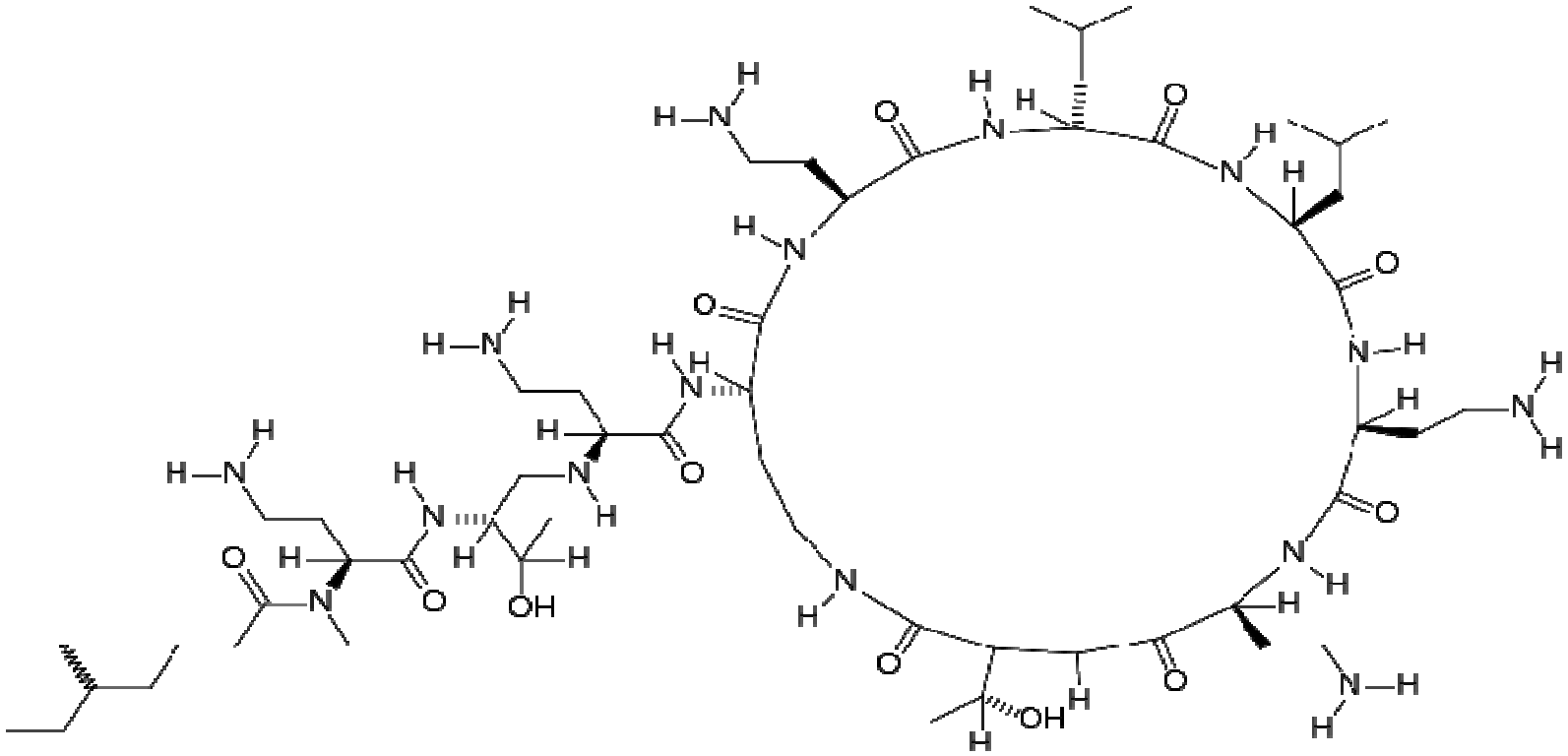
Colimycine: actualités

William Couet, PharmD, PhD

Gericco, 29 mars 2013

La colistine: polypeptide cyclique



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***

Breakpoints EUCAST : S ≤ 2 mg/l R > 2 mg/l

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

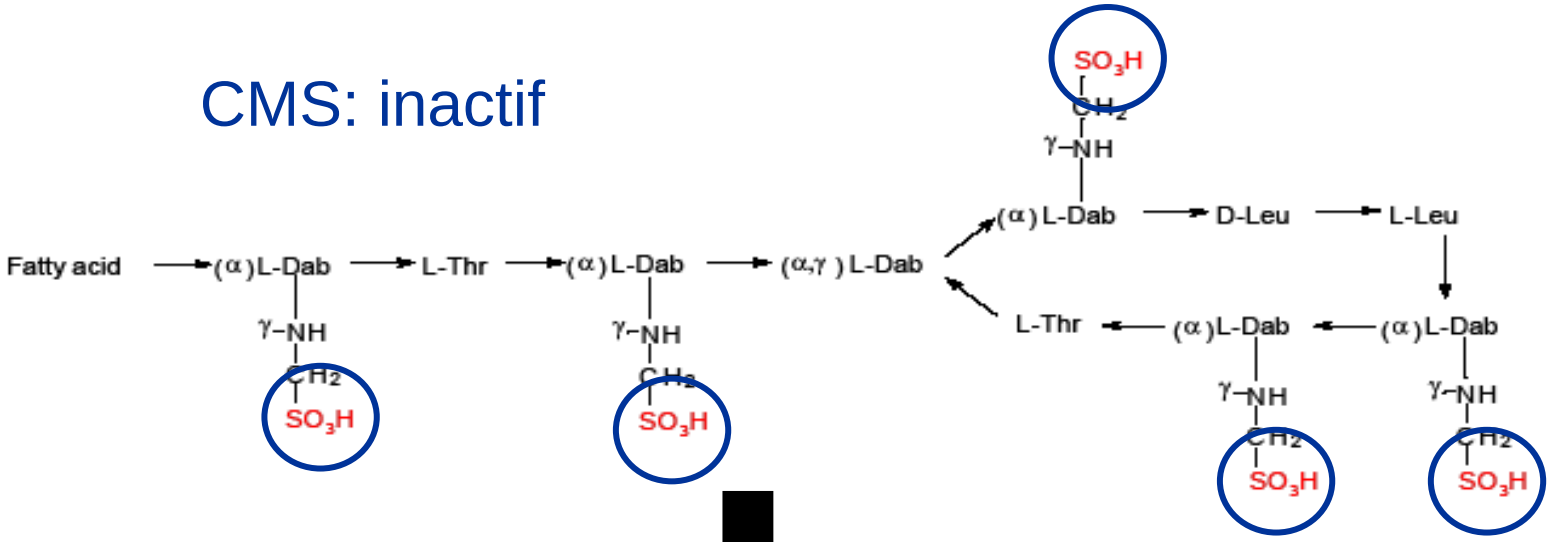
Increasing multidrug resistance in Gram-negative bacteria, in particular *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and *Klebsiella pneumoniae*, presents a critical problem. Limited therapeutic options have forced infectious disease clinicians and microbiologists to reappraise the clinical 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

