JNI 21es Journées Nationales d'Infectiologie
Poitiers et la région Nouvelle Aquitaine
Palais des Congrès du Futuroscope
du mercredi 9 septembre 2020 au vendredi 11 septembre 2020

# PK/PD : comment adapter la posologie des antibiotiques ? Au cours des infections du SNC.

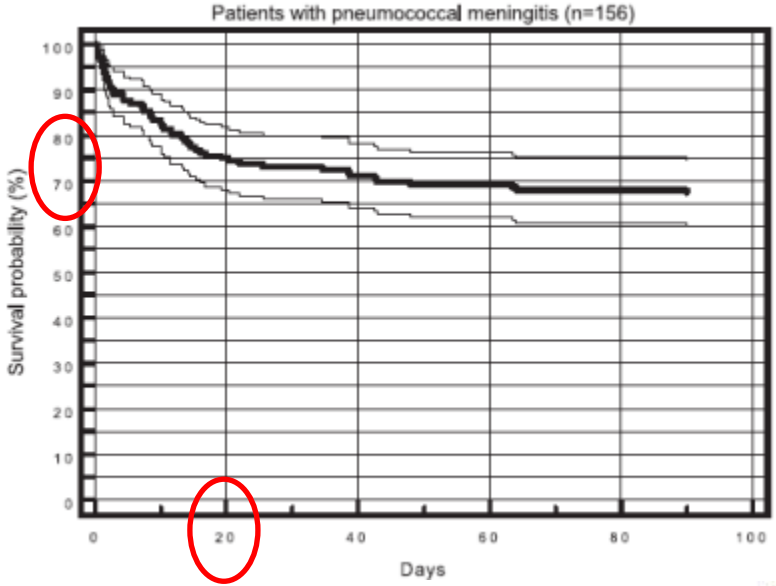
Pr Claire DAHYOT-FIZELIER
Service d'Anesthésie-Réanimation-Médecine Péri-Opératoire
INSERM U1070 - Pharmacologie des agents anti-infectieux
Poitiers

# Conflits d'intérêt

- **Aucun**

# Detrimental role of delayed antibiotic administration and penicillin-nonsusceptible strains in adult intensive care unit patients with pneumococcal meningitis: The PNEUMOREA prospective multicenter study*

Marc Auburtin, MD; Michel Wolff, MD; Julien Charpentier, MD; Emmanuelle Varon, MD; Yves Le Tulzo, MD, PhD; Christophe Girault, MD; Ismaël Mohammedi, MD; Benoît Renard, MD; Bruno Mourvillier, MD; Fabrice Bruneel, MD; Jean-Damien Ricard, MD; Jean-François Timsit, MD, PhD




Crit Care Med 2006 Vol. 34, No. 11

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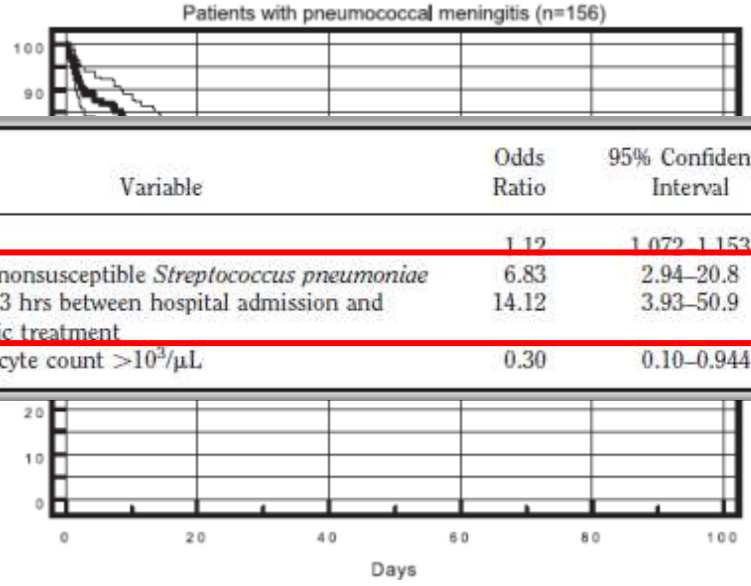


