Colistine: applications cliniques

Nicolas Grégoire, PharmD, PhD

DESC infectiologie, 13 Octobre 2015

THE LANCET Infectious Diseases

Review

Colistin: the re-emerging antibiotic for multidrug-resistant Gram-negative bacterial infections

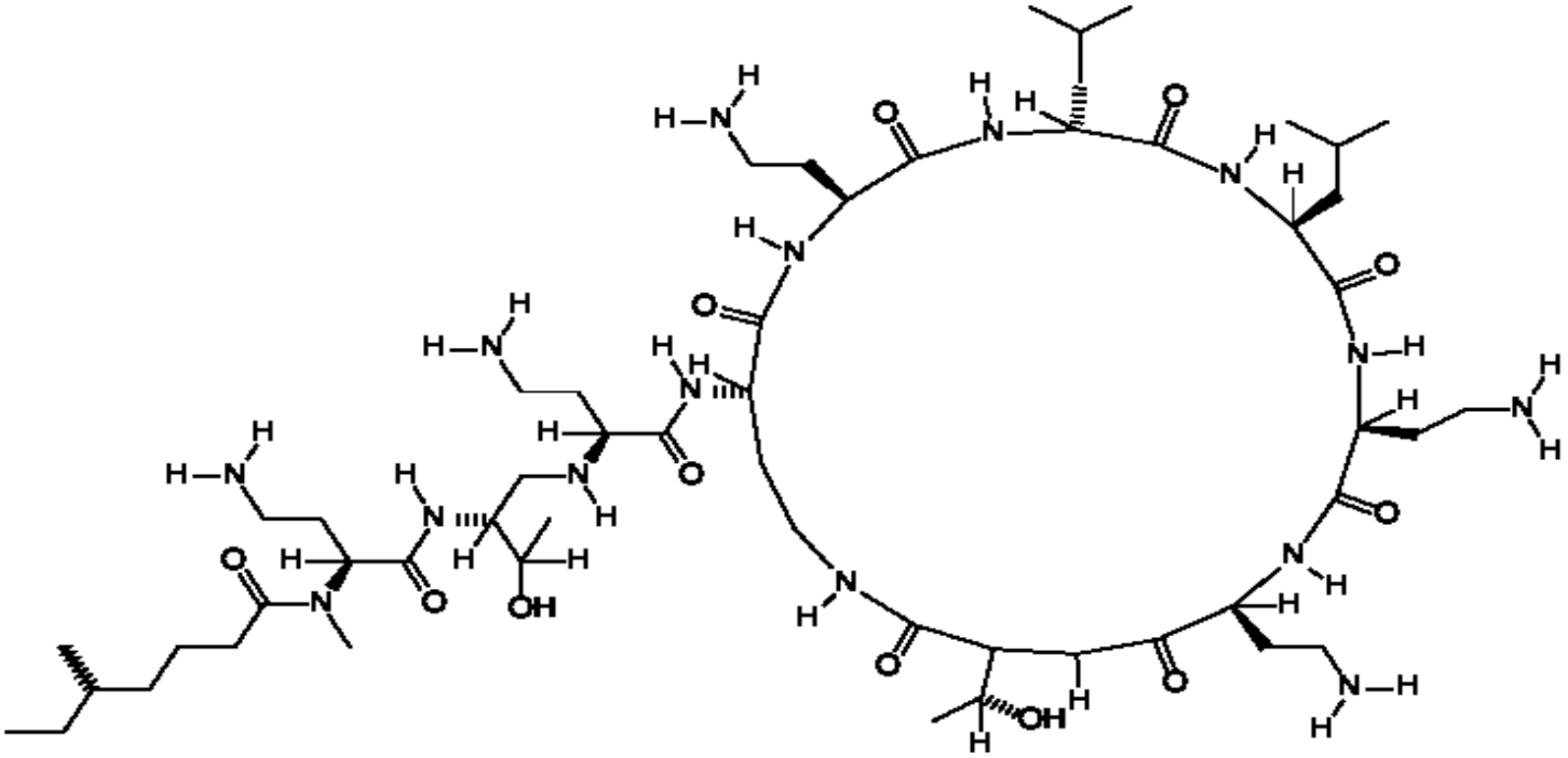
Jian Li, Roger L Nation, John D Turnidge, Robert W Milne, Kingsley Coulthard, Craig R Rayner, David L Paterson

Increasing multidrug resistance in Gram-negative bacteria, in particular *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and *Klebsiella pneumoniae*, presents a critical problem. Limited therapeutic options have forced infectious disease clinicians and microbiologists to reappraise the clinical application of colistin, a polymyxin antibiotic discovered more than 50 years ago. We summarise recent progress in understanding the complex chemistry, pharmacokinetics, and pharmacodynamics of colistin, the interplay between these three aspects, and their effect on the clinical use of this important antibiotic. Recent clinical findings are reviewed, focusing on evaluation of efficacy, emerging resistance, potential toxicities, and combination therapy. In the battle against rapidly emerging bacterial resistance we can no longer rely entirely on the discovery of new antibiotics; we must also pursue rational approaches to the use of older antibiotics such as colistin.

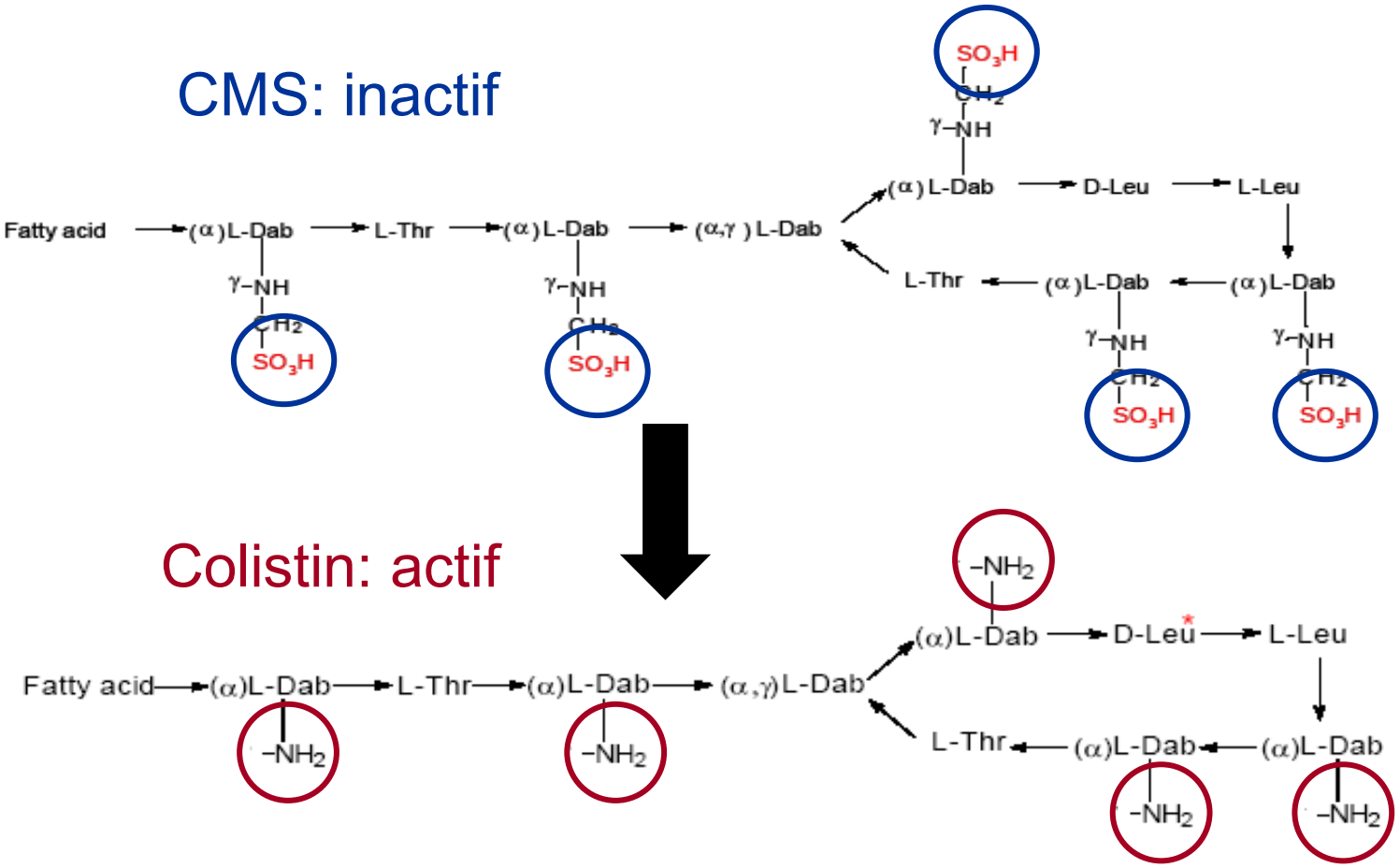
Lancet Infect Dis 2006; 6: 589–601

Facility for Anti-Infective Drug Development and Innovation, Victorian College of Pharmacy, Monash University, Parkville, Victoria, Australia (J Li PhD, Prof R L Nation PhD, C R Rayner PharmD); Division of Laboratory Medicine (Prof J D Turnidge FRACP) and

La colistine: polypeptide cyclique



Administration sous forme de prodrug



Mécanisme d'action

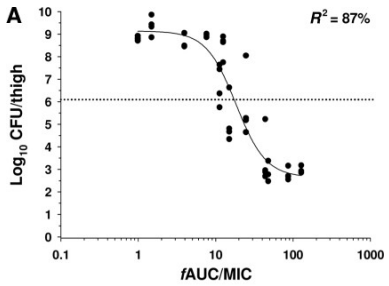
- Fixation aux lipopolysaccharides (LPS) et aux phospholipides de la membrane externe des BGN, augmentant sa perméabilité
- Bactéricide concentration-dépendant
- Resistance est peu fréquente

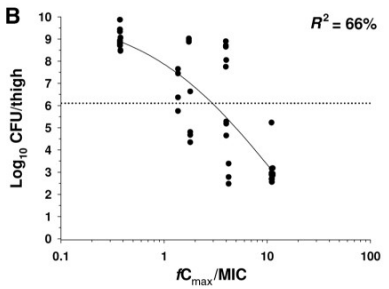
Spectre

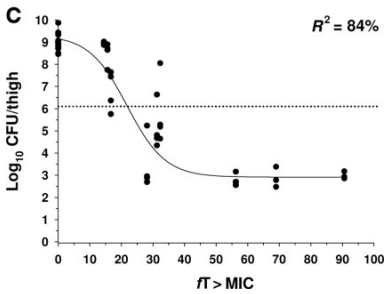
Aérobies à Gram négatif

- ***Acinetobacter***
- *Aeromonas*
- *Citrobacter*
- ***Enterobacter***
- ***E. coli***
- ***K. pneumoniae***
- *H. influenzae*
- *Moraxella*
- ***P. aeruginosa***
- *Salomonella*
- *Shigella*
- ***S. maltophilia***

Pharmacodynamie



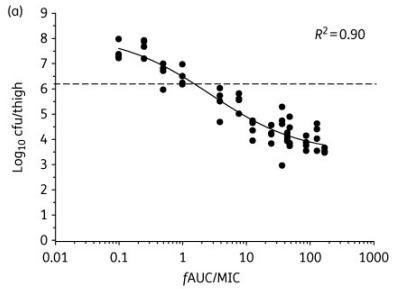


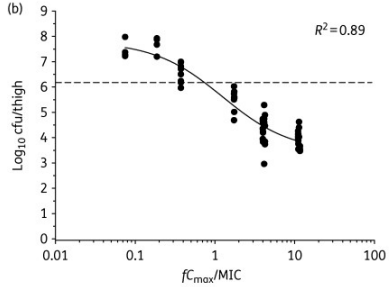


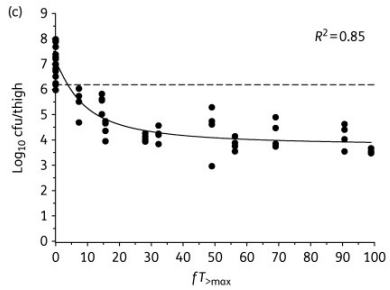
Pseudomonas aeruginosa

f.AUC/MIC

48







Acinetobacter baumannii

Antimicrob Agents Chemother. 2010 54(3):1117-24.

