# Last-resort antibiotics in cancer: dosing challenges

Pr William Couet, PharmD, PhD

*27 april 2013*

# *How to select last resort antibiotics ?*

- Antimicrobial spectrum of activity

  Gram(+) : Linezolid, Daptomycin…

  Gram(-) : Colistin

- But also quick bactericidal activity (febrile neutropenia)

# *Last resort antibiotics for Gram (+) :* Linezolid

Better antimicrobial activity than vancomycin on various *Staph.* species

Comparable clinical efficacity and safety in nonneutrapenic patients with:

- Nosocomial pneumonia due to Gram (+) *(Rubinstein E, CID 2001)*
- MRSA infections *(Steven DL, CID 2002)*

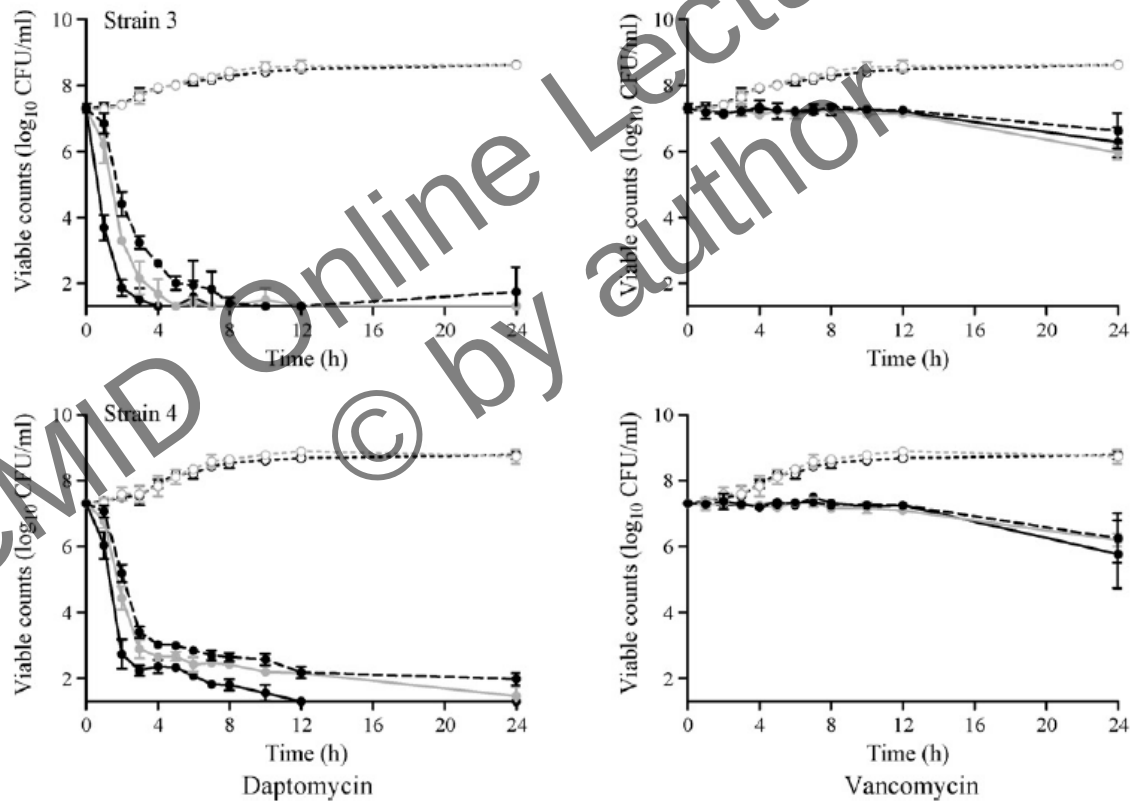
Confirmed in neutropenic patients with cancer *(Jaksic B et al., CID 2006)*

But bacteriostatic activity precluding rapid killing

# *Last resort antibiotics for Gram (+)* : Daptomycin



## *Rapid initial killing related to unbound concentration*




*(Torrico M. et al., IJAA, 2010)*

# *Daptomycin pharmacokinetics*

- Extensive protein binding (> 90%)

- Limited extravascular distribution (Vd = 100 mL/Kg) due to high MW and low lipophylicity, leading to relatively high systemic concentrations

- Elimination: renal (50% excreted unchanged), no circulating metabolites

- Elimination half-life: 6-12 h

*(Kim A., et al, AAC, 2008)*

# *Pharmacokinetics in cancer patients*



- Protein binding: fu = 6  2%  (~ 0.10% in HV)

- Vd = 180  50 mL/Kg  (vs 98  5 mL/Kg HV or 80  37mL/Kg in Crit Care patients) due to fluid supply ?

- $CL_T$= 15.0±6.1 mL/h/Kg vs 10.5±5.0 mL/h/Kg in Crit Care patients

- But which Dose is the best ?  6 mg/Kg/24h or in practice 8 - 10 mg/Kg/24h

*(Bubalo JS., et al, AAC, 2009)*

# *Daptomycin dosing adjustment*



## Efficacy

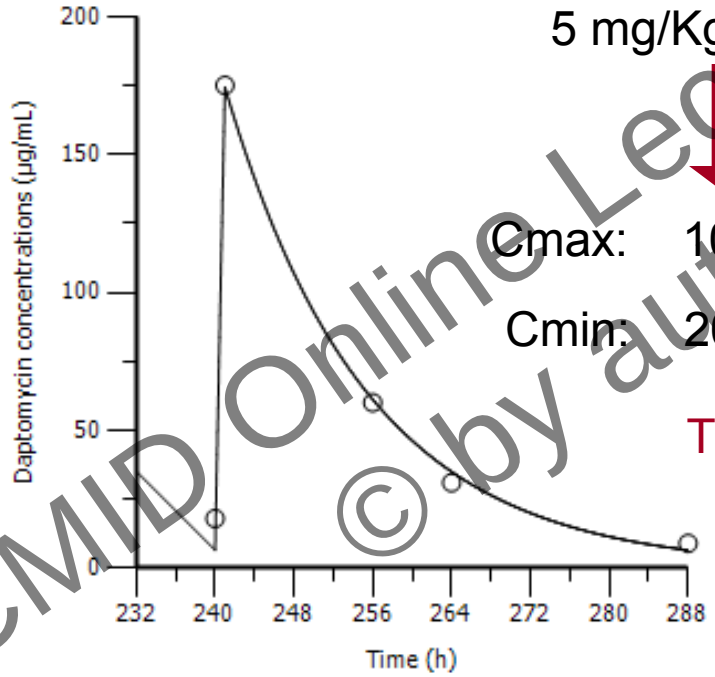
- AUC/ MIC is considered as the relevant PK-PD index to predict efficacy

- But an optimal threshold has not been defined yet

## Toxicity

- By contrast, CPK elevation related to musculoskeletal adverse events is most likely to occur when residual concentration (Cmin) ≥ 24.3 mg/L

# *Case report: patient with renal insufficiency not under dialysis*




5 mg/Kg every 24h vs 10 mg/Kg every 48h ?

Cmax: 103 µg/mL vs 174 µg/mL

Cmin: 20.7 µg/mL vs 6.5 µg/mL

Threshold Cmin < 24.3 µg/mL

**Figure 1.** Daptomycin experimental (open squares) and predicted (solid line) concentrations 10 days after adjusting daptomycin dosing regimen to 10mg/kg infused over 1h every 48h in a patient with $CR_{creat}$ = 23 mL/min

*(Marchand S. et al, AAC, 2013)*

# *Last resort antibiotics for Gram (-) :* Colistin



ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, June 2007, p. 1905–1911 Vol. 51, No. 6
0066-4804/07/$08.00+0 doi:10.1128/AAC.01015-06


## Colistin Is Effective in Treatment of Infections Caused by Multidrug-Resistant *Pseudomonas aeruginosa* in Cancer Patients▽

Ray Y. Hachem,[1]* Roy F. Chemaly,[1] Corine A. Ahmar,[2] Ying Jiang,[1] Maha R. Boktour,[1] Georges Abou Rjaili,[2] Gerald P. Bodey,[1] and Issam I. Raad[1]

*Department of Infectious Diseases, The University of Texas M. D. Anderson Cancer Center, Houston, Texas,[1] and Staten Island University Hospital, Staten Island, New York[2]*