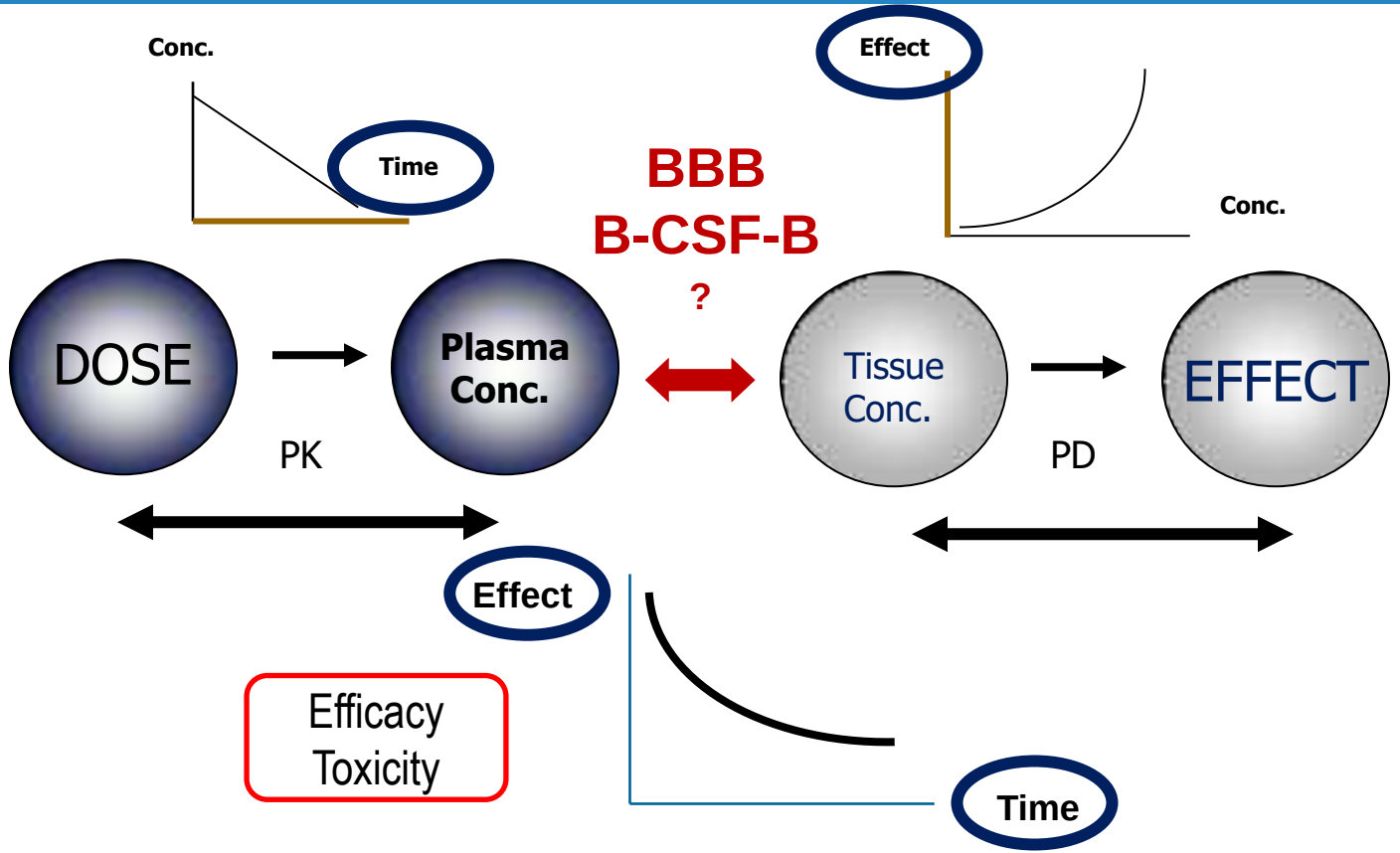

| Variable | Odds Ratio | 95% Confidence Interval | *p* Value |
|---|---|---|---|
| SAPS II[a] | 1.12 | 1.072–1.153 | .002 |
| Penicillin-nonsusceptible *Streptococcus pneumoniae* | 6.83 | 2.94–20.8 | $<10^{-4}$ |
| Interval >3 hrs between hospital admission and antibiotic treatment | 14.12 | 3.93–50.9 | $<10^{-4}$ |