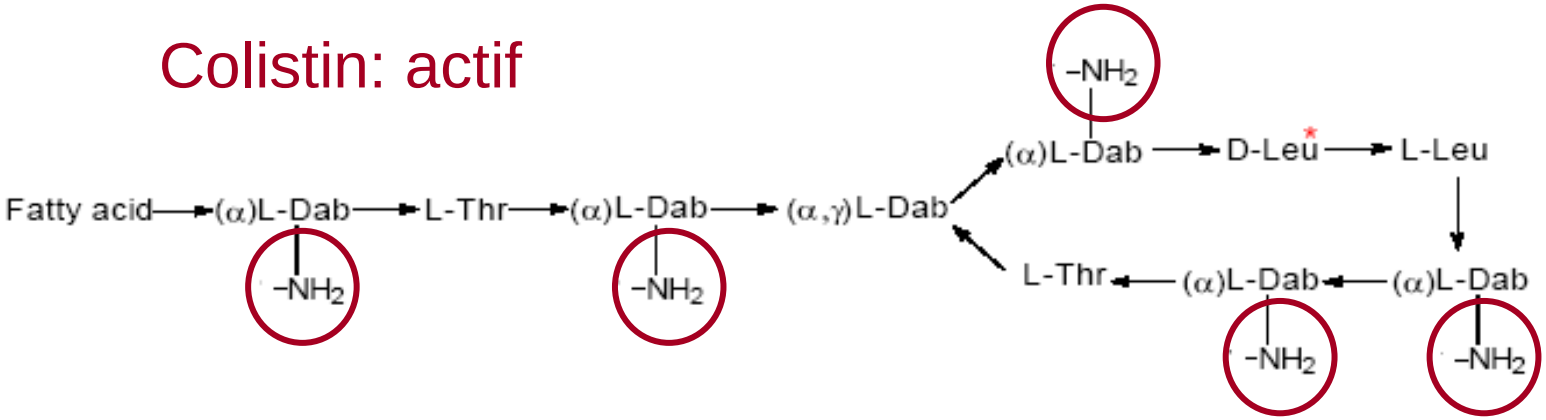
Facility for Anti-Infective Drug Development and Innovation, Victorian College of Pharmacy, Monash University, Parkville, Victoria, Australia (J Li PhD, Prof R L Nation PhD, C R Rayner PharmD); Division of Laboratory Medicine (Prof J D Turnidge FRACP) and

Administration sous forme de prodrug

CMS: inactif

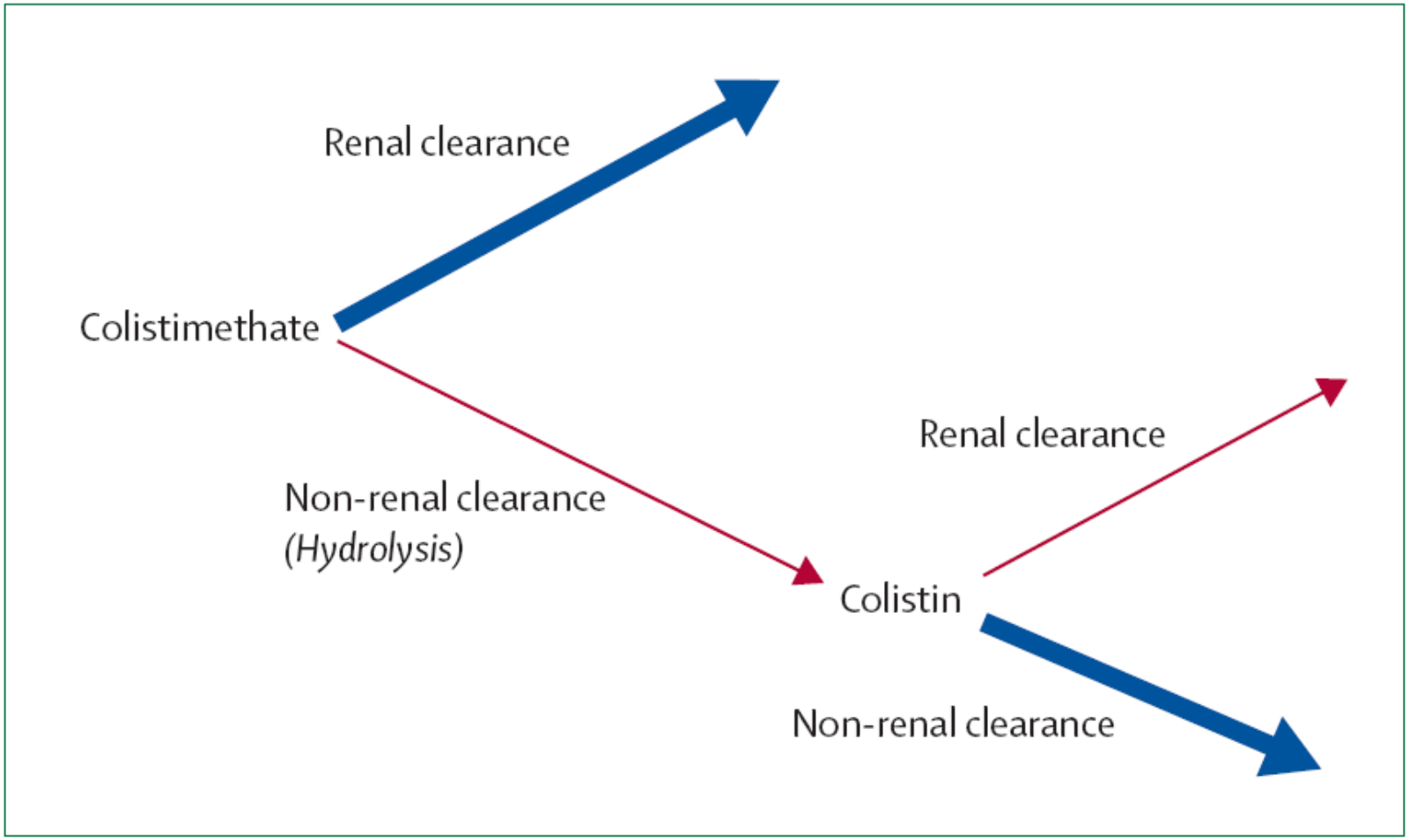


Colistin: actif



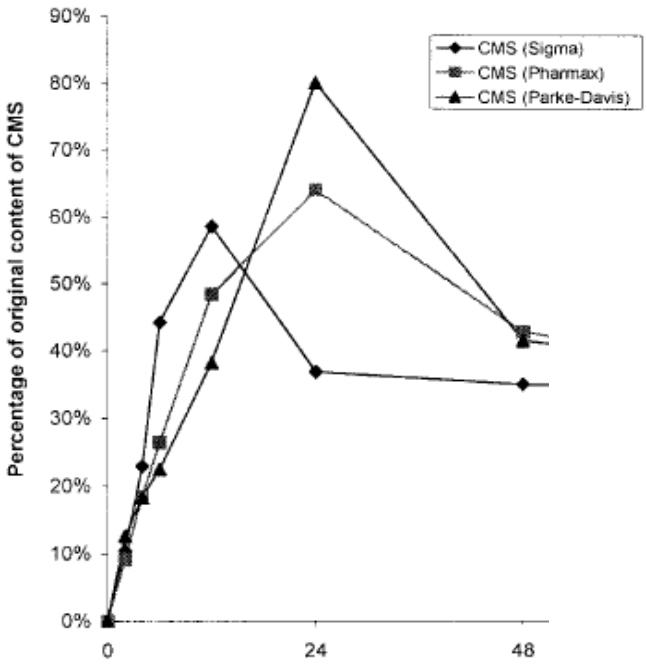
Pharmacocinétique du CMS et de la colistine

