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The role of phamacokinetic monitoring in the clinical management of severe infections: colistin

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Inserm U1070 - Poitiers

- No financial conflict of interest
- Potential intellectual conflict of interest:
  - *PHRC National Coli-Pop*
  - *EU-project AIDA "Old drugs for new bugs"*
  - *JPIAMR project Co-Action (Polymyxin B)*

Ils redécouvrent la Colistine

Nouvelle République du Centre Ouest

THE LANCET Infectious Diseases

Review

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

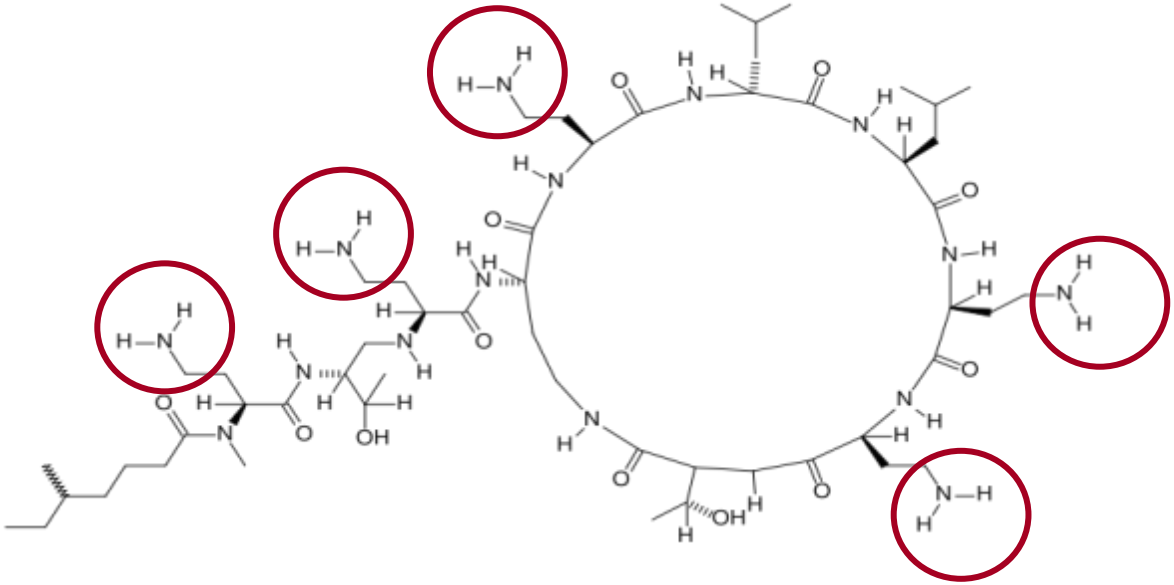
Jian Li, Roger L Nation, John D Turnidge, Robert W Milne, Kingsley Coulthard, Craig R Rayner, David L Paterson

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

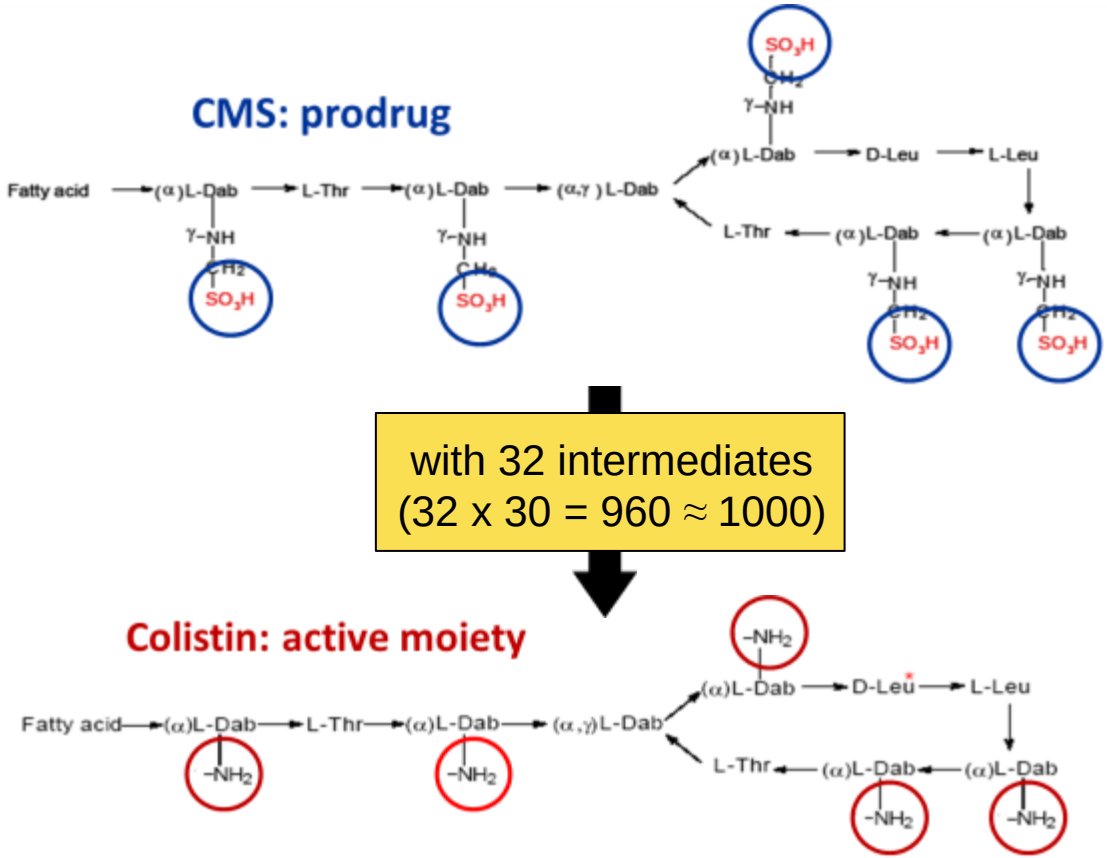
Facility for Anti-Infective Drug Development and Innovation, Victorian College of Pharmacy, Monash University, Parkville, Victoria, Australia (J Li PhD, Prof R L Nation PhD, C R Rayner PharmD); Division of Laboratory Medicine (Prof J D Turnidge FRACP) and