# *Rapid bactericidal effect of Colistin*



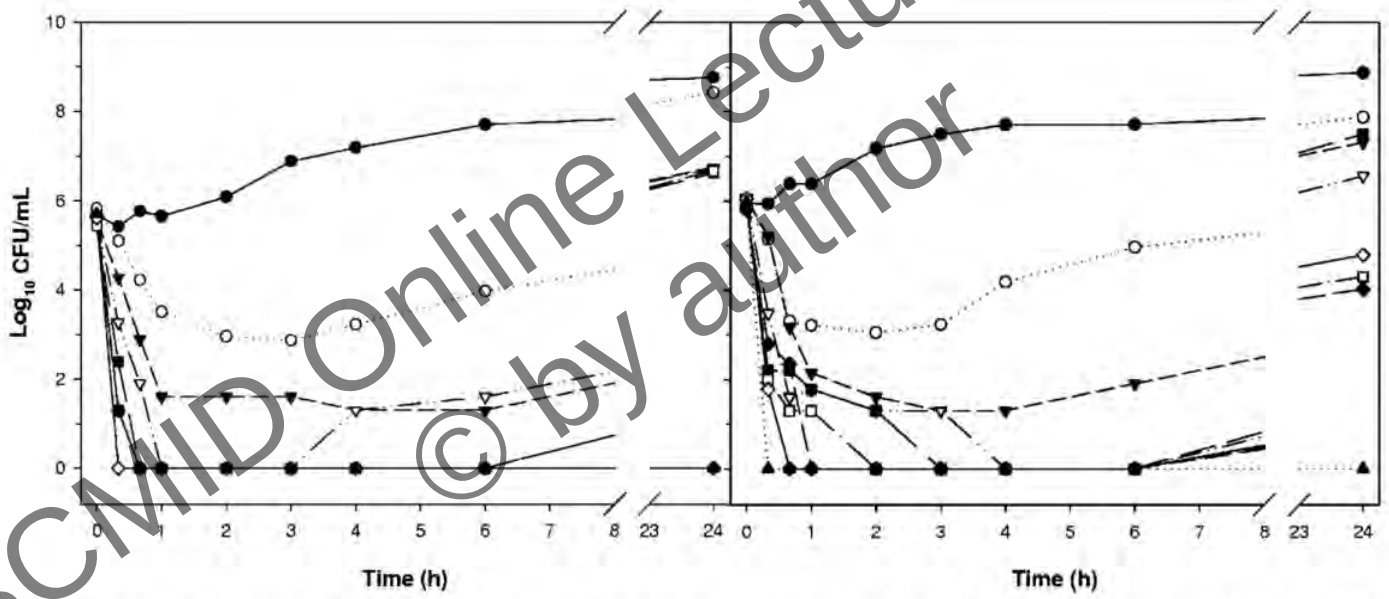



FIG. 2. Killing curves for ATCC 19606 (left panel) and isolate 6 (right panel) by colistin. Symbols: ●, control; ○, 0.5× MIC; ▼, 1× MIC; ▽, 2× MIC; ■, 4× MIC; □, 8× MIC; ◆, 16× MIC; ◇, 32× MIC; ▲, 64× MIC.