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

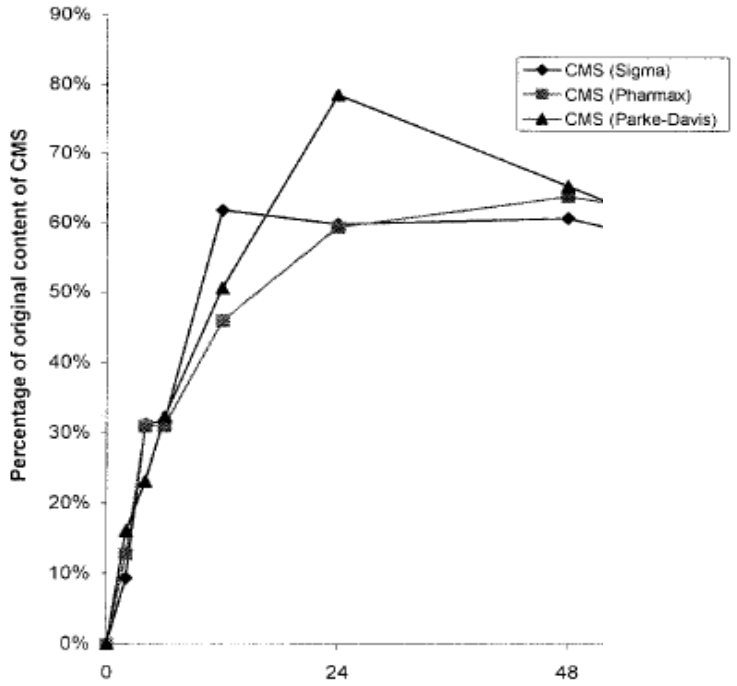


Le « problème de stabilité » du CMS

% de CMS converti en colistine à 37°C



Tampon Phosphate

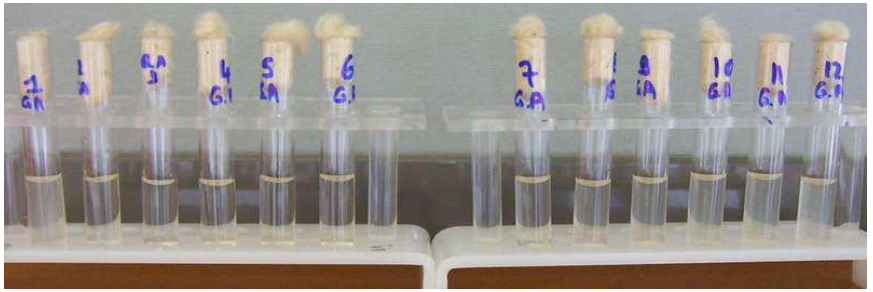


Plasma

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

Choix de la méthode de dosage

Initialement : dosage microbiologique



- Manque de précision

- Manque de spécificité: (hydrolyse du CMS en colistine pendant lapériode d’incubation)

A éviter…

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, May 2010, p. 1941–1948 Vol. 54, No. 5
0066-4804/10/$12.00 doi:10.1128/AAC.01367-09

Assay of Colistin and Colistin Methanesulfonate in Plasma and Urine by Liquid Chromatography-Tandem Mass Spectrometry▽

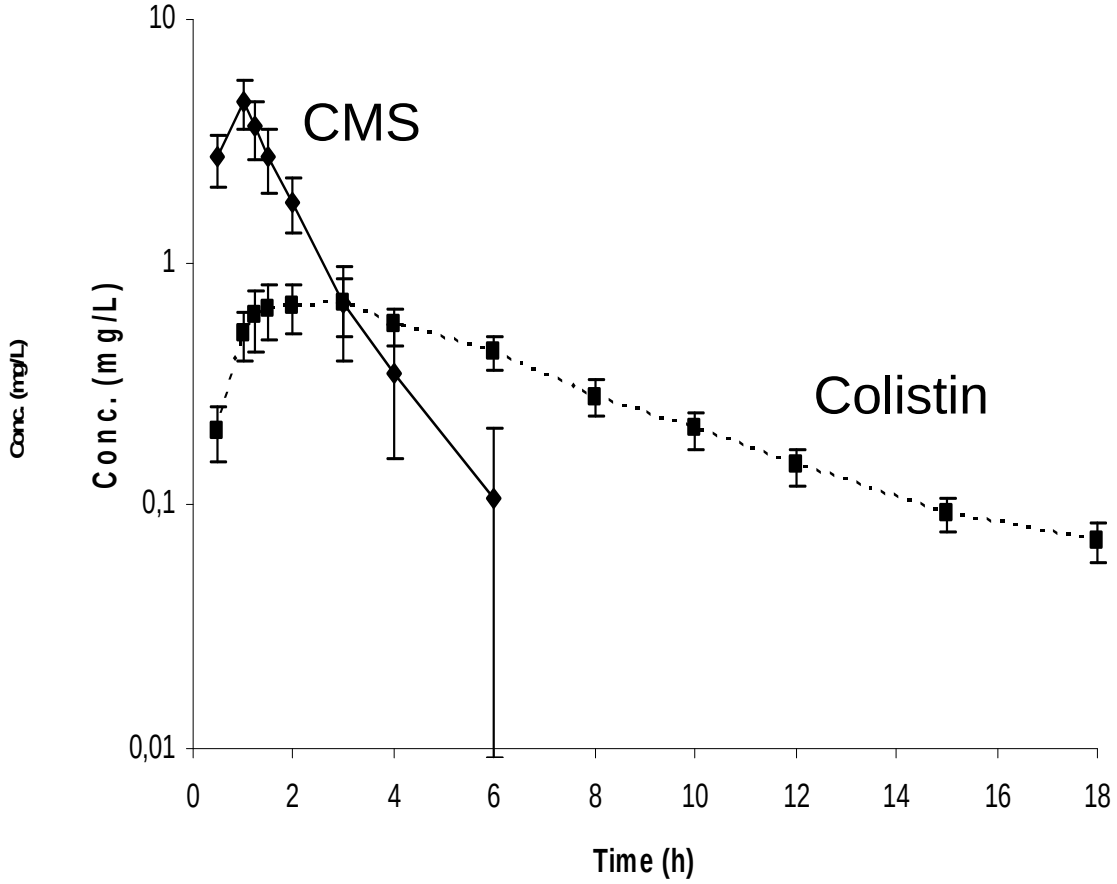
Patrice Gobin,[1,3] Florian Lemaître,[1,3] Sandrine Marchand,[1,2,3] William Couet,[1,2,3]* and Jean-Christophe Olivier[1,2]

