , liaison compétitive à l'albumine







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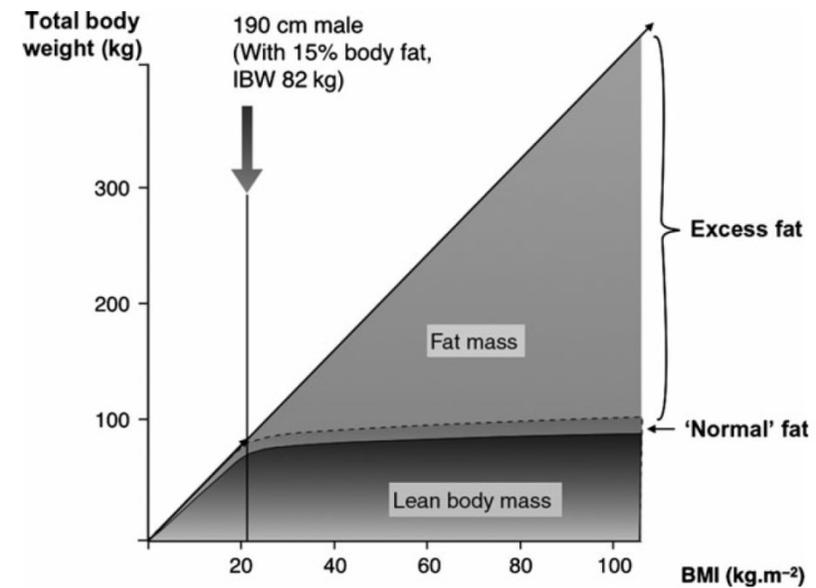
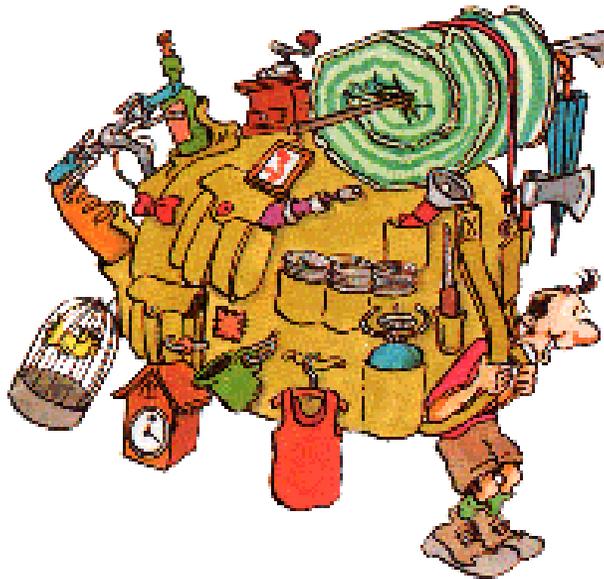
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Nightingale, Anesthesia, 2015

Problématique

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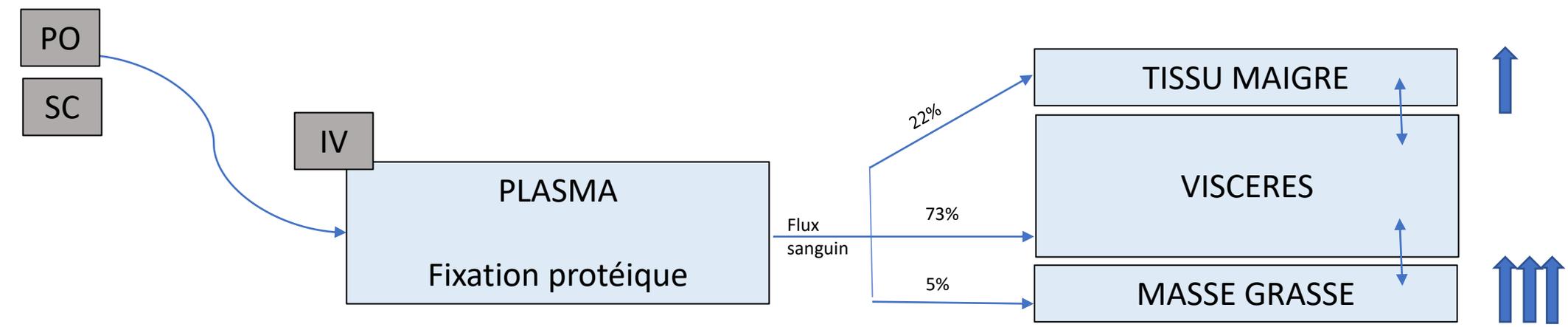
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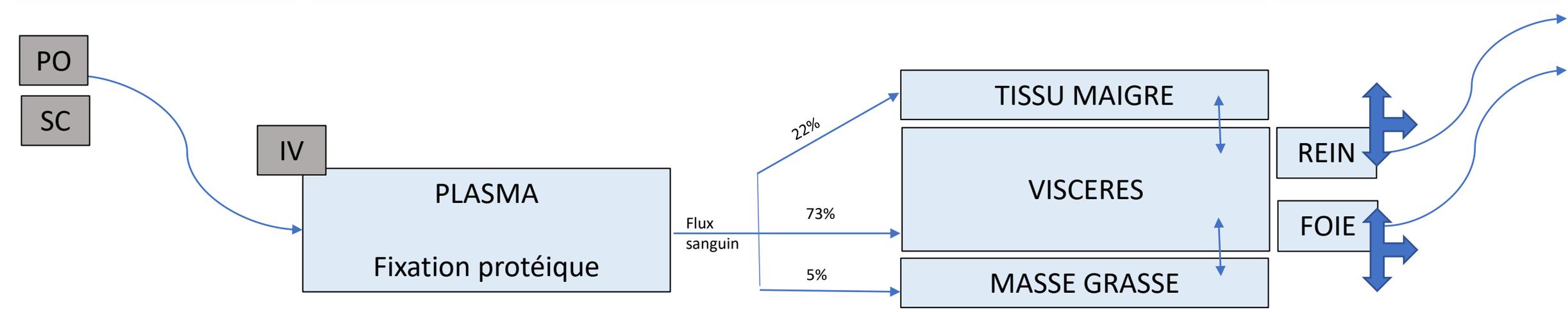
Conclusion

| Variable | Formules |
|---|--|
| Indice de masse corporelle (IMC) [kg/m ²] | $IMC = TBW / (taille [m])^2$ |
| Surface corporelle (BSA) [m ²] | $BSA = TBW^{0,425} \times taille (cm)^{0,725} \times 0,007184$ |
| Poids idéal (IBW) [kg] | $IBW = K + 2,3 \times [(taille [cm] / 2,54) - 60]$ K = 50 (homme) ou 45,5 (femme) |
| Masse maigre (LBW) [kg] | $LBW = 1,1 \times TBW - 0,0128 \times IMC$ (homme) $LBW = 1,07 \times TBW - 0,0148 \times IMC$ (femme) |
| Poids normal prédit (PNWT) [kg] | $PNWT = 1,57 \times TBW - 0,0183 \times IMC \times TBW - 10,5$ (homme) $PNWT = 1,75 \times TBW - 0,0242 \times IMC \times TBW - 12,6$ (femme) |



Volume de distribution des médicaments

- Hydrophiles : ↑
- Lipophiles : ↑↑↑



Problématique

Obésité

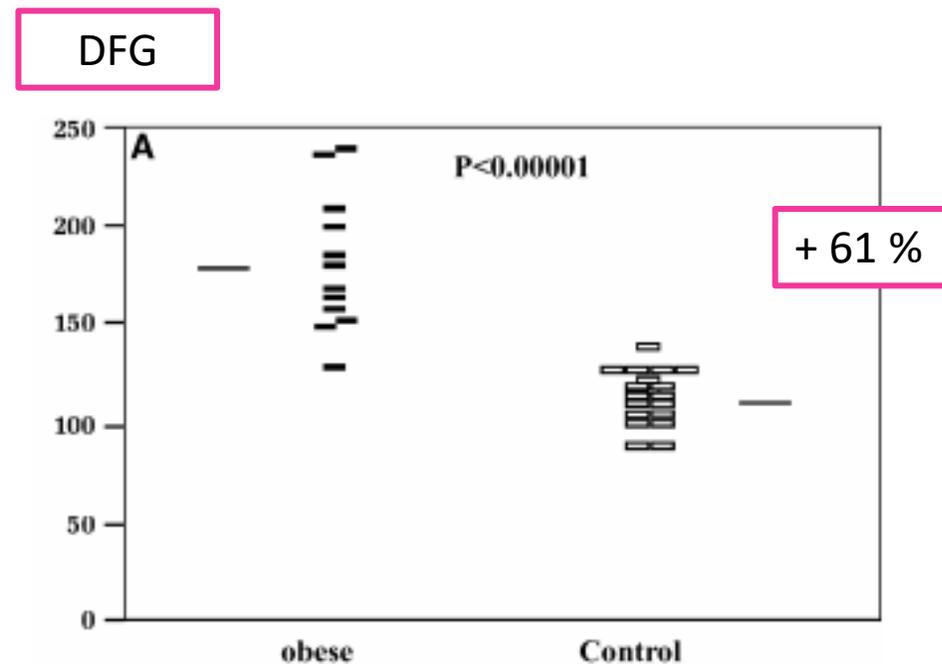
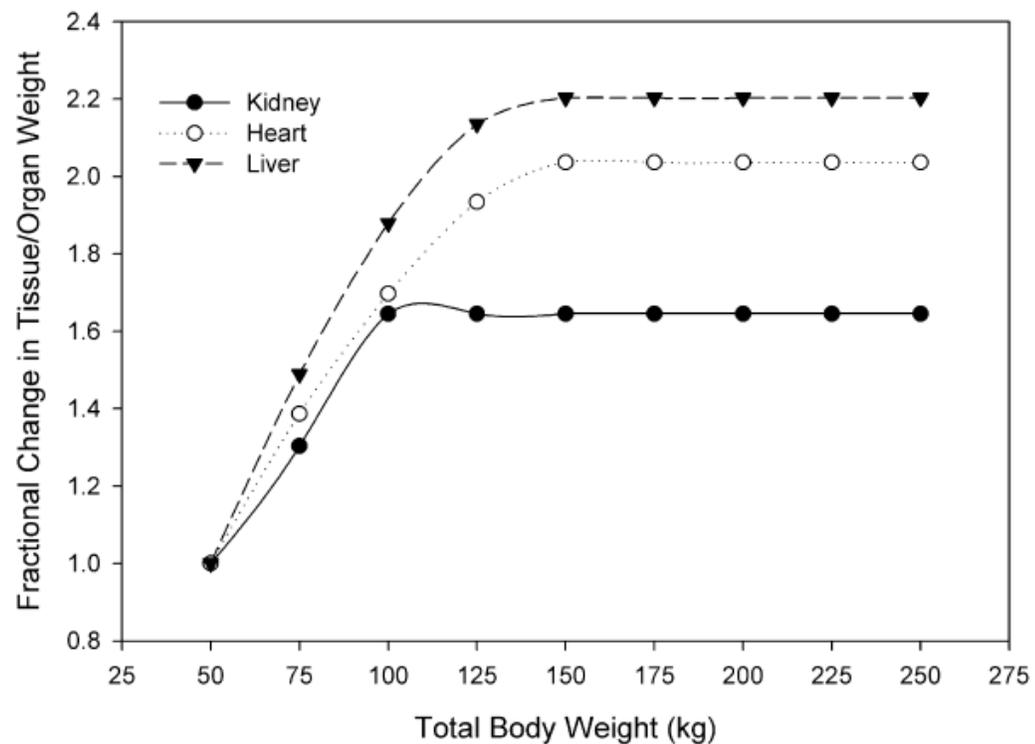
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Chagnac, Nephrol Dial Transplant, 2008
Young, J Toxicol Environ Health, 2009
Pai, Advances in Chronic Kidney Disease, 2010

Problématique

Obésité

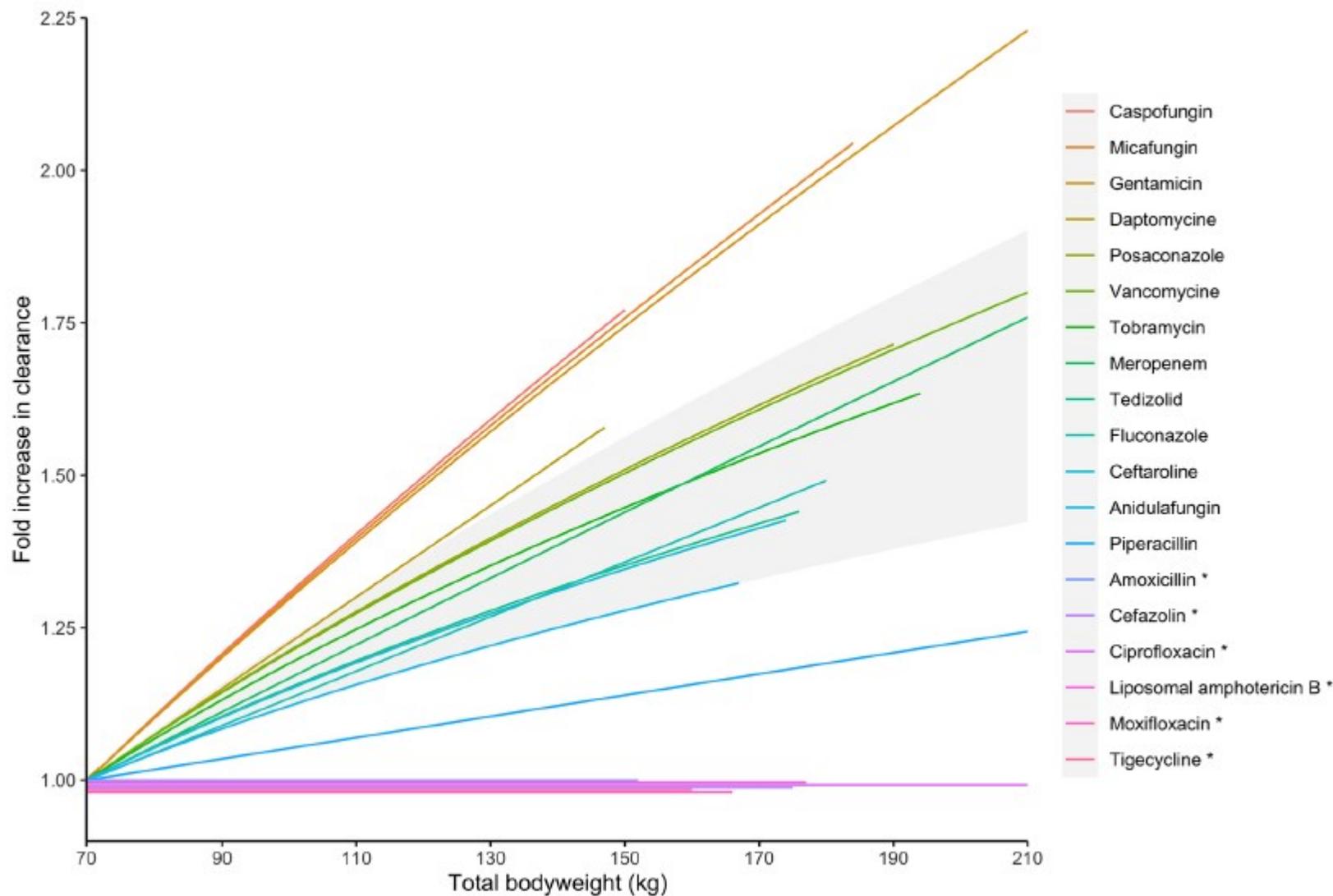
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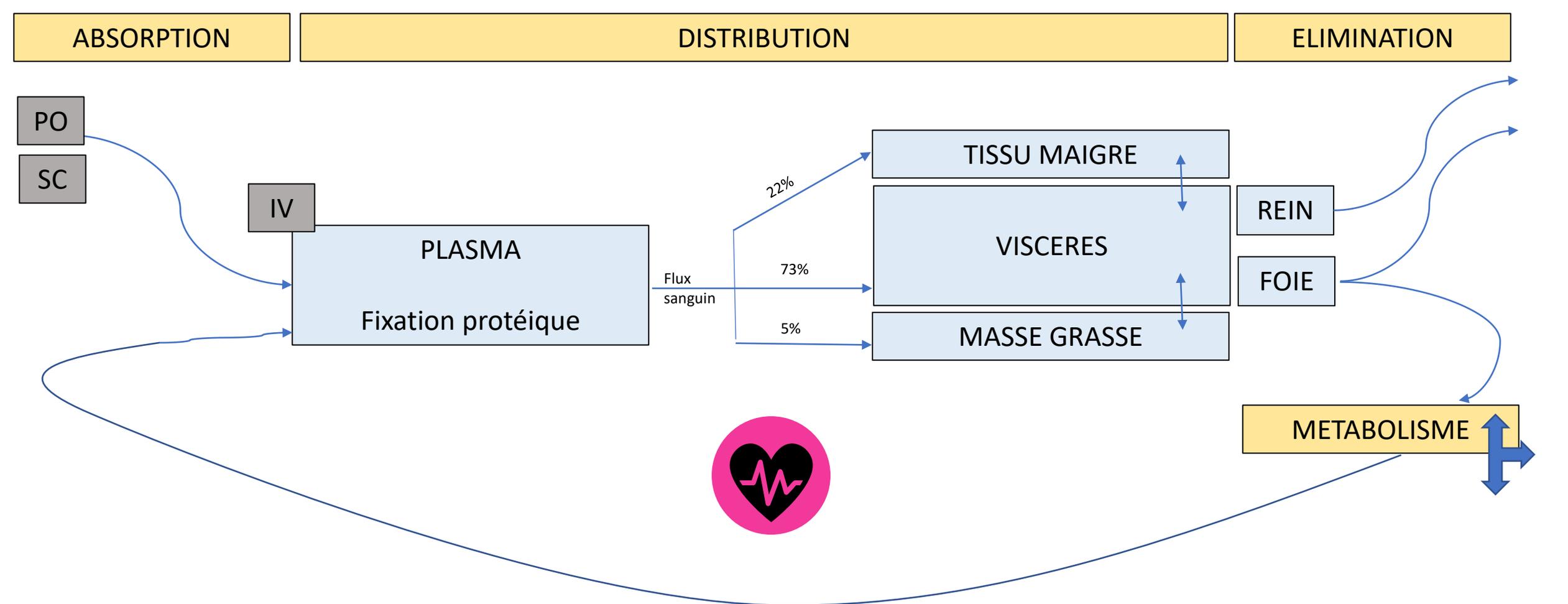
Agé

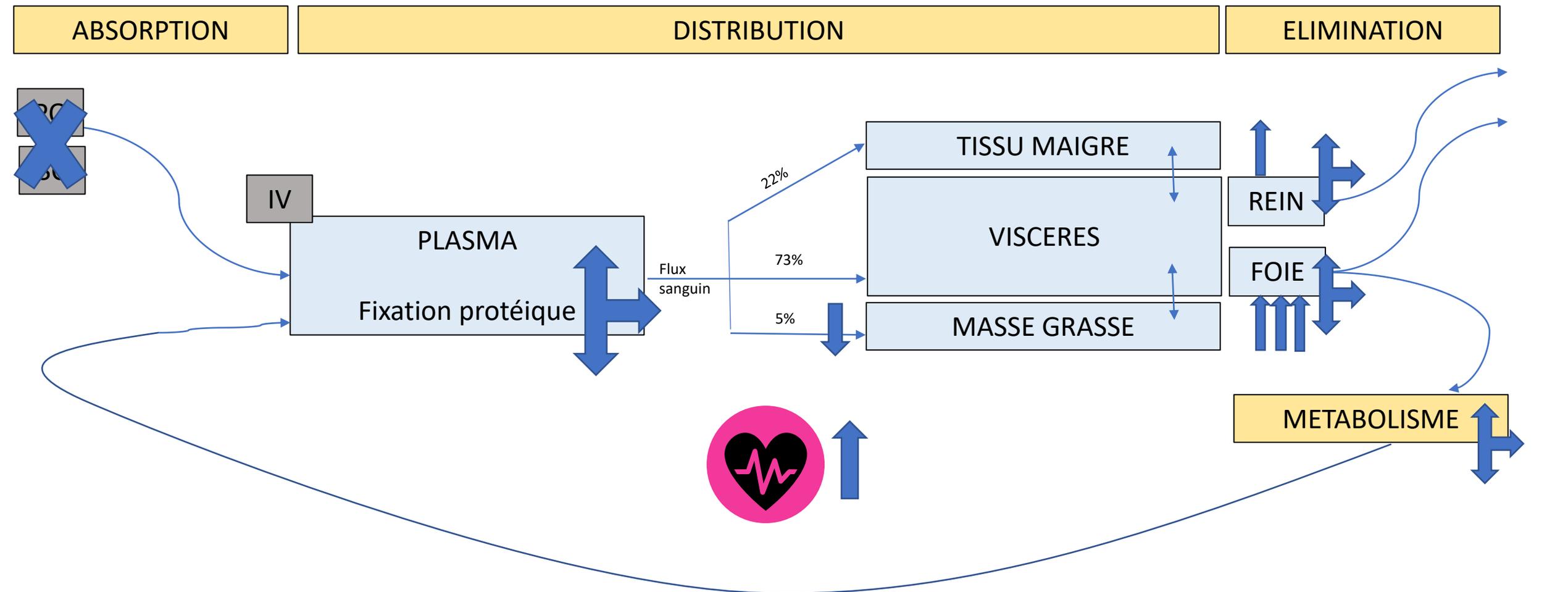
Jeune

Conclusion



van Rhee, 2024







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Pharmacocinétique : Étude du devenir des médicaments dans l'organisme