Mixture of about 30 cationic compounds…

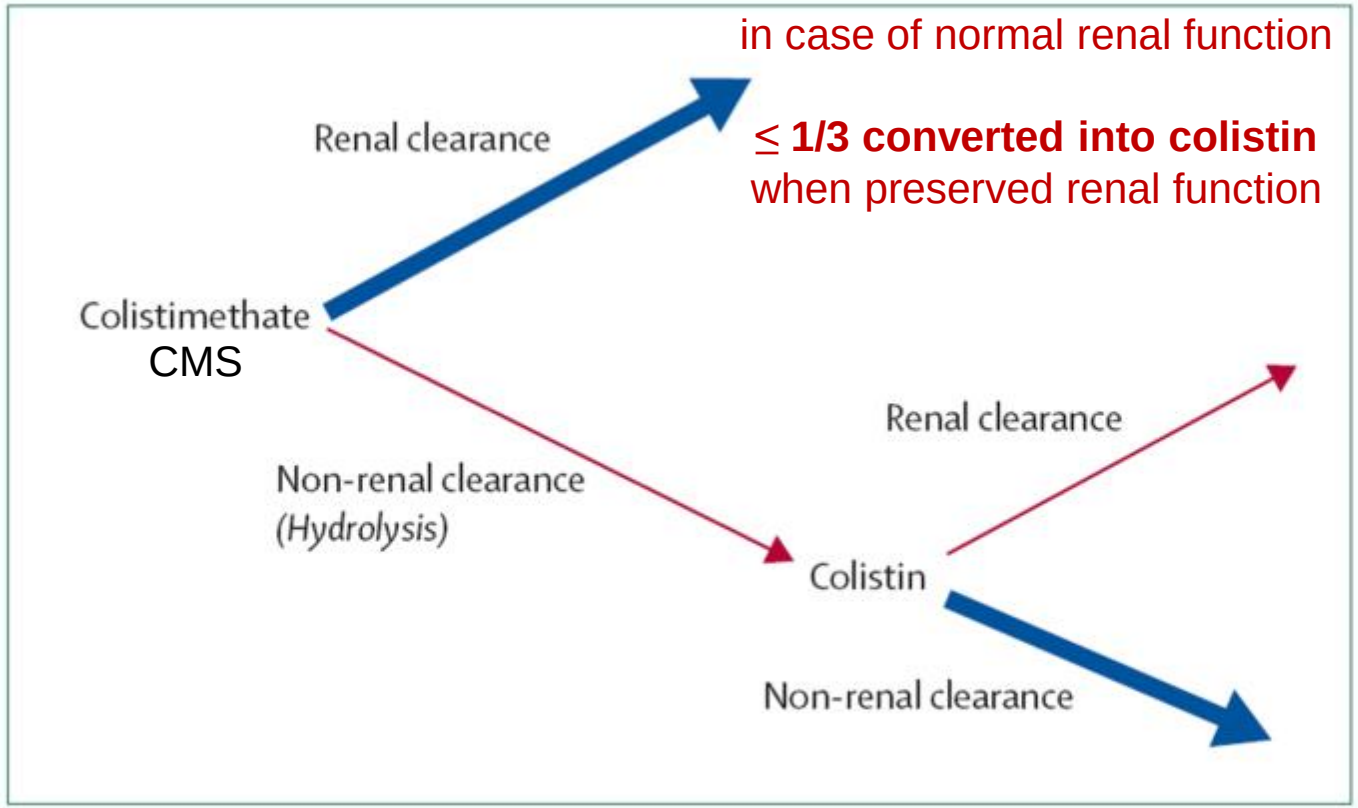


… with coli A and coli B accounting for about 80% of total

Colistin is administered as an inactive anionic prodrug: CMS

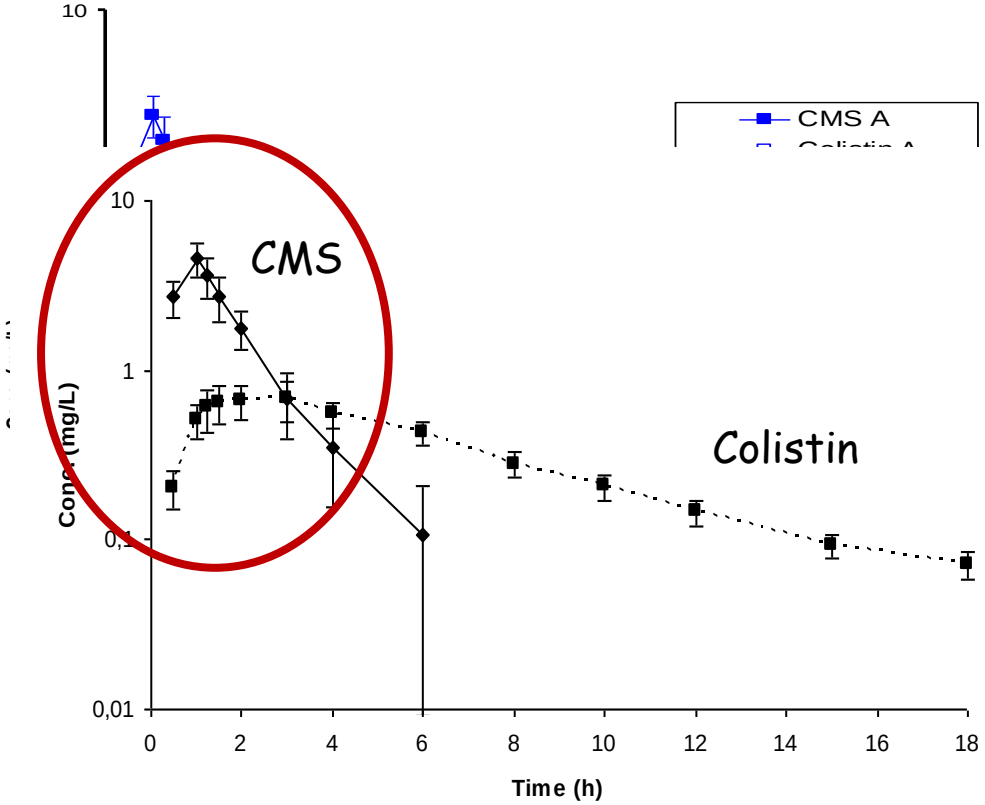


Schematic Colistin PK



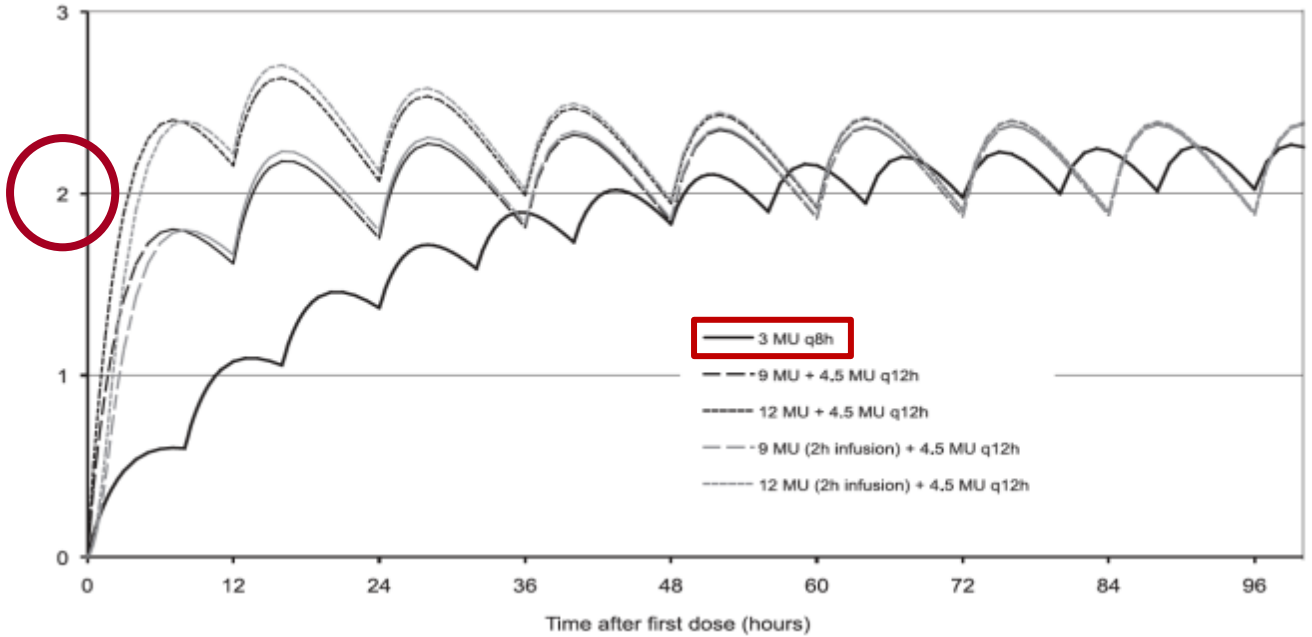
(from Li et al., Lancet Inf Dis, 2006)

Colistin PK in healthy volunteers (1 MIU single dose)