Université de Poitiers 1431

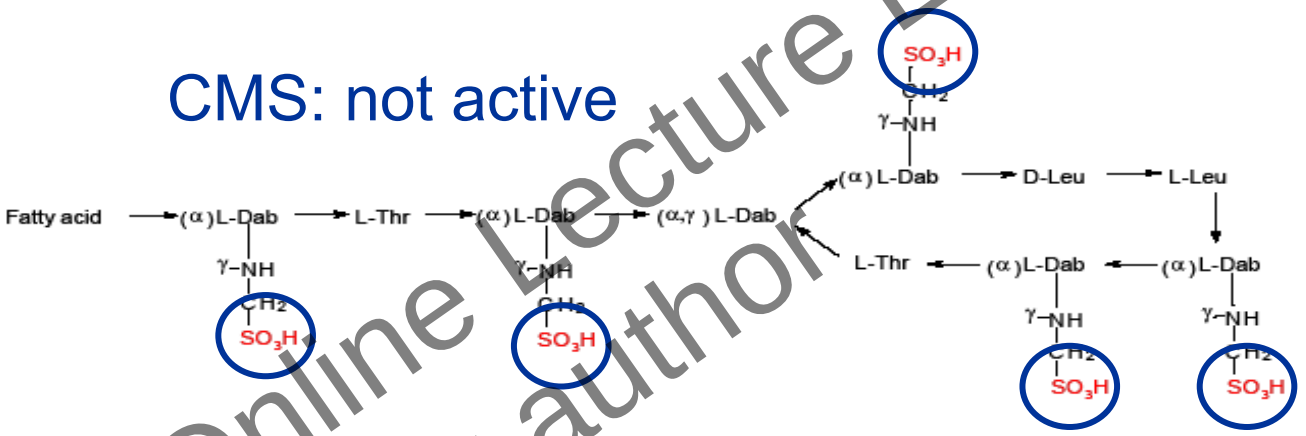
*(Li J et al., AAC, 2006)*

# *Colistin is adminsitered as a prodrug*

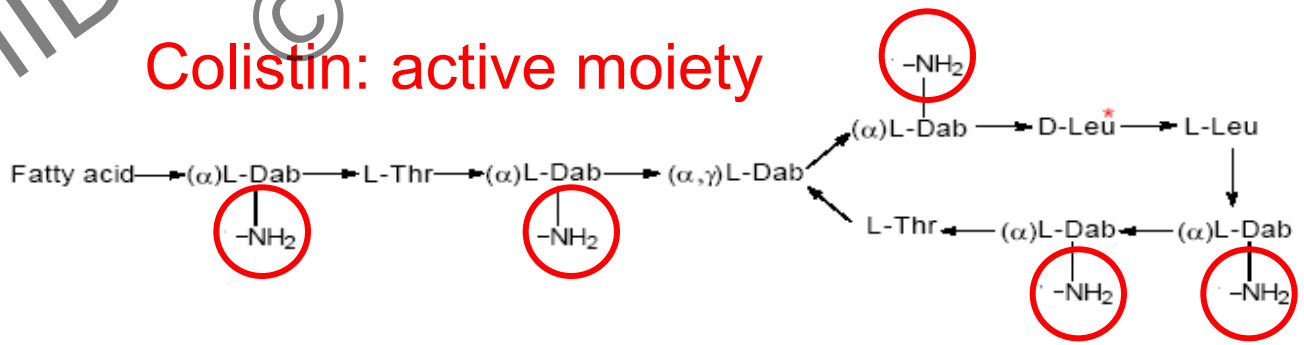




## CMS: not active

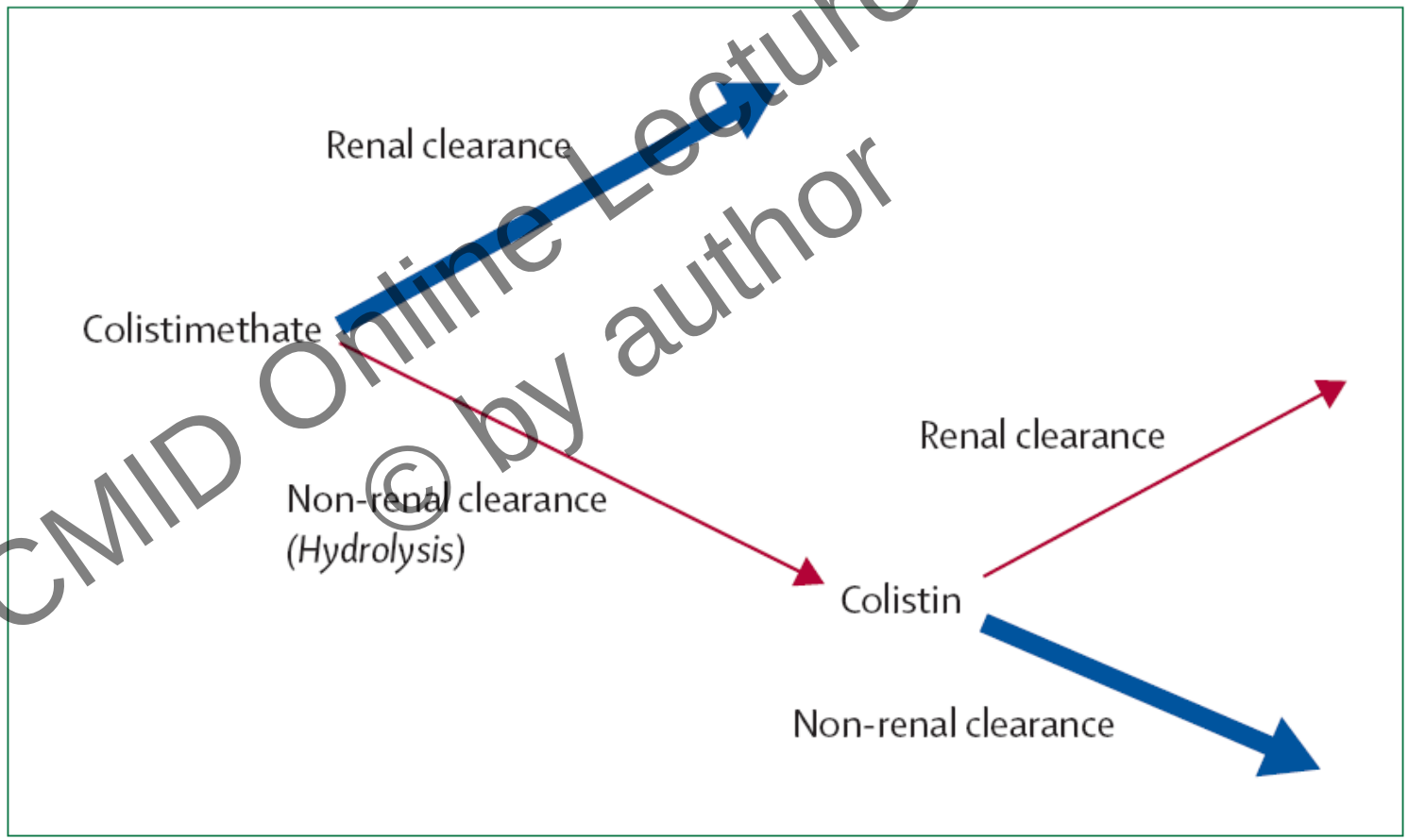



## Colistin: active moiety



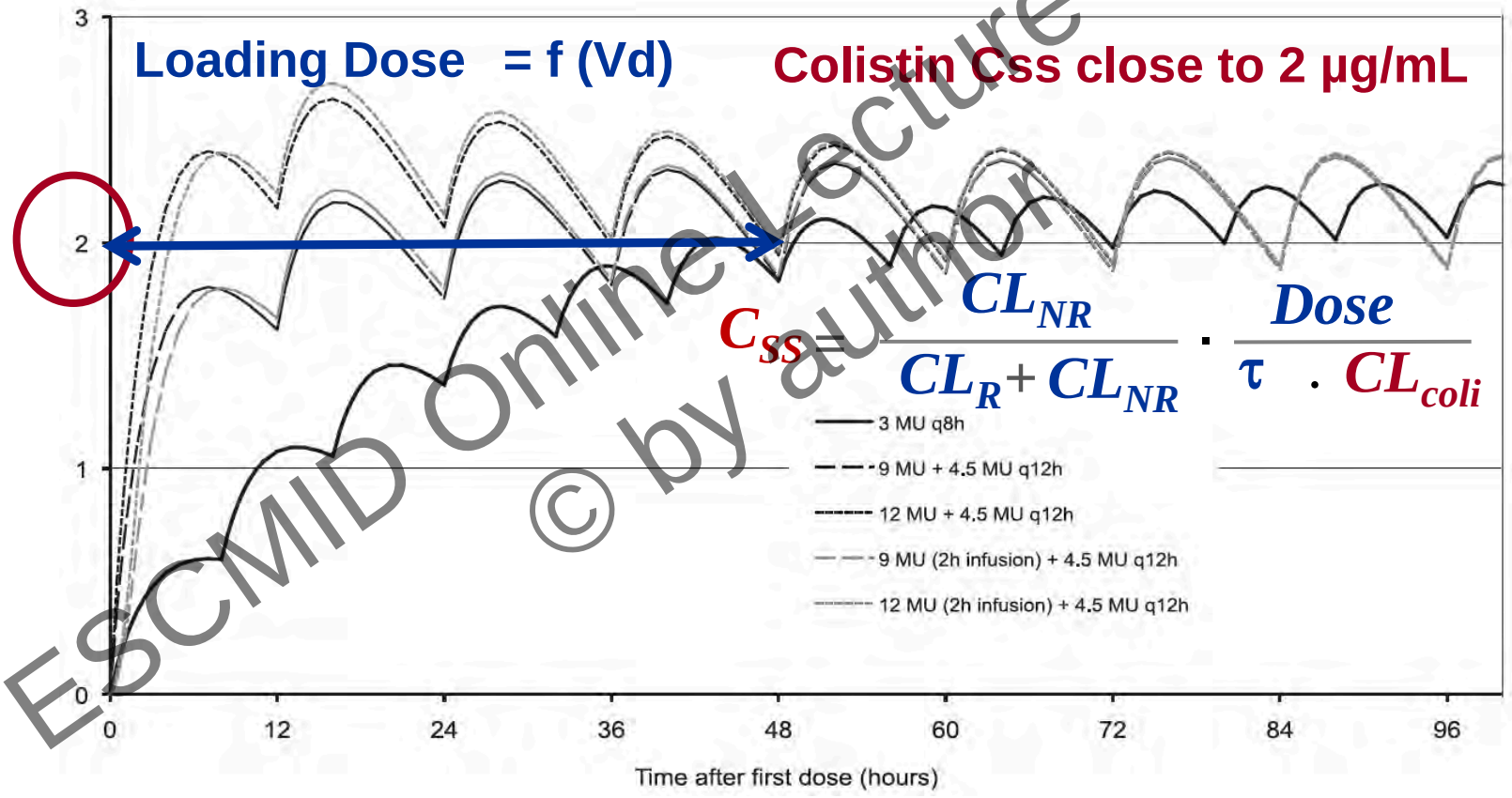
# *CMS and colistin disposition*






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