J Antimicrob Chemother. 2010 65(9):1984-90.

- **Efficacy**

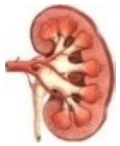
$$\frac{AUCu_{0-24h}}{CMI} = \frac{C_{ss,u}^{avg} \times 24}{CMI} \approx 48$$

$$\hookrightarrow \quad C_{ss,u}^{avg} \approx 2 \times CMI \xrightarrow[fu = 50\%]{\text{Assuming}} \boxed{C_{ss}^{avg} \approx 4 \times CMI}$$

En conc. totale

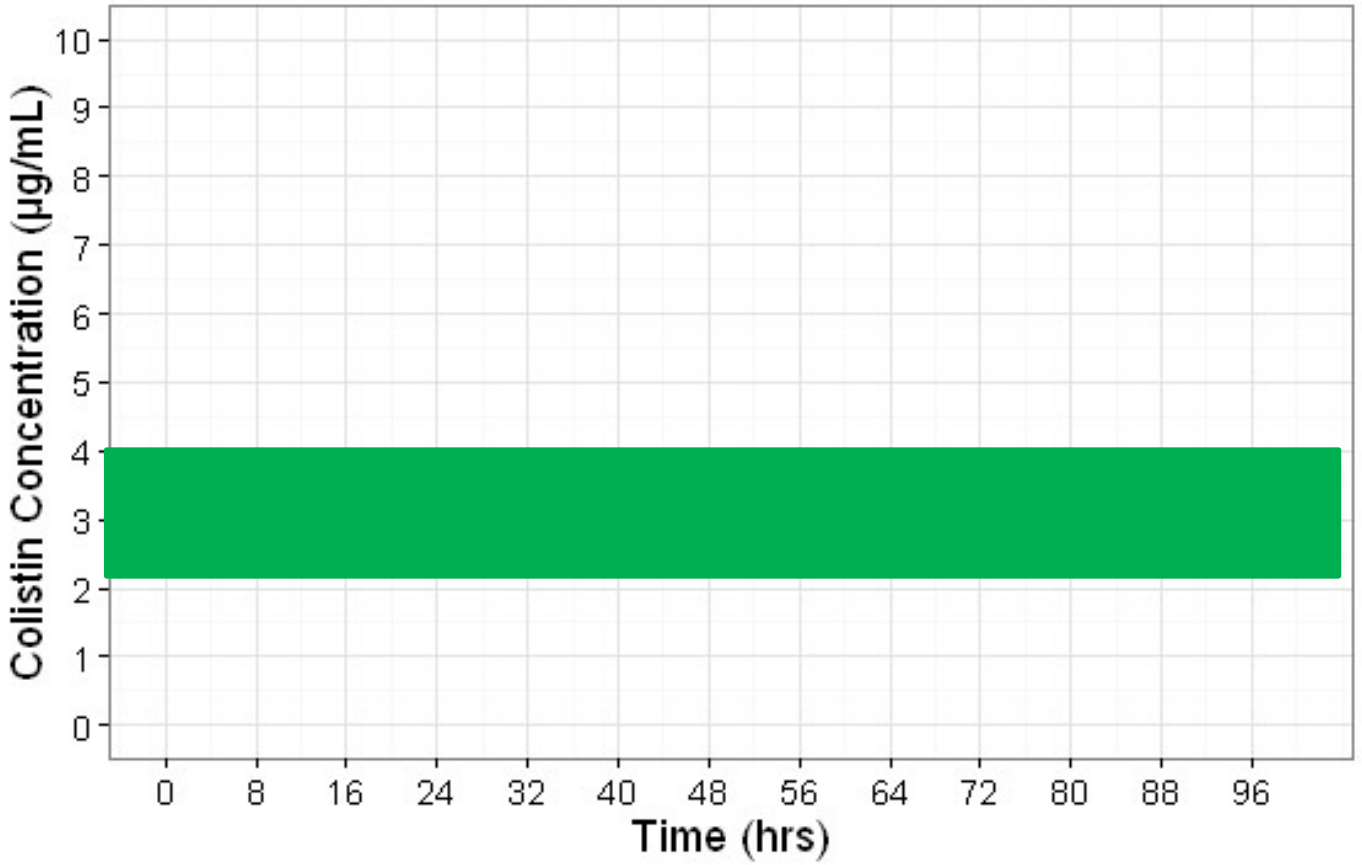
- **Toxicity**

 CNS

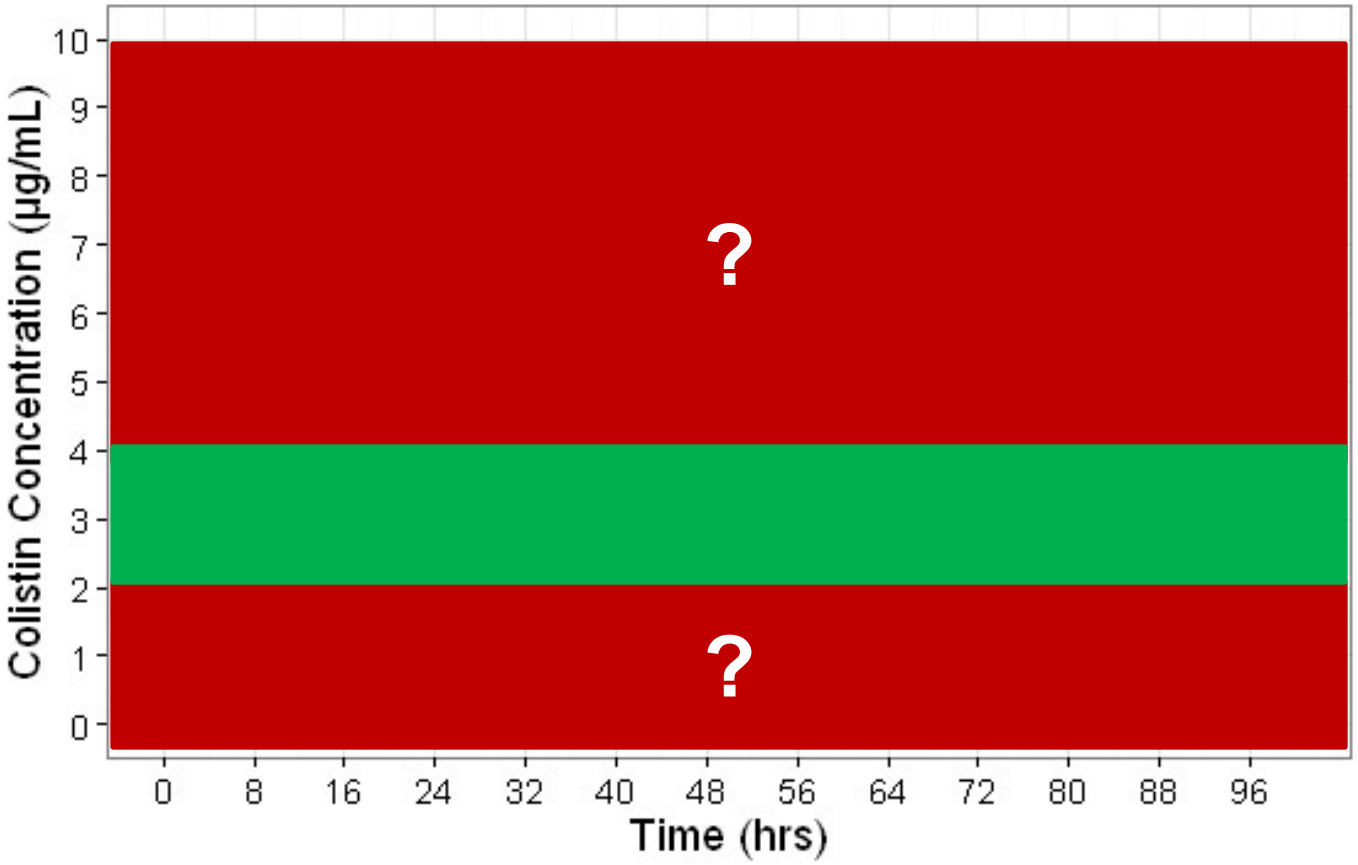
 Renal

Suggested target for total conc. in plasma: 2 – 4 µg/mL

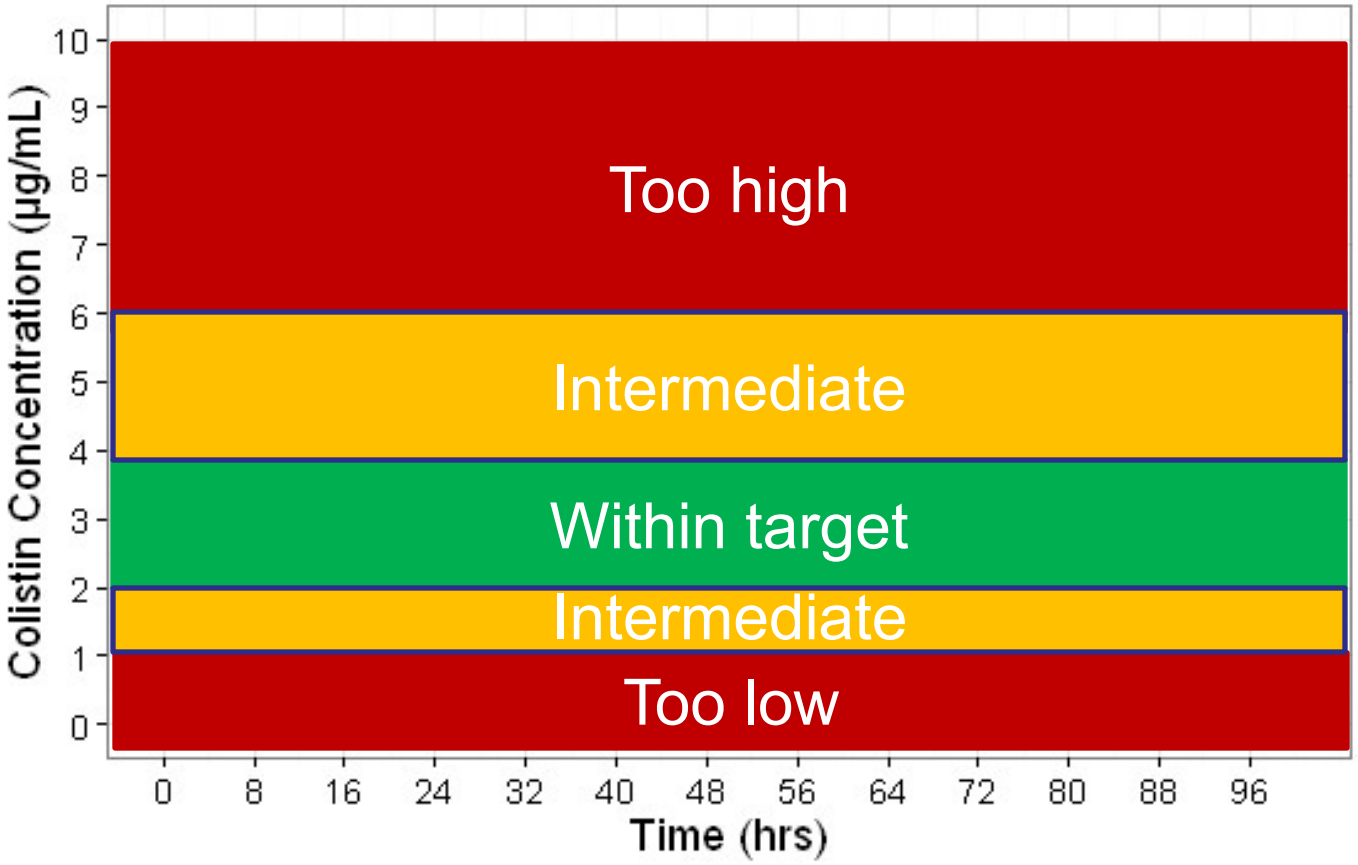
(EUCAST Break-points / Side effects)