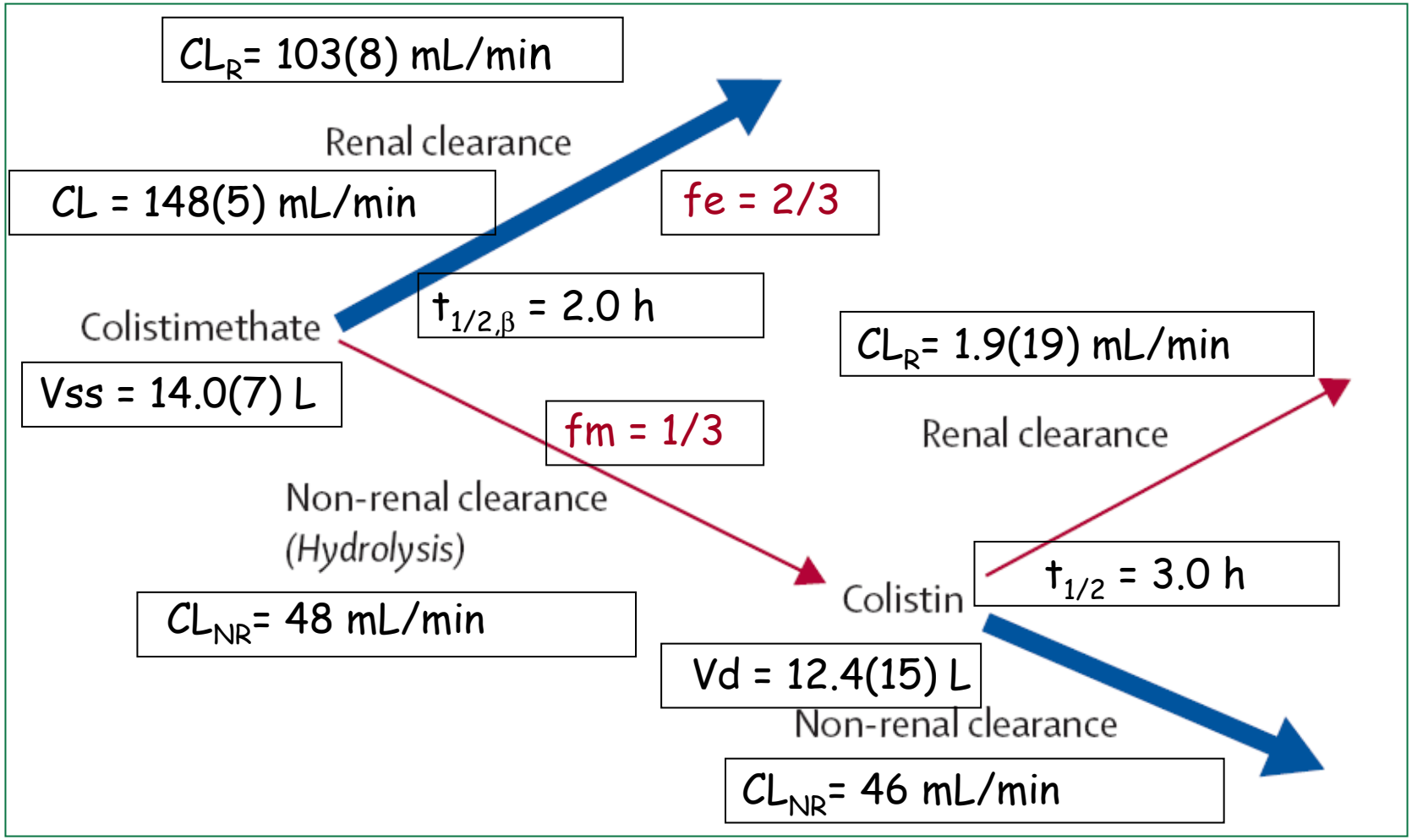
INSERM, ERI 23, 40 Avenue du Recteur Pineau, Poitiers 86000, France[1]; Université de Poitiers, Faculté de Médecine et de Pharmacie, 6 Rue de la Milétrie, Poitiers 86000, France[2]; and CHU Poitiers, 2 Rue de la Milétrie, Poitiers 86000, France[3]