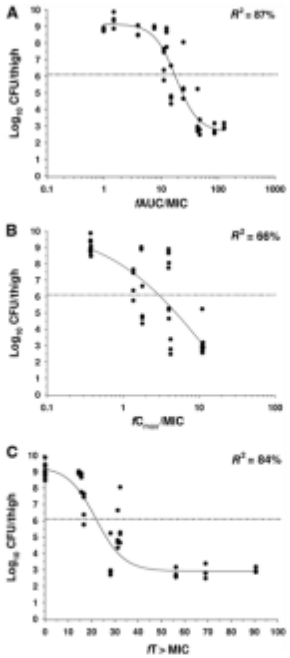
(Couet W, et al, CPT, 2011)

Colistin PK in ICU patients with preserved renal function (3 MIU / 8h)



(Plachouras D. et al., AAC, 2009)

Colistin PK-PD index

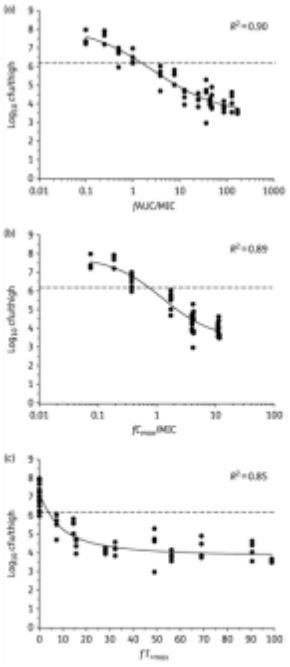


Pseudomonas aeruginosa

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

f.AUC/MIC

48



Acinetobacter baumannii

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