| CSF leukocyte count $>10^3/\mu L$ | 0.30 | 0.10–0.944 | .04 |

Crit Care Med 2006 Vol. 34, No. 11

# Antibiothérapie précoce dans les objectifs thérapeutiques….

# PKPD pour optimiser les régimes posologiques ?

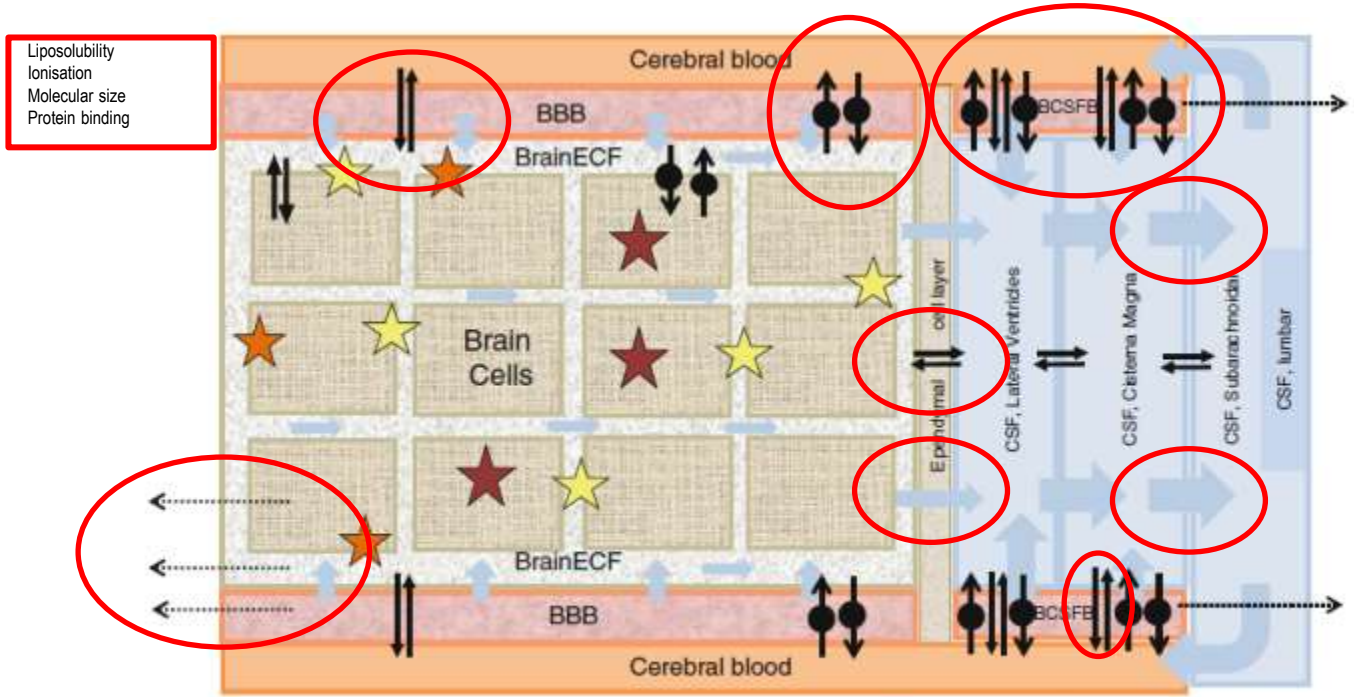
# PK-PD modeling ?