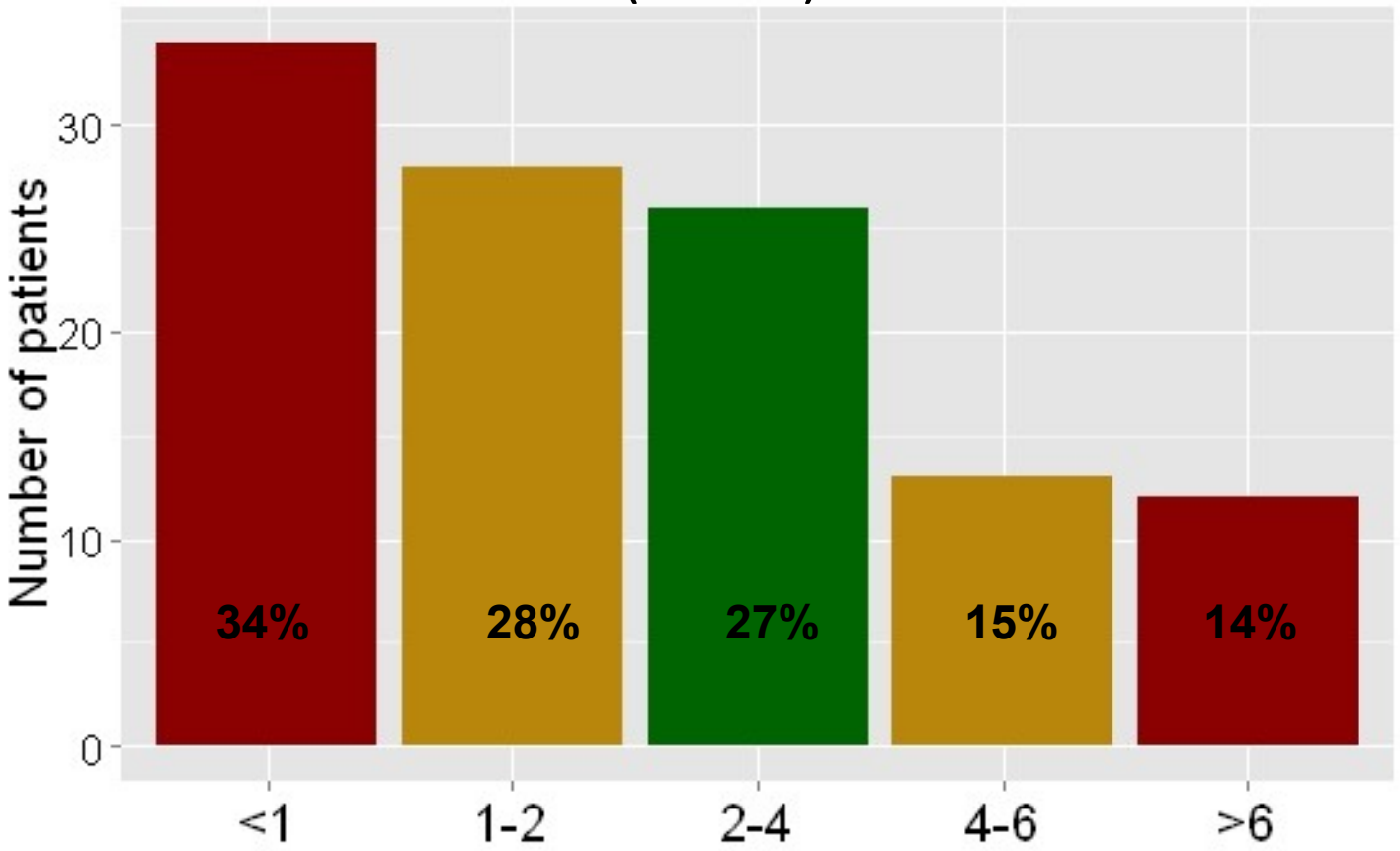
What if Ccoli < 2 µg/mL or Ccoli > 4 µg/mL ?



2 intermediate zones: 1-2 µg/mL and 4-6 µg/mL

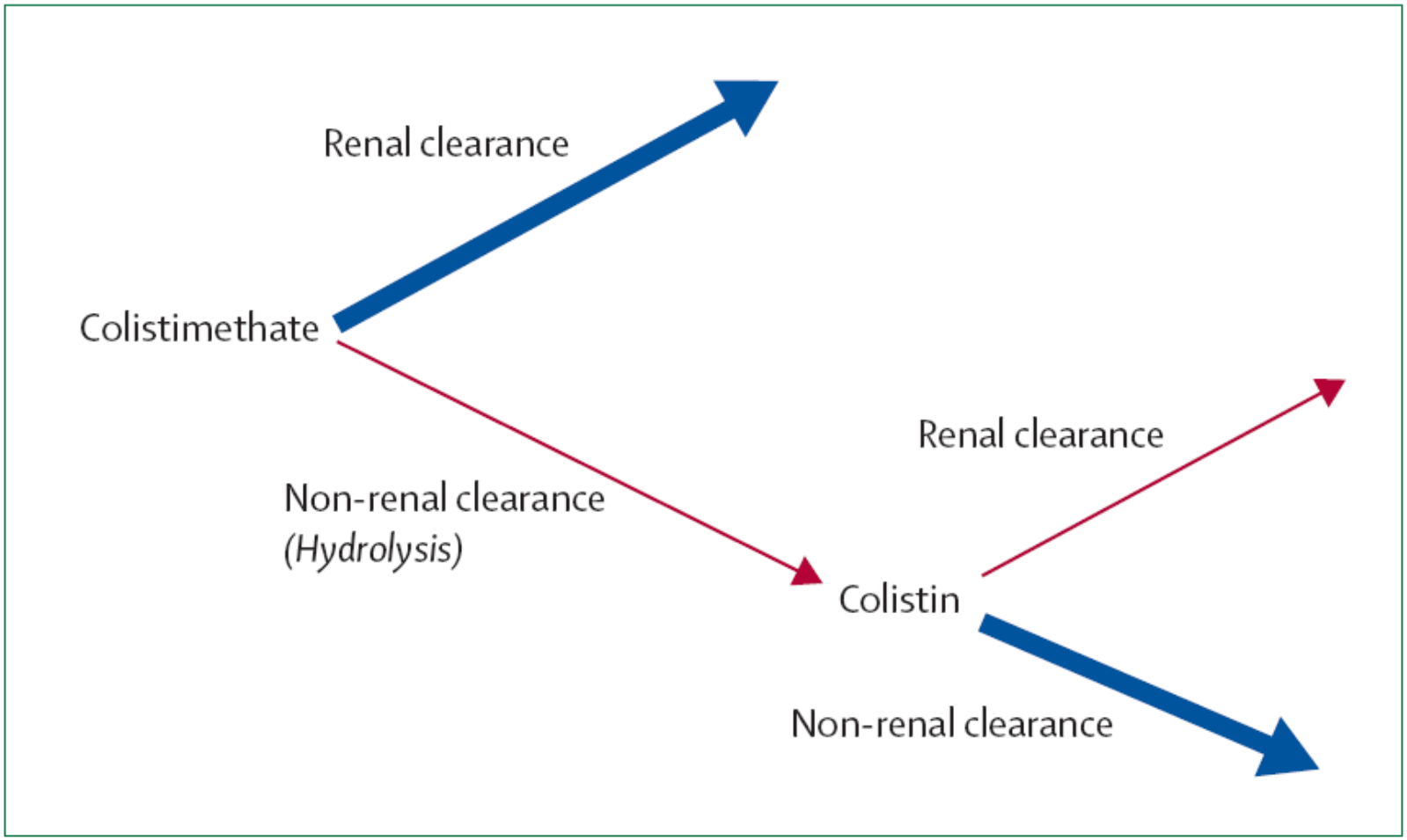


Measured Colistin trough Concentrations at steady-state
in Non-Hemodialyzed patients at the Poitiers University Hospital in 2013
(n=113)



Pharmacocinétique du CMS et de la colistine

(from Li et al., Lancet Inf Dis, 2006)

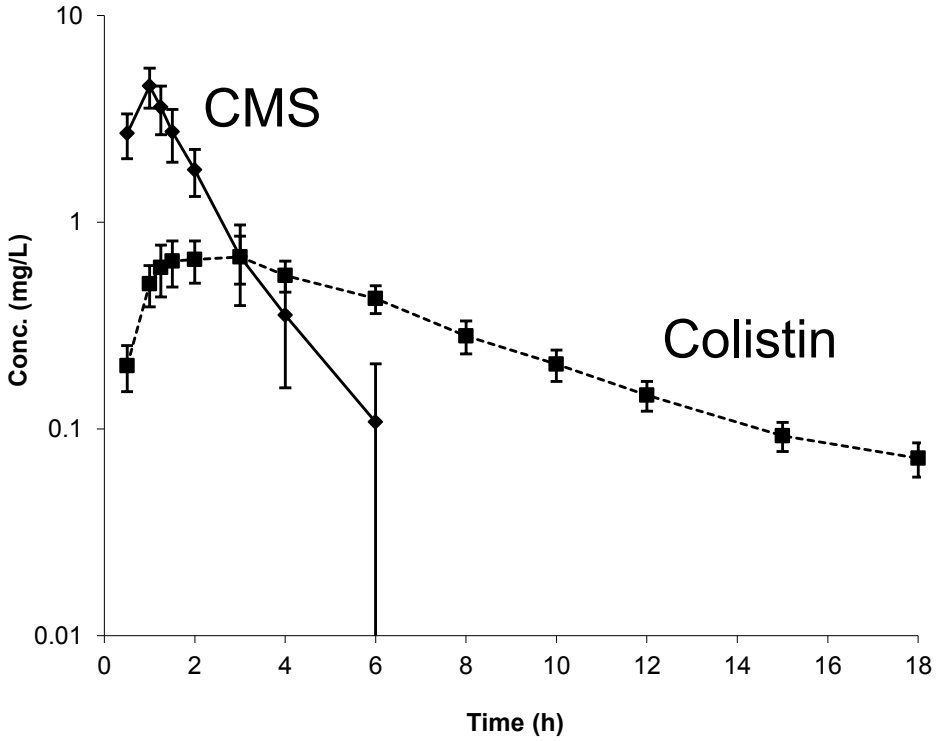


nature publishing group ARTICLES

Pharmacokinetics of Colistin and Colistimethate Sodium After a Single 80-mg Intravenous Dose of CMS in Young Healthy Volunteers