- **Efficacy**

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

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

Is colistin a good candidate for TDM ?

1- Increase activity

2- Limit toxicity

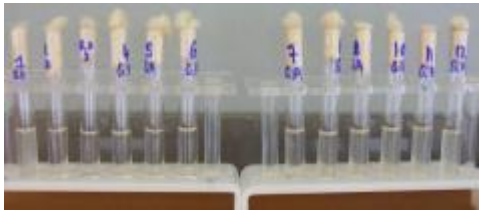
} Narrow therapeutic window and high PK variability

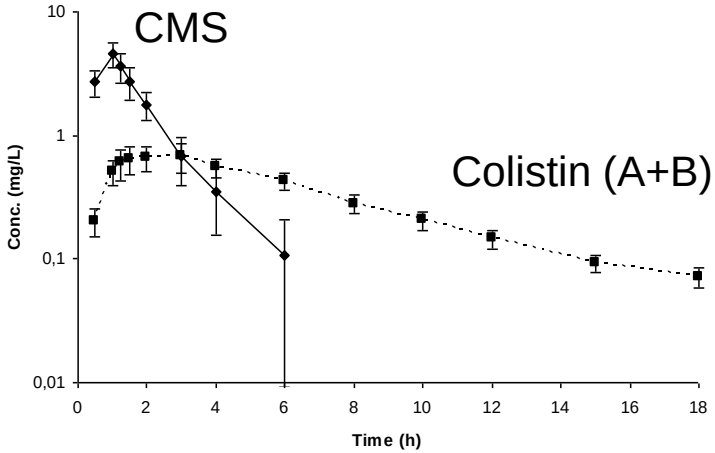
3- Avoid resistance

What are the challenges ?