ADEM chez le patient obèse :

Absorption :

- pour administration per os, peu modifiée
- voie sous cutanée imprévisible

Distribution :

- modification de la fixation protéique
- augmentation du débit cardiaque
- augmentation des volumes de distribution

Élimination :

- variation de la clairance de la créatinine

Métabolisme :

- modifications histopathologiques hépatiques
- augmentation des réactions de phase 2



| Antibiotiques | Hydrophiles | Lipophiles |
|---|--|---|
| Classes | β-lactamines Aminosides Vancomycine | Fluoroquinolones Macrolides Tigécycline |
| Caractéristiques pharmacocinétiques de base | Volume de distribution « réduit » Clairance rénale Faible pénétration tissulaire | Grand volume de distribution Clairance hépatique Grand pénétration tissulaire |
| Changements dus à l'obésité | Volume de distribution peu modifié Clairance rénale accrue (sauf In Rn) | Volume de distribution accru Effets variables sur la clairance hépatique |
| Posologie chez l'obèse | Poids idéal théorique ou poids ajusté | Poids réel recommandé |

Problématique

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CIPROFLOXACINE

- 17 volontaires obèses et 11 non obèses
- Ciprofloxacine 400 mg IV
- Dosage à T0 et 10, 20, 30, 40, 50 min et 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 6, 8, 10, 12, 14, 16, et 24 H

Table II. Pharmacokinetic parameters of ciprofloxacin in obese and normal-weight volunteers

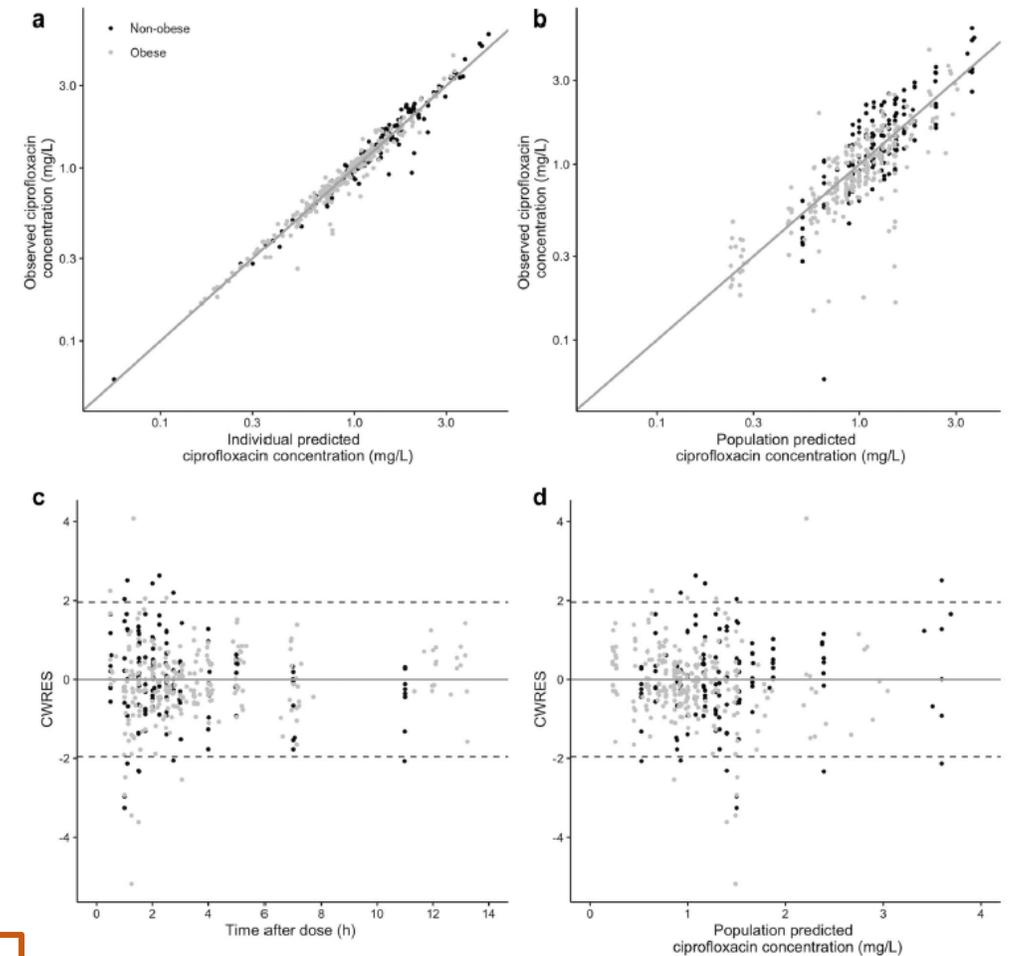
| <i>Pharmacokinetic parameters</i> | <i>Obese subjects</i> | <i>Normal subjects</i> |
|--|-----------------------------|------------------------|
| C_{max} ($\mu\text{g/ml}$) | $2.66 \pm 0.53^*$ | 3.11 ± 0.61 |
| t_{max} (hr) | 0.86 ± 0.26 | 0.95 ± 0.12 |
| AUC ($\mu\text{g} \cdot \text{hr/ml}$) | $7.72 \pm 1.49^*$ | 9.27 ± 1.51 |
| CL (ml/min) | $897.44 \pm 159.57^*$ | 744.44 ± 120.51 |
| CL _R (ml/min) | $637.58 \pm 128.89^*$ | 495.47 ± 137.85 |
| CL _{NR} (ml/min) | 267.74 ± 80.02 | 238.28 ± 58.34 |
| $t_{1/2}$ (hr) | 4.26 ± 0.66 | 4.00 ± 0.34 |
| V _{SS} (L) | $269.17 \pm 51.64^\ddagger$ | 219.03 ± 35.80 |
| V _{SS} (L/kg TBW) | $2.46 \pm 0.42^\ddagger$ | 3.06 ± 0.31 |
| F _u (%) | 69.74 ± 6.07 | 66.16 ± 10.90 |

Se baser sur IBW + 45% d'excès de poids

CIPROFLOXACINE

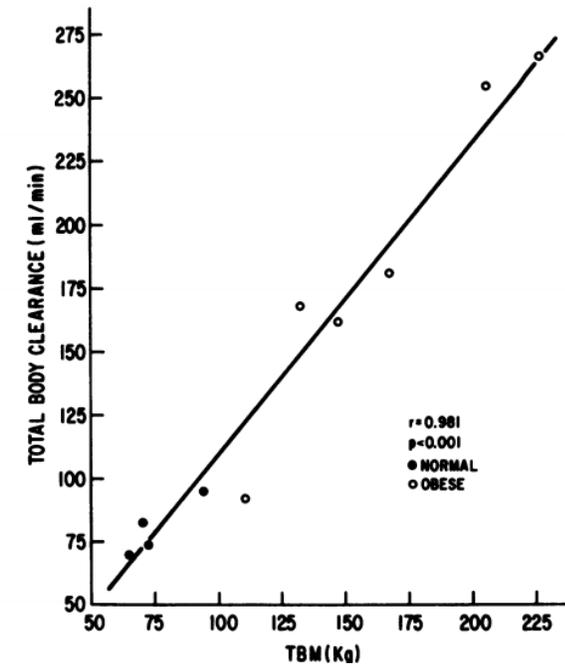
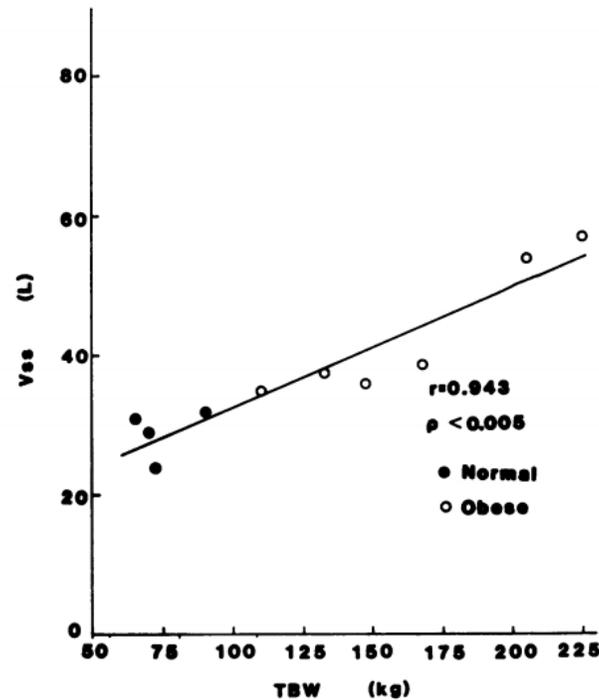
- 20 patients obèses
 - Ciprofloxacine 400 mg IV (n = 10)
 - Ciprofloxacine 500 mg PO (n = 10)
- 8 patients non obèses
 - Ciprofloxacine 500 mg PO puis Ciprofloxacine 400 mg IV à H3
- 11 à 17 dosages sur 12H
- Modelling et simulation

Même biodisponibilité, clairance et volume de distribution
mais concentrations tissulaires plus faibles chez l'obèse



VANCOMYCINE

- 6 patients obèses, 4 non obèses
- Vancomycine 1g IV sur 40 min
- Dosages
 - Avant injection
 - Mi dose
 - Fin perfusion
 - 5, 10, 20, 30, 45 minutes
 - 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16 et 24H



Dose initiale de Vancomycine basée sur TBW puis ajustement selon dosages

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VANCOMYCINE

- 20 patients obèses (per chirurgie bariatrique)
- 8 non obèses
- Vancomycine
 - Obèse : 12,5 mg/kg
 - Non obèse : 1g
- Dosages
 - Mi dose
 - Fin perfusion
 - 15, 30 minutes
 - 1, 1.5, 2, 3, 4, 6, 12, 24 et 48H

| Parameter | Morbidly obese group (n = 20) | Nonobese group (n = 8) |
|--|----------------------------------|---------------------------|
| Weight (kg) | 139.0 (110.6–234.6) | 69.5 (60.0–84.7) |
| Height (cm) | 173.5 (159–189) | 182.5 (166–190) |
| BMI (kg m ⁻²) | 45.5 (40.8–65.7) | 21.2 (20.4–25.0) |
| Age | 38.0 (23–54) | 25.5 (20–55) |
| Serum creatinine (μmol L ⁻¹) ^a | 72 (41–101) | 70 (60–86) |
| GFR (mL min ⁻¹) | 141.4 (80.7–260.7) | 117.9 (88.1–147.0) |
| MDRD (mL min ⁻¹) | 138.3 (89.5–220.6) | 115.4 (72.8–144.7) |
| CKD-EPI (mL min ⁻¹) | 148.1 (95.5–221.6) | 125.3 (77.1–139.3) |
| CG-TBW (mL min ⁻¹) | 249.2 (166.0–431.8) | 140.1 (87.9–157.3) |
| CG-LBW (mL min ⁻¹) | 122.0 (83.1–191.0) | 140.1 (87.9–157.3) |

Bolus 1500 mg puis dose journalière 35 mg/kg (max 5500 mg)

Problématique

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AMINOSIDES

| Author, year | Antibiotic studied | Main findings |
|--------------------------|----------------------------------|---|
| Schwartz et al, 1978 [1] | Gentamicin, tobramycin | Vd in obese subjects closely approximates Vd in normal subjects when using the formula: $ABW = IBW + 0.4 \times (TBW - IBW)$ |
| Blouin et al, 1979 [2] | Tobramycin | Tobramycin loading dose based on $ABW = IBW + 0.58 \times (TBW - IBW)$ |
| Korsager, 1980 [4] | Gentamicin | Gentamicin uptake in adipose tissue = 43.7% of uptake in total body mass of normal-weight patients |
| Bauer et al, 1980 [3] | Amikacin | Amikacin loading dose based on $ABW = IBW + 0.38 \times (TBW - IBW)$ |
| Bauer et al, 1983 [5] | Gentamicin, tobramycin, amikacin | Loading dose based on $ABW = IBW + 0.4 \times (TBW - IBW)$ |
| Leader et al, 1994 [11] | Gentamicin | Initial dose based on calculation of ClCr by Cockcroft equation with $IBW + 0.4 \times (TBW - IBW)$ |
| Traynor et al, 1995 [8] | Tobramycin | The TBW/IBW ratio predicts Vd. For patients with TBW/IBW ratio ≥ 1.25 , doses based on $ABW = IBW + 0.43 \times (TBW - IBW)$ |
| Wurtz et al, 1997 [10] | Aminoglycosides | DWCF = 0.4, therefore $ABW = IBW + 0.4 \times (TBW - IBW)$ |
| Pai et al, 2007 [12] | Aminoglycosides | Dosing of aminoglycosides should be based on ABW |

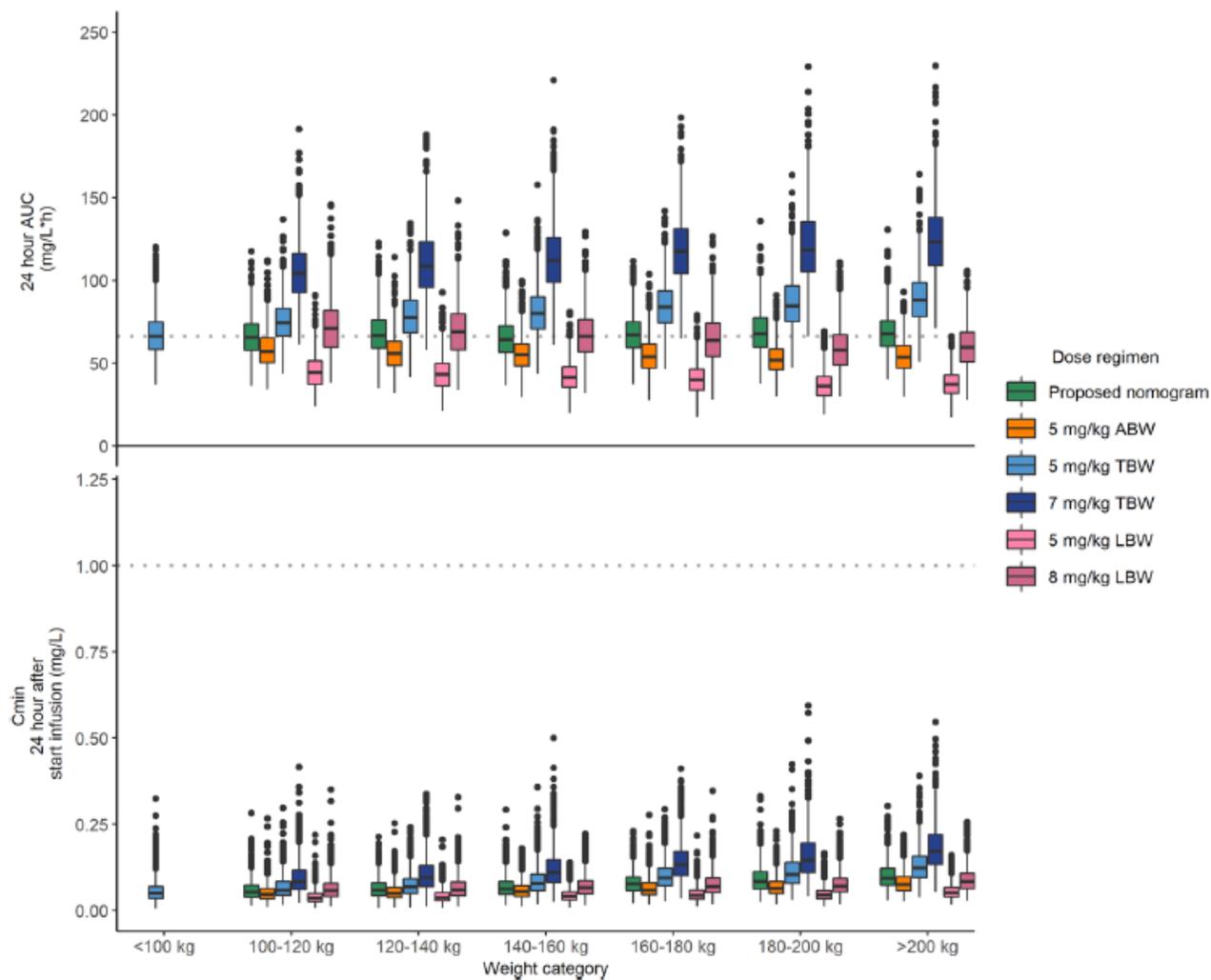
Dose de charge sur Poids Ajusté avec facteur correctif de 0,4 puis selon dosages

AMINOSIDES

Table 3 Proposed dose nomogram [based on a 5 mg/kg 'dose weight', calculated as $70 \times (TBW/70)^{0.73}$] for selecting the gentamicin dose in obese individuals with normal renal function (> 60 mL/min)

| TBW (kg) | Gentamicin dose (mg) |
|----------|----------------------|
| < 100 | Dose on TBW |
| 100–120 | 480 |
| 120–140 | 560 |
| 140–160 | 600 |
| 160–180 | 680 |
| 180–200 | 760 |
| 200–220 | 800 |

TBW total body weight



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PIPERACILLINE - TAZOBACTAM

- 9 patients obèses en réanimation
- Pip/Taz 4,5g/6h sur 30 min
- Dosages après 4^e, 5^e ou 6^e dose
- Simulation de Monte Carlo

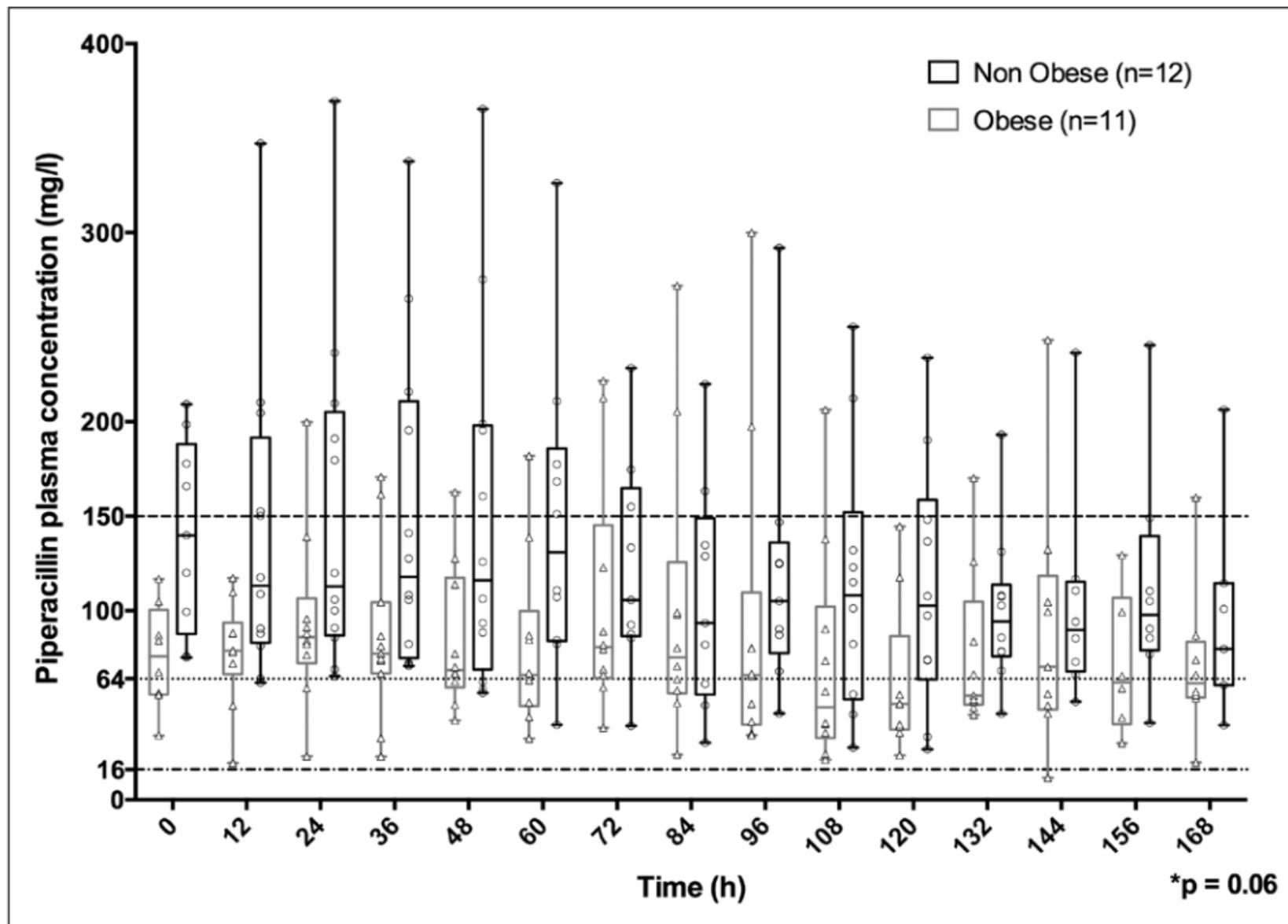
| Piperacillin-Tazobactam Dosage Regimen | Infusion Time, hrs | Piperacillin MIC, mg/L | Probability of Target Attainment, % |
|--|--------------------|------------------------|-------------------------------------|
| 3.375 g every 8 hrs | 0.5 | 16 | 100 |
| | | 32 | 34 |
| | | 64 | 0 |
| 3.375 g every 8 hrs | 4 | 16 | 100 |
| | | 32 | 29 |
| | | 64 | 0 |
| 3.375 g every 6 hrs | 0.5 | 16 | 100 |
| | | 32 | 78 |
| | | 64 | 0 |
| 3.375 g every 6 hrs | 4 | 16 | 100 |
| | | 32 | 62 |
| | | 64 | 0 |
| 4.5 g every 8 hrs | 0.5 | 16 | 100 |
| | | 32 | 91 |
| | | 64 | 0 |
| 4.5 g every 8 hrs | 4 | 16 | 100 |
| | | 32 | 93 |
| | | 64 | 0 |
| 4.5 g every 6 hrs ^b | 0.5 | 16 | 100 |
| | | 32 | 100 |
| | | 64 | 3 |
| 4.5 g every 6 hrs | 4 | 16 | 100 |
| | | 32 | 100 |
| | | 64 | 1 |

MIC = minimum inhibitory concentration.