# *Colistin PK in Critical Care patients*





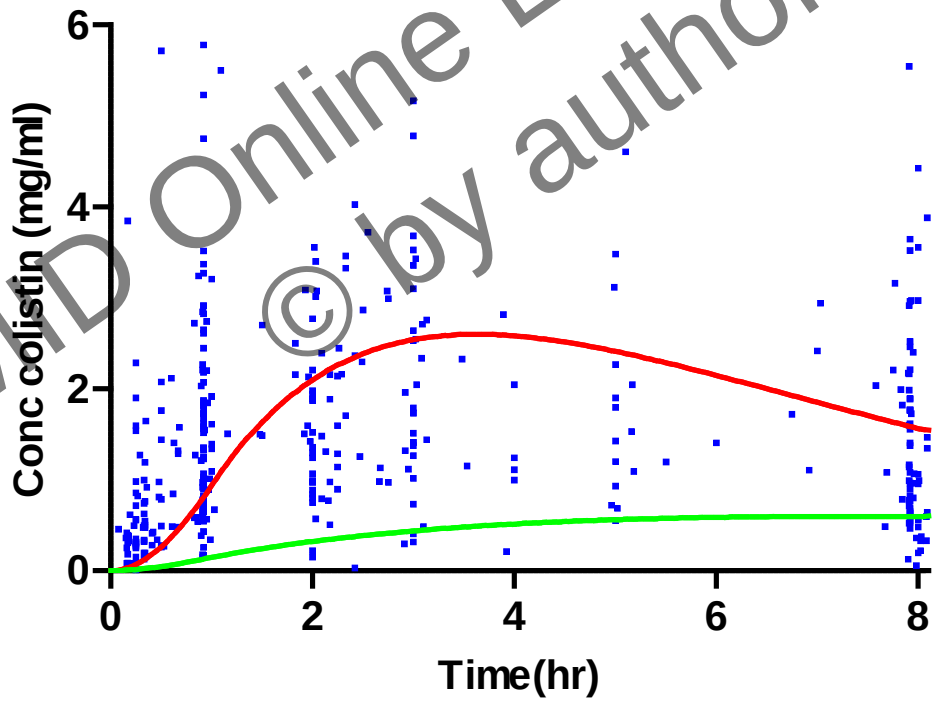

Université de Poitiers 1431

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

# *Colistin PK in Critical Care Patients*

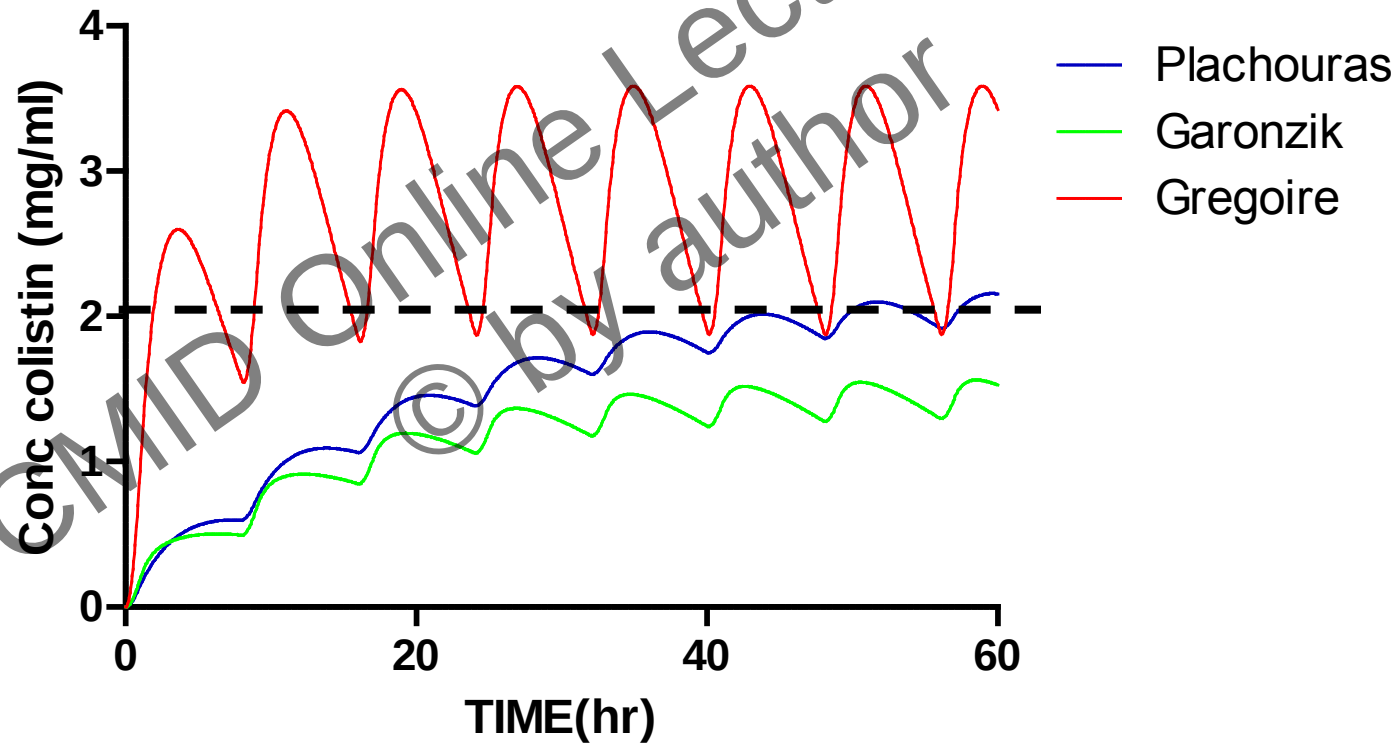


Colistin concentrations after the 1st injection of CMS to 70 Critical Care patients normalized to 3 MIU