# Utility of CSF in translational neuroscience

Elizabeth C. M. de Lange

BHE ≠ BHL




**CSF « Bulk flow »**

Fig. 3 Simplified and schematic representation passive and active transport processes, metabolism, and fluid flow, that all govern the concentration–time profile of the free drug at different sites in the CNS, and therewith CNS drug effects



J Pharmacokinet Pharmacodyn (2013) 40:315–326

# Posologies basées sur les études dans le LCR…

# Variabilité de la distribution des ATB dans le LCR

< 10%

30 à 70%

| | CSF penetration (CSF:plasma)* in uninflamed meninges | CSF penetration (drug in CSF:plasma)* in inflamed meninges |
|---|---|---|
| β-lactams | | |
| Benzylpenicillin | 0·02 | 0·1 |
| Amoxicillin/ampicillin | 0·01 | 0·05 |
| Cefotaxime | 0·1 | 0·2 |
| Ceftriaxone | 0·007 | 0·1 |
| Meropenem | 0·1 | 0·3 |
| Aminoglycosides | | |
| Gentamicin | 0·01 | 0·1 |
| Amikacin | No data | 0·1 |
| Glycopeptides | | |
| Vancomycin | 0·01 | 0·2 |
| Teicoplanin | 0·01 | 0·1 |
| Fluoroquinolones | | |
| Ciprofloxacin | 0·3 | 0·4 |
| Moxifloxacin | 0·5 | 0·8 |
| Levofloxacin | 0·7 | 0·8 |
| Others | | |
| Chloramphenicol | 0·6 | 0·7 |
| Rifampicin | 0·2 | 0·3 |
| Newer agents | | |
| Cefepime | 0·1 | 0·2 |
| Linezolid | 0·5 | 0·7 |
| Daptomycin | No data | 0·05 |
| Tigecycline | No data | 0·5 |

Inflammation augmente la perméabilité des barrières

Advances in treatment of bacterial meningitis

Lancet 2012; 380: 1693-702

# Advances in treatment of bacterial meningitis

*Diederik van de Beek, Matthijs C Brouwer, Guy E Thwaites, Allan R Tunkel*

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| β-lactams | | |
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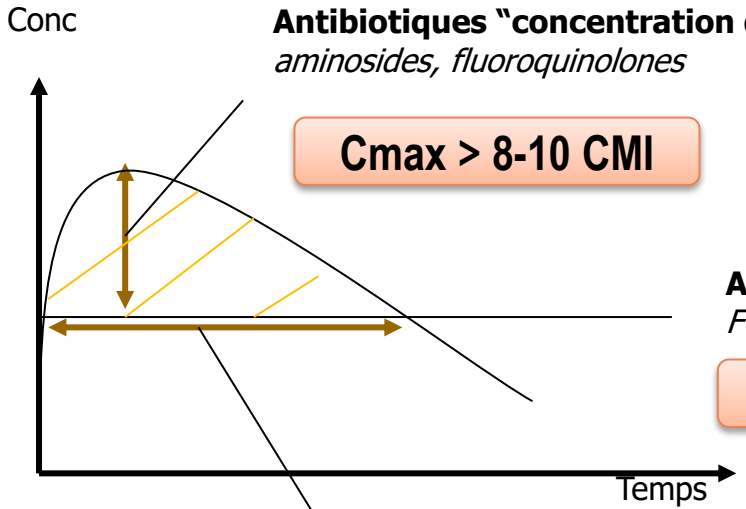
**Molécules hydrophiles : Facteur 2 to 10**

Cibles PD atteintes ?

**Moins d'effet pour les molécules à « bonne diffusion »**

Lancet 2012; 380: 1693-702

# Quels objectifs thérapeutiques ?




**Antibiotiques "concentration dépendants"**
*aminosides, fluoroquinolones*

Bolus

**Cmax > 8-10 CMI**

Cible adaptée au LCR ?