^aPharmacodynamic target was $\geq 50\%$ time above MIC of unbound drug.

PIPERACILLINE -
TAZOBACTAM

- Bolus de 4g sur 30 minutes
- Puis 16g/24H IVSE
- Dosages à H1 de la fin du bolus puis toutes les 12H pendant 7 jours



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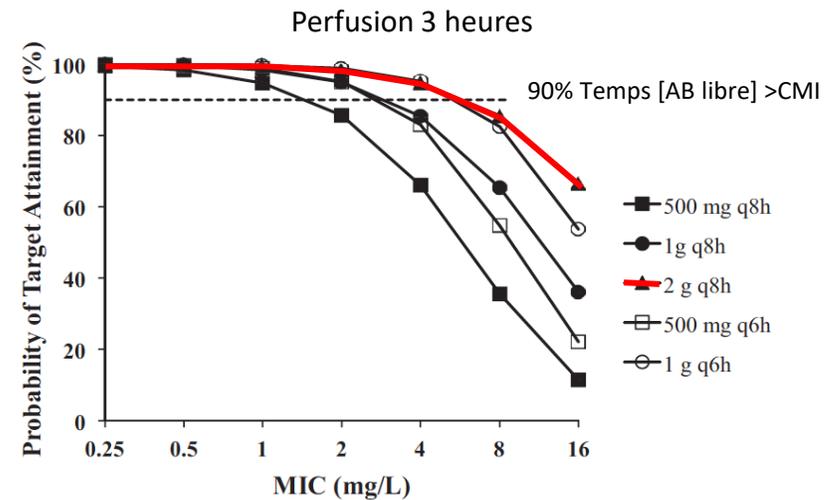
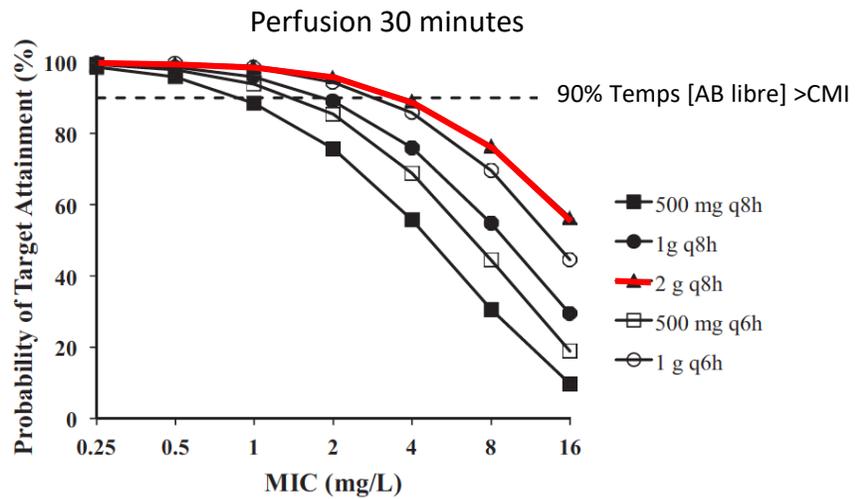
PIPERACILLINE -
TAZOBACTAM

| Targeted Minimum Inhibitory Concentration (mg/L) | Probability of Target Attainment (%) | | | | | |
|--|--------------------------------------|----------|--------------------|----------|----------------------|----------|
| | PTZ 12 g/1.5 g/24 hr | | PTZ 16 g/2 g/24 hr | | PTZ 20 g/2.5 g/24 hr | |
| | Obese | Nonobese | Obese | Nonobese | Obese | Nonobese |
| 16 | 90 | 100 | 100 | 100 | 100 | 100 |
| 32 | 88 | 100 | 91 | 100 | 100 | 100 |
| 64 | 21 | 65 | 44 | 98 | 75 | 100 |
| 150 | 0 | 8 | 12 | 27 | 18 | 42 |

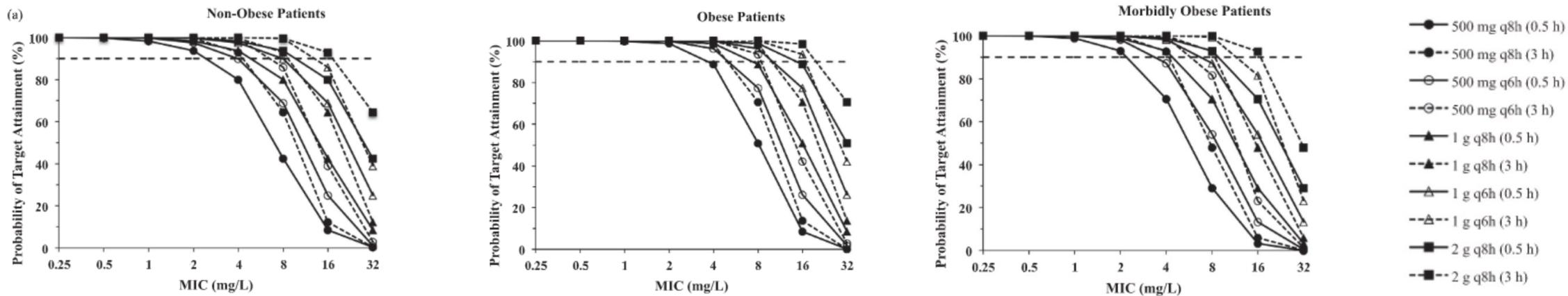
Utiliser dose maximale

MEROPENEME

- 9 patients obèses morbides $\geq 40 \text{ kg/m}^2$
- 5 schémas posologiques administrés sur 30 minutes ou 3 heures



MEROPENEME



Chung, ACCP, 2017

Doses « normales » maximales en perfusion longue

Problématique

Obésité

Maigreur

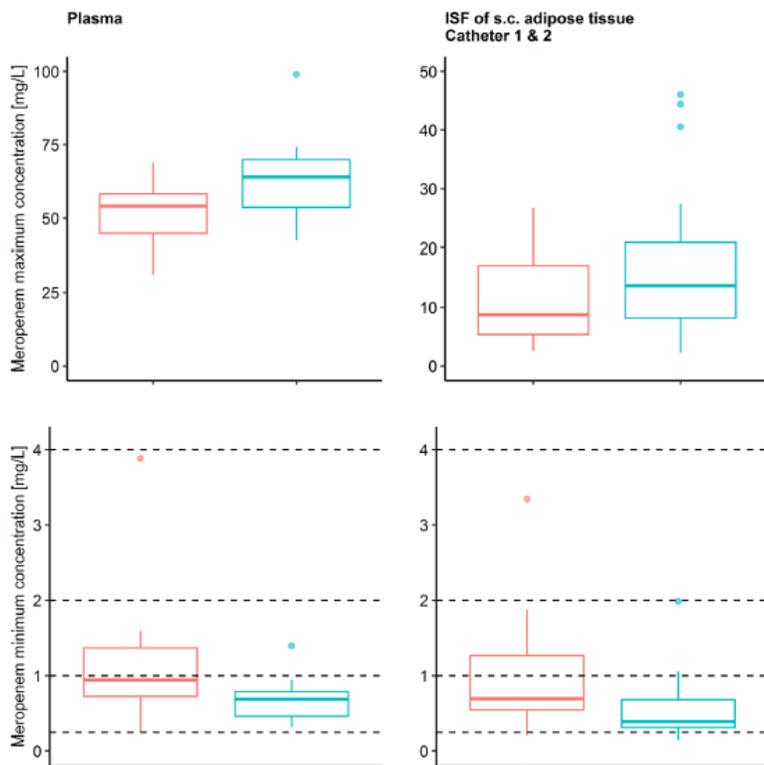
Musclé

Agé

Jeune

Conclusion

MEROPENEME

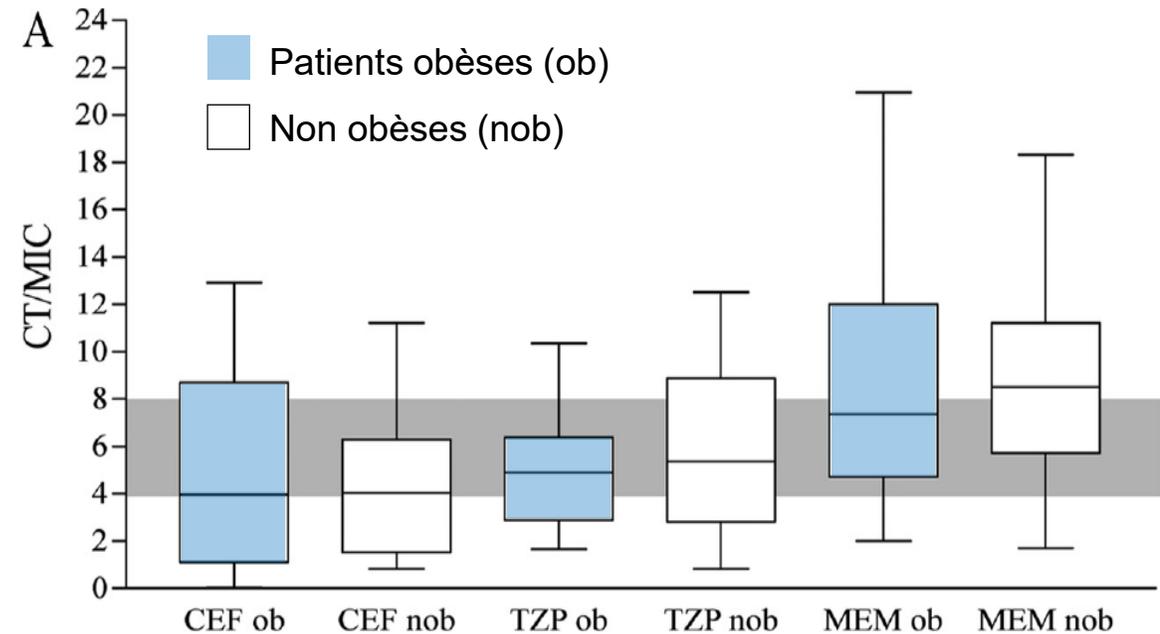


- 15 patients obèses (rouge) et 15 non obèses (bleu)
- Méropénème 1 g
- Mesures plasma- and microdialyse

Gradient plasma/tissu

β LACTAMINES

- Etude monocentrique rétrospective belge
- 49 patients obèses (IMC 40 kg/m²),
- 59 non obèses (IMC 22 kg/m²)
- Traitement pour infection sévère en réanimation
- 12 patients CEF :
 - 2g puis dose médiane journalière 6 g [2-6]
- 19 TZP :
 - 4 g puis dose médiane journalière 16g [12-16]
- 37 MEM :
 - 1 g puis dose médiane journalière 3g [2-3]
- Dosage à T0 et T2



Concentration cible /CMI = ratio concentration / CMI entre 4 et 8 fois la CMI à 70% du temps entre 2 doses pour CEF, 50% pour TZP et 40% pour MEM (Breakpoints for *P aeruginosa*)

Concentrations adéquates :

- CEF : 25 %
- TZP : 47 %
- MEM : 49 %

Surdosage 25 %
Sous-dosage 32 %

Problématique

Obésité

Maigreur

Musclé

Agé

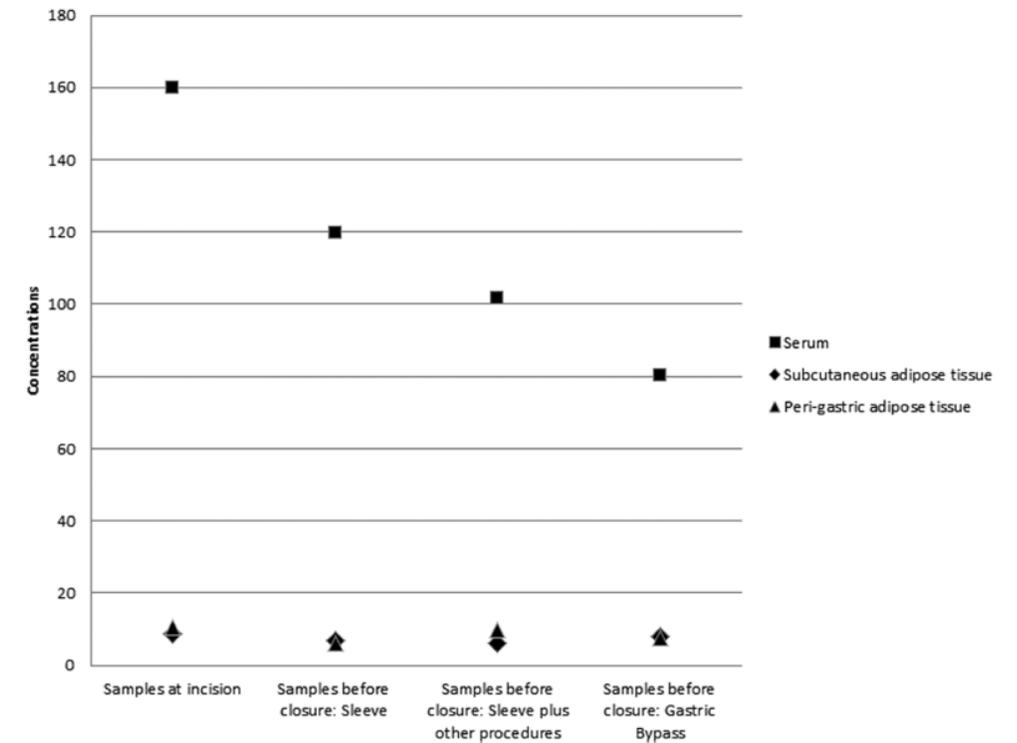
Jeune

Conclusion

CEFAZOLINE

- 2013 : reco ASHP, augmenter doses Céfazo en prophylaxie chez l'obèse (2g versus 1g + réinjection à H4)
- Etude prospective de pharmacocinétique monocentrique américaine
- 37 patients + chirurgie bariatrique
- Injection de 2 g de Céfazoline 3 à 5 minutes avant l'incision
- Prélèvement à l'incision et à la fermeture
 - Sang
 - Tissus adipeux sous cutané
 - Tissus adipeux péri gastrique

Mean Cefazolin Concentrations (mg/L or mg/kg)



Nouvelle reco antibioprophylaxie SFAR 2024 : pas d'augmentation des doses de céphalosporines

Problématique

Obésité

Maigreur

Musclé

Agé

Jeune

Conclusion

CEFAZOLINE

Lack of Pharmacokinetic Basis of Weight-Based Dosing and Intra-Operative Re-Dosing with Cefazolin Surgical Prophylaxis in Obese Patients: Implications for Antibiotic Stewardship

Sharon Blum,¹ Cheston B. Cunha,² and Burke A. Cunha³

- **There are no comparative studies to support this approach, which is based largely on the theory “more must be better.”**
- Weight-based dosing of cefazolin in the obese is flawed, because it does not take into account PK factors, which are critical in the obese.
 - Cefazolin is a water-soluble (hydrophilic) antibiotic that does not penetrate adipose tissue regardless of IV dose.
 - Importantly, adipose tissue is not a valid target tissue in clean–clean-contaminated SSI prophylaxis, as it does not become infected.
 - Cefazolin displays time-dependent killing kinetics so that as long as serum/tissue concentrations are above the minimum inhibitory concentration (MIC) of SSI pathogens, there is no enhanced killing with higher concentrations relative to concentration-dependent antibiotics.
- It should be kept in mind that prophylaxis involves no inoculum (minimal dose needed) whereas infection presents a high inoculum (full dose needed). Certainly, if cefazolin 1 by (IV push is sufficient for serious infection, how can a 2- or 3-g doses be anything but excessive when there is no infection (no inoculum)?

Problématique

Obésité

Maigreur

Musclé

Agé

Jeune

Conclusion

OBESSE PATIENT

Cephalosporin

Same doses (<BMI 50 kg/m²)

Vancomycin

Same doses (total weight)
Adjust injection duration

Clindamycin

BMI 30-45 kg/m² : 900 mg
BMI 45-60 kg/m² : 1200 mg
BMI > 60 kg/m² : 1600 mg

Gentamicin

6-7 mg/kg
(adjusted weight)



Problématique

Obésité

Maigreur

Musclé

Agé

Jeune

Conclusion



Problématique

Obésité

Maigreur

Musclé

Agé

Jeune

Conclusion





Population hétérogène +++

Problématique

Obésité

Maigreur

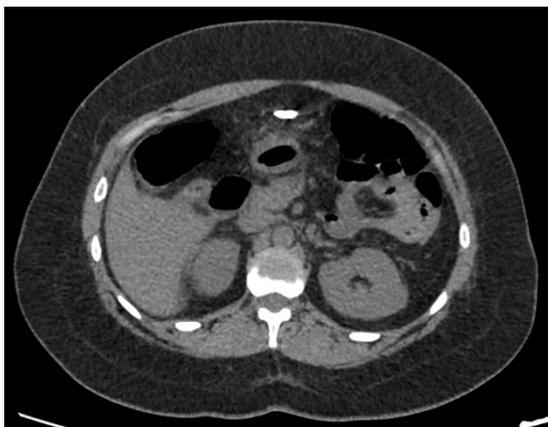
Musclé

Agé

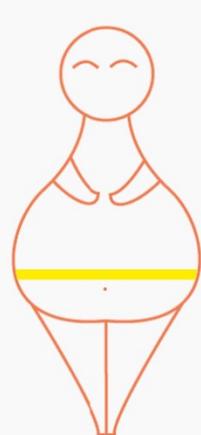
Jeune

Conclusion

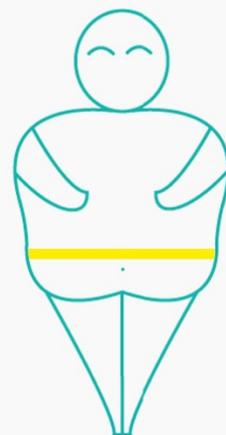
Femme IMC 47 kg/m²



Différentes localisation de la masse adipeuse

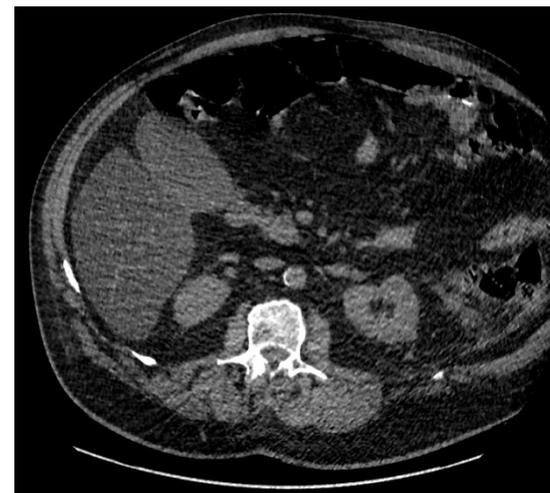


Obésité gynoïde



Obésité androïde

Homme IMC 46 kg/m²



Problématique

Obésité

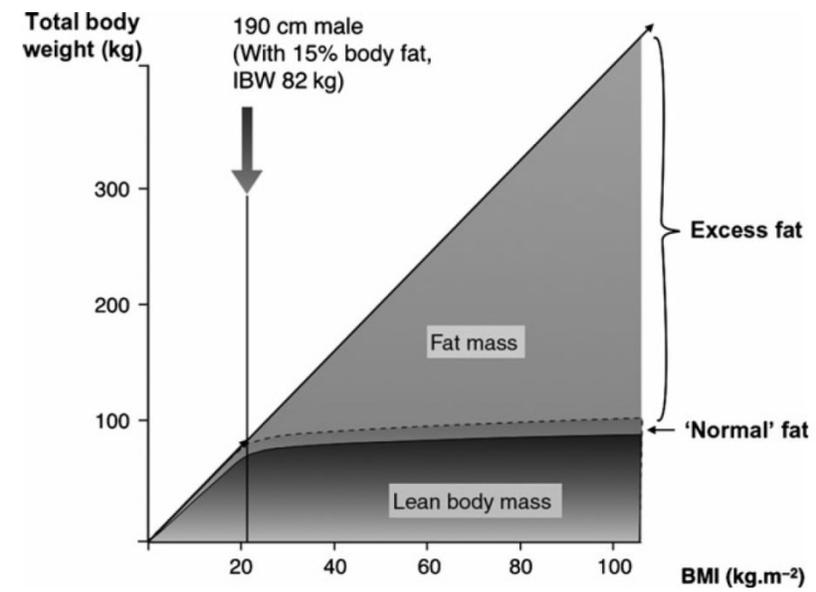
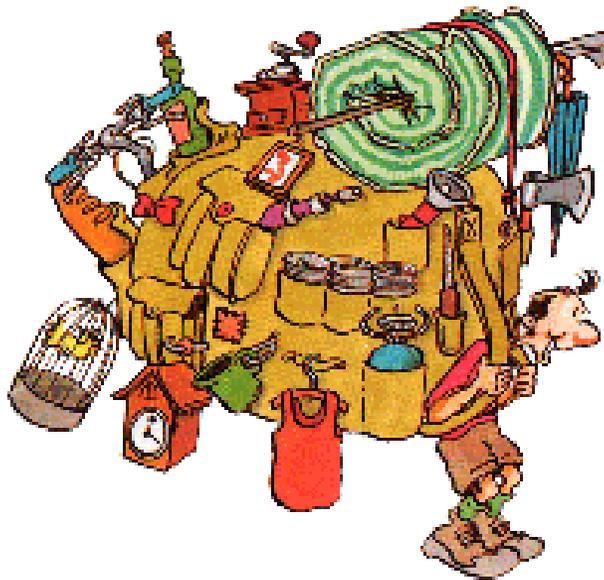
Maigreur

Musclé

Agé

Jeune

Conclusion



Nightingale, Anesthesia, 2015

Problématique

Obésité

Maigreur

Musclé

Agé

Jeune

Conclusion



Photo la voix du Nord

Distinguer
les obèses ayant une
activité physique
conservée
(masse musculaire
+++)

De ceux qui ne peuvent plus se
mobiliser (perte masse musculaire)



Problématique

Obésité

Maigreur

Musclé

Agé

Jeune

Conclusion



OBESE ???