1 – Measure concentrations

From bioassay…





… to HPLC and LC-MS/MS assay

Only Colistin (not CMS) is quantified

Due to potential pre-analytical CMS degradation, avoid « Cmax » determination

What are the challenges ?

1 - Measure concentrations

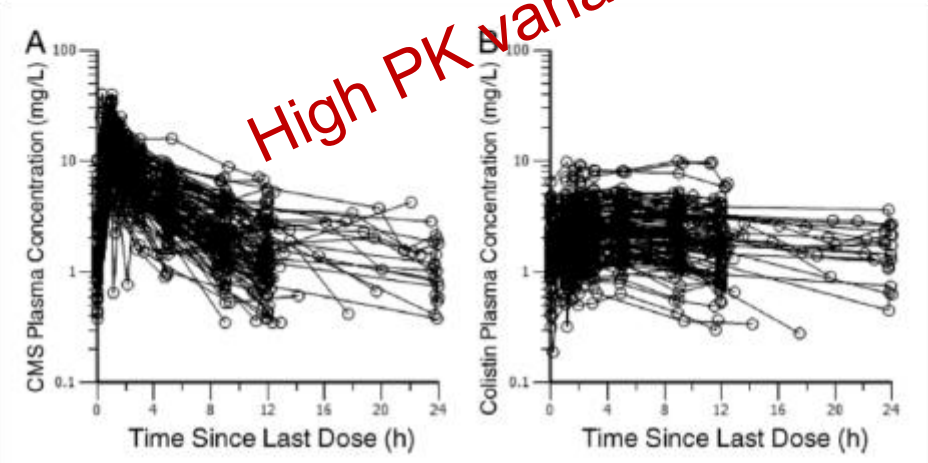
2 - Manage PK variability

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]*‡

High PK variability



Colistin concentrations at steady-state = 2 µg/mL

Rate of formation = Rate of elimination

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

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

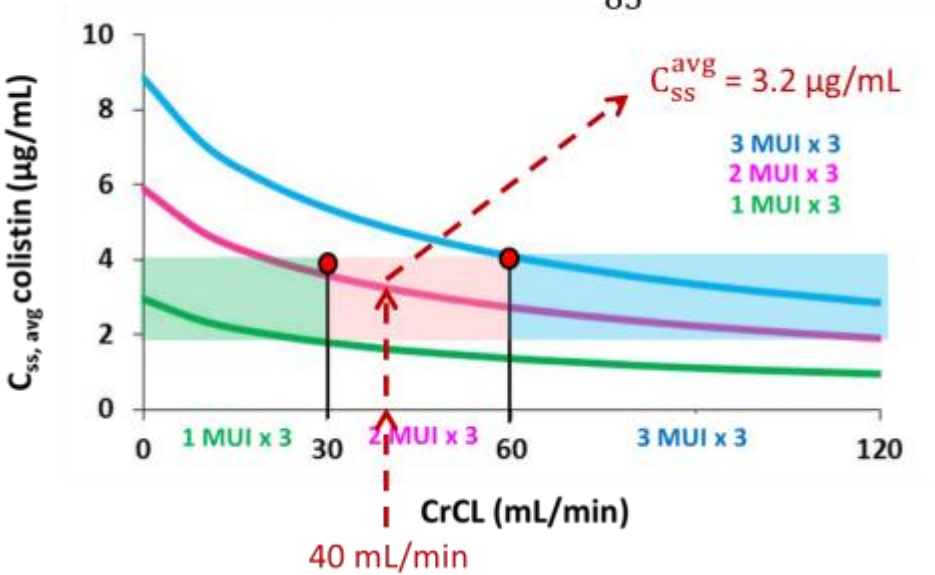
GFR

Limited impact on Css

Uncontrolled

Predicted Css of colistin in a typical « french » ICU patient with CLcreat = 40 mL/min