W Couet[1,2,3], N Grégoire[1,2], P Gobin[1,3], PJ Saulnier[4], D Frasca[1,2,3], S Marchand[1,2,3] and O Mimoz[1,2,4]

CLINICAL PHARMACOLOGY & THERAPEUTICS | VOLUME 89 NUMBER 6 | JUNE 2011



AAC
Journals.ASM.org

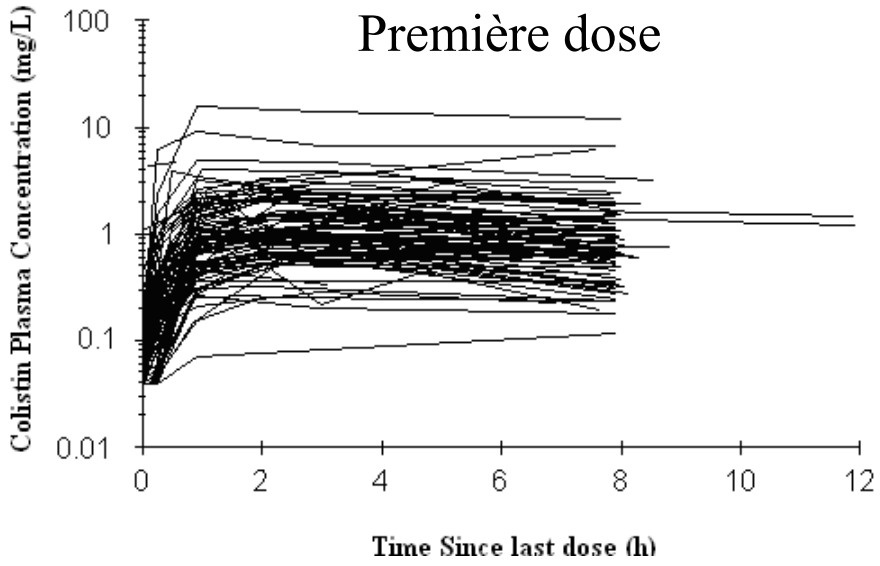
New Colistin Population Pharmacokinetic Data in Critically Ill Patients Suggesting an Alternative Loading Dose Rationale

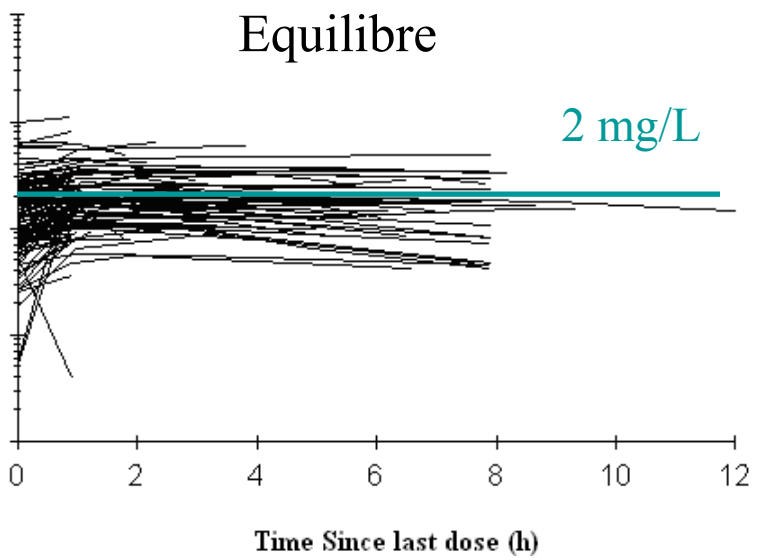
N. Grégoire,[a,b] O. Mimoz,[a,b,c] B. Mégarbane,[d] E. Comets,[e,f,g] D. Chatelier,[c] S. Lasocki,[h] R. Gauzit,[i] D. Balayn,[c] P. Gobin,[a,c] S. Marchand,[a,b,c] W. Couet[a,b,c]

INSERM U1070, Poitiers, France[a]; Université de Poitiers, Poitiers, France[b]; CHU Poitiers, Poitiers, France[c]; Hôpital Lariboisière, Paris, France[d]; INSERM CIC 0203, Université Rennes 1, Rennes, France[e]; IAME, UMR 1137, INSERM, Paris, France[f]; IAME, UMR 1137, Université Paris Diderot, Sorbonne Paris Cité, Paris, France[g]; Hôpital Bichat, Paris, France[h]; Hôpital Hôtel Dieu, Paris, France[i]

Pharmacocinétique de la colistine

- Forte variabilité inter et intra-individuelle

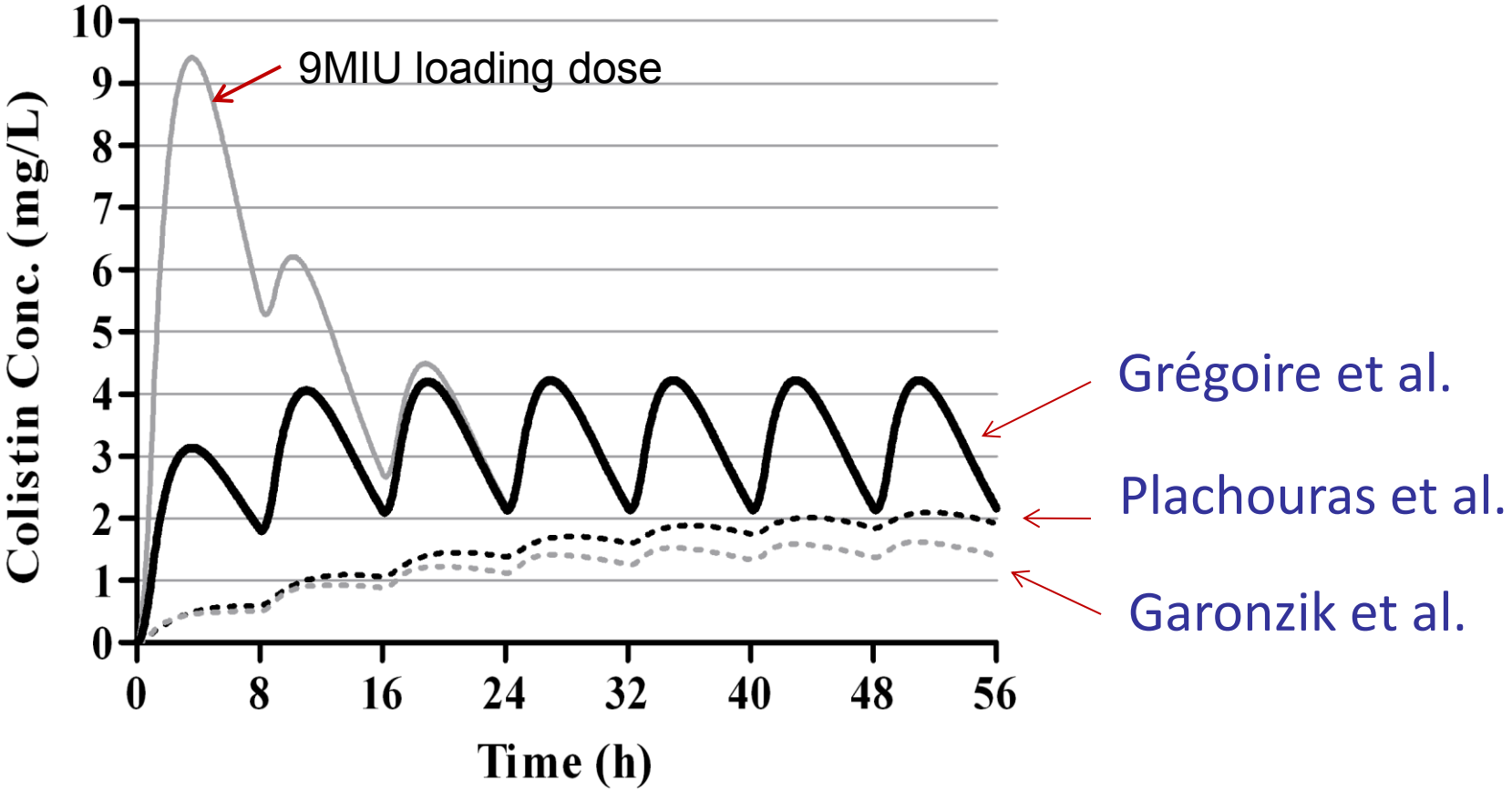




Dose médiane: 6MUI/j en 3 adm.

Predicted concentrations

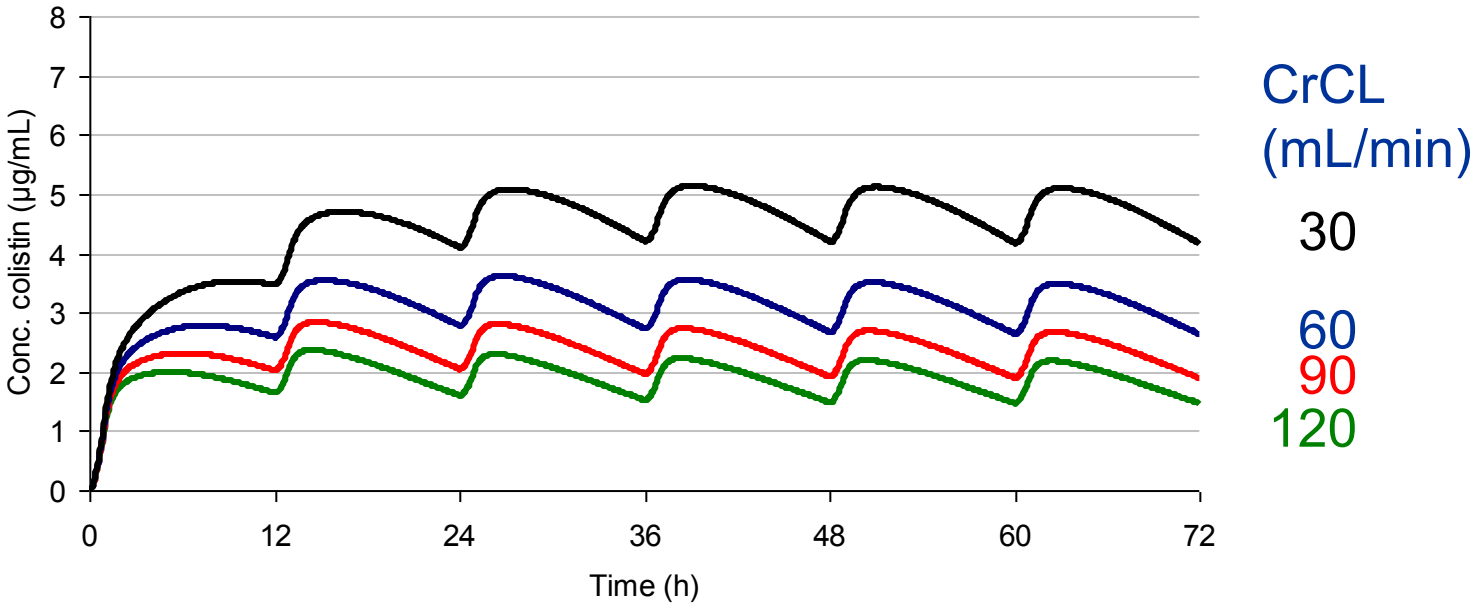
(Clcreat = 90 mL/min and CMS: 3MIU / 8h)