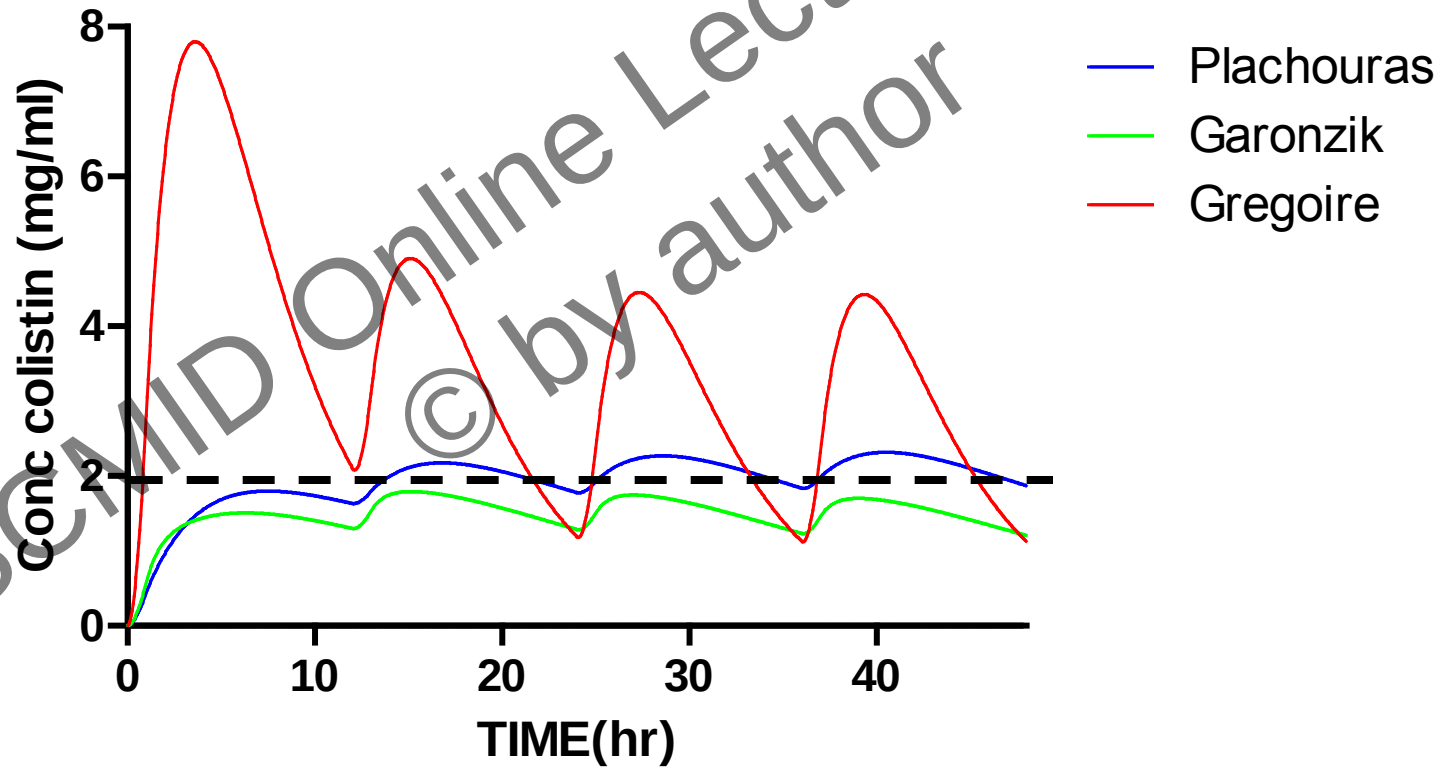

Plachouras prediction

# *Comparative colistin PK in Critical Care Patients:*
## *without loading dose*

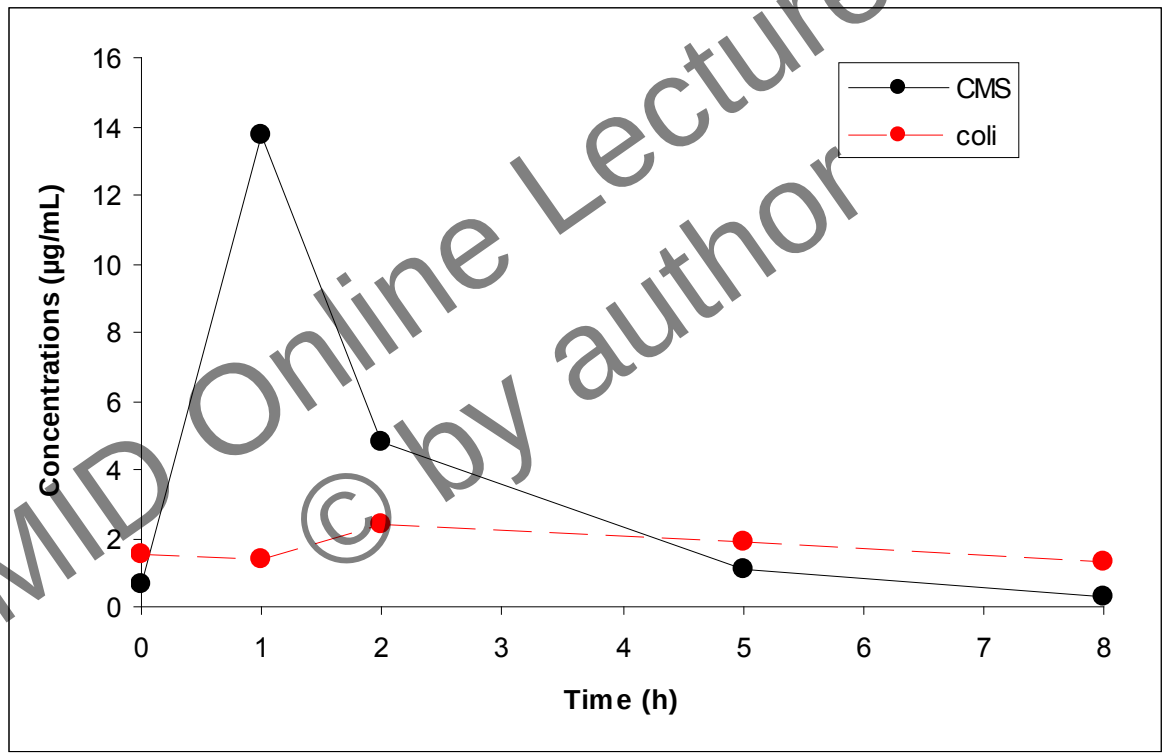


# *Comparative colistin PK in Critical Care Patients:*
## *with 9MIU loading dose*





# *CMS and colistin PK in a 57Kg cancer patient with normal renal function receiving CMS 3MIU/8h*

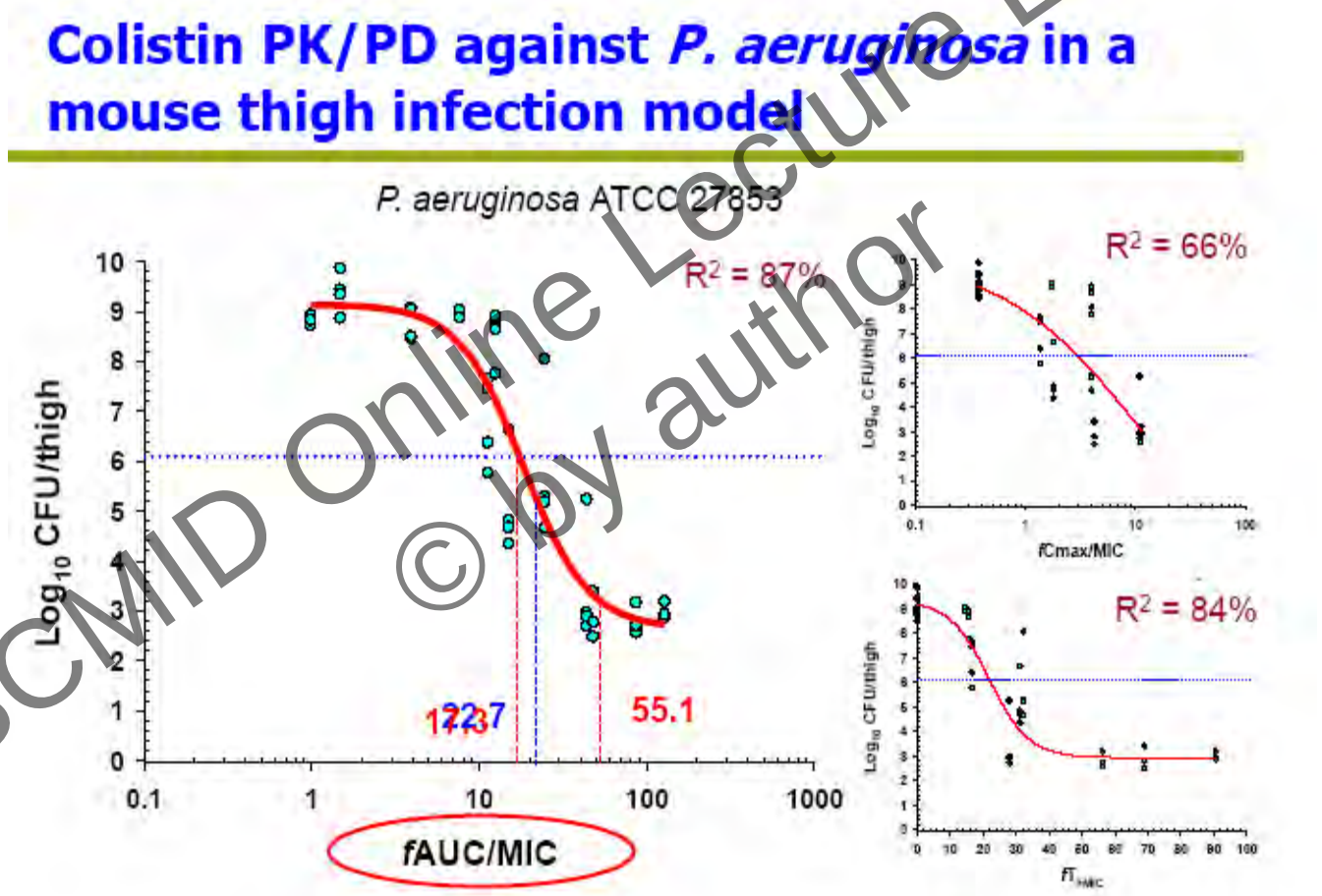





*(unpublished data)*

# *PK-PD index to predict colistin effect*

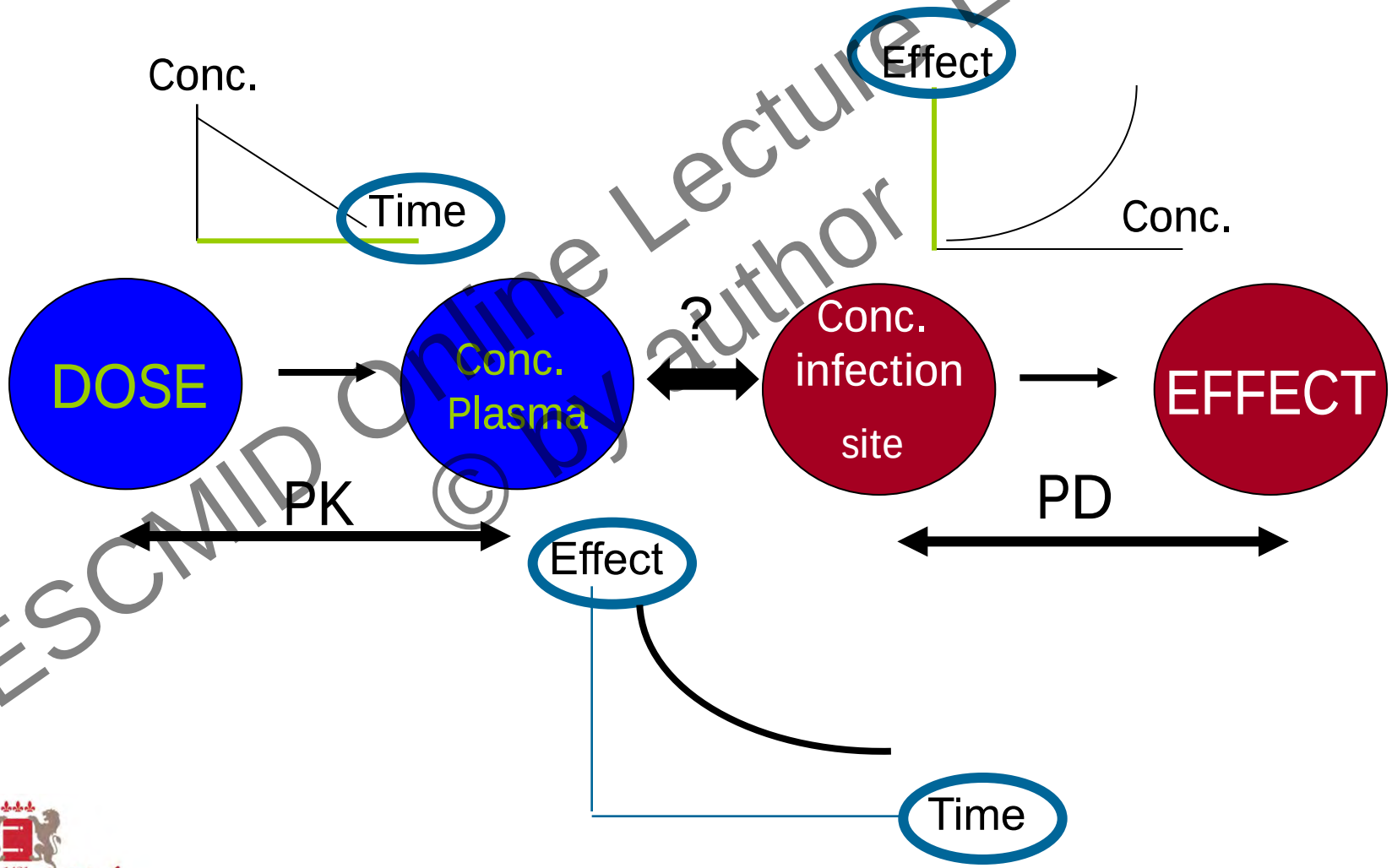




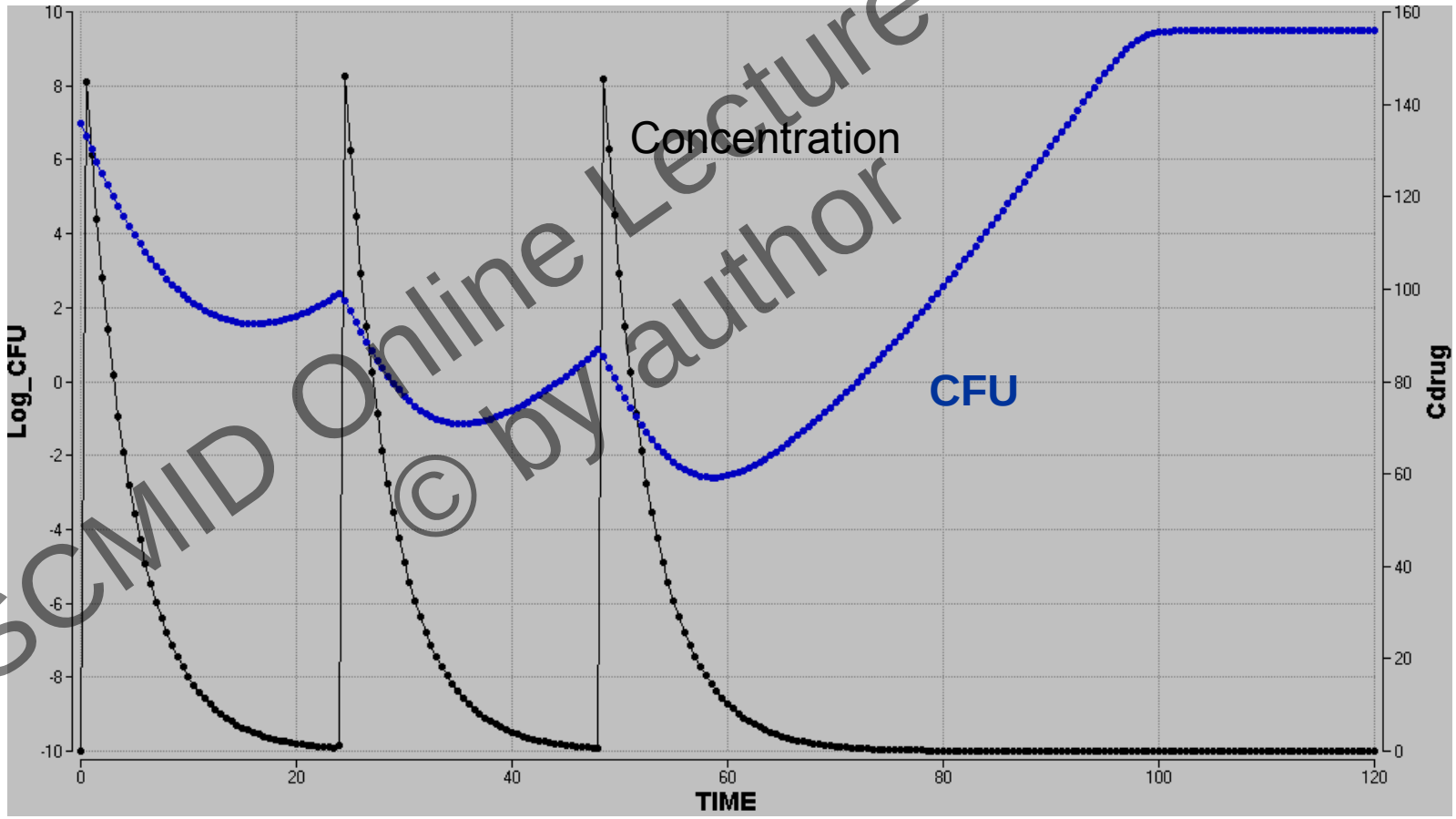



*(Dudhani et at., AAC, 2011)*

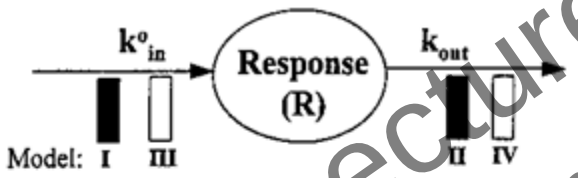
# *PK-PD modeling principle*



# *Predicted time course of effect*



# PD: Indirect effect model




$$\frac{dR}{dt} = k_{in} \cdot \{1+H_1(t)\} - k_{out} \cdot \{1+H_2(t)\} \cdot R$$

| Model | $H_1(t)$ | $H_2(t)$ | Condition |
|---|---|---|---|
| I | $-\left(\frac{I_{max} \cdot C_p}{IC_{50} + C_p}\right)$ | 0 | $0 < I_{max} \leq 1$ |
| II | 0 | $-\left(\frac{I_{max} \cdot C_p}{IC_{50} + C_p}\right)$ | $0 < I_{max} \leq 1$ |
| III | $\left(\frac{S_{max} \cdot C_p}{SC_{50} + C_p}\right)$ | 0 | $0 < S_{max}$ |