$$CL_{R,CMS} = 68.5 \times \left(\frac{CL_{CREAT}}{85}\right)^{0.85}$$



Effect of inter-patients variability : *Monte Carlo simulations*

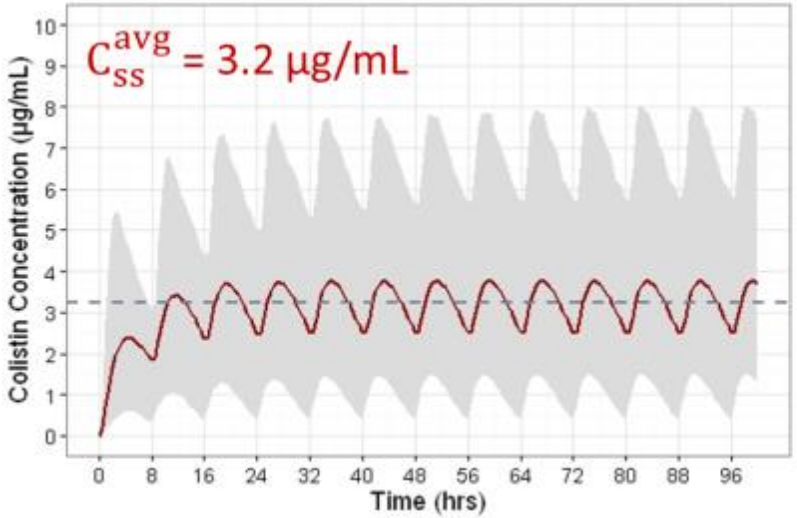
COLIPOP

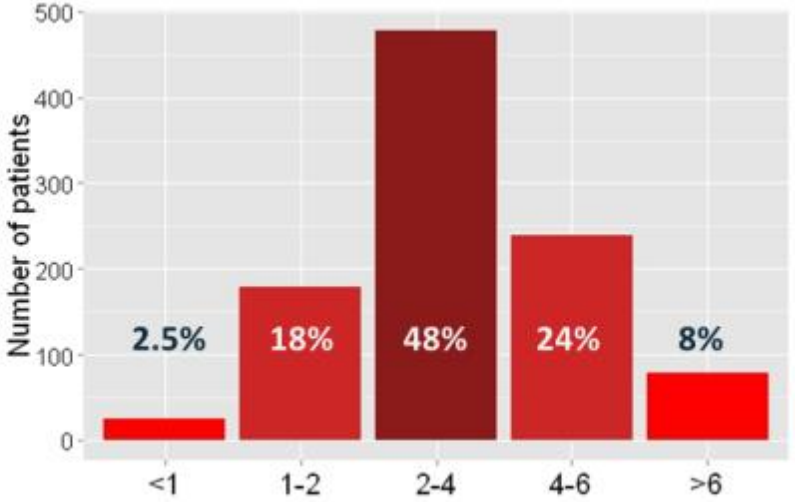
$CL_{R,CMS}$	36 mL/min
$CL_{NR,CMS}$	43.7 mL/min
V_{CMS}	15.7 L
CL_{COLI}	37.7 mL/min
V_{COLI}	10.2 L

CLcreat = 40 mL/min

2MUI x 8h

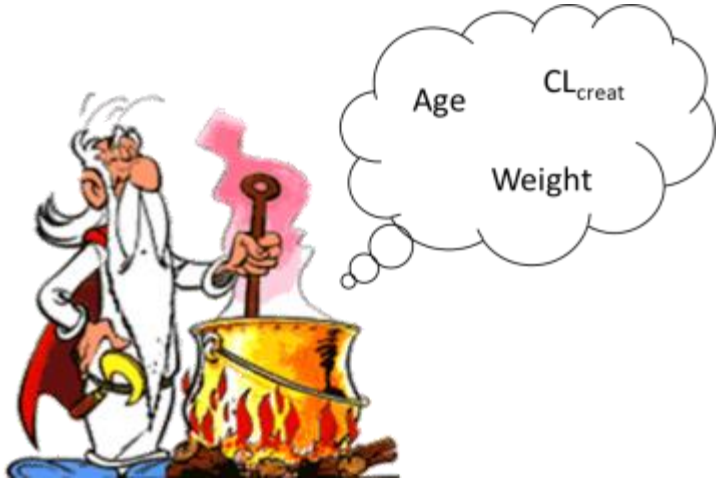
Simulated Css of colistin in a typical « french » population of ICU patient with CLcreat = 40 mL/min receiving 2 MIU / 8h