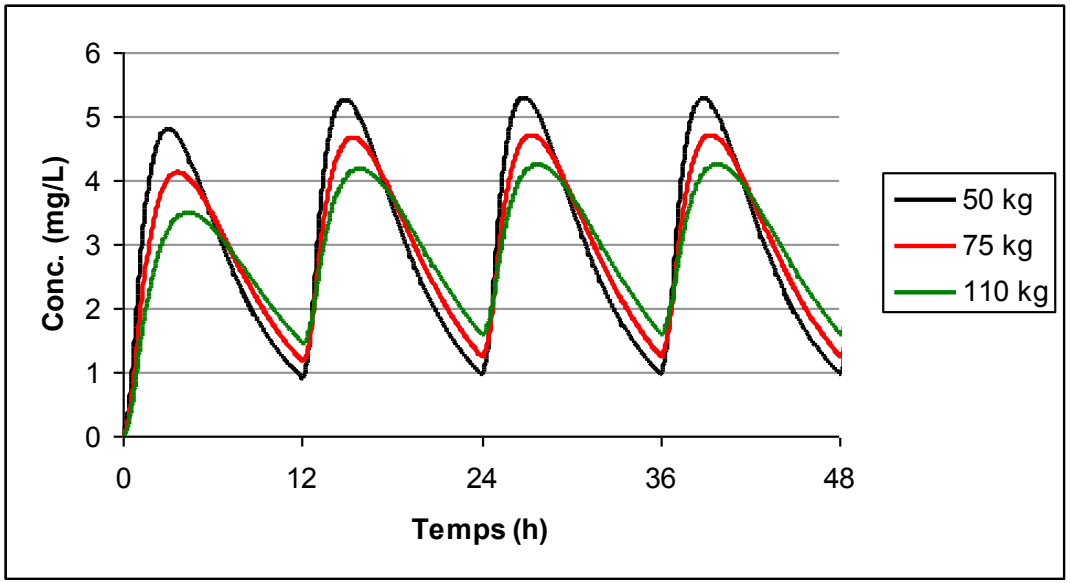
(Grégoire. et al., AAC)

Effet de la clairance de la créatinine sur les concentrations de colistine à l'équilibre

Dose de charge + 4.5 MUI / 12h



Effet du poids sur les concentrations de colistine



$$V_{CMS} = 19.2 \times (\frac{Poids}{77})$$

Effet sur la dose de charge mais pas sur la concentration à l'équilibre

L'ajustement de la dose d'entretien au poids n'a pas de justification (Vidal®)

Le patient de réanimation

- **Dose de charge**

  Dose de charge (MUI)=Css_{target} x 1/15 x Poids (Kg)

  Limite à 10 MUI

- **Dose entretien**

  Dose quotidienne (MUI)=Css_{target} x (0.05xCrCL+1)

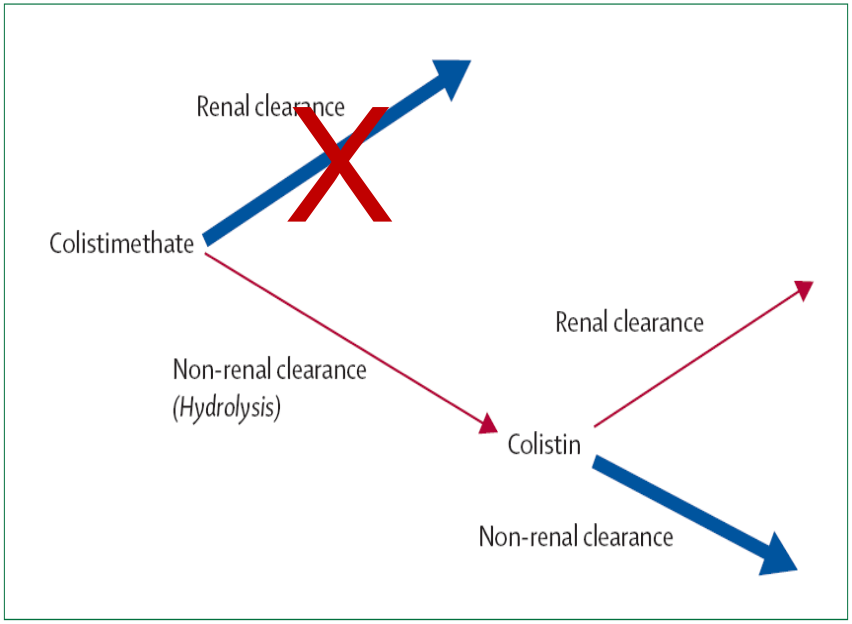
Css target	CrCL (mL/min)	Dose d'entretien quotidienne (MUI)
2 mg/L	120	10 (dose maxi)
	50	7
	10	3

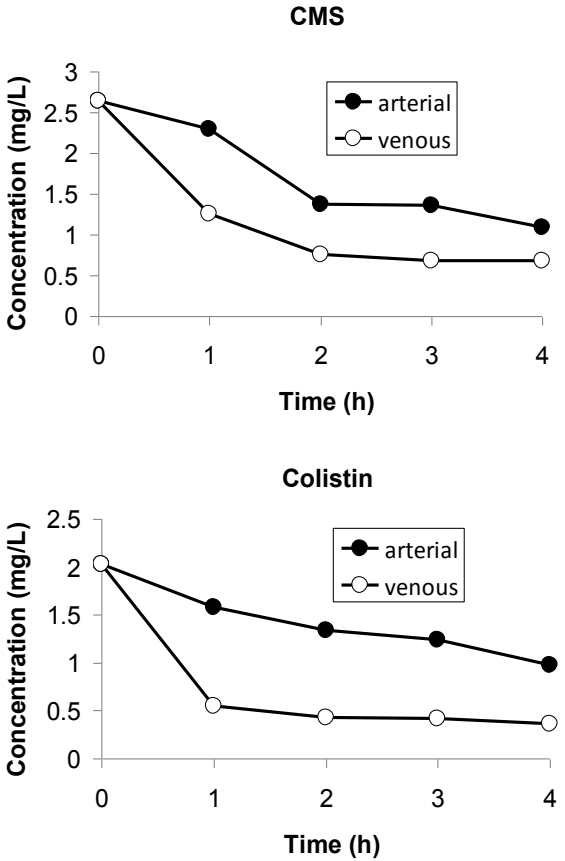
Garonzik et al. (2011)

Le patient avec une fonction rénale normale

- Difficile d ’atteindre des concentrations efficaces
- Css prédit pour un traitement de 3 MUI /8h est faible (2-3 mg/L selon les auteurs)
- Pluri-thérapie conseillée
- Suivi de la fonction rénale

Quid du patient hémodialysé ?





(Marchand S., et al., J Antimicrob Chemother. 2010)

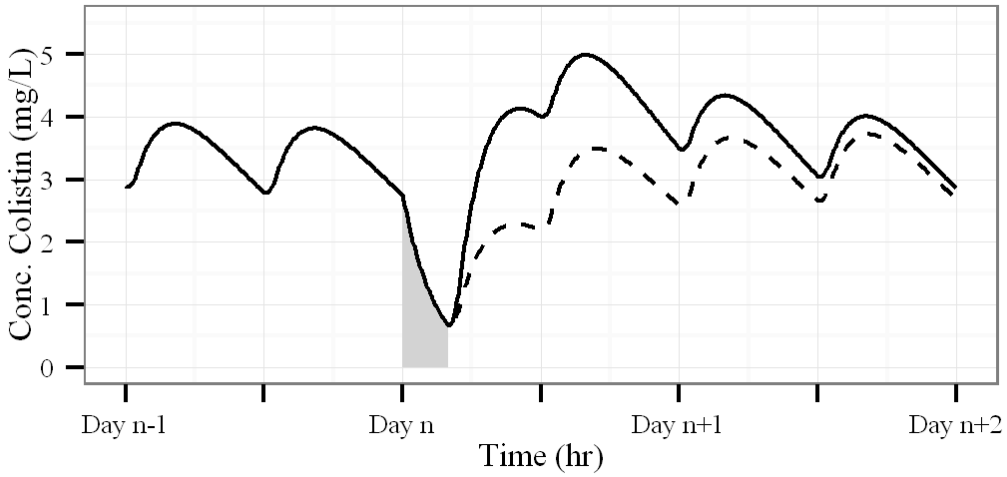
Patient hémodialysé

- Fonction rénale dégradée: fortes concentrations de colistine
- CMS et colistine sont dialysés

		Clairance CMS	Clairance Colistine
Hemodialyse	Marchand et al. (2010)	90 mL/min	133 mL/min
	Garonzik et al. (2011)	95 mL/min	57 mL/min
Hemofiltration	Li et al. (2005)	11 mL/min	12 mL/min
	Garonzik et al. (2011)	64 mL/min	34 mL/min

Patient hémodialysé

- Effet séance hémodialyse de 4h



Simulations of colistin plasma concentration-time profiles in ICU-HD patients receiving a 4-hour HD session on Day n and dosed with1.5 MIU q12h of CMS. The CMS dose planned before the HD session was postponed immediately after the session and was either 1.5 MIU (dash line) or 3 MIU (solid line)

Patient hémodialysé
Recommandations hors séances

- Dose de charge

  Dose de charge (MUI)=Css_{target} x 1/15 x Poids (Kg)

- Dose entretien

  Dose quotidienne (MUI)=Css_{target} x 1

Garonzik et al. (2011)

Patient hémodialysé
Recommandations les jours de séance

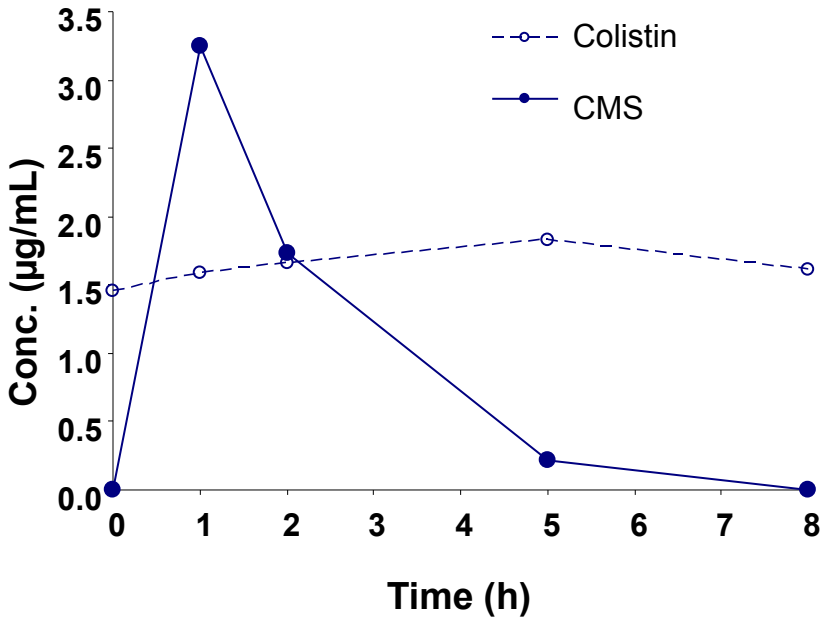
- Hémofiltration continue
  - Garonzik: 3 MUI /12h pour Css_{target}=1 mg/L