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

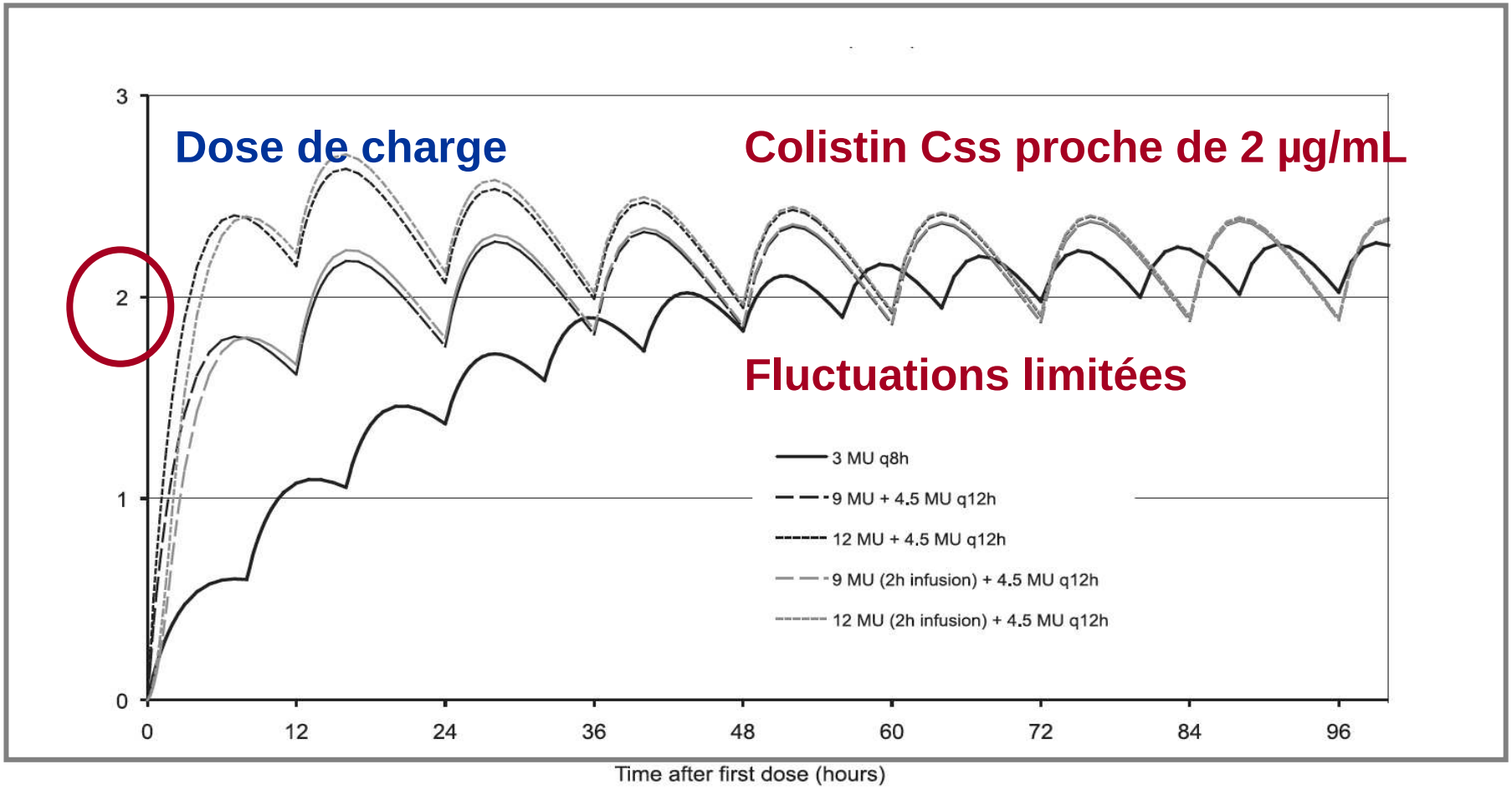



CL_R= 103(8) mL/min
Renal clearance
CL = 148(5) mL/min
fe = 2/3
$t_{1/2,\beta}$ = 2.0 h
Colistimethate
Vss = 14.0(7) L
fm = 1/3
Non-renal clearance
(Hydrolysis)
CL_{NR}= 48 mL/min
CL_R= 1.9(19) mL/min
Renal clearance
$t_{1/2}$ = 3.0 h
Colistin
Vd = 12.4(15) L
Non-renal clearance
CL_{NR}= 46 mL/min

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Aug. 2009, p. 3430–3436 Vol. 53, No. 8
0066-4804/09/$08.00+0 doi:10.1128/AAC.01361-08

Population Pharmacokinetic Analysis of Colistin Methanesulfonate and Colistin after Intravenous Administration in Critically Ill Patients with Infections Caused by Gram-Negative Bacteria▽†

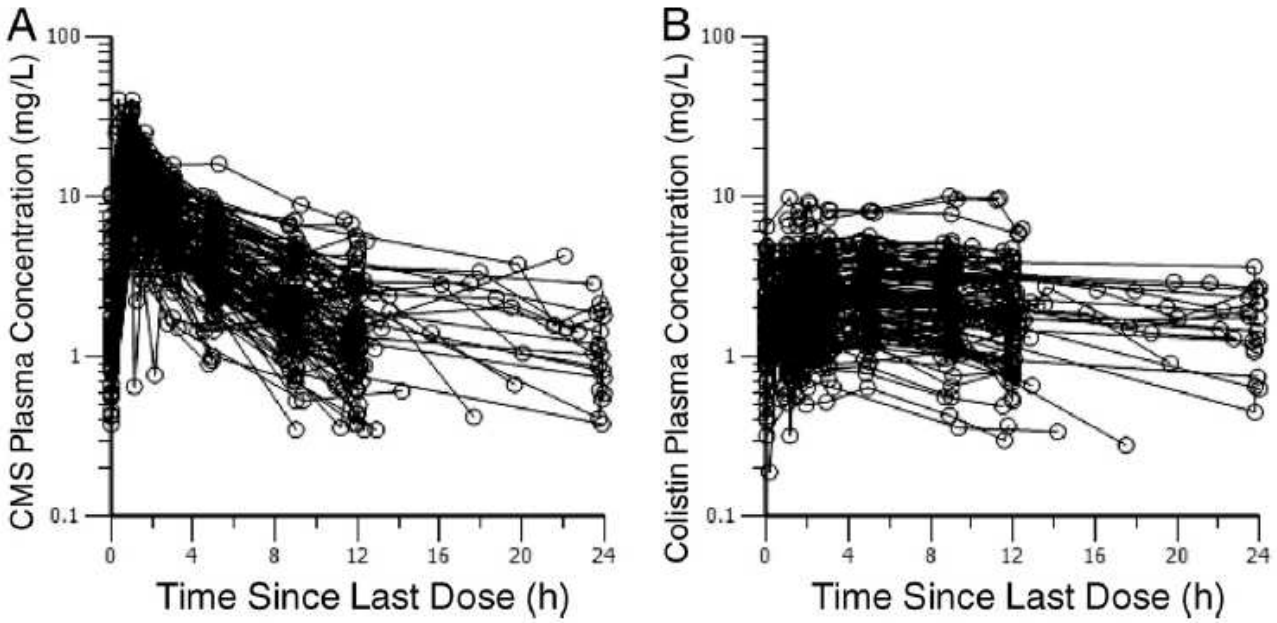
D. Plachouras,[1]* M. Karvanen,[2] L. E. Friberg,[3] E. Papadomichelakis,[4] A. Antoniadou,[1] I. Tsangaris,[4] I. Karaiskos,[1] G. Poulakou,[1] F. Kontopidou,[1] A. Armaganidis,[4] O. Cars,[2] and H. Giamarellou[1]



ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, July 2011, p. 3284–3294 Vol. 55, No. 7
0066-4804/11/$12.00 doi:10.1128/AAC.01733-10

Population Pharmacokinetics of Colistin Methanesulfonate and Formed Colistin in Critically Ill Patients from a Multicenter Study Provide Dosing Suggestions for Various Categories of Patients[▽]

S. M. Garonzik,[1]† J. Li,[2]† V. Thamlikitkul,[3] D. L. Paterson,[4] S. Shoham,[5] J. Jacob,[2] F. P. Silveira,[6]‡ A. Forrest,[1]‡ and R. L. Nation[2]*‡



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

Colistin conc. à l'état stable

Vitesse de formation = Vitesse d'élimination

$$\frac{fm \,.\, Dose}{\tau} = CL_{coli} \cdot C_{SS}$$

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

DFG

Impact limité

Imprévisible

Faut-il doser la colistine ?