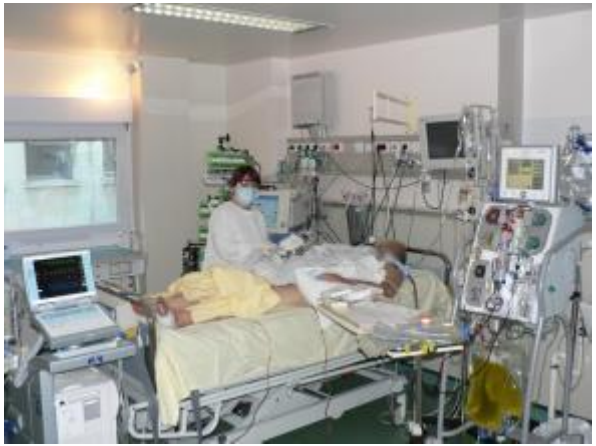




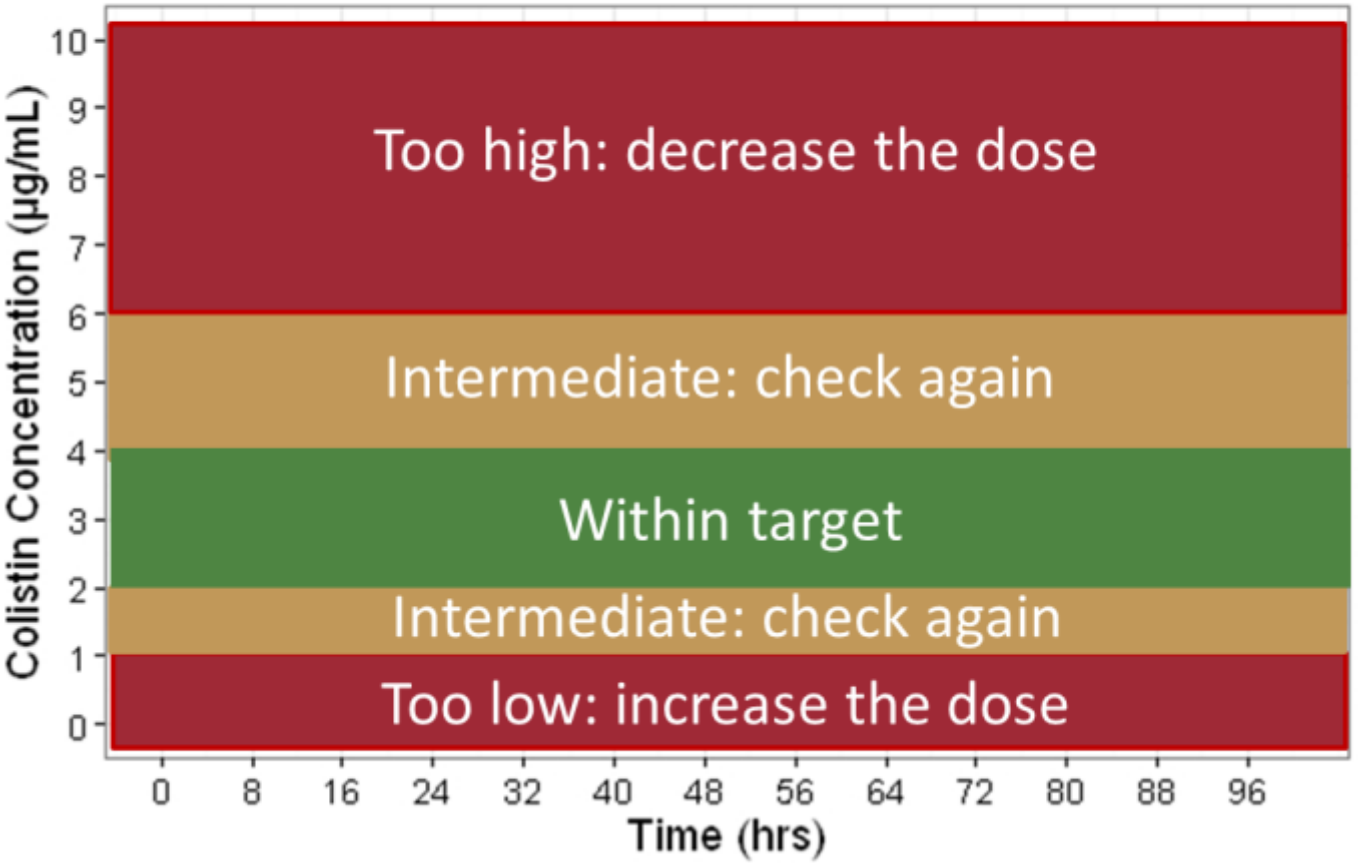
Could we use a bayesian TDM approach with 1 or 2 early plasma concentrations for selecting the optimal dosing regimen?