- Hémodialyse discontinue
  - administration après la séance d ’HD, dose x 2

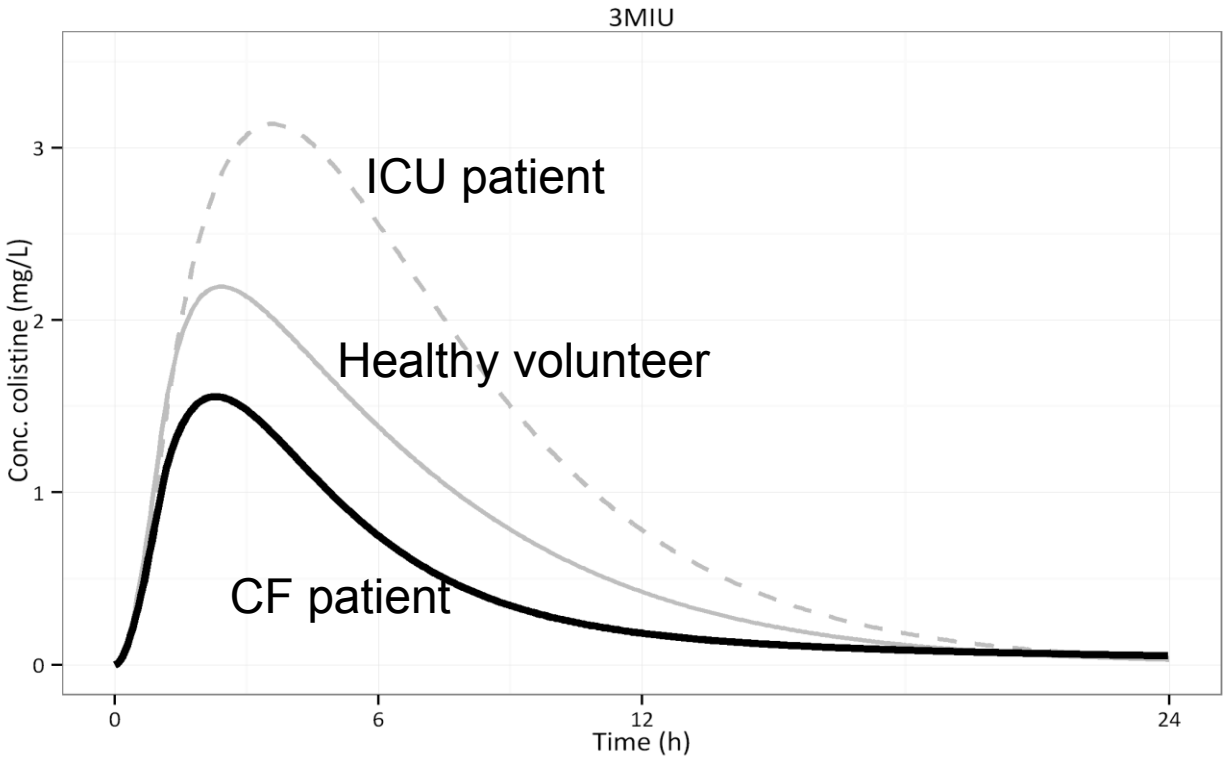
Patient obèse

- Effet du poids sur le volume de distribution
- Les données actuelles justifient l'utilisation d 'une dose de charge élevée mais dose d 'entretien « normale »

Ex: Patient 42 ans, 140 Kg, CLcréat: 70 mL/min, CMS 1.5 MIU/8h



Patient mucoviscidose



- Concentrations de colistine inférieures chez le patient mucoviscidose après administration iv
- Faire des administrations en aérosol

Patient grand brûlé

- La présence d'un œdème diminue la vitesse de transformation du CMS en colistine (↓ concentrations de colistine)
- Pour un traitement par CMS à 4 MUI /12h prédiction Css_{coli} = 2 mg/L
- Etude en cours (Percy)

Lee, 2012, Population Pharmacokinetic Analysis of Colistin in Burn Patients; World Conference on Pharmacometrics (WCoP)

Patient sous aérosol (2MIU)

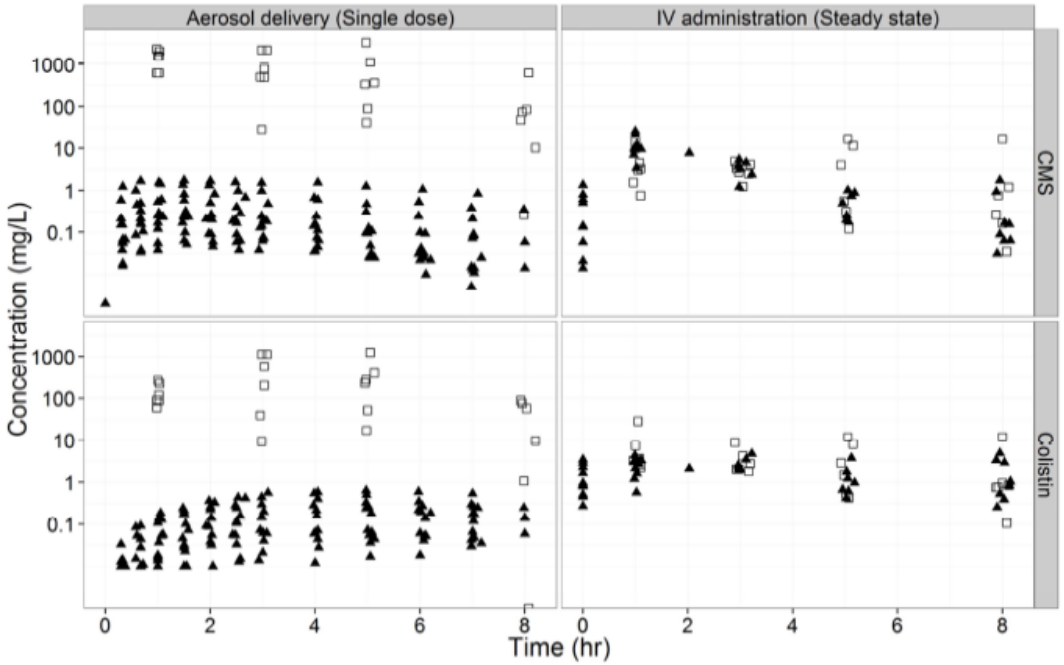


Figure 1: CMS (top panel) and colistin (bottom panel) concentrations in ELF (open squares) and plasma (filled triangles) following a single dose aerosol delivery or IV administrations at steady state.

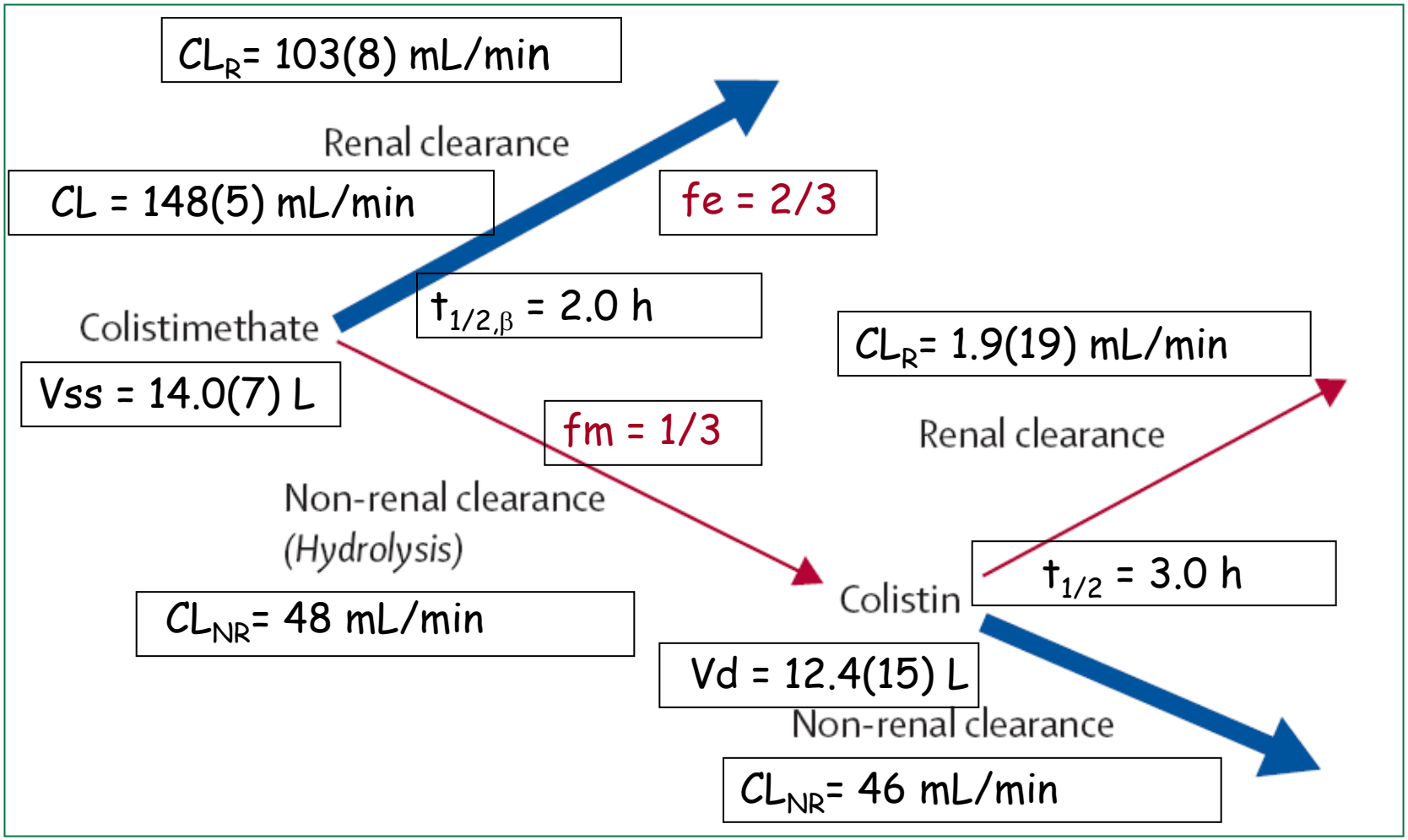
- Le passage systémique est faible (10%)
- Les concentrations sont nettement plus fortes dans les poumons que dans le plasma

Ajustement individuel de posologie

- Justification
  - Index thérapeutique étroit
  - Forte variabilité inter-individuelle

- Méthode d'ajustement
  - A priori
  - Suivi des concentrations (therapeutic drug monitoring)

On connaît les valeurs moyennes des paramètres



CL_{creat}: le principal paramètre à considérer pour ajuster les posologies

TABLE 3. Suggested loading dose and daily maintenance doses of CMS[a]

Dose	Category of critically ill patient	Dosing suggestions
Loading dose	All patient categories	Equation 9: Loading dose of CBA (mg) = colistin $C_{ss,avg}$ target[b] × 2.0 × body wt (kg).[c] See caveat in footnote *c*. First maintenance dose should be given 24 h later.
Maintenance dose	Not on renal replacement	Equation 10: Daily dose of CBA (mg) = colistin $C_{ss,avg}$ target[b] × (1.50 × CrCL + 30).[d] Recommended dosage intervals based on CrCL: <10 ml/min/1.73 m^2, every 12 h, 10-70 ml/min/1.73 m^2 every 12 (or 8) h, and >70 ml/min/1.73 m^2 every 12 (or 8) h. See important caveat in footnote *d*.
	Receiving intermittent hemodialysis	Daily dose of CBA on a non-HD day to achieve each 1.0-mg/liter colistin $C_{ss,avg}$ target[b] = 30 mg[e]. Supplemental dose of CBA on a HD day[f]: add 50% to the daily maintenance dose if the supplemental dose is administered during the last hour of the HD session, or add 30% to the daily maintenance dose if the supplemental dose is administered after the HD session. Twice-daily dosing is suggested.
	Receiving continuous renal replacement	Daily dose of CBA to achieve each 1.0-mg/liter colistin $C_{ss,avg}$ target = 192 mg.[g] Doses may be given every 8-12 h.