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

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

Expected: 3.4 µg/mL

42 mL/min

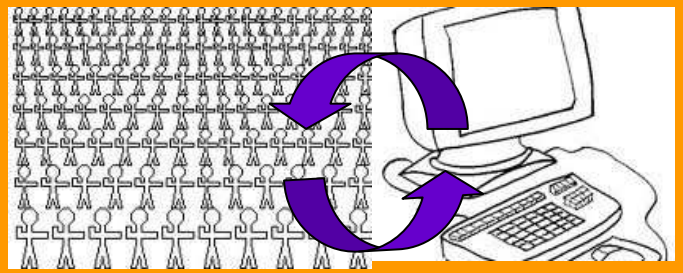
Initial guess: 35 mL/min

Observed: 8.1 µg/mL

Revised: 15 mL/mn

Suivi thérapeutique de la colistine

Database
For PK Pop



Dosage

CHU de Poitiers

Ajustement bayesien

CHU CLERMONT FERRAND CENTRE HOSPITALIER UNIVERSITAIRE

CHU DE REIMS

CHRU HÔPITAUX DE TOURS

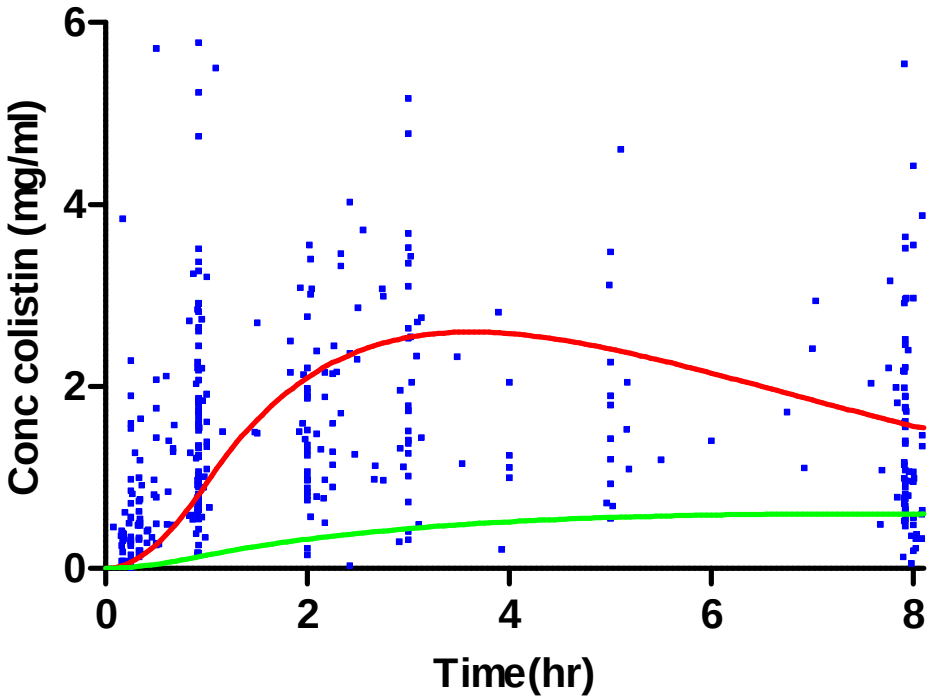
CENTRE HOSPITALIER UNIVERSITAIRE DE NANTES

Les Hôpitaux Universitaires de STRASBOURG

Nouvelle étude chez le patient de réanimation non HD

(PHRC National)

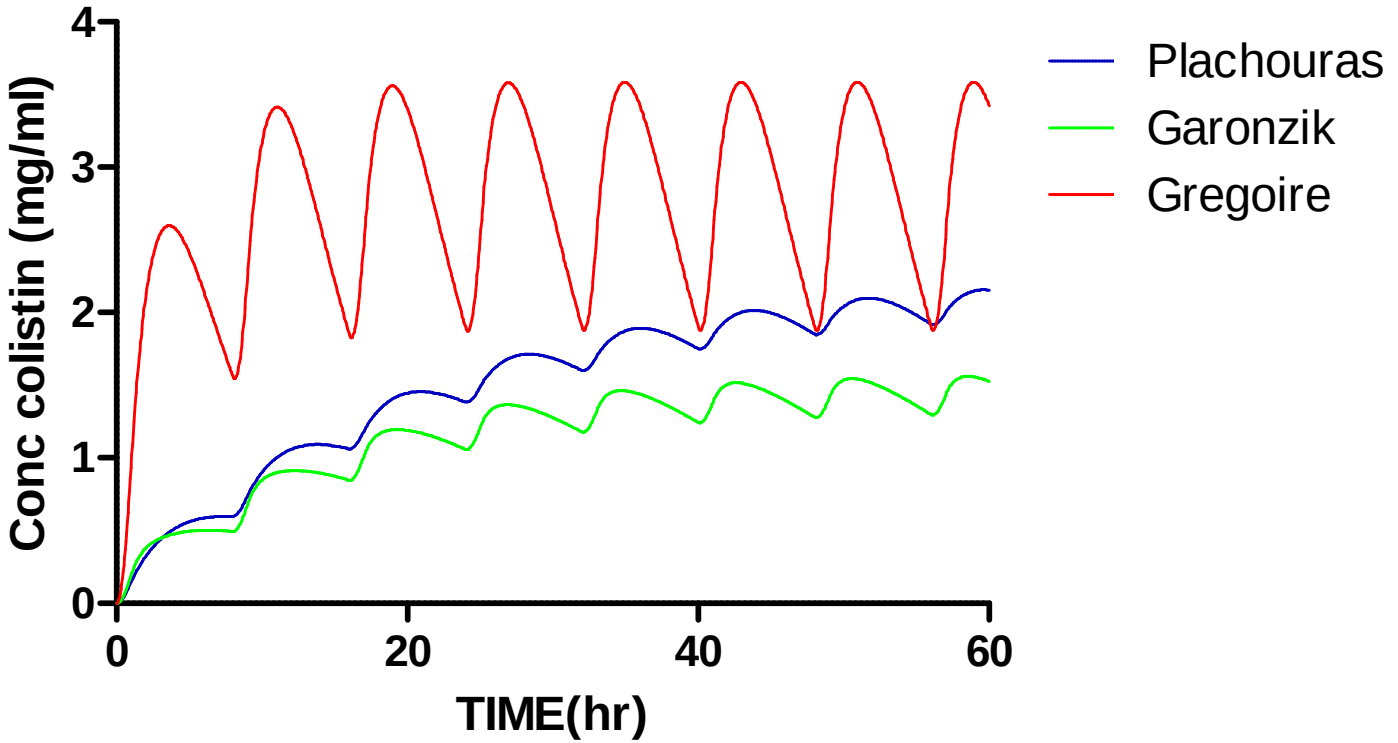
Concentrations de colistine après la 1ère injection de CMS
chez 70 patients de réanimation
après normalisation de la dose à 3 MUI