Probably not …

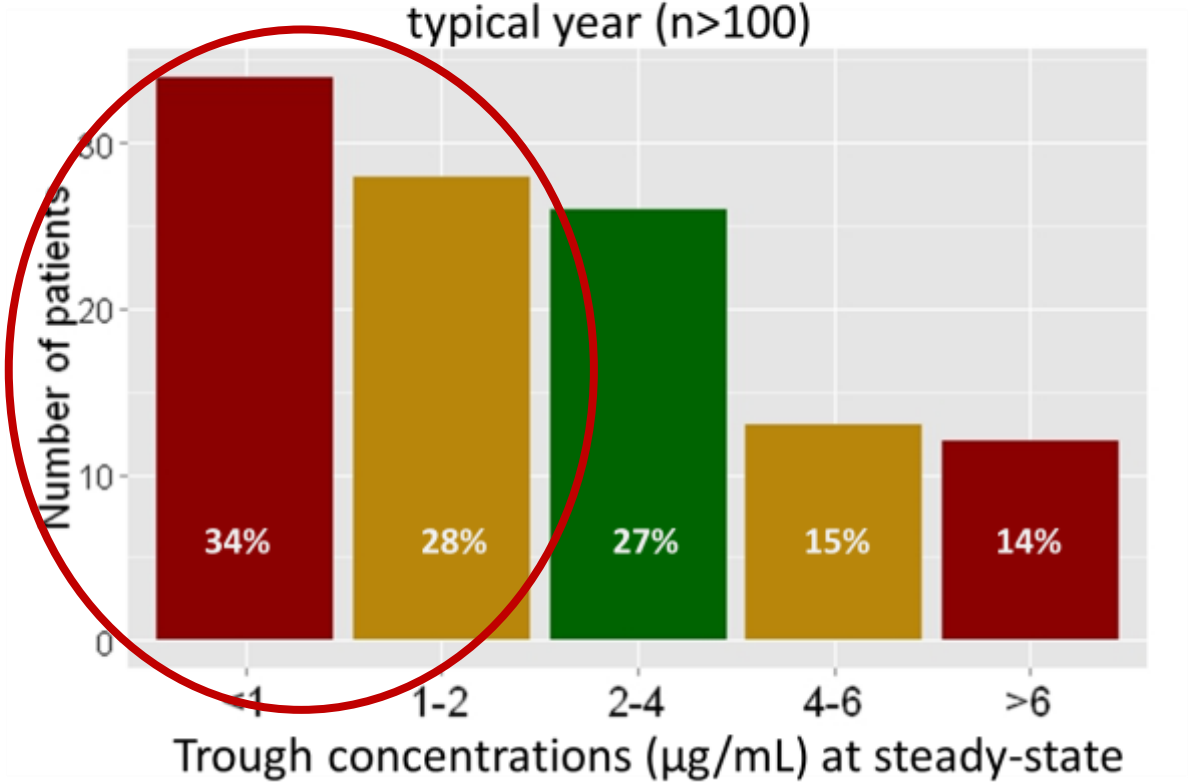




In every day practice



Measured Colistin **trough concentrations** at steady-state in Non-Hemodialyzed patients at the Poitiers University Hospital in a typical year (n>100)



What are the challenges ?

1 - Measure concentrations

2 - Manage PK variability

3 - Define a concentration target

In every day practice colistin is not administered alone

Typical « french patient » with Clcreat = 40 mL/min

Colistin: 2 MIU / 8h

Css = 2-4 µg/mL

Optimal dosing alone

But combined ???

Amikacin: 20 mg/kg

Cmax = 60-80 µg/mL

Balance between increased efficacy (synergy)

and nephrotoxicity

REVIEW 10.1111/j.1469-0691.2011.03667.x

Colistin pharmacokinetics: the fog is lifting

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1) Inserm ERI-23, CHU, Service de Toxicologie et Pharmacocinétique, UFR Médecine-Pharmacie, Université de Poitiers and 2) Intensive Care Unit, University Hospital of Poitiers, Poitiers, France

Abstract

Colistin is a re-emerging old antibiotic that is used to treat multidrug-resistant infections in critically ill patients. It corresponds to a mixture of at least 30 different compounds administered as inactive derivatives. Therefore, colistin pharmacokinetics are quite difficult to investigate and complex to predict. However specific chromatographic methods have been made available in recent years, leading to a series of modern pharmacokinetic studies after intravenous administration of the prodrug to critical-care patients; these have been conducted by a few groups and have only been recently published. The objective of this article was to conduct a critical review of these very informative modern pharmacokinetic studies and to provide prospective thoughts.

Keywords: Colistin, critical-care patients, pharmacokinetics, prodrug, simulations
Article published online: 14 September 2011
Clin Microbiol Infect 2012; **18:** 30–39