The Lancet Diabetes & Endocrinology Commission

Definition and diagnostic criteria of clinical obesity

Francesco Rubino, David E Cummings, Robert H Eckel, Ricardo V Cohen, John P H Wilding, Wendy A Brown, Fatima Cody Stanford, Rachel L Batterham, I Sadaf Farooqi, Nathalie J Farpour-Lambert, Carel W le Roux, Naveed Sattar, Louise A Baur, Katherine M Morrison, Anoop Misra, Takashi Kadowaki, Kwang Wei Tham, Priya Sumithran, W Timothy Garvey, John P Kirwan, José-Manuel Fernández-Real, Barbara E Corkey, Hermann Toplak, Alexander Kokkinos, Robert F Kushner, Francesco Branca, Jonathan Valabhji, Matthias Blüher, Stefan R Bornstein, Harvey J Grill, Eric Ravussin, Edward Gregg, Noor B Al Busaidi, Nasreen F Alfaris, Ebaa Al Ozairi, Lena M S Carlsson, Karine Clément, Jean-Pierre Després, John B Dixon, Gauden Galea, Lee M Kaplan, Blandine Laferrère, Martine Laville, Soo Lim, Jesús R Luna Fuentes, Vicki M Mooney, Joseph Nadglowski Jr, Agbo Urudinachi, Magdalena Olszanecka-Glinianowicz, An Pan, François Pattou, Philip R Schauer, Matthias H Tschöp, Maria T van der Merwe, Roberto Vettor, Geltrude Mingrone

Executive summary

Current BMI-based measures of obesity can both underestimate and overestimate adiposity and provide inadequate information about health at the individual level, which undermines medically-sound approaches to health care and policy. This Commission sought to define clinical obesity as a condition of illness that, akin to the notion of chronic disease in other medical specialties, directly results from the effect of excess adiposity on the function of organs and tissues. The specific aim of the Commission was to establish objective criteria for disease diagnosis, aiding clinical decision making and prioritisation of therapeutic interventions and public health strategies. To this end,

measurement of body fat, where available, or at least one anthropometric criterion (eg, waist circumference, waist-to-hip ratio, or waist-to-height ratio) in addition to BMI, using validated methods and cutoff points appropriate to age, gender, and ethnicity. In people with very high BMI (ie, >40 kg/m²), however, excess adiposity can pragmatically be assumed, and no further confirmation is required. We also recommend that people with confirmed obesity status (ie, excess adiposity with or without abnormal organ or tissue function) should be assessed for clinical obesity. The diagnosis of clinical obesity requires one or both of the following main criteria: evidence of reduced organ or tissue function due to obesity (ie, signs, symptoms, or

Lancet Diabetes Endocrinol 2025

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January 14, 2025
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For the Arabic, Chinese, French, German, Greek, Hindi, Italian, Japanese, Polish, Portuguese, Spanish, and Swedish translations of the Executive summary see Online for appendix 1

Metabolic and Bariatric Surgery (Prof F Rubino) and Division of Diabetes & Nutritional Sciences (Prof G Mingrone), School of Cardiovascular and Metabolic

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NEWS | 14 January 2025

New obesity definition sidelines BMI to focus on health

Fresh approach to diagnosing the condition looks at how excess body fat affects the body.

Problématique

Obésité

Maigreur

Musclé

Agé

Jeune

Conclusion

The Lancet Diabetes & Endocrinology Commission

Definition and diagnostic criteria of clinical obesity



- **Obésité** : **adiposité excessive**, avec ou sans répartition ou fonction anormale du tissu adipeux, dont les causes sont multifactorielles et toujours partiellement comprises.
- **Obésité pré clinique** : un état d'excès d'adiposité avec fonction préservée des autres tissus et organes et une variation variable, mais généralement augmenté, risque de développer une obésité clinique et plusieurs autres maladies non transmissibles
- **Obésité clinique** : maladie systémique et chronique, caractérisée par l'altération des fonctions des tissus, des organes, de l'individu tout entier, ou une combinaison des deux, en raison d'un excès d'adiposité. L'obésité clinique peut entraîner de graves lésions des organes cibles, provoquant une altération de la vie et potentiellement mettant la vie en danger.

Problématique

Obésité

Maigreur

Musclé

Agé

Jeune

Conclusion

The Lancet Diabetes & Endocrinology Commission

Definition and diagnostic criteria of clinical obesity



- **IMC** : ne doit être utilisé que comme une mesure substitut du risque sanitaire au niveau de la population, par exemple pour les études épidémiologiques, ou à des fins de dépistage, plutôt que comme mesure individuelle de la santé.
- **Diagnostic de l'obésité** : l'excès de l'adiposité doit être confirmée soit par une mesure de la graisse corporelle, si disponible, ou au moins un critère anthropométrique (par exemple, le tour de taille, le rapport taille/hanche, ou rapport taille/hauteur) en plus de l'IMC, en utilisant des méthodes et des seuils validés adaptés à l'âge, au sexe et à l'origine ethnique. Chez les personnes avec un IMC très élevé (c'est-à-dire $>40 \text{ kg/m}^2$), mais excès d'adiposité peut être supposé de manière pragmatique, et pas plus loin une confirmation est requise.

Problématique

Obésité

Maigreur

Musclé

Agé

Jeune

Conclusion

Bien choisir l'antibiotique :

- Spectre adapté, CMI basse
- Fenêtre thérapeutique large
- Facilement dosable

Augmenter les doses selon les principes théoriques et les études existantes

DOSER +++ l'antibiotique et adapter la posologie

Surveiller l'efficacité et la survenue d'effets indésirables

Problématique

Obésité

Maigreur

Musclé

Agé

Jeune

Conclusion

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 Guilhaumou¹, Sihem Benaboud², Youssef Bennis³, Claire Dahyot-Fizelier⁴, Eric Dailly⁵, Peggy Gandia⁶, Sylvain Goutelle⁷, Sandrine Lefeuvre⁸, Nicolas Mongardon⁹, Claire Roger¹⁰, Julien Scala-Bertola¹¹, Florian Lemaitre¹² and Marc Garnier^{13*} 

Conclusions: The experts strongly suggest the use of personalized dosing, continuous or prolonged infusion and therapeutic drug monitoring when administering β LA in critically ill patients.

Problématique

Obésité

Maigreur

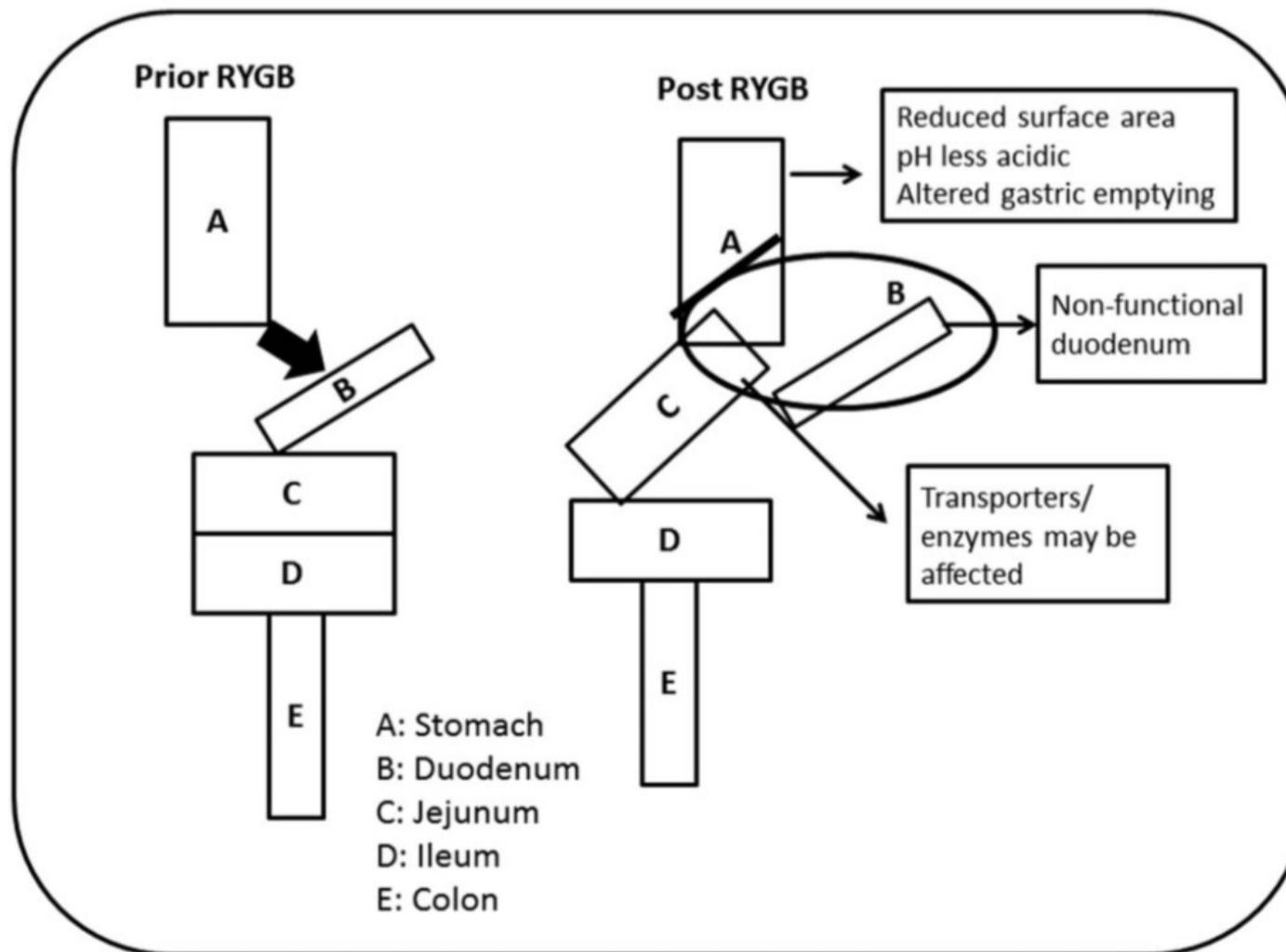
Musclé

Agé

Jeune

Conclusion

Administration per os
après chirurgie bariatrique ?



Problématique

Obésité

Maigreur

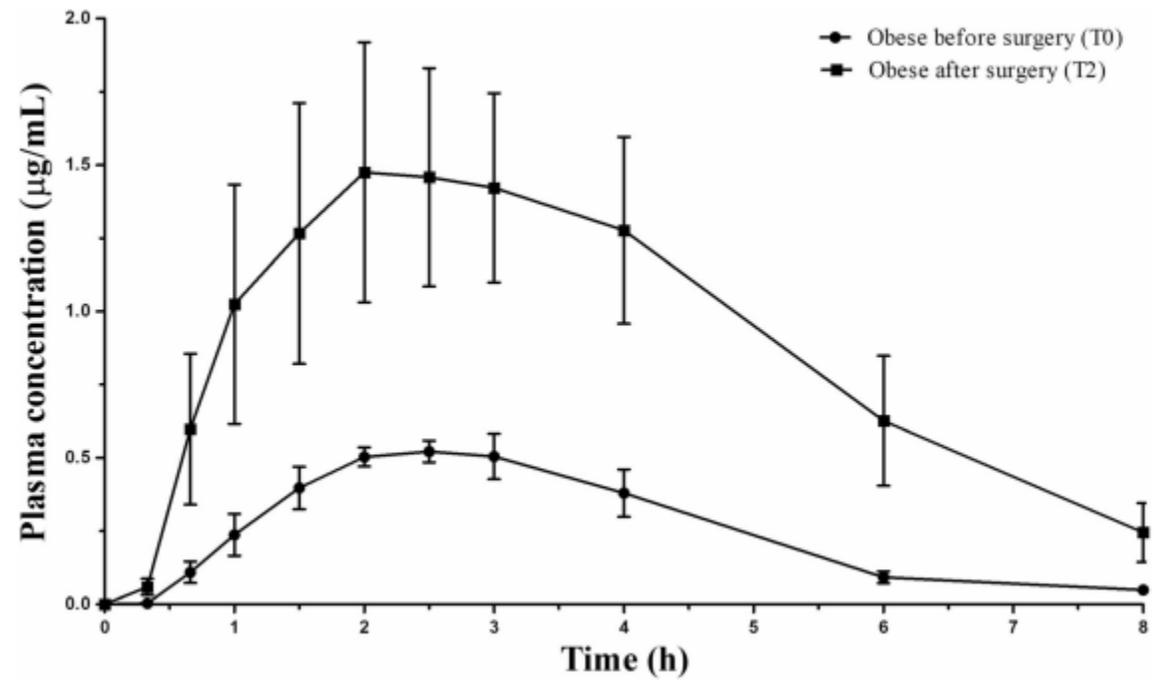
Musclé

Agé

Jeune

Conclusion

- 8 patients volontaires « sains »
- Amoxicilline 500 mg PO à jeun
- Avant et 2 mois après chirurgie bariatrique
- Dosage à H0, 20 min, 40 min, 1, 1.5, 2, 2.5, 3, 4, 6, et 8 h post-dose



Problématique

Obésité

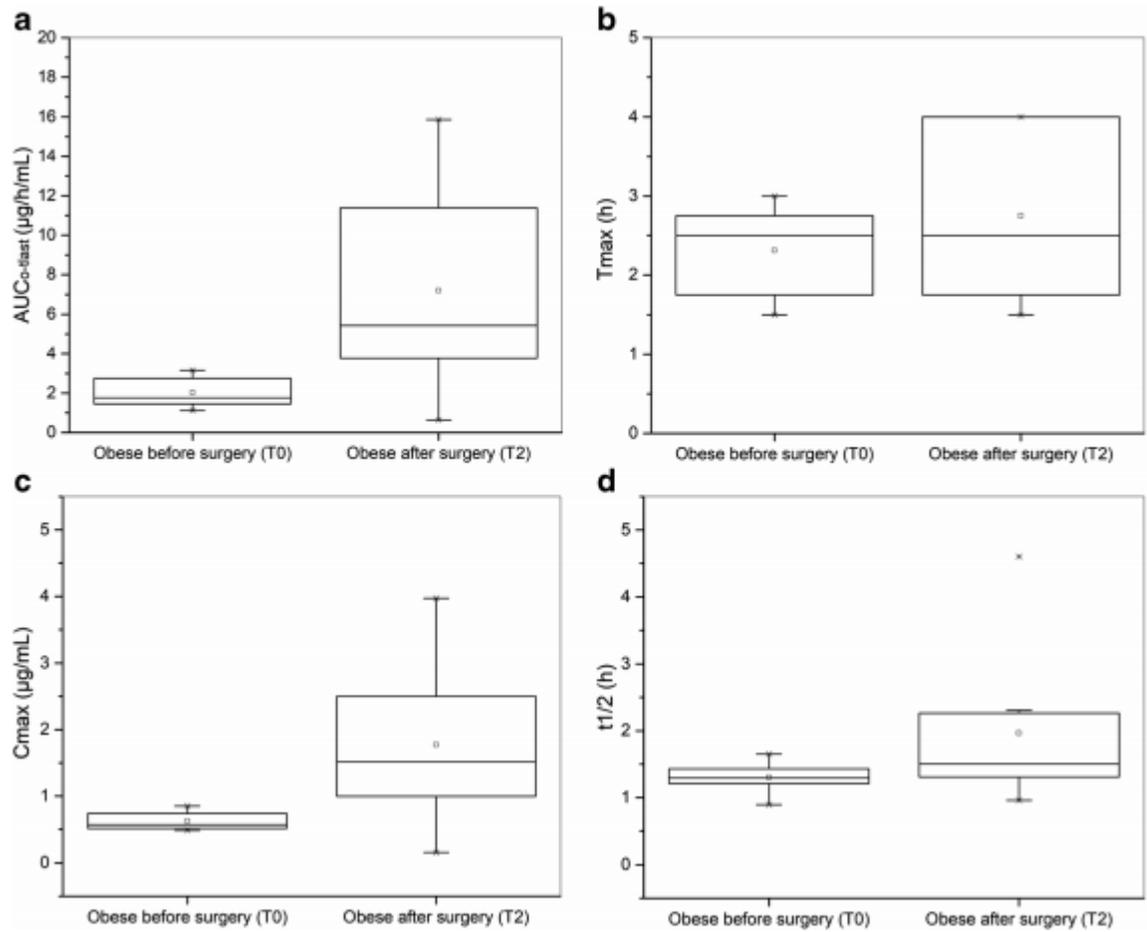
Maigreur

Musclé

Agé

Jeune

Conclusion





Repeated Piperacillin-Tazobactam Plasma Concentration Measurements in Severely Obese Versus Nonobese Critically Ill Septic Patients and the Risk of Under- and Overdosing*

Boris Jung, MD, PhD^{1,2}; Martin Mahul, MD, MSc^{1,2}; Dominique Breilh, PharmD, PhD³; Rachel Legeron, PharmD³; Jeremy Signe, MD^{2,4}; Helene Jean-Pierre, MD⁴; Anne-Catrin Uhlemann, MD, PhD⁵; Nicolas Molinari, PhD⁶; Samir Jaber, MD, PhD^{1,2}

Objective: Obesity and critical illness modify pharmacokinetics of antibiotics, but piperacillin-tazobactam continuous IV infusion pharmacokinetics has been poorly studied in obese critically ill patients. We aimed to compare pharmacokinetics of piperacillin in severely obese and nonobese patients with severe sepsis or septic shock. We hypothesized that plasma concentration variability would expose the critically ill to both piperacillin under- and overdosing.

Methods: Prospective comparative study. Consecutive critically ill severely obese (body mass index, > 35 kg/m²) and non-

obese patients (body mass index, < 30 kg/m²) were treated with 16 g/2 g/24 hr continuous piperacillin-tazobactam infusion. Piperacillin plasma concentration was measured every 12 hours over a 7-day period by high-pressure liquid chromatography. Unbound piperacillin plasma concentration and fractional time of plasma concentration spent over 64 mg/L (4-fold the minimal inhibitory concentration for *Pseudomonas aeruginosa*) were compared between the two groups. We performed 5,000 Monte Carlo simulations for various dosing regimens and minimal inhibitory concentration and calculated the probability to spend 100% of the time over 64 mg/L.