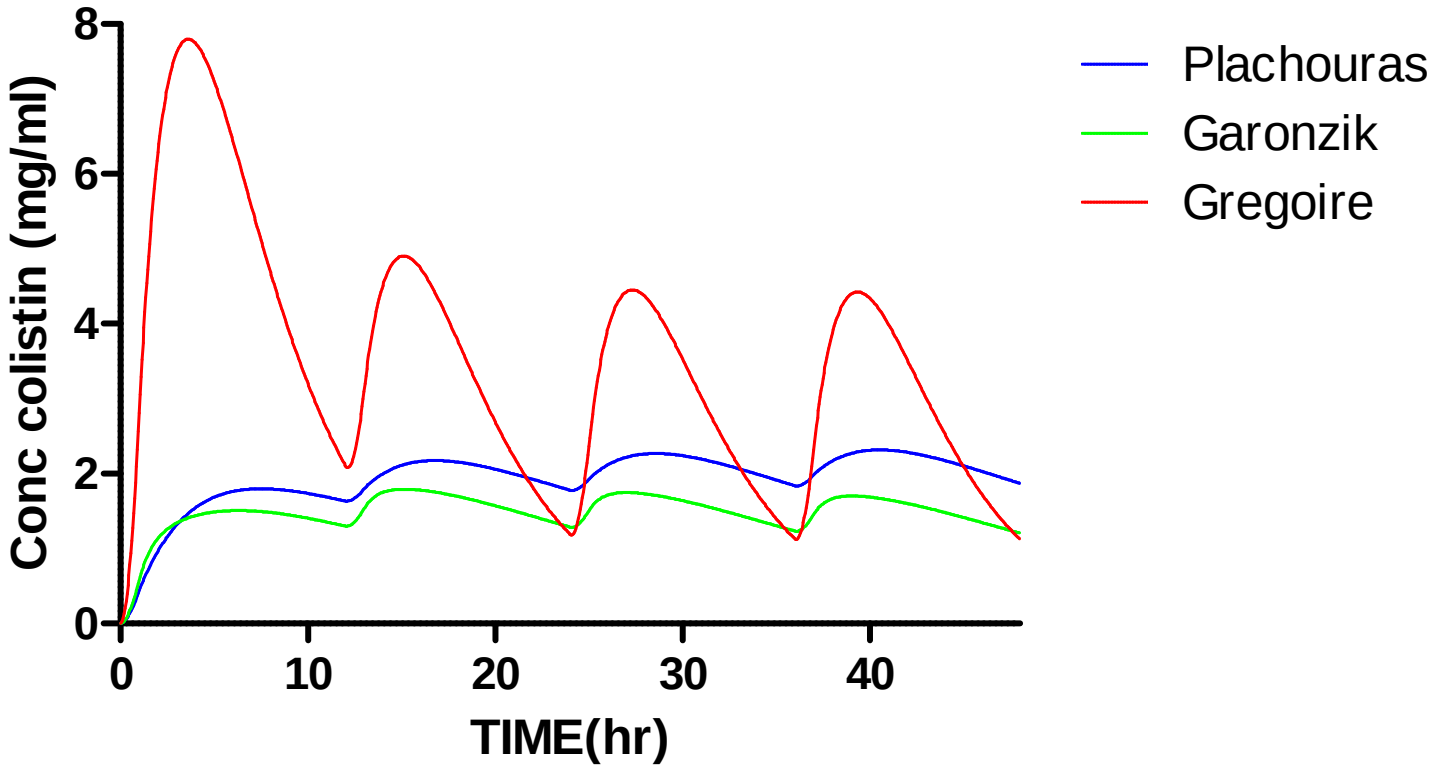
Plachouras

?

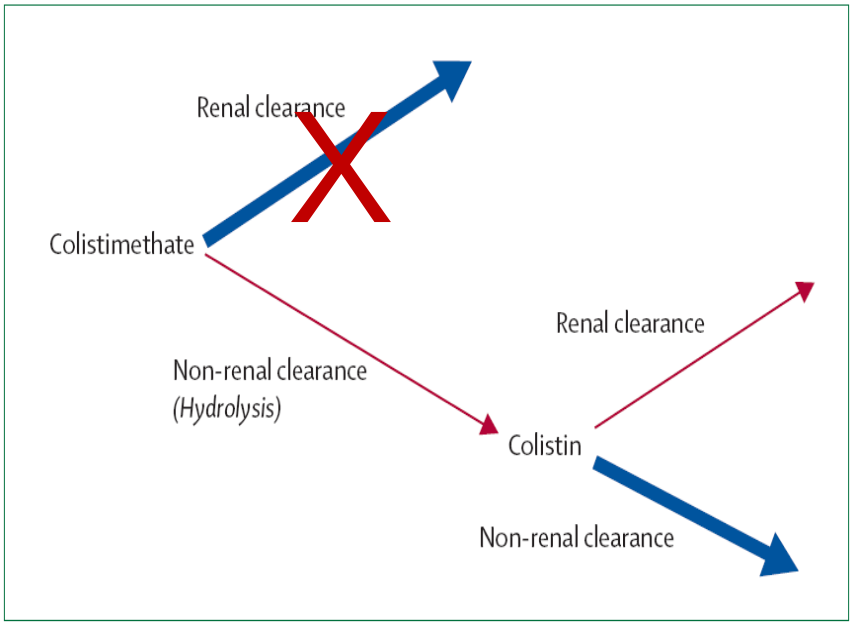
Simulations: Doses d’entretien 3 MIU/8h

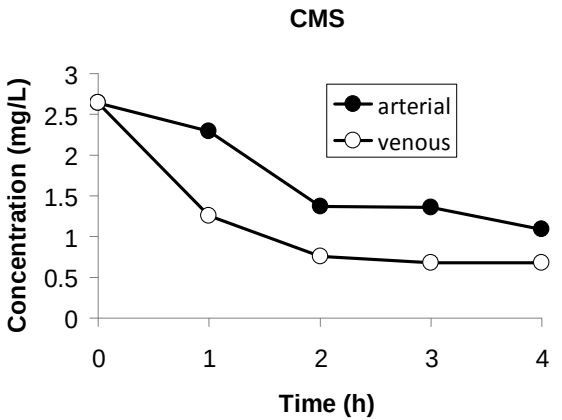


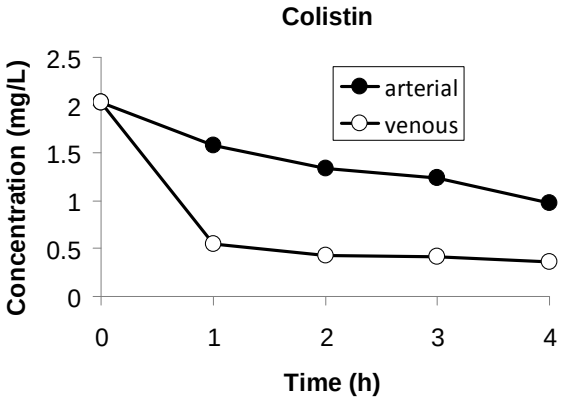
Simulations: Dose de charge 9 MIU + Doses d'entretien 3 MIU/8h



Quid du patient hémodialysé ?







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

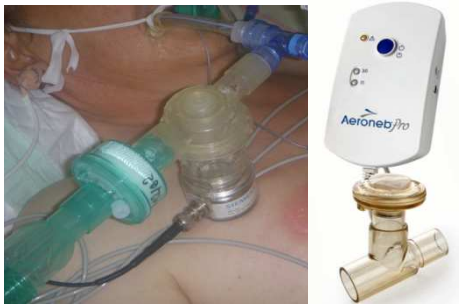
Adminsitration en aérosol

Pen Century®

(Marchand S. et al., AAC, 2010)