| IV | 0 | $\left(\frac{S_{max} \cdot C_p}{SC_{50} + C_p}\right)$ | $0 < S_{max}$ |

Key: $IC_{50}$ Inhibition  $SC_{50}$ Stimulation



(Jusko et al., 1994)

# PK-PD model to predict decay and regrowth

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, June 2010, p. 2379–2384 Vol. 54, No. 6
0066-4804/10/$12.00 doi:10.1128/AAC.01478-08


## Semimechanistic Pharmacokinetic-Pharmacodynamic Model with Adaptation Development for Time-Kill Experiments of Ciprofloxacin against *Pseudomonas aeruginosa*▽

Nicolas Grégoire,[1]† Sophie Raherison,[2]† Claire Grignon,[1] Emmanuelle Comets,[3] Manuella Marliat,[1] Marie-Cécile Ploy,[2] and William Couet[1]*

*Université de Poitiers, CHU Poitiers, INSERM Eri-23, Poitiers, France[1]; Université de Limoges, EA3175, INSERM Avenir, Limoges, France[2]; and Université de Paris, INSERM U-738, Paris, France[3]*

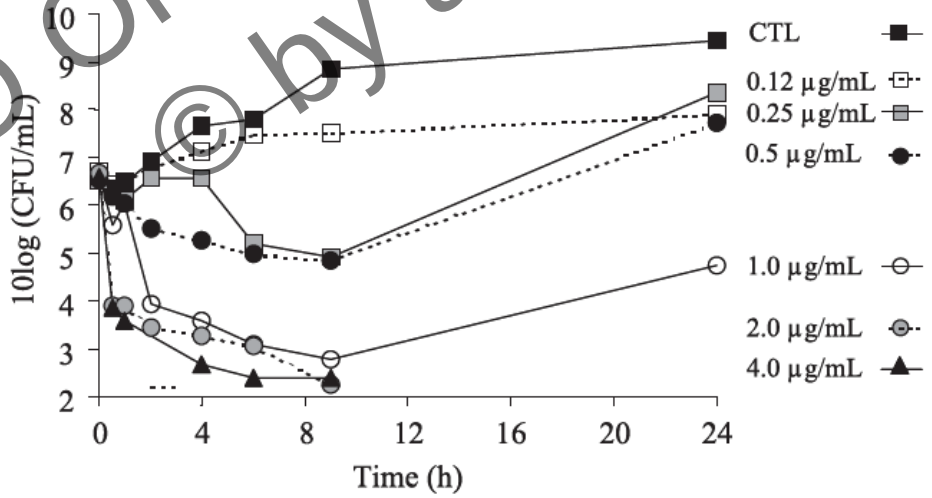
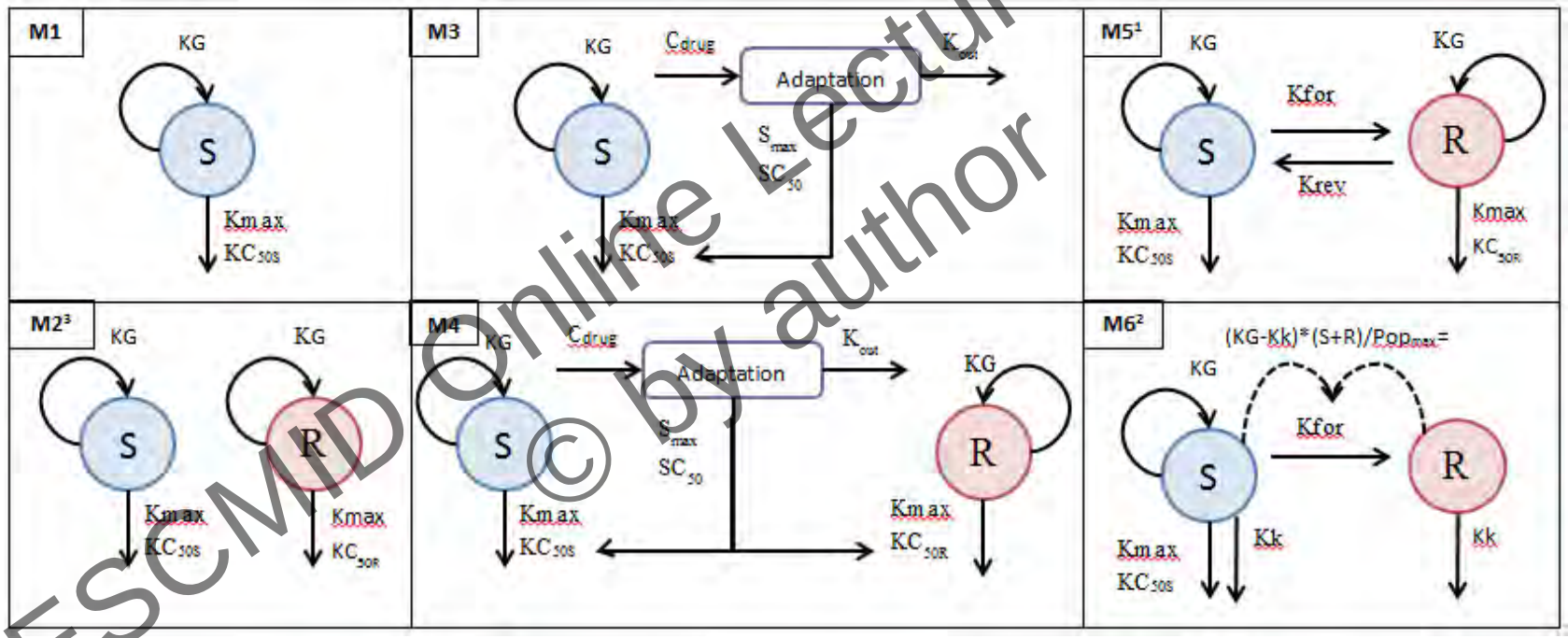



FIG. 1. Representative time-kill curves for *P aeruginosa* exposed to ciprofloxacin at concentrations ranging from 0 to 4.0 µg/ml. CTL, control.