Results: We enrolled 11 severely obese and 12 nonobese patients and obtained 294 blood samples. We did not observe a statistically significant difference in piperacillin plasma concentrations over time between groups. The fractional time over 64 mg/L was 64% (43–82%) and 93% (85–100%) in obese and nonobese patients, respectively, $p = 0.027$ with intra- and intergroup variability. Five non-obese and two obese patients experienced potentially toxic piperacillin plasma concentrations. When 64 mg/L was targeted, Monte Carlo simulations showed that 12 g/1.5 g/24 hr was inadequate in both groups and 16 g/2 g/24 hr was adequate only in nonobese patients.

Conclusion: Using a conventional dosing of 16 g/2 g/24 hr continuous infusion, obese patients were more likely than nonobese patients to experience piperacillin underdosing when facing high minimal inhibitory concentration pathogens. The present study suggests that piperacillin drug monitoring might be necessary in the sickest patients who are at the highest risk of unpredictable plasma concentration exposing them to overdose, toxicity, underdosing, and treatment failure. (*Crit Care Med* 2017; 45:e470–e478)

Key Words: Monte Carlo simulation; obesity; piperacillin-tazobactam; population pharmacokinetic; septic shock

*See also p. 923.

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Drs. Jung and Mahul contributed equally to the study.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (<http://journals.lww.com/ccmjournal>).

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Review

Effect of obesity on the pharmacokinetics of antimicrobials in critically ill patients: A structured review

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ABSTRACT

The increased prevalence of obesity presents challenges for clinicians aiming to provide optimised antimicrobial dosing in the intensive care unit. Obesity is likely to exacerbate the alterations to antimicrobial pharmacokinetics when the chronic diseases associated with obesity exist with the acute pathophysiological changes associated with critical illness. The purpose of this paper is to review the potential pharmacokinetic (PK) changes of antimicrobials in obese critically ill patients and the implications for appropriate dosing. We found that hydrophilic antimicrobials (e.g. β -lactams, vancomycin, claptomycin) were more likely to manifest altered pharmacokinetics in critically ill patients who are obese. In particular for β -lactam antibiotics, obesity is associated with a larger volume of distribution (V_d). In obese critically ill patients, piperacillin is also associated with a lower drug clearance (CL). For daptomycin, these PK changes have been associated with reduced achievement of pharmacodynamic (PD) targets when standard drug doses are used. For vancomycin, increases in V_d are associated with increasing total body weight (TBW), meaning that the loading dose should be based on TBW even in obese patients. For daptomycin, an increased V_d is not considered to be clinically relevant. For antifungals, little data exist in obese critically ill patients; during fluconazole therapy, an obese patient had a lower V_d and higher CL than non-obese comparators. Overall, most studies suggested that standard dosage regimens of most commonly used antimicrobials are sufficient to achieve PD targets. However, it is likely that larger doses would be required for pathogens with higher minimum inhibitory concentrations.

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1. Introduction

Obesity is a growing public health concern and is associated with increased morbidity and mortality compared with non-obese individuals [1–3]. Obesity is a well known risk factor for community- and hospital-acquired infections as well as hospital and intensive care unit (ICU) admission [4–6]. Critically ill obese patients in particular are at a higher risk of infection and commonly require antimicrobial therapy [7,8]. However, delivering optimal antimicrobial therapy in this population is considered to be a great challenge. To date, there are few studies summarising the published

data and providing clinical guidance for effective dosing in these patients.

Understanding antimicrobial pharmacokinetic (PK) behaviour is crucial to optimise antimicrobial therapy for critically ill obese patients. However, antimicrobial pharmacokinetics is often altered by the pathophysiology associated with critical illness [9,10] and may be further changed in the presence of obesity. Both antimicrobial volume of distribution (V_d) and clearance (CL) can be highly variable in critically ill and obese patients [11,12]. Standard dosage regimens of antimicrobials, particularly those that are mainly eliminated through the kidneys, may result in fluctuations of plasma concentrations in critically ill patients that may require dosing regimen adjustments to ensure optimal antimicrobial concentrations are achieved [13]. Optimised antimicrobial dosing in the ICU requires an understanding of antimicrobial pharmacokinetics/pharmacodynamics and possible PK changes caused by critical illness.

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CURRENT OPINION

Patients with Obesity Should be Recognised as a Special Patient Population During Drug Development of Antibacterial and Antifungal Agents; A Call to Action

K. P. van Rhee^{1,2,3}  · C. A. J. Knibbe^{3,4}  · P. D. van der Linden¹  · R. J. M. Brüggemann^{5,6} 

Table 2 Overview of the proposed dosing recommendations for patients with obesity compared to dose adjustments for renal and hepatic insufficiency

| | Patients with obesity | Renal insufficiency* | Hepatic insufficiency* | References |
|--------------------------|--|---|---|------------|
| Amoxicillin | No dose adjustment required based on bodyweight | eGFR 30–10 mL/min: 50 % reduced maintenance dose eGFR < 10 mL/min: 75 % reduced maintenance dose | No dose adjustment required | 11 |
| Anidulafungin | 25 % increased loading- and maintenance dose for TBW > 140 kg | No dose adjustment required | No dose adjustment required | 18 |
| Caspofungin | Individuals with obesity will have low caspofungin concentrations despite being on the recommended doses No dosing advice provided | No dose adjustment required | CP-A: no dose adjustment required CP-B: 50 % reduced maintenance dose CP-C: No data | 25 |
| Cefazolin | No dose adjustment required based on exposure in plasma Surgical prophylaxis: Consider a 50 % dose increase for BMI > 40 kg/m ² | eGFR 40–70 mL/min: 50 % reduced daily dose eGFR 20–40 mL/min: 80 %–85 % reduced daily dose eGFR 5–20 mL/min: 90 %–95 % reduced daily dose | No dose adjustment required | 7 |
| Ceftazidime | No dose adjustment required based on bodyweight. | eGFR 30–50 mL/min: 33 % reduced daily dose eGFR 10–30 mL/min: 50 % reduced daily dose eGFR < 10 mL/min: 66 % reduced daily dose | No dose adjustment required | 24 |
| Ciprofloxacin | No dose adjustment required based on exposure in plasma Skin and soft tissue infection: 120–160 kg: increase dosing frequency to 3 dd > 160 kg: increase dosing frequency to 4 dd | 30–60 mL/min: 50 % reduced daily dose < 30 mL/min: 75 % reduced daily dose | No dose adjustment required | 6 |
| Daptomycin | No dose adjustment required based on body weight | eGFR 10–30 mL/min 100 % prolonged dosing interval | No dose adjustment required | 23 |
| Fluconazole | 50 % increased loading dose for males > 140 kg | eGFR < 50 mL/min 50 % reduced maintenance dose | No dose adjustment required | 10 |
| Gentamicin | Up to 25 % dose reduction compared to TBW based dose depending on total body weight | Up to 90 % reduced daily dose depending on severity of renal insufficiency, apply TDM | No dose adjustment required | 16, 32 |
| Liposomal amphotericin B | Cap dosing weight at 100 kg | No data | No data | 14 |
| Meropenem | No dose adjustment required based on body weight Dose adjustment not needed for pathogen with MIC ≤ 2 mg/L. Higher dosages may be needed for less sensitive pathogens | eGFR 26–50 mL/min 33 % reduced daily dose eGFR 10–25 mL/min 66 % reduced daily dose eGFR < 10 mL/min 85 % reduced daily dose | No dose adjustment required | 21 |
| Micafungin | Increase maintenance dose by 50–100 % if TBW > 125 kg and MIC 0.016–0.032 mg/L. Consider alternative therapy for overweight individuals if MIC > 0.32 mg/L | No dose adjustment required | CP-A/B: no dose adjustment required CP-C: Insufficient data | 15 |
| Moxifloxacin | No dose adjustment required based on body weight | No dose adjustment required | Insufficient data | 22 |
| Piperacillin | No dose adjustment required based on body weight | eGFR 40–20 mL/min up to 33 % reduced daily dose eGFR < 20 mL/min 33 %–50 % reduced daily dose | No dose adjustment required | 26 |
| Posaconazole | In case of treatment, increase loading and maintenance dose by 33 % for individuals with TBW 140–190 kg and by 66 % for individuals with TBW > 190 kg | No dose adjustment required | No dose adjustment required | 12 |

Problématique

Obésité

Maigreur

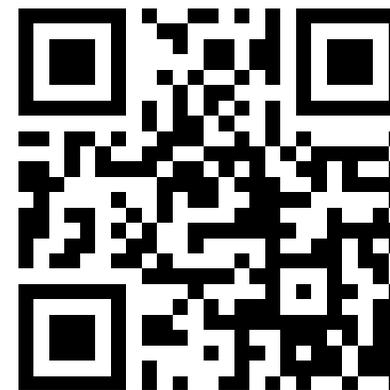
Musclé

Agé

Jeune

Conclusion

Abxbmi.com
Infectiologie.com



Problématique

Obésité

Maigreur

Musclé

Agé

Jeune

Conclusion



Giacometti

- 2 à 5% de la population française
- Tendance à la baisse
- Modifications physiologiques +++ si dénutrition (vs maigreur constitutionnelle)

Problématique

Obésité

Maigreur

Musclé

Agé

Jeune

Conclusion

- 36 patients : 18 LBW + 18 contrôles
- Administration de Méropénème
 - Dose de charge 2 g
 - Dose selon fonction rénale
 - Perfusion continue
- Dosage résiduel après 3 à 4 jours de traitement
- Seul facteur associé à surdosage : altération fonction rénale

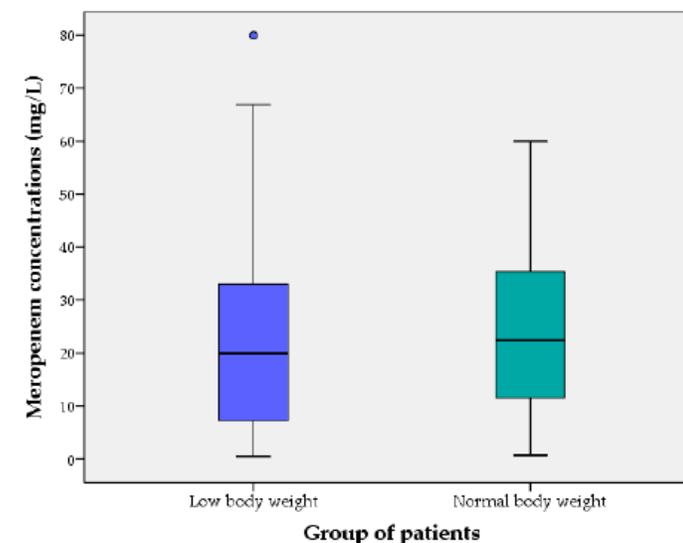


Table 2. PK/PD and toxicity data of the two groups.

| Variable | LwBW Group (Cases, n = 18) | NBW Group (Controls, n = 18) | p Value |
|--|-------------------------------|---------------------------------|---------|
| $C_{\min,ss}$, mg/L | 19.9 (22.2) | 22.4 (25.8) | >0.999 |
| Optimal PK/PD $100\% fT_{\geq 1-10 \times MIC}$, n (%) * | 6 (33.3) | 3 (16.7) | 0.443 |
| Subtherapeutic levels $100\% fT_{< MIC}$, n (%) * | 1 (5.6) | 1 (5.6) | >0.999 |
| Supratherapeutic PK/PD $100\% fT_{> 10 \times MIC}$, n (%) * | 11 (61.1) | 14 (77.8) | 0.278 |
| Toxicity thresholds | | | |
| $C_{\min,ss} > 44.5$ mg/L, n (%) ** | 3 (16.7) | 1 (5.6) | 0.603 |
| $C_{\min,ss} > 64.2$ mg/L, n (%) *** | 2 (11.1) | 0 (0) | 0.486 |
| DILI, n (%) | 2 (11.1) | 0 (0) | 0.486 |

Problématique

Obésité

Maigreur

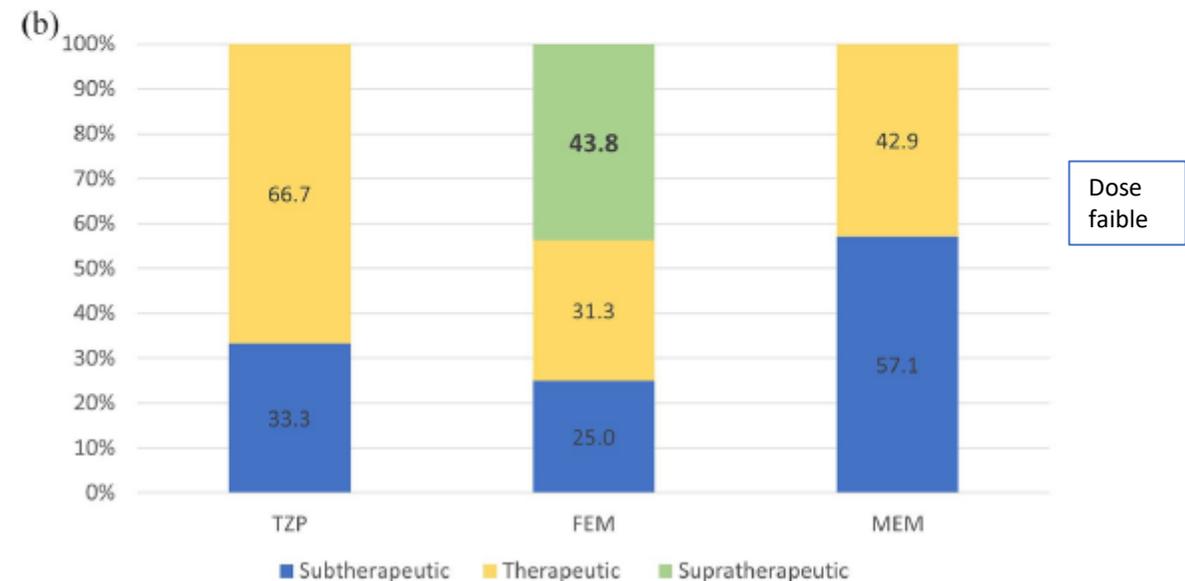
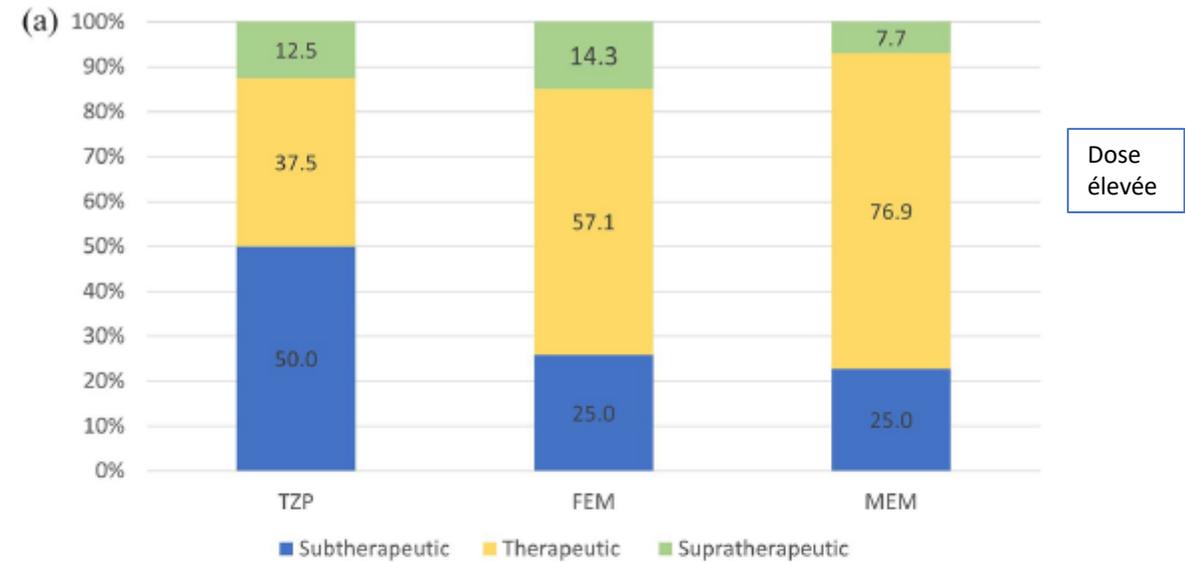
Musclé

Agé

Jeune

Conclusion

- 72 patients LBW
 - 29 TZP
 - 23 FEP
 - 20 MEM
- Dose élevée définie en fonction des standards pédiatriques
 - TZP 400 mg/kg/j
 - FEP 150 mg/kg/j
 - MEM 60 mg/kg/j
- Dosage de la concentration résiduelle



Problématique

Obésité

Maigreur

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Conclusion

Table 2. PK/PD target attainment for β -lactam antibiotics.

| PK/PD target and serum concentration | Piperacillin/ tazobactam (29) | Cefepime (23) | Meropenem (20) | <i>p</i> Value |
|--|----------------------------------|-------------------|-------------------|----------------|
| Free trough concentration | 35.89 \pm 42.07 | 34.95 \pm 30.50 | 8.76 \pm 12.50 | 0.02* |
| 100% fT > MIC | 18 (62.1%) | 17 (73.9%) | 14 (70%) | 0.65 |
| 100% fT > 4 MIC | 3 (10.3%) | 11 (47.8%) | 6 (30%) | 0.01* |
| Supratherapeutic concentration ^a | 1 (3.4%) | 8(34.8%) | 1 (5%) | 0.002* |
| Serum concentration within therapeutic range | 17 (58.6%) | 9 (39.1%) | 13 (65%) | 0.193 |
| Subtherapeutic concentration ^b | 11 (38.0%) | 6 (26.1%) | 6 (30%) | 0.65 |

Problématique

Obésité

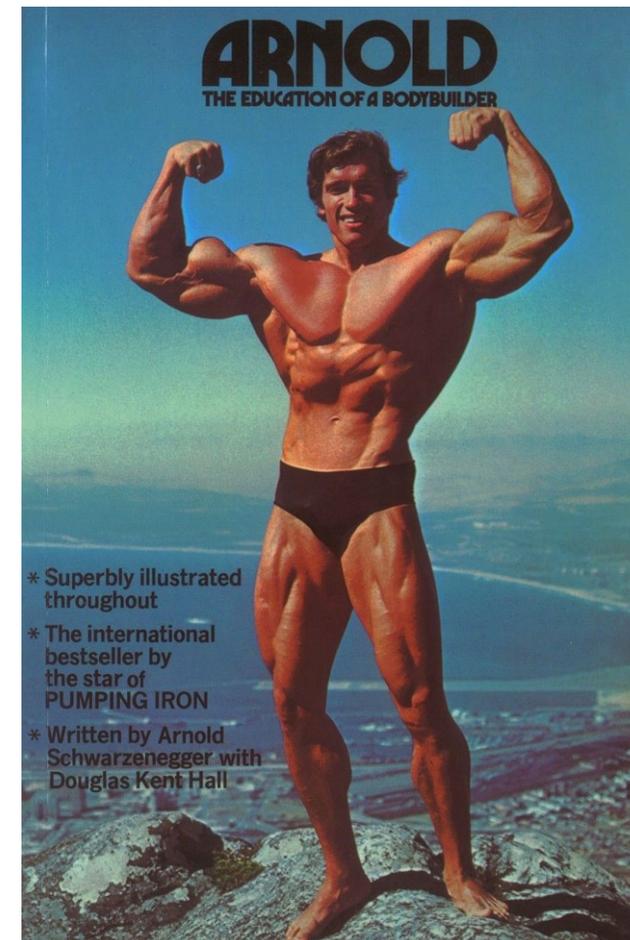
Maigreur

Musclé

Agé

Jeune

Conclusion



Pas de données

Augmentation de la masse maigre +++

Y a-t-il des âges extrêmes en réanimation ?