Etude chez le patient de réanimation

-Patients: n = 12 (male and female)
54 ± 19 years old,
CrCL: 134 ± 53 mL/min



Aeroneb Pro®

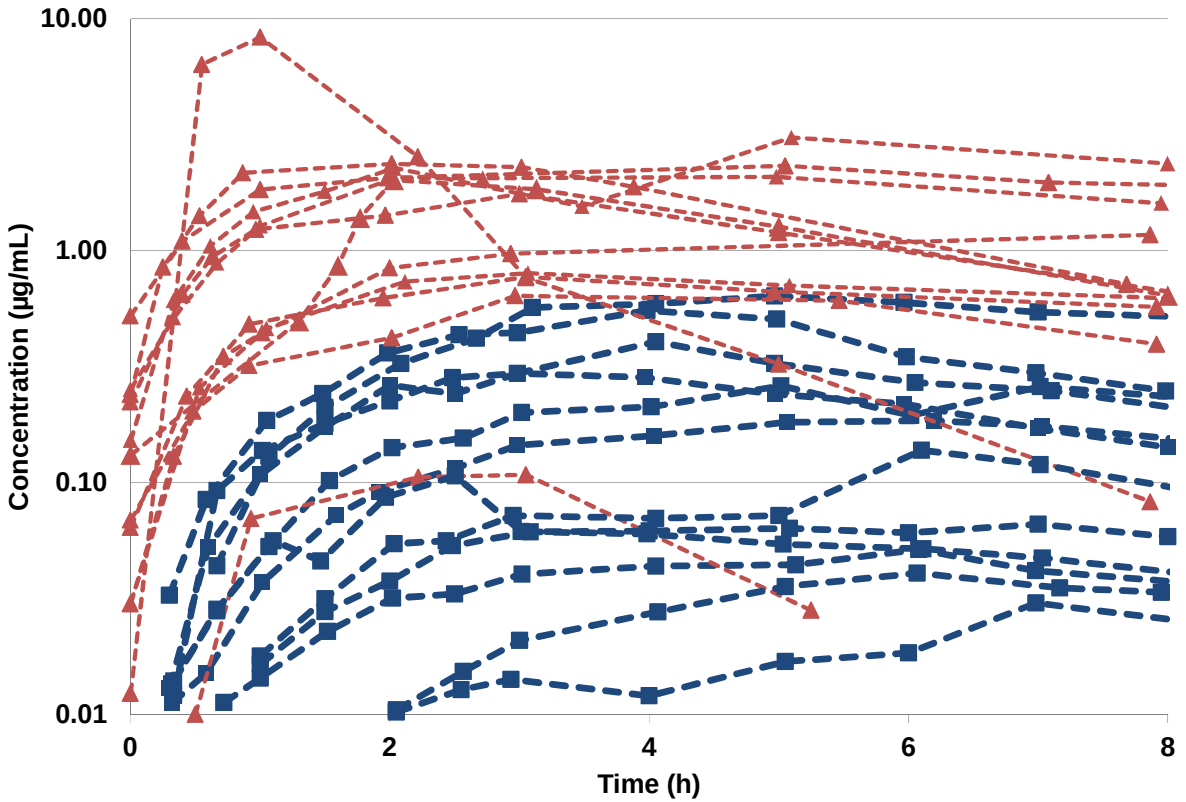
-CMS dosing: 2 MIU Nebulized (30 min)
then infused IV over 30 min

- Sampling: Blood (n= 276) and mini-BAL (n=48)

- Assay: CMS and colistin in plasma and BAL by LC-MS/MS

- PK analysis: simultaneous analysis (S-ADAPT):
of CMS and colistin
in plasma and ELF
after Nebulization and IV infusion

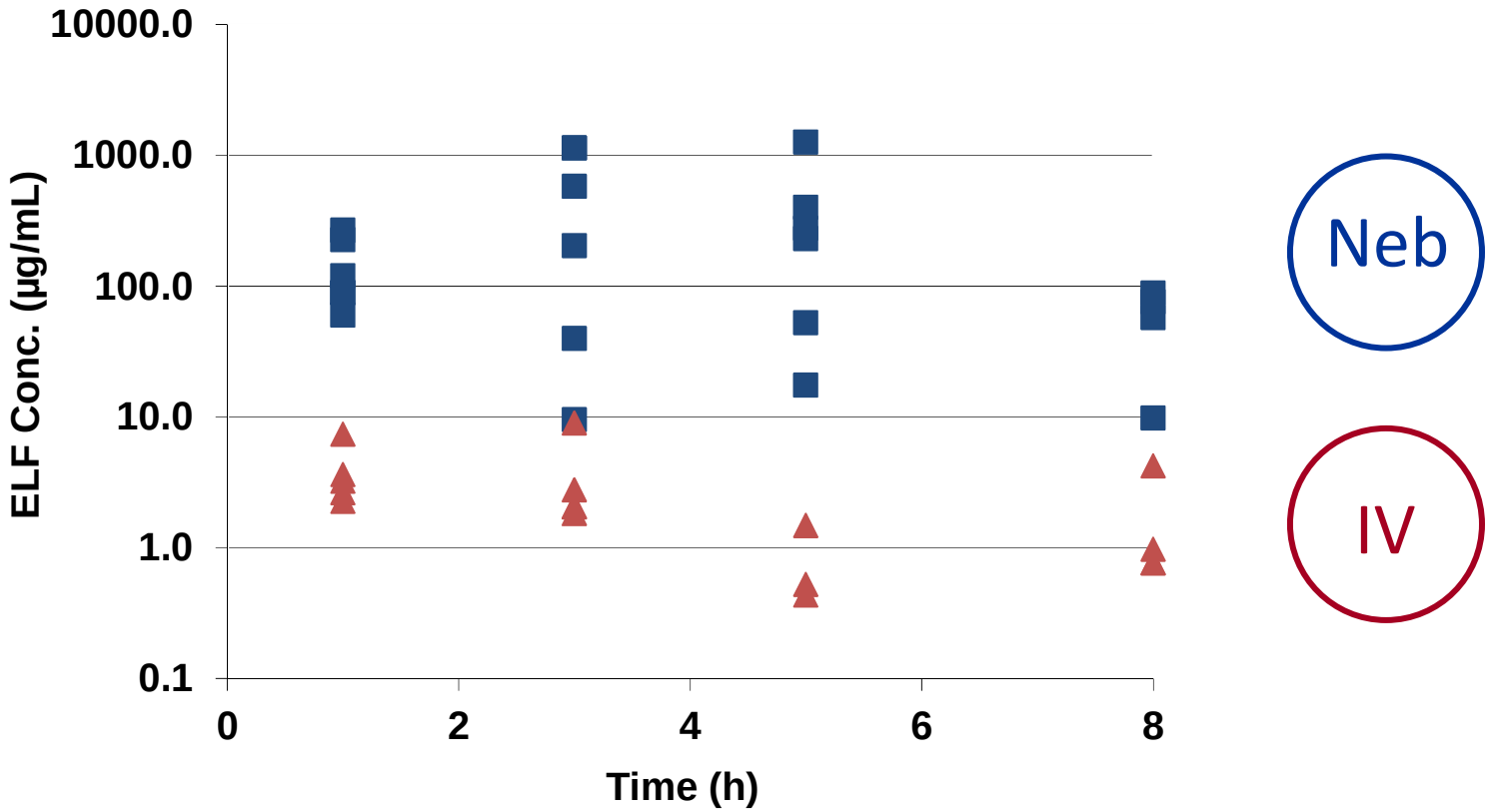
Effet de la voie d'administration sur les concentrations plasmatiques de colistine



IV

Neb

Effet de la voie d'administration sur les conc. de colistine dans le liquide alvéolaire



Remerciements:

- Nicolas Grégoire
- Patrice Gobin
- Sandrine Marchand
- Olivier Mimoz

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the EU-project AIDA
(grant Health-F3-2011-278348)