# *Multiplicity of PK-PD model to predict regrowth*



## Adaptation



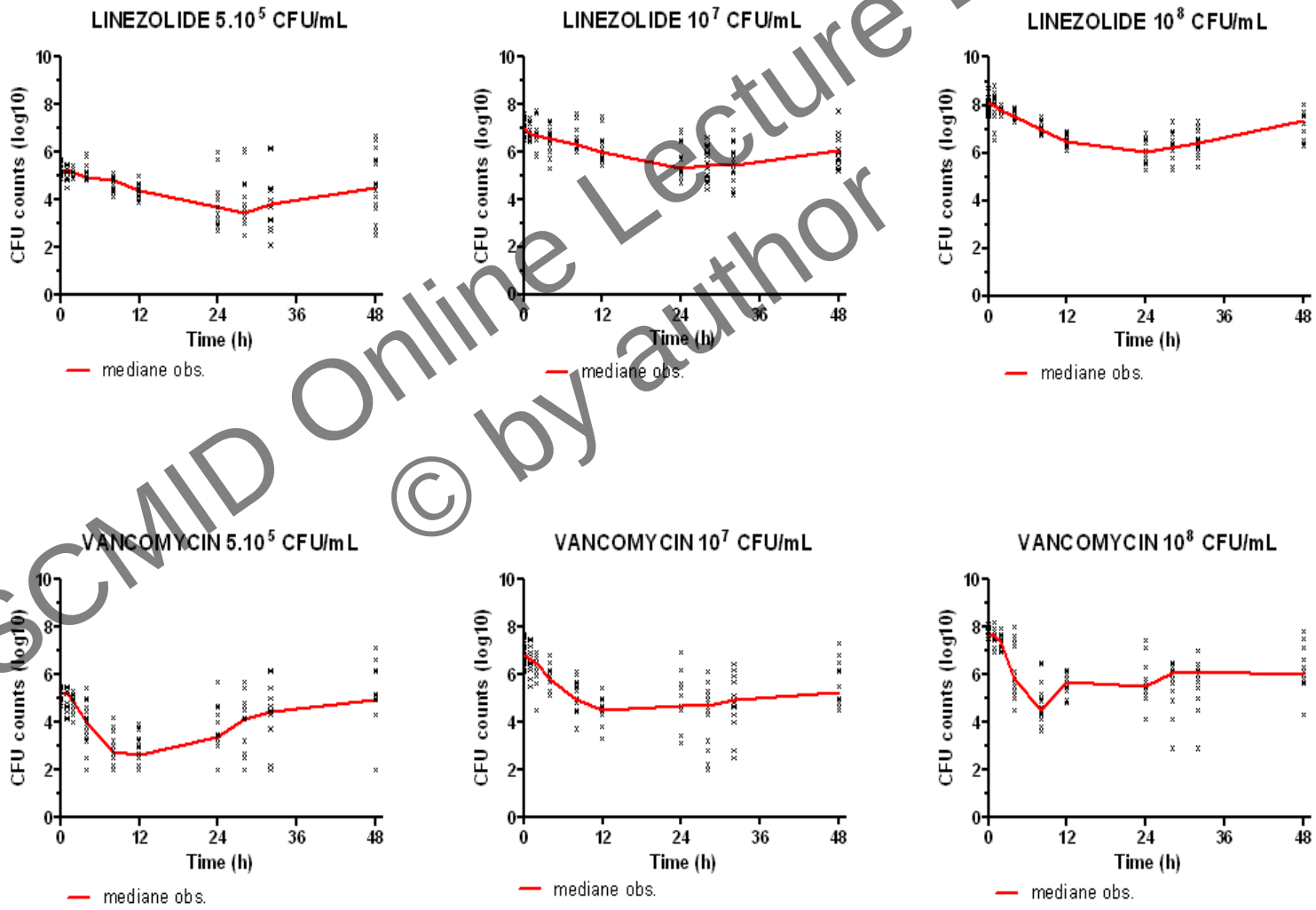

2 Sub-pop (S and R)

Université de Poitiers 1431

*(Jacobs M. et al., poster ECCMID 2013)*

# *Semi-mechanistic models for bacteriostatic versus bactericidal effects with regrowth*

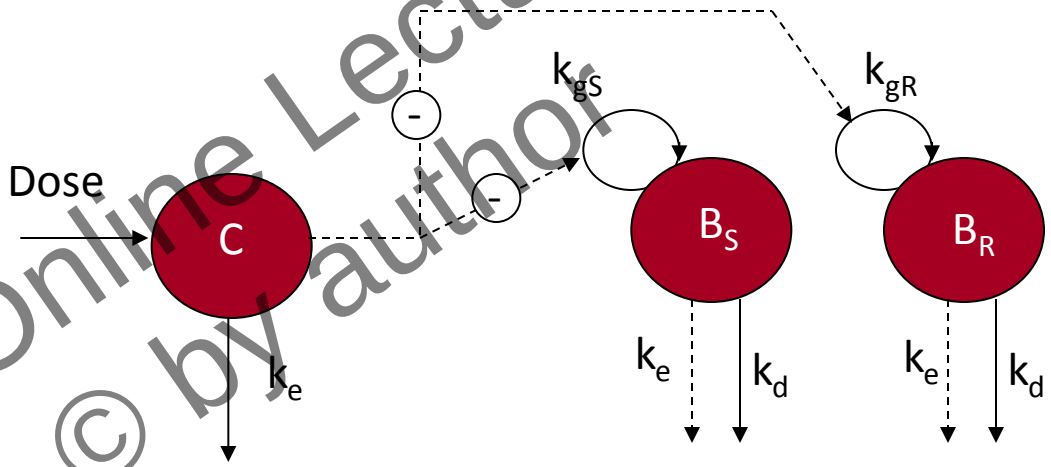




# PK-PD model for linezolid: growth inhibition + 2 sub-populations



## Bacteriostatic → Growth Inhibition ($k_g$)




$$\frac{dB_S}{dt} = K_{gS} \cdot \left(1 - \frac{B_S + B_R}{N_{max}}\right) \cdot \left(1 - \frac{I_{max\,S} \cdot C}{IC_{50\,S} + C}\right) \cdot B_S - \left(K_d + K_e\right) \cdot B_S$$

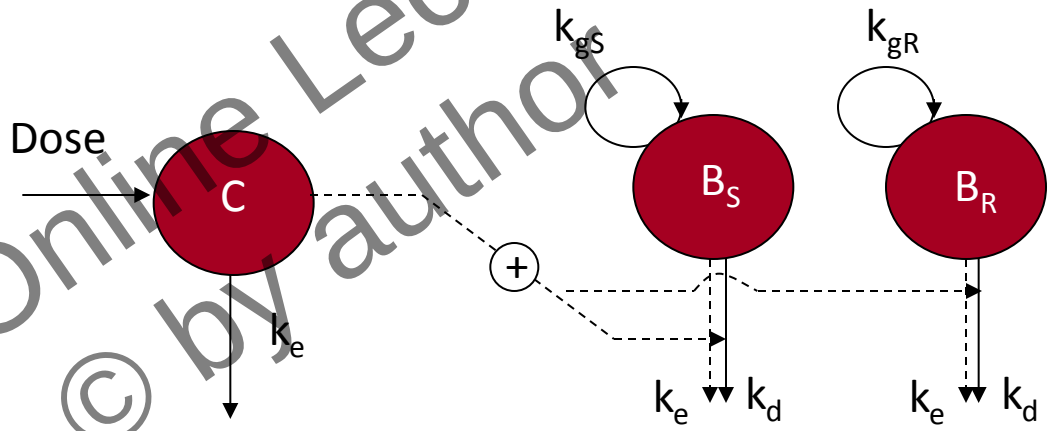
$$\frac{dB_R}{dt} = K_{gR} \cdot \left(1 - \frac{B_S + B_R}{N_{max}}\right) \cdot \left(1 - \frac{I_{max\,R} \cdot C}{IC_{50R} + C}\right) \cdot B_R - \left(K_d + K_e\right) \cdot B_R$$