- 500 000 patients très âgés/an en USI en Europe
- 15-20% des patients admis en USI > 80 ans
- “Very Old Intensive Care Patients” (VIP)

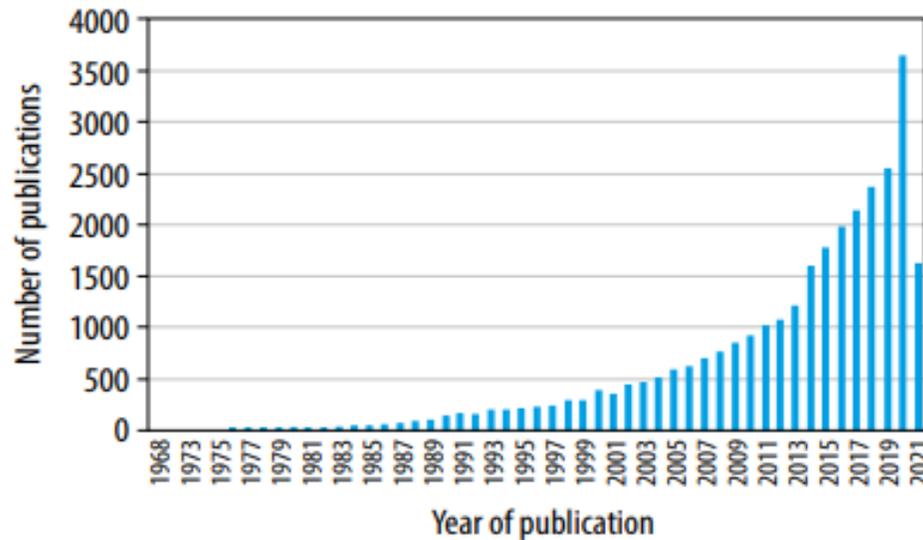
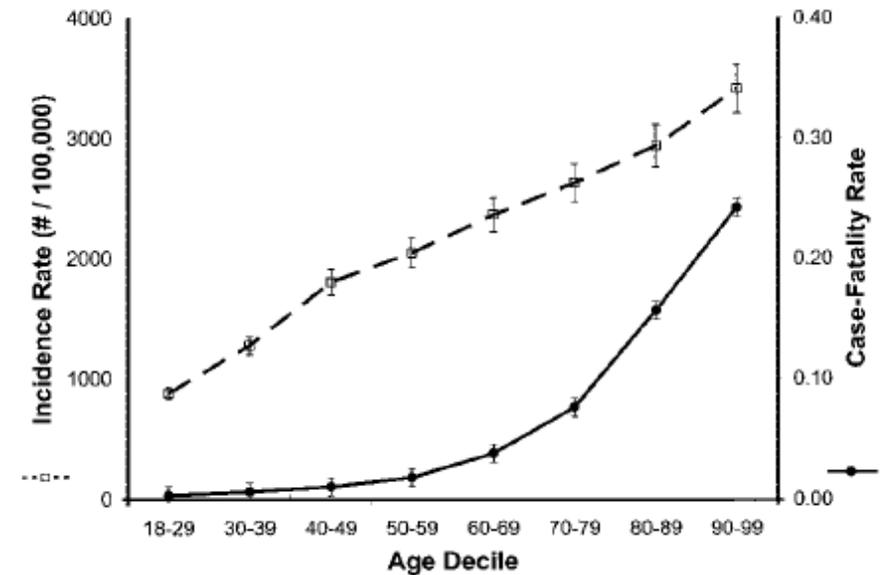


FIGURE 2. Number of publications in PubMed with the search terms “old” and “intensive care” 1968–2021



Van Heerden PV, et al. *Anaesthesiol Intensive Ther.* 2021
 Aliberti MJR, et al. *Intensive Care Med.* 2022
 Martin GS, et al. *Crit Care Med.* 2006

Problématique

Obésité

Maigreur

Musclé

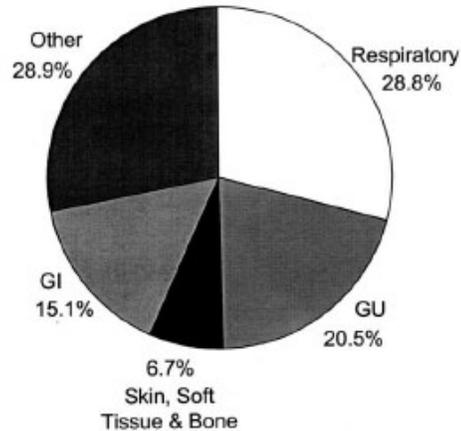
Agé

Jeune

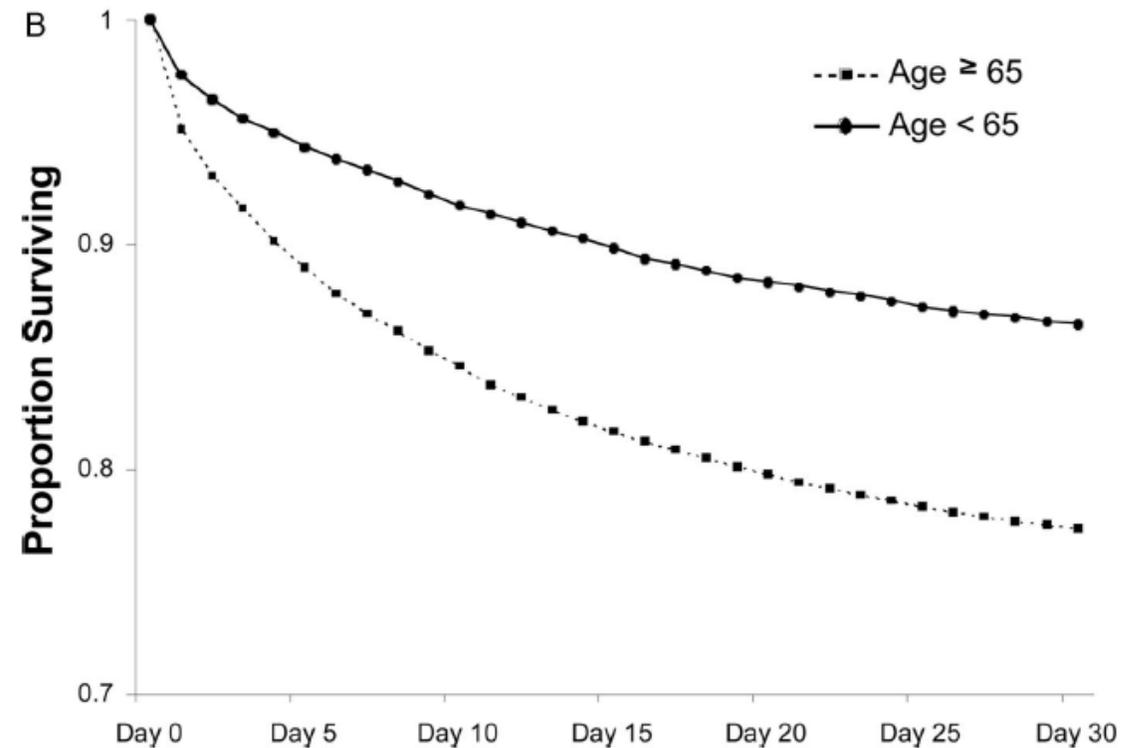
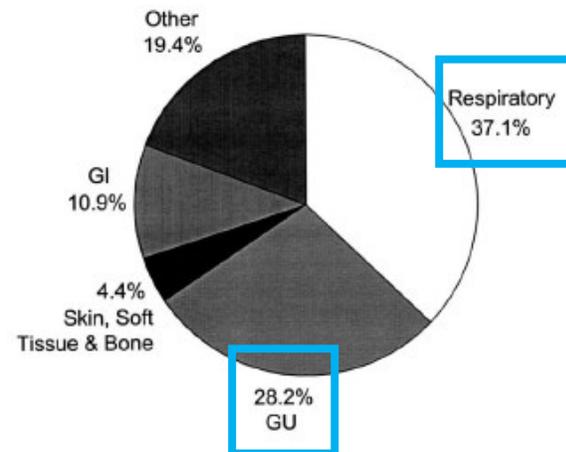
Conclusion

Mortalité plus élevée

< 65 Years of Age



≥ 65 Years of Age



Problématique

Obésité

Maigreur

Musclé

Agé

Jeune

Conclusion

Mortalité plus élevée

- Cohorte prospective internationale nichée dans EUROBACT-2 : adultes hospitalisés pour bactériémie nosocomiale dans 219 USI entre 2019 et 2021
- Comparaison de patients âgés ≥ 75 years et de jeunes adultes
- 2111 patients dont 563 (27%) ≥ 75 ans

Table 2 Management of HA-BSI among 2111 individuals, according to age category, adjustments for center

| | 18–75 years N= 1548 (73%) | ≥ 75 years N= 563 (27%) | Adjusted p^a |
|---|------------------------------|---------------------------------|----------------|
| Clinical status on day #28 | | | |
| Discharged, N (%) | 312 (20.2) | 67 (11.9) | <0.001 |
| All-cause mortality, N (%) | 520 (33.6) | 281 (49.9) | <0.001 |
| All-cause mortality (excluding individuals whose death was preceded by a decision to withhold or withdraw life-sustaining treatment) ^b , N (%) | 374 (26.8) | 200 (41.8) | <0.001 |

Problématique

Obésité

Maigreur

Musclé

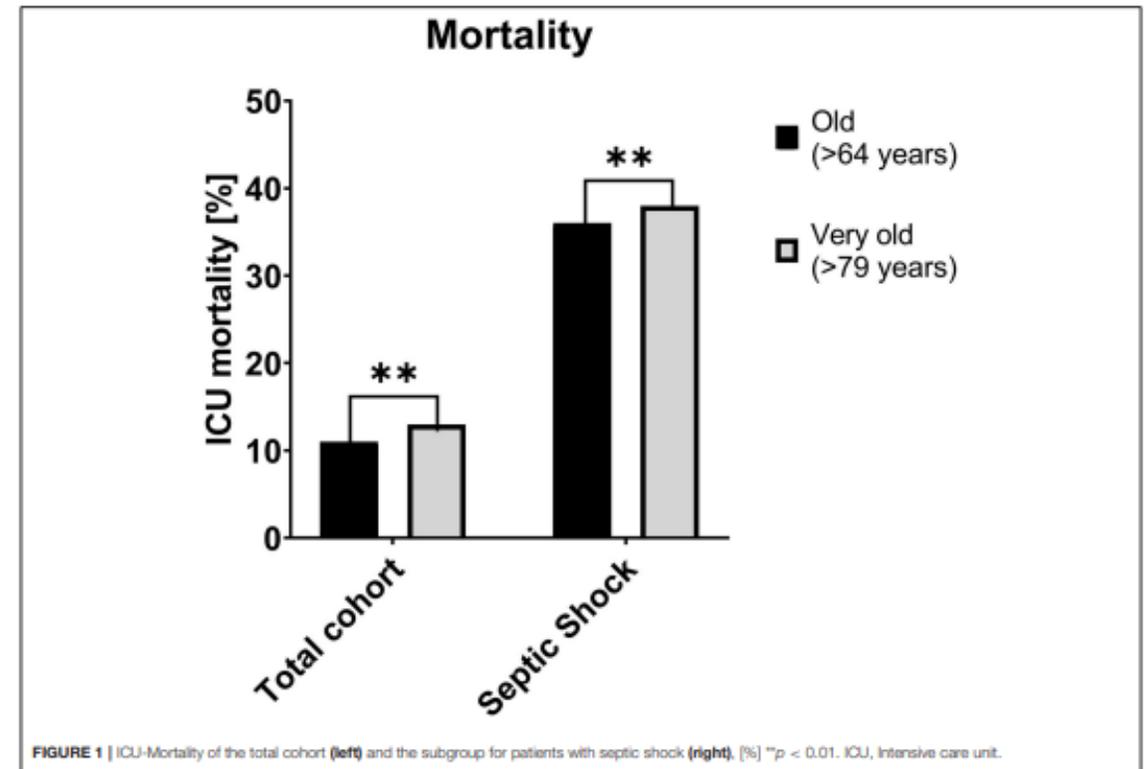
Agé

Jeune

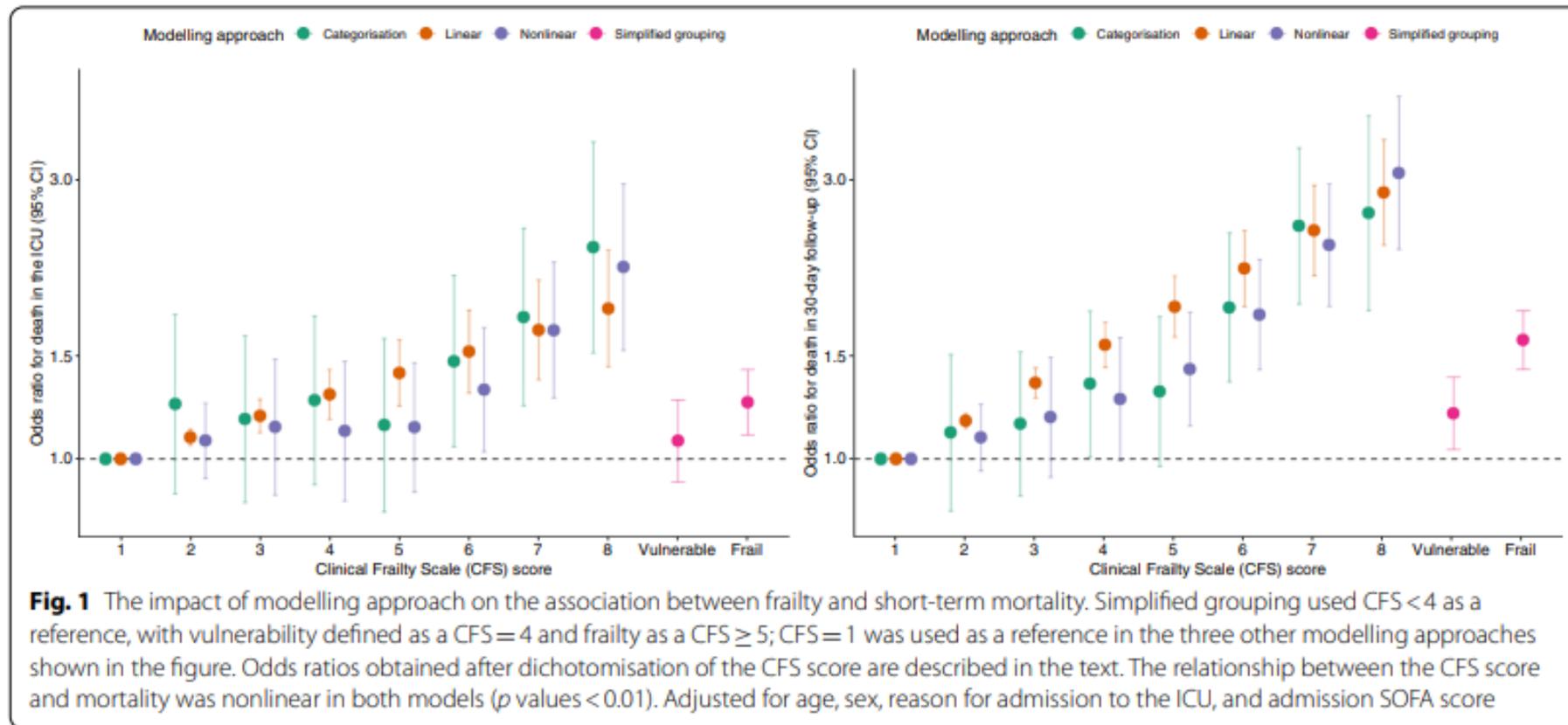
Conclusion

« VIP » : mortalité encore plus élevée

- 9 385 patients avec sepsis : 6 184 âgés (65-79 ans) et 3 201 très âgés (> 80 ans)
- Mortalité due au sepsis plus élevée chez les patients très âgés (13 vs 11 % ; $p = 0,005$)
- Avoir > 80 ans associé à un risque plus élevé de mortalité en USI (aOR 1,32, 95 % CI 1,09-1,59 ; $p = 0,004$).
- Même résultats dans le sous-groupe choc septique

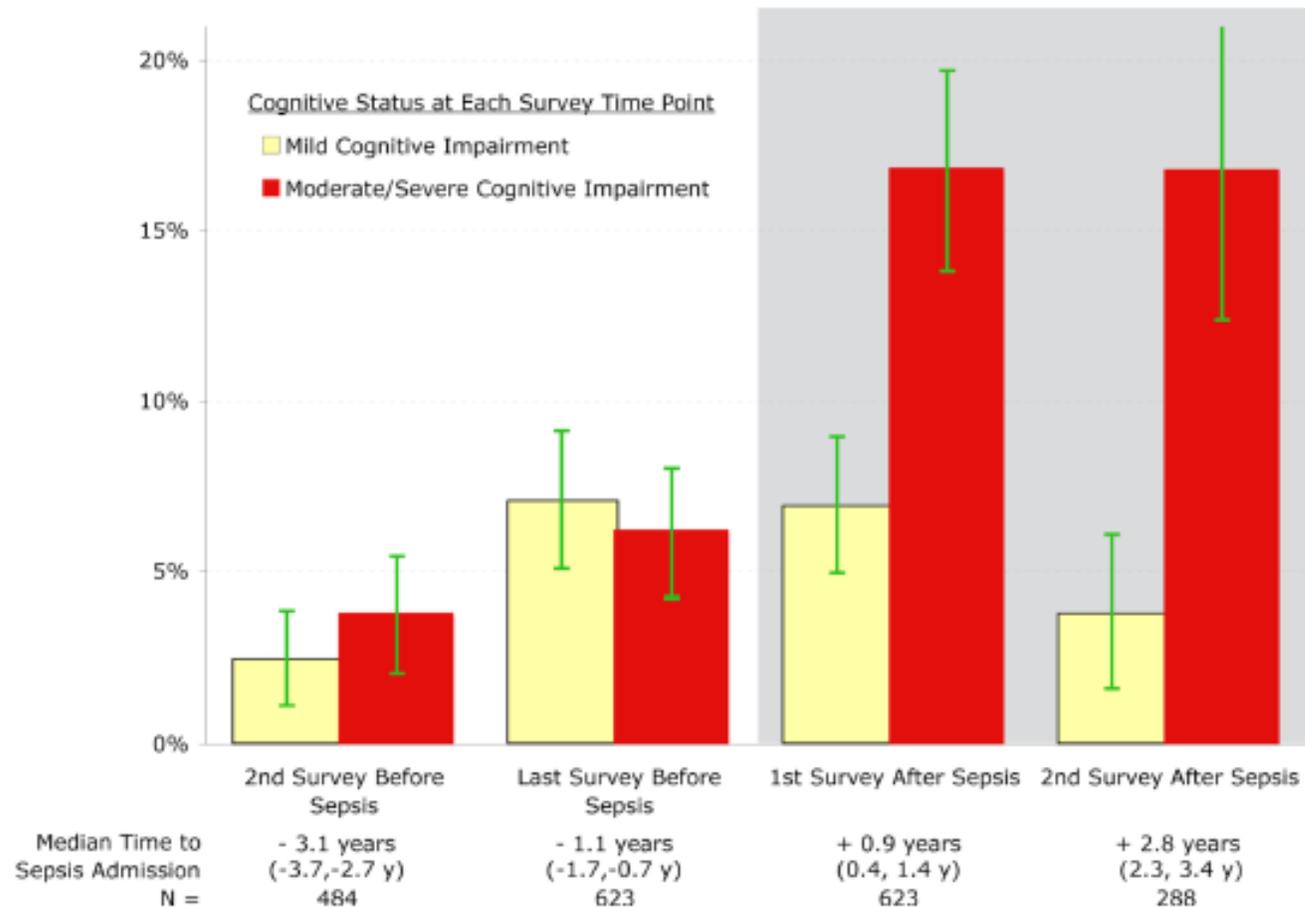


Mortalité associée à la fragilité





Déclin cognitif



Problématique

Obésité

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Agé

Jeune

Conclusion



Patient âgé : plus de risque d'effets indésirables

- 10,6% des passages au SAU des > 65 ans liés à un effet indésirable d'un médicament
- Dont 25% liés à un antibiotique
- **Antibiotiques = médicaments les plus pourvoyeurs d'effets indésirables**
- « Primum non nocere »

⇒ ATB que si absolument nécessaire

⇒ Monothérapie

⇒ Durée la plus courte

⇒ Adaptation de la posologie au poids et au DFG

- Erreur de posologie chez 34% de 1044 patients > 80 ans hospitalisés

... applicable à la
réanimation ?