[a] Expressed as mg of colistin base activity (CBA) for various categories of critically ill patients. The suggested maintenance daily dose would commence 24 h after administration of a CMS loading dose. Example: To target a colistin $C_{ss,avg}$ of 2.5 mg/liter, a 55-kg patient with a CrCL of 40 ml/min/1.73 m^2 would receive a loading dose of 275 mg CBA followed in 24 h by commencement of a maintenance regimen of 225 mg CBA/day in 2 to 3 equally divided doses.

[b] Colistin $C_{ss,avg}$ target is expressed in mg/liter. This target should be based on MIC, site, and severity of infection.

[c] Use the lower of ideal or actual body weight, expressed in kg. At this time, we suggest caution in the use of a loading dose greater than 300 mg CBA (see the text for more details).

[d] Based upon the population PK analysis for 101 critically ill patients not on continuous renal replacement therapy. Colistin $C_{ss,avg}$ target expressed in mg/L. Creatinine clearance (CrCL) expressed in ml/min/1.73 m^2. Although the Jelliffe equation was used to estimate CrCL in this study, other means (e.g., Cockcroft and Gault equation) may be used to estimate CrCL which would then be normalized to a body surface area of 1.73 m^2. See text for caveat regarding use of the algorithm in patients with CrCL values > 70 ml/min/1.73 m^2 or when targeting a "high" colistin $C_{ss,avg}$, both being circumstances where the algorithm may predict daily doses of CBA substantially greater than the current upper limit in the product label.

[e] Based upon use of equation 10 and setting CrCL to zero.

[f] Supplemental dose of CMS to achieve a similar colistin $C_{ss,avg}$ on a HD day as occurs on a non-HD day. It is assumed that the hemodialysis session occurs toward the end of a CMS dosage interval.

[g] Based on the population PK analysis for 4 critically ill patients receiving continuous renal replacement therapy.

Mais en fait 3 paramètres déterminent Css

Faut-il monitorer les concentrations ?

CASE REPORT

Journal of Infection (2011)

Convulsions and apnoea in a patient infected with New Delhi metallo-β-lactamase-1 *Escherichia coli* treated with colistin

Herbert D. Spapen [a,*], Patrick M. Honore [a], Nicolas Gregoire [b], Patrice Gobin [b], Jouke de Regt [a], Geert A. Martens [c], Denis Pierard [d], William Couet [b]

24 mL/min

3 MIU / 8h

$$C_{SS} = \frac{CL_{NR}}{CL_R + CL_{NR}} \cdot \frac{Dose}{\tau \cdot CL_{coli}}$$

42 mL/min

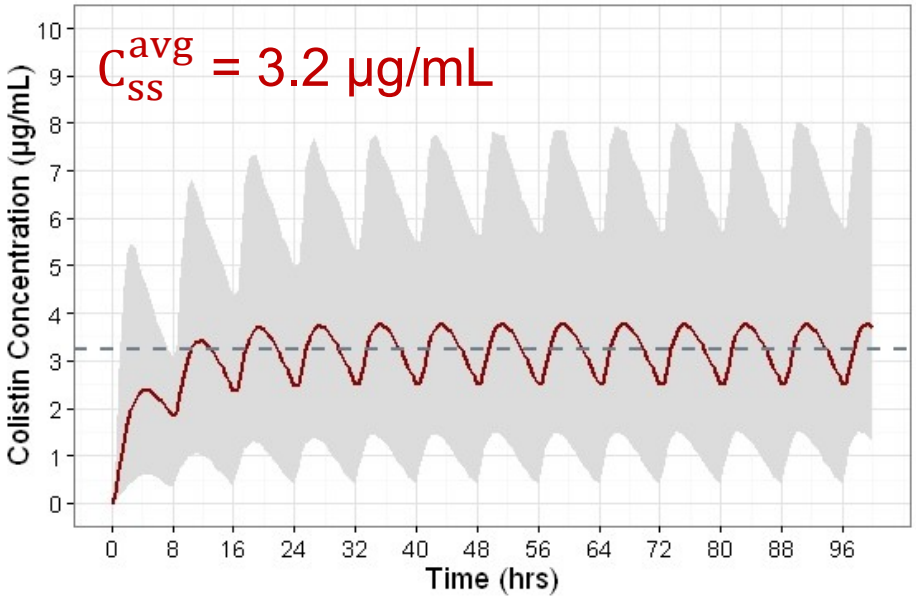
Prédiction *a priori*: 35 mL/min

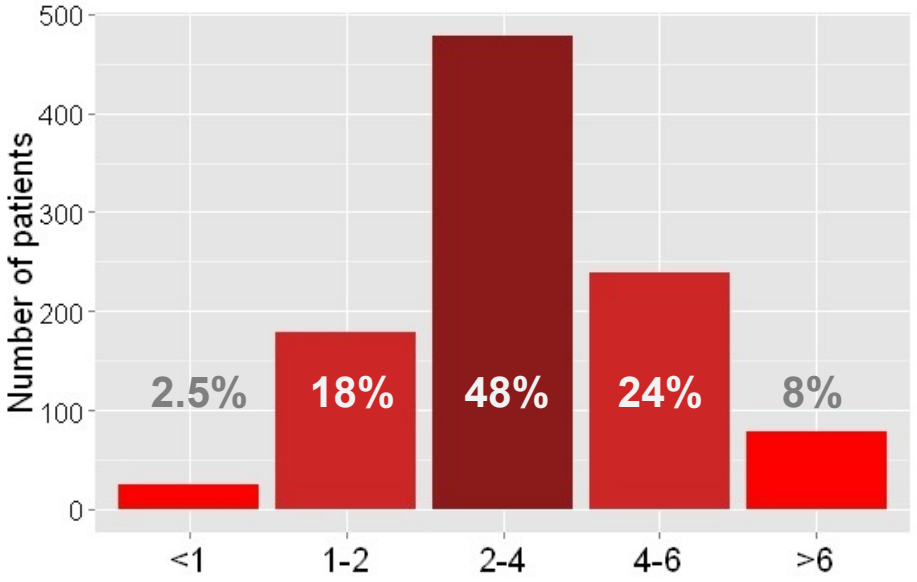
Prédit *a priori*: 3.4 µg/mL

Mesurée: 8.1 µg/mL

CL_{coli} Corrigée: 15 mL/min

Simulated colistin plasma concentrations versus time in typical COLI POP PATIENTS with CLcreat = 40 mL/min receiving 2 MIU / 8h





Monitorage des concentrations (TDM)

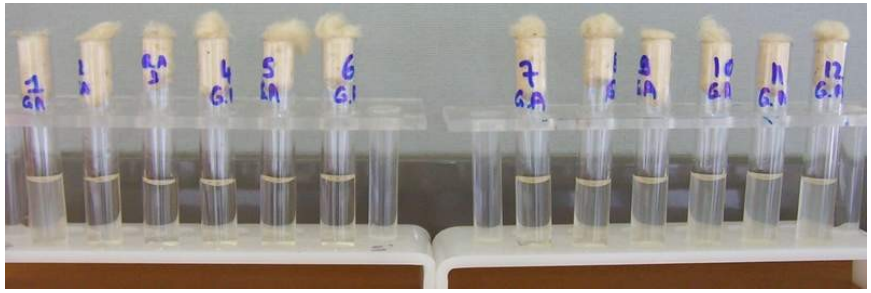
- La part de la variabilité inter-individuelle expliquée par CrCL et WT est faible