# *PK-PD model for vancomycin: death stimulation + 2 sub-populations*





## Bactericidal → Death Stimulation (kd)

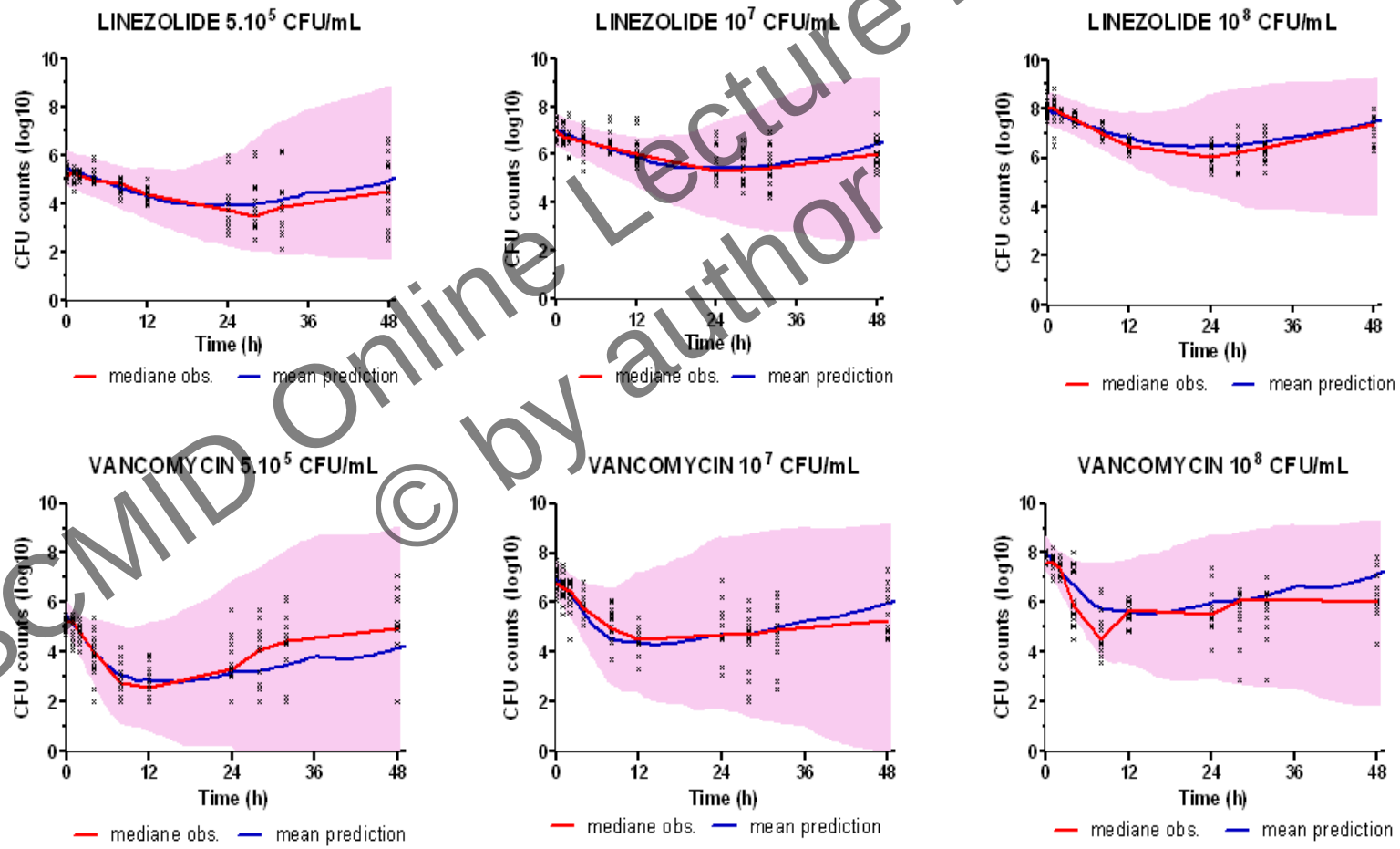



$$\frac{dB_S}{dt} = K_{gS} \cdot \left(1 - \frac{B_S + B_R}{N_{\max}}\right) \cdot B_S - \left(\frac{K_{kS} \cdot C}{EC_{50S} + C} + K_d + K_e\right) \cdot B_S$$

$$\frac{dB_R}{dt} = K_{gR} \cdot \left(1 - \frac{B_S + B_R}{N_{\max}}\right) \cdot B_R - \left(\frac{K_{kR} \cdot C}{EC_{50R} + C} + K_d + K_e\right) \cdot B_R$$

# *Modeling result*

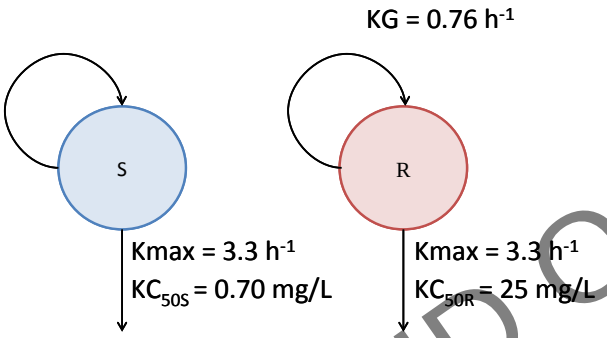


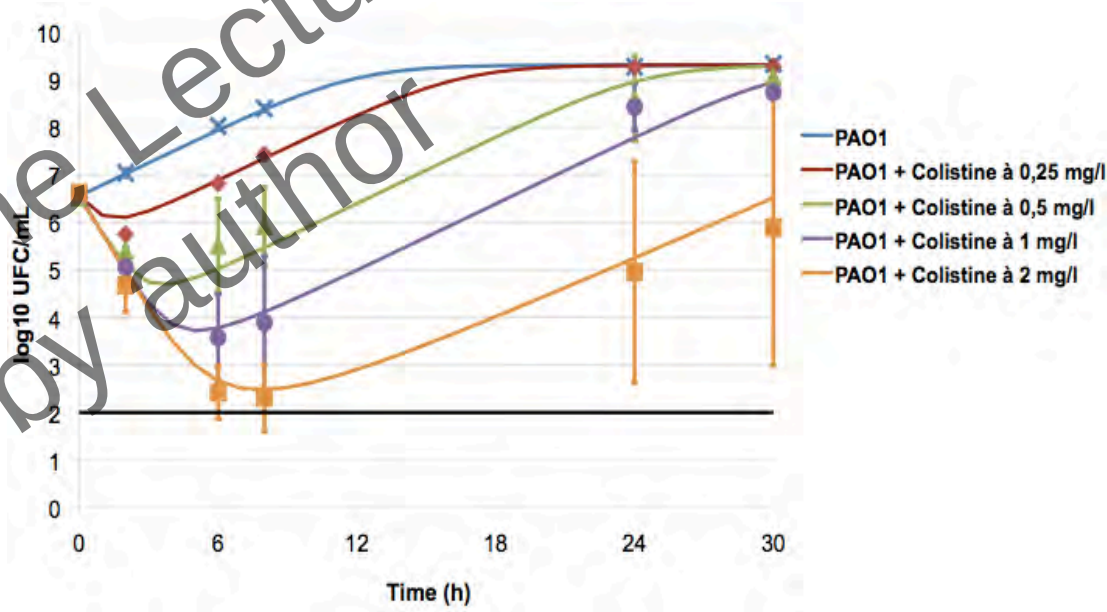



*(Grégoire N. et al., ECCMID, 2013)*

# *Semi mechanistic PD model to characterize the colistin quick bactericidal effect*





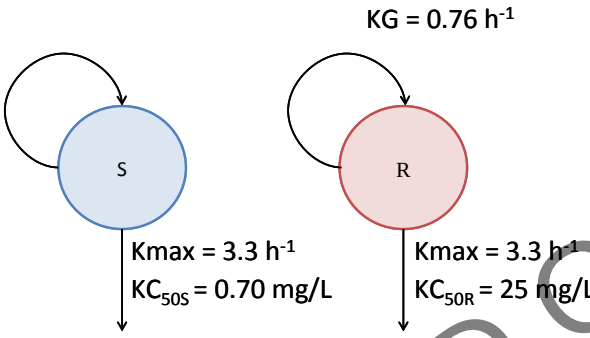






Université de Poitiers 1431

*(Boisson M. et al., internal report)*

# *Predicted effect of colistin within ELF after Aerosol vs IV adminsitration of CMS*



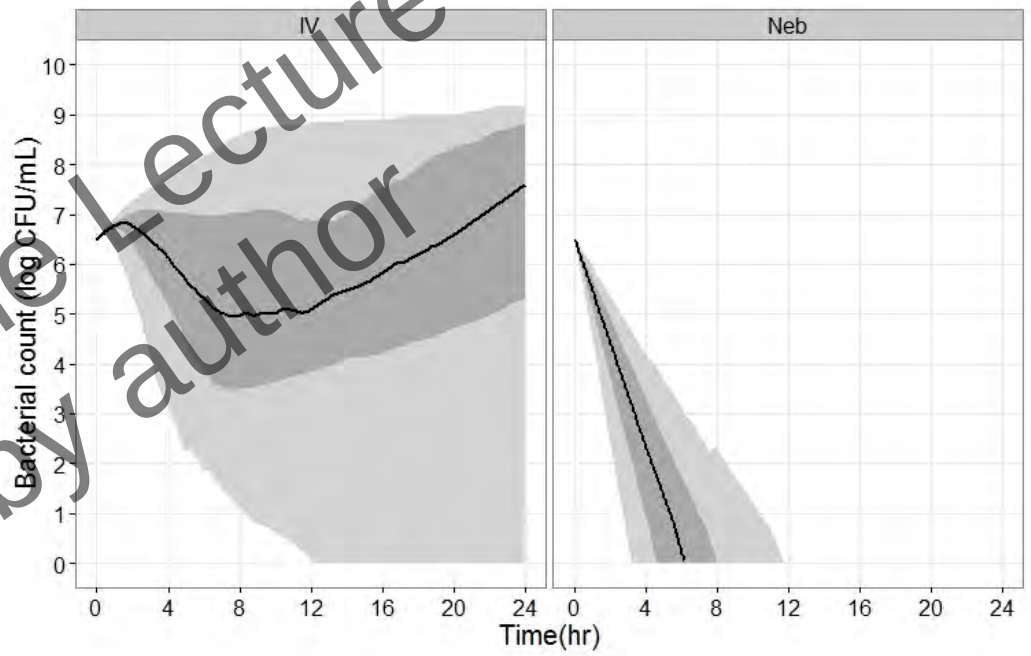




*Fig. 6: Predicted bacterial count over time following dosing with 2 MIU of CMS IV (left) or nebulized (right).*

# Conclusion

- Not so many new « last resort » antibiotics

- PK modifications are expected in cancer patients

    - But not always well documented

    - And potentially difficult to interpret

- PK without PD is not enough

# Acknowledgements:

- France Roblot
- Matthieu Jacobs
- Nicolas Grégoire
- Patrice Gobin
- Sandrine Marchand
- Olivier Mimoz

*Part of this work was financially supported by:*

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