Problématique

Obésité

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Jeune

Conclusion

Table 3. Common antimicrobial-induced adverse events in elderly persons.

| Antimicrobial class/agent | Adverse event |
|---------------------------------|---|
| Aminoglycosides | Nephrotoxicity and ototoxicity |
| Anti-tuberculosis | Hepatotoxicity |
| Isoniazid | Peripheral neuropathy |
| Rifampin | Red-orange discoloration of urine, tears, and sweat and drug interactions |
| β -Lactams | Diarrhea, drug fever, interstitial nephritis, rash, thrombocytopenia, anemia, and neutropenia |
| Carbapenems | Seizure |
| Clindamycin | Diarrhea and <i>Clostridium difficile</i> -associated colitis |
| Fluoroquinolones | Nausea, vomiting, CNS effects, decreased seizure threshold, and QT prolongation |
| Linezolid | Thrombocytopenia and anemia |
| Macrolides and azalides | Gastrointestinal intolerance, QT prolongation, and ototoxicity |
| Erythromycin and clarithromycin | Cholestatic hepatitis and drug interactions |
| Amantadine and rimantadine | CNS effects |
| Tetracyclines | Photosensitivity |
| Minocycline | Vertigo |
| Triazole antifungals | |
| Itraconazole and voriconazole | Gastrointestinal intolerance, hepatotoxicity, and drug interactions |
| Voriconazole | Photosensitivity and visual disturbances |
| Trimethoprim-sulfamethoxazole | Blood dyscrasias, drug fever, hyperkalemia, and rash |

- Néphrotoxicité : aminosides, glycopeptides, **amoxicilline**
- Confusion : fluoroquinolones, béta-lactamines dont **cefepime**
- Troubles digestifs : colite à *Clostridioides difficile*

Colite à *Clostridium difficile*

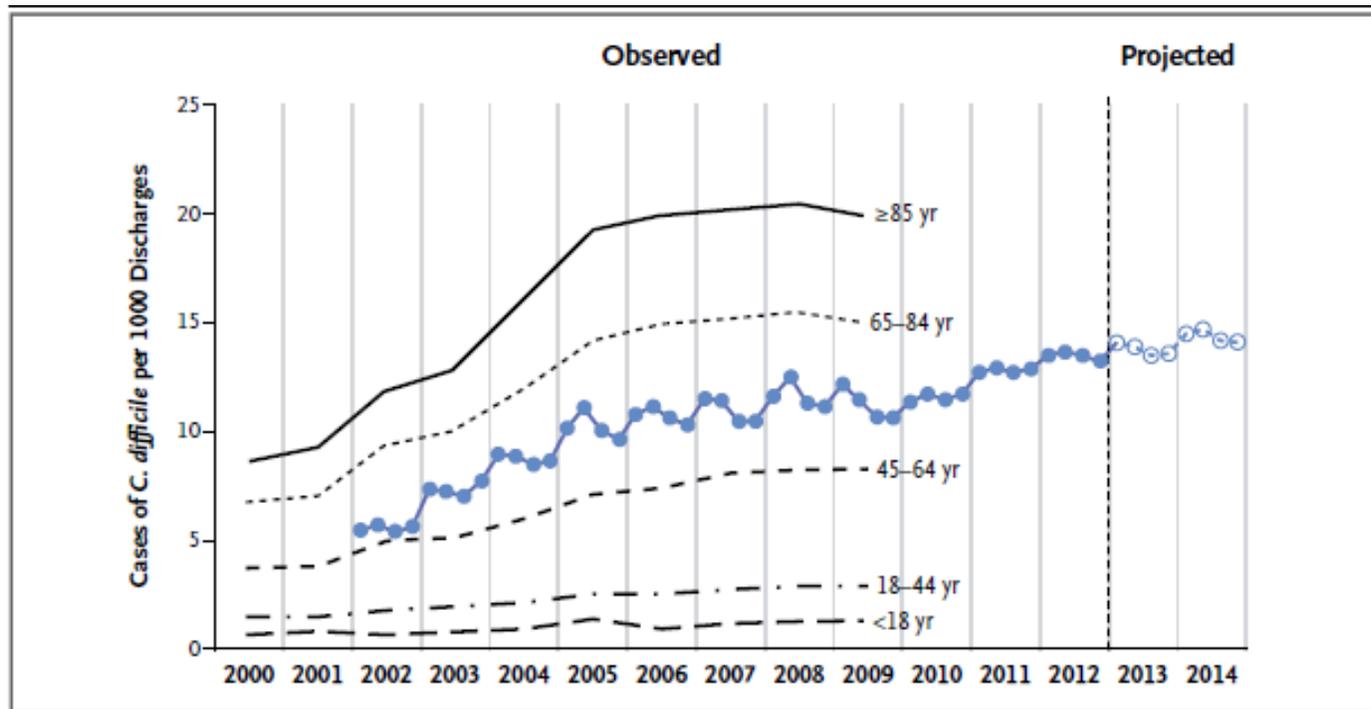


Figure 2. Incidence of Nosocomial *Clostridium difficile* Infection.

The overall incidence of nosocomial *C. difficile* infection is shown by year (blue), as is the incidence according to patient age (black). Data are from Steiner et al.¹⁸ and Lessa et al.²⁴

Table 1. Antibiotic Classes and Their Association with *Clostridium difficile* Infection.*

| Class | Association with <i>C. difficile</i> Infection |
|-------------------------------|--|
| Clindamycin | Very common |
| Ampicillin | Very common |
| Amoxicillin | Very common |
| Cephalosporins | Very common |
| Fluoroquinolones | Very common |
| Other penicillins | Somewhat common |
| Sulfonamides | Somewhat common |
| Trimethoprim | Somewhat common |
| Trimethoprim-sulfamethoxazole | Somewhat common |
| Macrolides | Somewhat common |
| Aminoglycosides | Uncommon |
| Bacitracin | Uncommon |
| Metronidazole | Uncommon |
| Teicoplanin | Uncommon |
| Rifampin | Uncommon |
| Chloramphenicol | Uncommon |
| Tetracyclines | Uncommon |
| Carbapenems | Uncommon |
| Daptomycin | Uncommon |
| Tigecycline | Uncommon |

Problématique

Obésité

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Jeune

Conclusion



Patient âgé : plus d'interactions médicamenteuses

- Polymédication : 58.4% des > 75 ans ont ≥ 6 médicaments
- Diminution des concentrations de l'ATB : antiacides, calcium/fer et quinolones
- Diminution des concentrations du médicament : AVK et rifampicine
- Augmentation des concentrations du médicament : AVK et ATB, dabigatran et clarithromycine, ADO et cotrimoxazole, colchicine et pristinamycine
- Toxicités cumulées : médicaments qui allongent le QT et quinolones ou macrolides, corticoïdes et quinolones, néphrotoxiques et cotrimoxazole



... applicable à la
réanimation ?

Problématique

Obésité

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Jeune

Conclusion

Table 2. Drug interactions among antimicrobials prescribed to elderly persons.

| Antimicrobial class/agent(s) | Interacting agent(s) | Potential clinical effect |
|---------------------------------|--|--|
| Aminoglycosides | Amphotericin B, cyclosporin, cisplatin, loop diuretics, tacrolimus, and vancomycin | Additive nephrotoxicity |
| Amoxicillin and ampicillin | Allopurinol | Rash |
| Fluoroquinolones | Pharmaceuticals containing aluminum, iron, magnesium, or zinc; antacids; and sucralfate | Decreased absorption of fluoroquinolones |
| Ciprofloxacin | Antiarrhythmics | Ventricular arrhythmia |
| | Calcium supplements | Decreased absorption of ciprofloxacin |
| | Theophylline | Increased theophylline concentration |
| | Warfarin | Increased anticoagulant effect |
| Linezolid | Serotonergic agents (SSRIs, TCAs, and MAOIs) | Serotonin syndrome |
| Macrolides | | |
| Azithromycin | Pharmaceuticals containing aluminum or magnesium | Decreased azithromycin absorption |
| Clarithromycin and erythromycin | Calcium channel blockers, HMG-CoA-reductase inhibitors, cyclosporine, digoxin, theophylline, and warfarin | Increased concentration or effect of interacting drug; increased concentration of macrolide (calcium channel blockers) |
| Metronidazole | Warfarin | Increased anticoagulant effect |
| | Alcohol (including alcohol-containing pharmaceuticals) | Disulfiram-like reaction |
| Rifampin | Antacids | Decreased rifampin absorption |
| | Antiarrhythmics, benzodiazepines, calcium-channel blockers, corticosteroids, digoxin, enalapril, estrogens and/or progestins, methadone, phenytoin, tamoxifen, theophylline, valproate, voriconazole, and warfarin | Decreased concentration or effect of interacting drug |
| Tetracyclines | Pharmaceuticals containing aluminum, calcium, iron, or magnesium; antacids; and bismuth subsalicylate | Decreased tetracycline absorption |
| | Digoxin | Digoxin toxicity |
| Triazole antifungals | Carbamazepine, phenobarbital, phenytoin, and rifampin | Decreased antifungal concentration |
| | Antiarrhythmics, benzodiazepines, calcium-channel blockers, corticosteroids, digoxin, HMG-CoA-reductase inhibitors, sulfonyleureas, and warfarin | Increased concentration or effect of interacting drug |
| Itraconazole, ketoconazole | Antacids, H ₂ -receptor antagonists, and proton-pump inhibitors | Decreased antifungal absorption |
| Voriconazole | Phenytoin and proton-pump inhibitors | Increased concentration or effect of interacting drug |
| Trimethoprim-sulfamethoxazole | Phenytoin | Increased phenytoin concentration |
| | Sulfonyleureas | Hypoglycemia |
| | Warfarin | Increased anticoagulant effect |

Problématique

Obésité

Maigreur

Musclé

Agé

Jeune

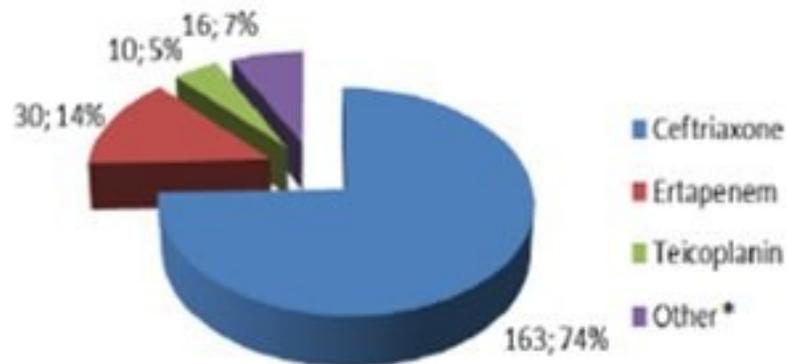
Conclusion



Sujet âgé : plus de difficultés de voie d'abord

- Voie orale : troubles de la déglutition
⇒ Médicament écrasable? Solution buvable?
- Alternative : la voie sous-cutanée ?

... non applicable à la réanimation



J Antimicrob Chemother 2023; **78**: 1–7

<https://doi.org/10.1093/jac/dkac383> Advance Access publication 14 November 2022

**Journal of
Antimicrobial
Chemotherapy**

Subcutaneously administered antibiotics: a review

Marie Jumpertz^{1,2}, Romain Guilhaumou³, Matthieu Million^{1,2}, Philippe Parola^{1,4}, Jean-Christophe Lagier^{1,2},
Philippe Brouqui^{1,2} and Nadim Cassir^{1,2*}

Problématique

Obésité

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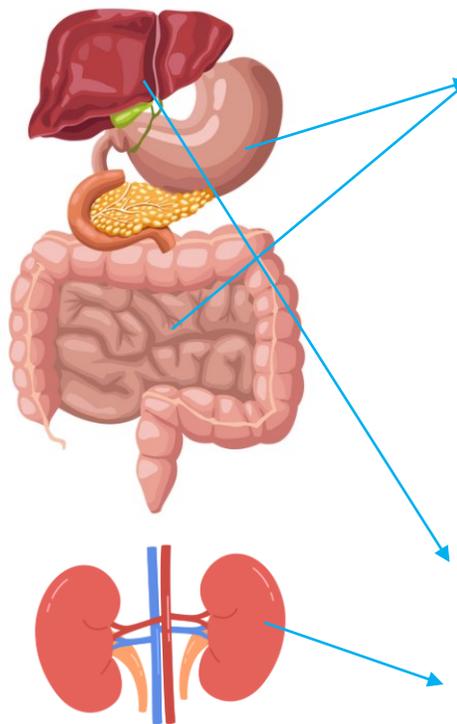
Jeune

Conclusion

Spécificité PK/PD chez le sujet âgé

⇒ Effet variable : **augmentation** ou diminution des concentrations sériques

⇒ Ex : 91 patients > 75 ans sous ATB > 7 jours : 51 (56%) surdosage



| Physiologic change | Potential pharmacokinetic effect |
|---|---|
| Absorption | |
| Increased gastric pH | Decreased absorption of pH-dependent antimicrobials and increased absorption of acid-labile antimicrobials |
| Decreased small bowel surface area | Decreased absorption |
| Decreased blood flow to small bowel | Decreased absorption |
| Decreased gastric emptying and gastrointestinal motility | Decreased or delayed absorption |
| Distribution | |
| Increased ratio of adipose tissue to lean tissue | Increased half-life of lipid-soluble antimicrobials |
| Decreased total body water | Increased concentration of water-soluble antimicrobials |
| Decreased plasma albumin level | Increased free concentration of acidic antimicrobials (e.g., penicillins, ceftriaxone, sulfonamides, and clindamycin) |
| Increased plasma α_1 -acid glycoprotein level | Decreased free concentration of basic antimicrobials (e.g., macrolides) |
| Metabolism | |
| Decreased phase 1 enzyme (cytochrome P-450) activity | Increased half-life of antimicrobials metabolized by phase 1 enzymes |
| Decreased hepatic blood flow | Decreased first-pass metabolism |
| Elimination, decreased renal blood flow and glomerular filtration rate | Increased half-life of renally eliminated antimicrobials |

Problématique

Obésité

Maigreur

Musclé

Agé

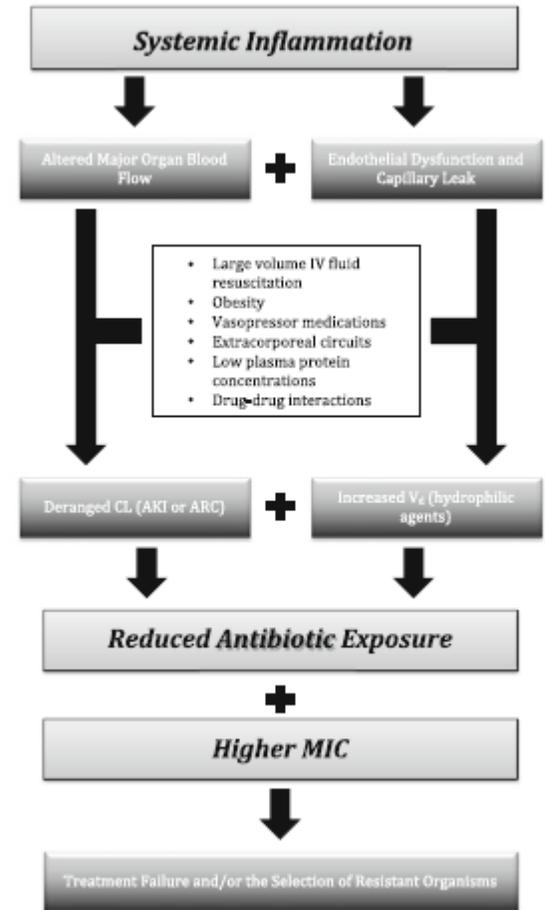
Jeune

Conclusion

Spécificité PK/PD en réanimation

- Augmentation du volume de distribution
 - Modification de la clairance rénale et hépatique
 - Thérapeutiques : EER, ECMO...
- ⇒ Effet variable : augmentation ou **diminution** des concentrations sériques

| | Timeline | | |
|----------------|---|---|--|
| | Day 1 | Day 2 | > Day 3 |
| Clinical | Norepinephrine High vascular filling Mechanical ventilation AKI +/- RRT or ECMO | Norepinephrine Stop vascular filling Mechanical ventilation AKI +/- RRT or ECMO | Norepinephrine weaning Extubation AKI +/- RRT |
| Microbiology | ? | Bacterial identification | |
| MIC | ? | ? | +/- Available |
| PK alterations | Under dosage | Under – overdosage | Overdosage |
| AM dosing | High doses | High or « normal » dose | « Depending on » |



Novy E, et al. *Antibiotics (Basel)*. 2023
 Udy AA, et al. *Intensive Care Med*. 2013

Problématique

Obésité

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Conclusion

Spécificités PK/PD chez le « VIP »

Physiologic change

Absorption

Increased gastric pH

Decreased small bowel surface area

Decreased blood flow to small bowel

Decreased gastric emptying and gastrointestinal motility

Distribution

Increased ratio of adipose tissue to lean tissue

Decreased total body water

Decreased plasma albumin level

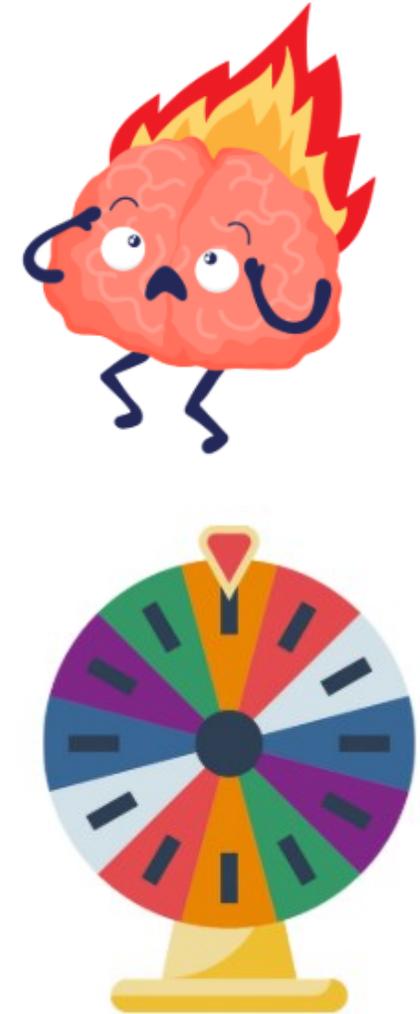
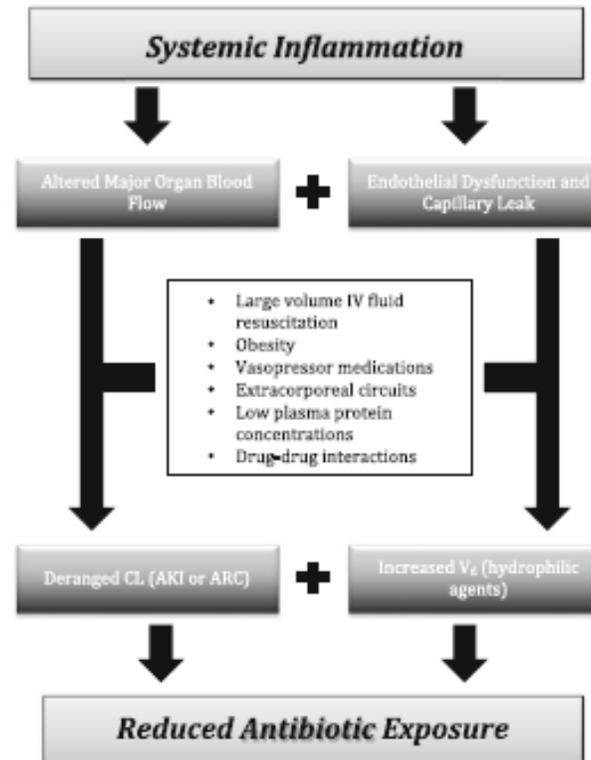
Increased plasma α_1 -acid glycoprotein level

Metabolism

Decreased phase 1 enzyme (cytochrome P-450) activity

Decreased hepatic blood flow

Elimination, decreased renal blood flow and glomerular filtration rate



Problématique

Obésité

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Conclusion

TDM = therapeutic drug monitoring

Table 1 Recommended indications for the use of therapeutic drug monitoring (TDM) of beta-lactam antibiotics. In cases of limited clinical data, these recommendations represent the authors' opinions

| Indications for beta-lactam TDM | Comments, references |
|--|--|
| Patients | |
| Critically ill | [8, 43, 47] |
| Augmented renal clearance | Low serum creatinine predicts subtherapeutic plasma concentrations [8, 45] |
| Obesity | [63] |
| Renal insufficiency | Particularly haemodialysis or CRRT patients [56] |
| Elderly | [62] |
| Cystic fibrosis | [55] |
| Infections | |
| Any severe/life-threatening infection | [47, 104] |
| Infections in anatomic sites with variable drug penetration, e.g.: | *Some beta-lactams have strong penetration into lung epithelial lining fluid; for these and for a non-life-threatening pneumonia, TDM may not be necessary |
| Osteomyelitis | |
| Prostatitis | |
| Meningitis | |
| Pneumonia* | |
| Infections with poor source control, e.g.: | |
| Endocarditis or other endovascular infection without a removable focus | |
| Incompletely drained abscess | |
| Loculated empyema | |
| Antibiotics | |
| Imipenem, meropenem and other carbapenems | These drugs are typically eliminated rapidly; patients may have undetectable trough levels [8, 46] |
| Cephalosporins | All cephalosporins can be monitored for efficacy, and cefepime should be monitored for both efficacy and toxicity [7] |
| Penicillins | These antibiotics may achieve only low (e.g. oral amoxicillin) and/or variable (e.g. piperacillin) plasma levels [8] |

Problématique

Obésité

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Conclusion

- M. D, 81 ans – 1,80 m – 87 kg – IMC 26,9 kg/m²
- Polyvasculaire : HTA sous bithérapie, AVC ischémique G en 1989 séquellaire (hémiparésie D)
- Adénocarcinome prostatique sous hormonothérapie
- Uropathie obstructive (lithiases): pose de JJ bilatérales en 2021, refus de changement depuis
- Traitement habituel :
 - XATRAL LP 10 mg : 1 cp le matin
 - AMLOR 5 mg matin : 1 gélule le matin
 - LISINOPRIL 20 mg : 1 cp le matin
 - OMEPRAZOLE 20 mg : 1 cp le matin
 - TRAMADOL 50: 1g matin, 1g midi, 1 g soir
 - DAFALGAN 1g: 3x1 comprimé/j

Problématique

Obésité

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Conclusion

- Adressé aux urgences pour douleur hypogastrique et dysurie alors qu'il ne sort plus de chez lui depuis une semaine dans un contexte de syndrome grippal.
- Conscient, T 36,4°C, PA 119/70 mmHg, FC 101 bpm, SpO2 100% en AA
- Examen clinique sans particularité sauf un globe urinaire