- Variabilité intra-individuelle forte

→ Suivi des concentrations au cours du temps

Choix de la méthode de dosage

à éviter



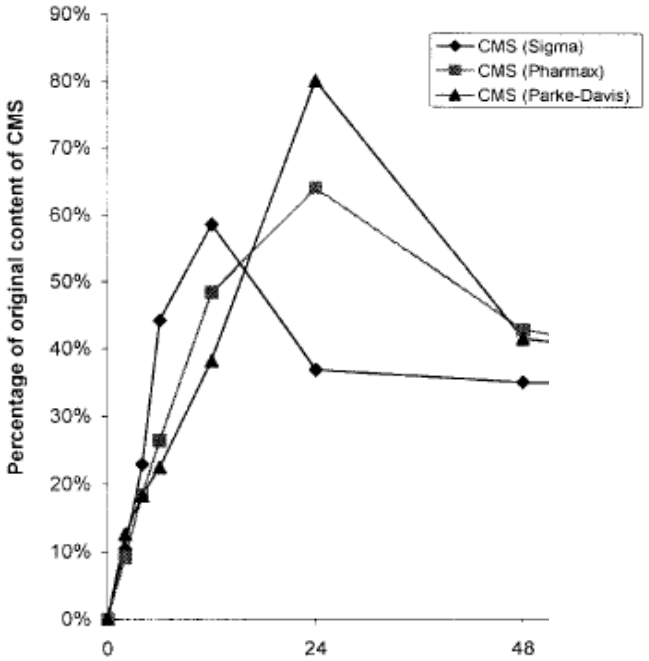
Méthodes microbiologiques

Méthodes chromatographiques séparant CMS et colistine

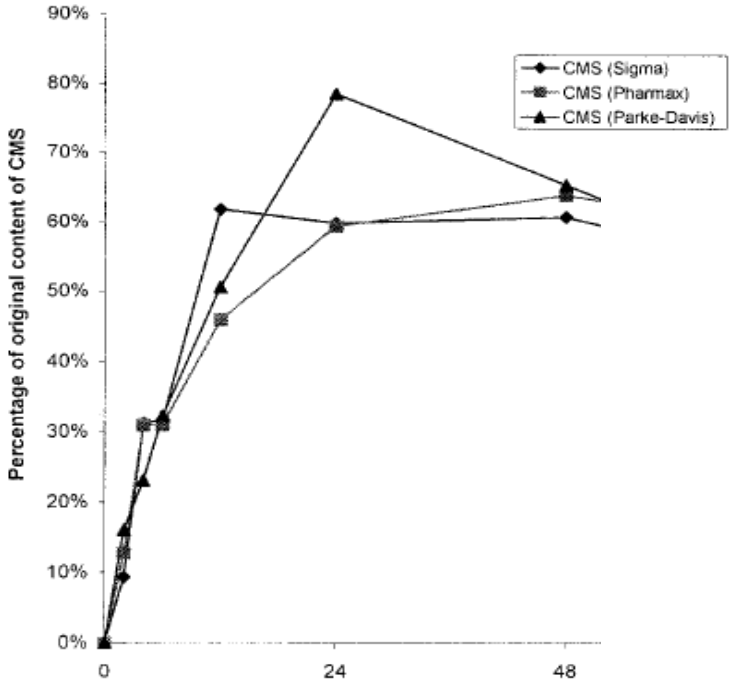
… à recommander

Le « problème de stabilité » du CMS

% de CMS converti en colistine à 37°C



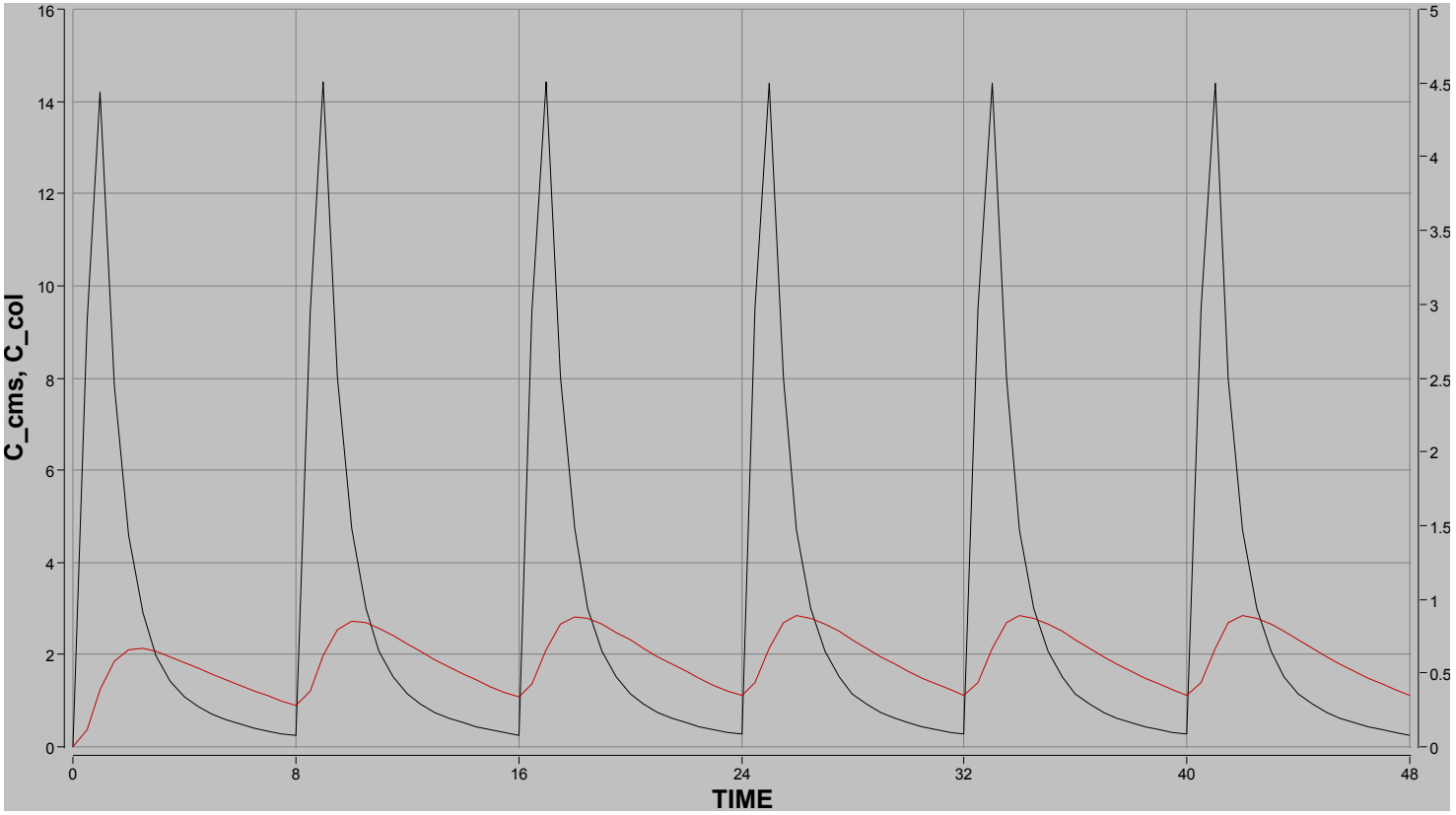
Tampon Phosphate



Plasma

(Antimicrob Agents Chemother. 2003 Apr;47(4):1364-70)

Quand faut-il prélever ?



Avant un début de perfusion: à la <u>résiduelle du CMS</u>

Analyse du résultat

- **Après la première dose (bayesien)**

L'analyse bayesienne permet de prédire le profile PK le plus probable pour le patient étant donnés les concentrations mesurées et la PK connue pour la population dont est issu ce patient (ex: réanimation, mucoviscidose,…)

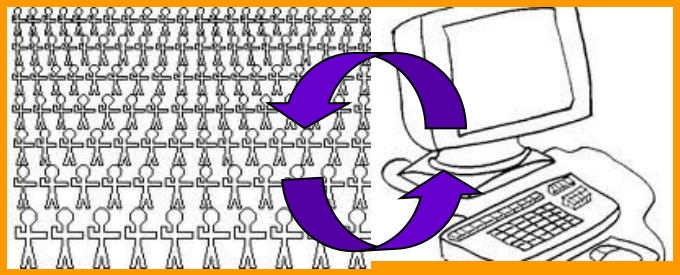
- **A l'équilibre (PK linéaire, faibles fluctuations)**

- **Du fait de la variabilité intra-individuelle il est conseillé de poursuivre le monitoring**

- **Adaptation de la posologie en fonction de la concentration cible et de la toxicité (range 2-4 mg/L voire plus)**

Suivi thérapeutique de la colistine

Database
For PK Pop



Dosage

CHU de Poitiers

CHU CLERMONT FERRAND CENTRE HOSPITALIER UNIVERSITAIRE

CHU DE REIMS

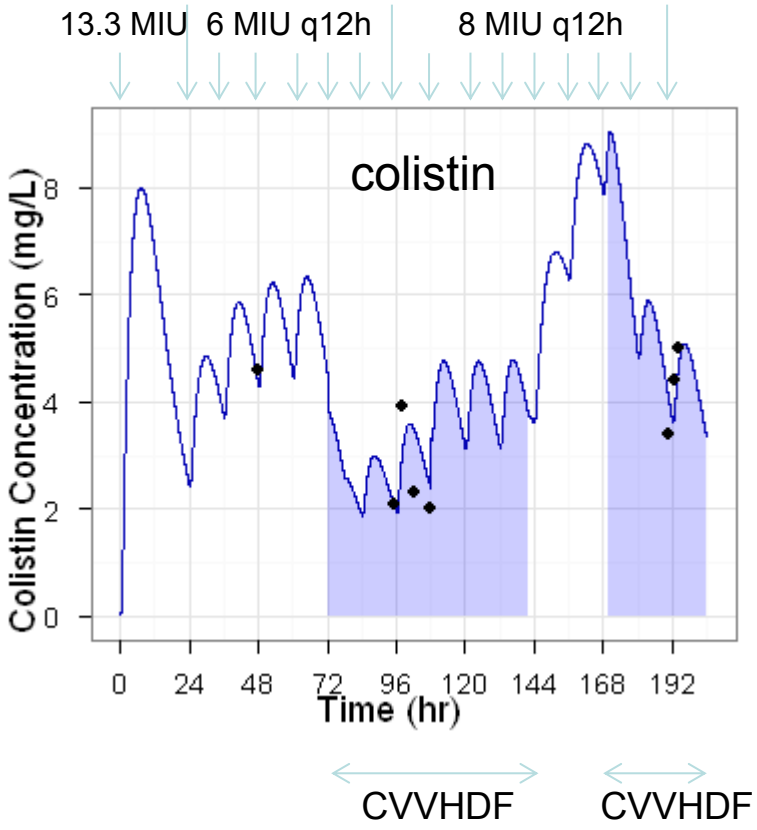
CHRU HÔPITAUX DE TOURS

CENTRE HOSPITALIER UNIVERSITAIRE DE NANTES

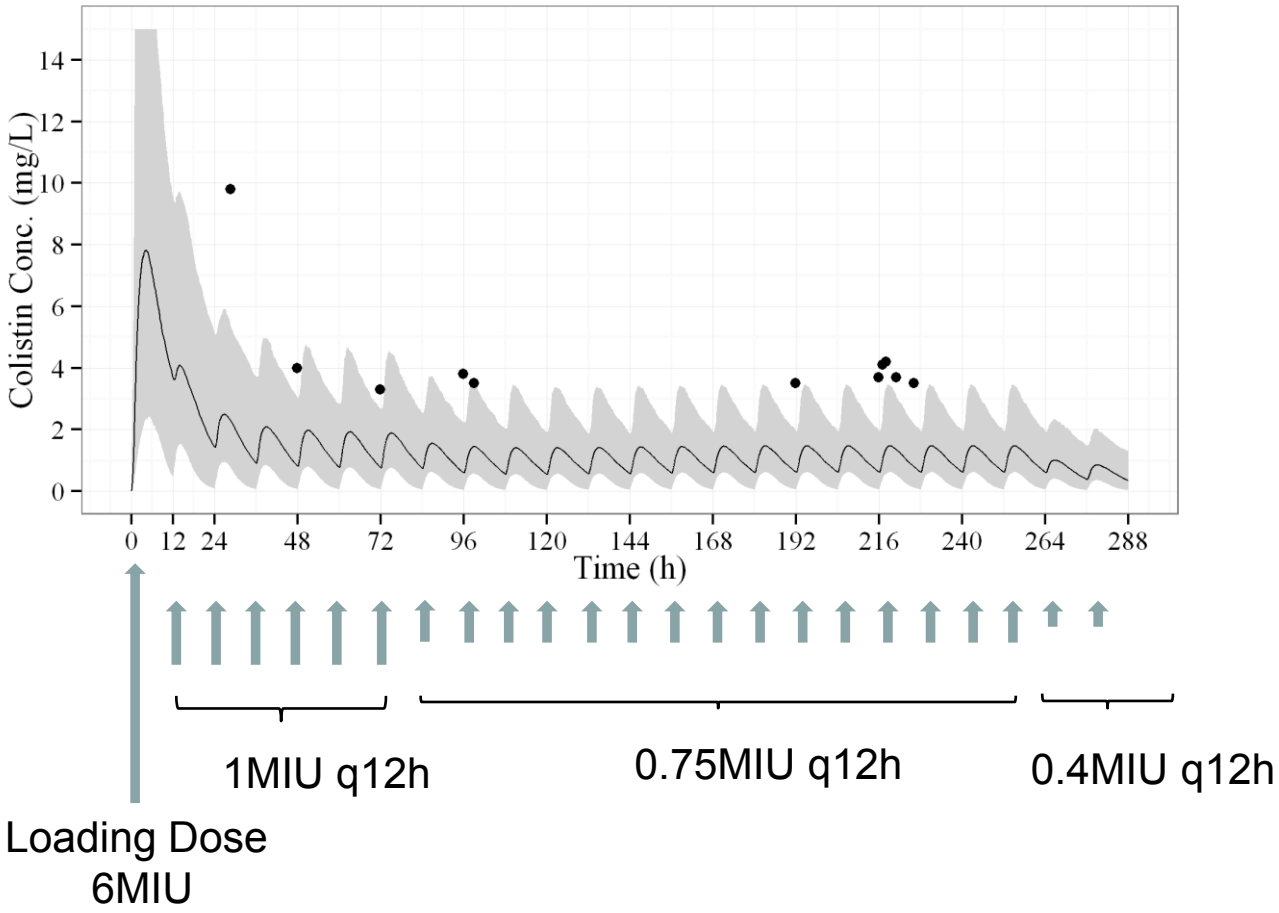
Les Hôpitaux Universitaires de STRASBOURG

Ajustement bayesien

Patient 64 ans, hémodialysé



Patient (61y – 67Kg) with estimated CLcreat between 10 and 15 mL/min



Analyse à posteriori. Ce patient n'était pas homogène avec la population de patients de réanimation utilisée pour la construction de l'intervalle de confiance (facteur à rechercher)

Conclusion

- La concentration de colistine à l'équilibre dépend de la fonction rénale
- Il est difficile d'atteindre des concentrations efficaces pour les patients avec une fonction rénale normale
- Intérêt de monitorer les concentrations de colistine au cours du temps par des méthodes chromatographiques

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