Problématique

Obésité

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Conclusion

| Sang veineux | | | |
|------------------------|-----------|----------|---|
| Température patient | | °C | 36.8 |
| pH | 7.34-7.38 | % Don... | 7.07 <input type="checkbox"/> |
| pCO2 | 43-49 | mm Hg | 15 <input type="checkbox"/> |
| pCO2 | 5.7-6.25 | kPa | 2.01 <input type="checkbox"/> |
| pO2 | 35-45 | mm Hg | 155 <input checked="" type="checkbox"/> |
| pO2 | 5.05-5.6 | kPa | 20.7 <input checked="" type="checkbox"/> |
| pH/T° patient | | | |
| pCO2/T° patient | 43-49 | | |
| pCO2/T° patient | 5.7-6.25 | | |
| pO2/T° patient | 35-45 | | |
| pO2/T° patient | 5.05-5.6 | | |
| CO2 total | 23.0-28.0 | mmol/L | 4.8 <input type="checkbox"/> |
| Bicarbonate | 23-28 | mmol/L | 4 <input type="checkbox"/> |
| Hémoglobine totale | 13.5-17.5 | g/dL | 10.2 <input type="checkbox"/> |
| HbO2 | 70.0-80.0 | % | 95.2 <input checked="" type="checkbox"/> |
| Carboxy Hb | 0.5-1.5 | % | 3.4 <input checked="" type="checkbox"/> |
| Méthémoglobine | <1.0 | % | 0.5 |
| Contenu en O2 | 14.0-16.0 | mL/dL | 14.1 |
| Lactate | 0.5-1.6 | mmol/L | 0.9 |
| Glucose | 3.9-5.8 | mmol/L | 3.5 <input type="checkbox"/> |
| Sodium | 136-146 | mmol/L | 137 |
| Potassium | 3.4-4.5 | mmol/L | 5.0 <input checked="" type="checkbox"/> |
| Calcium ionisé | 1.15-1.29 | mmol/L | 1.10 <input type="checkbox"/> |
| Calcium ionisé /pH 7.4 | 1.15-1.29 | mmol/L | ERREUR... |

| VIROLOGIE - MOLECULAIRE | | | |
|------------------------------|--|--|--|
| Coronavirus SARS-CoV-2 - BPO | | | |
| Détection de l'ARN | | | |
| Cycle seuil (Ct) | | | |
| Gène E | | | |
| Région Orf1 a/b | | | |
| Gène NSP2 | | | |
| Gène NSP2 cycle seuil (Ct) | | | |
| Gène N | | | |
| Gène N cycle seuil (Ct) | | | |

| BIOCHIMIE | | | |
|-------------------------|---------|----------|--|
| Indices plasmatiques | | | |
| Aspect du plasma | | | |
| Examens sanguins | | | |
| Glucose | 3.9-5.8 | mmol/L | |
| Sodium | 136-145 | mmol/L | 137 |
| Potassium | 3.5-4.5 | mmol/L | 4.9 <input checked="" type="checkbox"/> <input checked="" type="checkbox"/> |
| Chlorure | 98-107 | mmol/L | 111 <input checked="" type="checkbox"/> |
| CO2 total | 24-30 | mmol/L | 4.85 <input type="checkbox"/> |
| Trou anionique | -3-3 | mmol/L | 9.9 <input checked="" type="checkbox"/> |
| Protéines | 65-80 | g/L | 69 |
| Urée | 2.5-7.4 | mmol/L | 45.5 <input checked="" type="checkbox"/> |
| Créatinine | 59-104 | µmol/L | 877 <input checked="" type="checkbox"/> |
| DFG calculé par CKD-EPI | >90 | mL/mi... | 4.4 <input type="checkbox"/> |
| Valeurs normales | | | |

Problématique

Obésité

Maigreur

Musclé

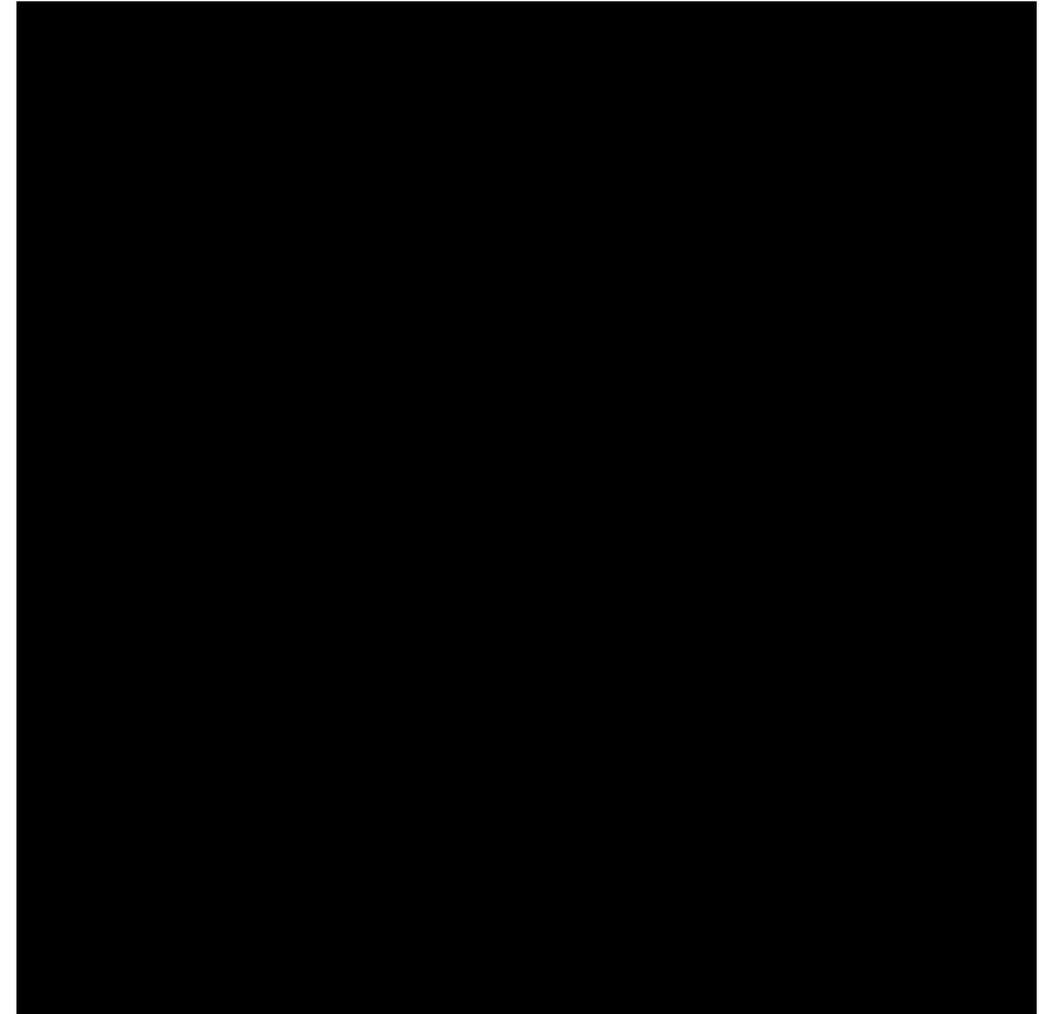
Agé

Jeune

Conclusion

| MICROBIOLOGIE - RENSEIGN... | | | |
|-----------------------------|-----|--|---|
| Pré-analytique | | | |
| Ensemencement manuel | | | Ensemencé manuellement. |
| BACTERIOLOGIE - URINES | | | |
| Examen macroscopique | | | |
| Aspect macroscopique | | | Léger trouble |
| Examen microscopique | | | |
| Cellules | | | Absence |
| Cristaux | | | Absence |
| Cylindres | | | Absence |
| Numération | | | |
| Hématies | /mL | | >10*6  |
| Leucocytes | /mL | | >10*6  |
| Coloration de gram | | | |
| . | | | Nombreux bacilles à Gram positif cory... |
| . | | | Quelques bacilles à Gram négatif |

- CEFOTAXIME
- Changement de JJ
- Prise en charge par l'équipe de réanimation



Problématique

Obésité

Maigreur

Musclé

Agé

Jeune

Conclusion

Méropénem* 500mg pdr inj fl (Arrow)

Gen

BCH - REA CHIR - ATB1

Discontinu avec durée

Intraveineuse

Condition : Dose de charge
Dose : 2 g à 11:32, à passer en 1 h

SOLUTION 1
Méropénem* 500mg pdr inj fl (Arrow) : 2 g, 40 ml
SODium CHLorure 0,9% - 50mL sol perf poche Freeflex (Fresenius) : 10 ml
Volume : 50 ml
Concentration : 0,04 g/ml

MEROPENEME J01DH02 21/03/2025 11:32 21/03/2025 11:32

1 j

PRÉPARATION À ADMINISTRER
SOLUTION 1 : 50 ml
Débit : 50 ml/h
Durée de la préparation : 1 h

Méropénem* 500mg pdr inj fl (Arrow)

Gen

BCH - REA CHIR - ATB1

Intraveineuse

Condition : dose d'entretien
2 g toutes les 8 heures (soit 6 g/j)

SOLUTION 1
Méropénem* 500mg pdr inj fl (Arrow) : 2 g, 40 ml
Volume : 40 ml

MEROPENEME J01DH02 21/03/2025 12:32 21/03/2025 12:32

1 j

PRÉPARATION À ADMINISTRER
SOLUTION 1 : 40 ml

Méropénem* 500mg pdr inj fl (Arrow)

Gen

Intraveineuse

Condition : dose d'entretien IVL sur 1h
Faire 1g sur sur 1h après chaque dialyse
1 g toutes les 12 heures (soit 2 g/j)

SOLUTION 1
Méropénem* 500mg pdr inj fl (Arrow) : 1 g, 20 ml
Volume : 20 ml

MEROPENEME J01DH02 21/03/2025 20:31 21/03/2025 20:31

1 j

PRÉPARATION À ADMINISTRER
SOLUTION 1 : 20 ml

Imipénème+Cilastatine* 500mg/500mg pdr perf fl (Arrow)

Gen

Intraveineuse

Condition : Dose d'entretien, sur 1h
Réfaire 500 mg sur 1h après chaque séance de dialyse
500 mg toutes les 12 heures (soit 1000 mg/j)

SOLUTION 1
Imipénème+Cilastatine* 500mg/500mg pdr perf fl (Arrow) : 500 mg, 20 ml
SODium CHLorure 0,9% - 50mL sol perf poche Freeflex (Fresenius) : 60 ml
Volume : 80 ml
Concentration : 6,25 mg/ml

IMPENEME ET CILASTATINE J01DH51 21/03/2025 18:30 26/03/2025 06:30 26/03/2025 17:57

5 j

PRÉPARATION À ADMINISTRER
SOLUTION 1 : 80 ml

| BACTERIOLOGIE - URINES | |
|--------------------------------|---|
| Examen macroscopique | |
| Aspect macroscopique | Léger trouble |
| Examen microscopique | |
| Cellules | Absence |
| Cristaux | Absence |
| Cylindres | Absence |
| Numération | |
| Hématies | >10*6 |
| Leucocytes | >10*6 |
| Coloration de gram | |
| . | Nombreux bacilles à Gram positif corynéformes |
| . | Quelques bacilles à Gram négatif |
| Culture et ou identification | |
| — | 1. Klebsiella pneumoniae 1.10e4 UFC/mL (ou g) |
| | 1. |
| BLSE | Positif |
| Identification par | Spectrom... |
| Méthode : Diffusion | V |
| CASFM/EUCAST 2023 V1 | V |
| Amoxicilline | R |
| Amoxicilline+ac. clavulanique | R |
| Amoxicilline+ac.clav.(cystite) | R |
| Ticarilline | R |
| Méccillinam | R |
| Céfotaxime | R |
| Ceftazidime | R |
| Céfépime | R |
| Imipénème | S |
| Ertapénème | S |
| Gentamicine | R |
| Amikacine | S |
| Acide nalidixique | R |
| Ofloxacine | R |
| Triméthoprim+ sulfaméthoxazole | R |
| Nitrofuranes | S |
| Fosfomycine | R |

+ Enterococcus faecalis

Problématique

Obésité

Maigreur

Musclé

Agé

Jeune

Conclusion

| PHARMACO - TOXICO - SERU... | | | |
|-----------------------------|-------|--|---|
| ATB : Imipénème | | | |
| Date début de traitement | | | Non Comm. |
| Voie d'administration | | | Non communiqué(e) |
| Posologie | | | 2/J |
| Dose | mg | | 500 |
| Dose/poids patient | mg/kg | | - |
| Heure de dernière prise | | | 23/03/2025 à 20:00 |
| Délai (Prise/Prélèvement) | | | 13h |
| Imipénème | mg/L | | 1.0 |
| Zones thérapeutiques | | | Absorption : Tmax = 60 min... ⓘ |
| Commentaire | | | La concentration plasmatiqu... ⓘ |

| PHARMACO - TOXICO - SERU... | | | |
|-----------------------------|-------|--|----------------------|
| ATB : Imipénème | | | |
| Date début de traitement | | | Non Co... |
| Voie d'administration | | | Non co... |
| Posologie | | | 2/J |
| Dose | mg | | 500 |
| Dose/poids patient | mg/kg | | - |
| Heure de dernière prise | | | Non Co... |
| Délai (Prise/Prélèvement) | | | - |
| Imipénème | mg/L | | 29.0 |
| Zones thérapeutiques | | | Absorpt... ⓘ |
| Commentaire | | | En l'abs... ⓘ |

Absorption : Tmax = 60 minutes après injection IM et en fin de perfusion IV.
 Distribution : la liaison aux protéines plasmatiques est faible (20 %). Sa distribution est bonne dans l'organisme (faible dans le LCR, ascite, bile, os, sécrétions bronchiques et pancréatiques, péricarde) avec un Vd = 0,14-0,23 L/kg.
 Métabolisme : par une dipeptidase située au niveau de la bordure en brosse des cellules du tubule rénal proximal.
 Excrétion : Principalement rénale (50-70 %). La demi-vie est égale à 1 heure. L'imipénème est dialysable.
 Les concentrations observées en fonction du mode d'administration sont les suivantes
 - Après administration IM de 500 mg => Pic : 10 mg/L
 - Après administration IVL de 1 g => Pic : 41-83 mg/L ; avec une fonction rénale normale, 8h après administration IV, la résiduelle est < 1 mg/L

Problématique

Obésité

Maigreur

Musclé

Agé

Jeune

Conclusion

Et chez les jeunes ?

- **Hyperclairance** ≥ 130 ml/mn/1.71m²
- Favorisée par le sepsis
- Risque de **sous-dosage** :
 - Beta-lactamines : 58% \geq CMI, et 31% \geq 4xCMI
 - Cefiderocol : posologie dédiée
- Augmentation du risque d'échec ?

Table 3 Drug therapeutic failure rates between ARC and non-ARC patients for often used antimicrobials

| | No ARC | ARC |
|---|--------------|---------------|
| No. of patients with failure | 8/62 (12.9%) | 18/66 (27.3%) |
| n failures/n patients on selected antimicrobial therapy (%) | | |
| Amoxicillin/ clavulanic acid | 1/24 (4.2) | 8/25 (32.0) |
| Cefuroxim | 2/11 (18.1) | 5/23 (21.7) |
| Piperacillin/ tazobactam | 2/17 (11.8) | 6/19 (31.6) |
| Meropenem | 2/7 (28.6) | 2/8 (25.0) |

ARC: Augmented renal clearance is a 24-hour urinary creatinine clearance > 130 mL/min per 1.73 m².

Problématique

Obésité

Maigreur

Musclé

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Jeune

Conclusion

Chez l'enfant en réanimation

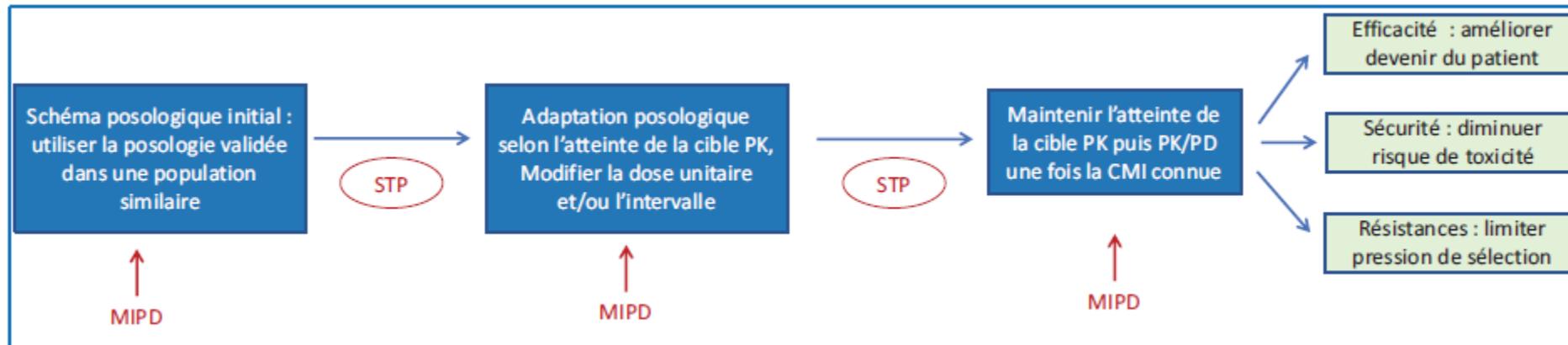
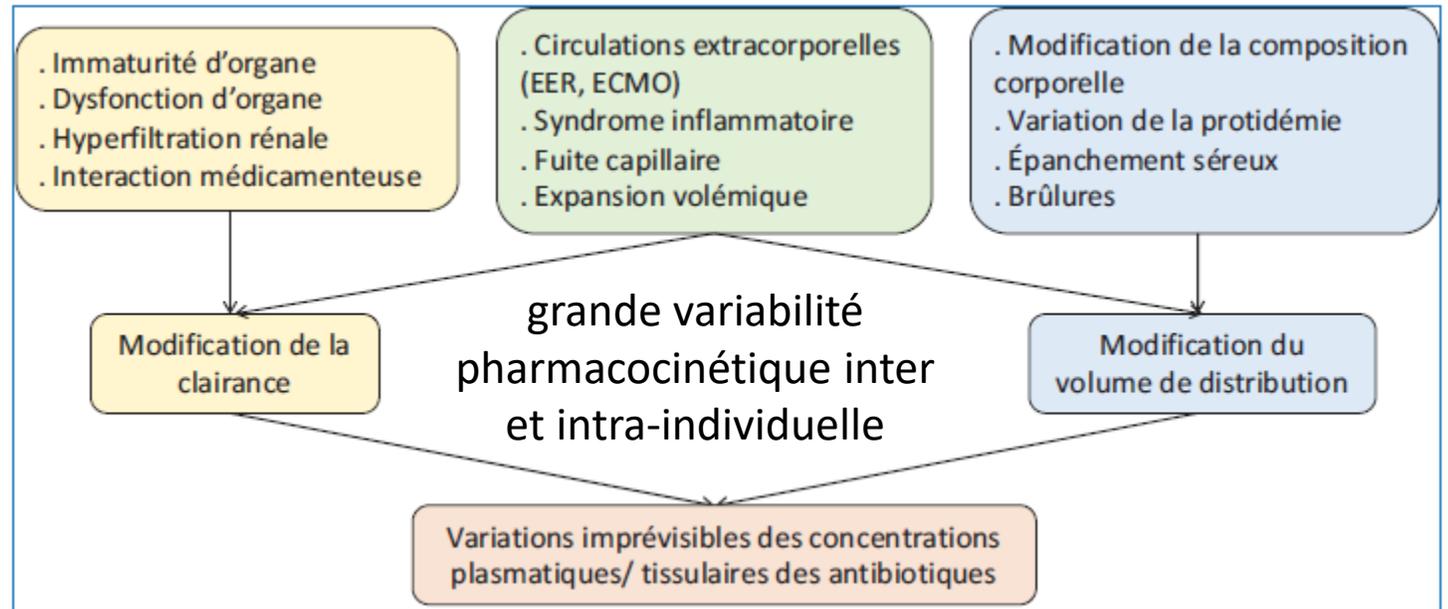
Mise au point pratique

Comment optimiser les posologies des antibiotiques chez l'enfant en situation critique ?

How to optimize the antibiotic dosing regimens in critically ill children

Agathe Béranger^{a,b}
Noémie de Cacqueray^{a,b}
Stéphanie Leroux^{c,d}

Perfectionnement en Pédiatrie 2025;8:48-56



Problématique

Obésité

Maigreur

Musclé

Agé

Jeune

Conclusion

- Situations toutes à risque de sur/sous dosage des antibiotiques
 - ⇒ Molécule les plus efficace + fenêtre thérapeutique large
 - ⇒ Adapter au poids et à la fonction rénale...
 - ⇒ Dosages

Merci de votre attention