**Antibiotiques "temps & conc° dépendants"**
*FQ, daptomycine, linezolide, Vancomycine*

**[SSC>CMI] > 80-120 à >600**

**Antibiotiques "temps dépendants"**
*β-lactamines, carbapénème, macrolides, linezolide*

Bolus ou **Perf Continues**

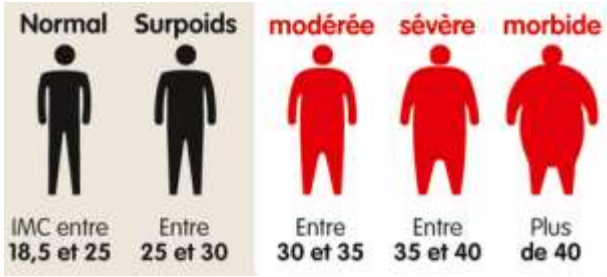
**[conc] ~ 90-100% Δt >MIC ou 4CMI**

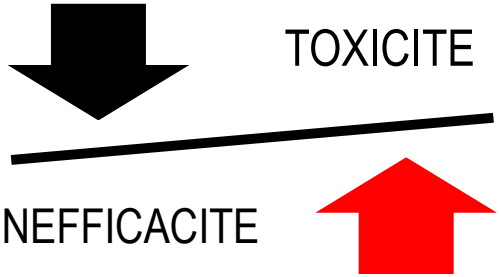
# Facteurs à considérer aussi….

Virulence bactérienne

« La cible » de Paul Sibuet.

Défaillances d'organes

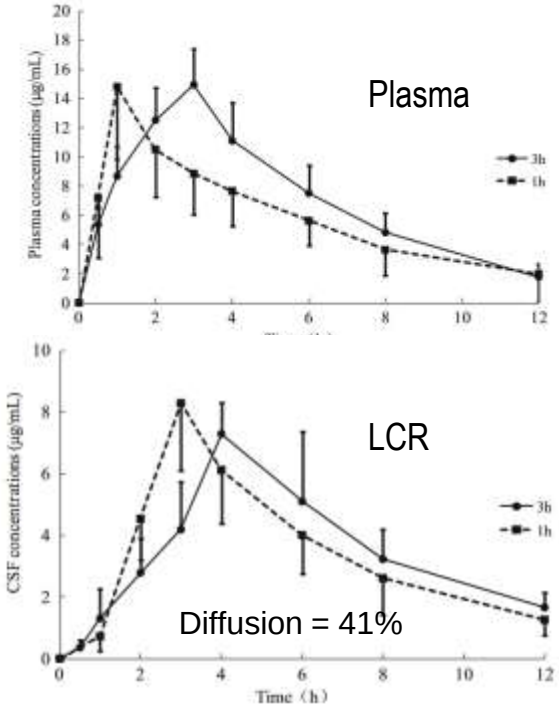


# Comment la PKPD peut-elle nous aider?

# Prolonged infusion of linezolid is associated with improved pharmacokinetic/pharmacodynamic (PK/PD) profiles in patients with external ventricular drains

Wenjun Zhao [1,2] · Lingti Kong [3] · Chenchen Wu [4] · Xiaofei Wu [2]




200mg/h pdt 3h

| MIC (μg/mL) | PTA (%) | | | |
|---|---|---|---|---|
| | Plasma | | CSF | |
| | $AUC_{0-24\ h}$/MIC | %T > MIC | $AUC_{0-24\ h}$/MIC | %T > MIC |
| 1 | 99.90 | 100 | 0.00 | 100 |
| 2 | 50.04 | 99.99 | 0.00 | 99.98 |
| 4 | 0.04 | 99.92 | 0.00 | 93.21 |
| 8 | 0.00 | 86.92 | 0.00 | 27.89 |

| MIC (μg/mL) | PTA (%) | | | |
|---|---|---|---|---|
| | Plasma | | CSF | |
| | $AUC_{0-24\ h}$/MIC | %T > MIC | $AUC_{0-24\ h}$/MIC | %T > MIC |
| 1 | 86.85 | 99.81 | 25.92 | 99.54 |
| 2 | 20.32 | 97.41 | 0.00 | 90.56 |
| 4 | 0.33 | 75.88 | 0.00 | 49.10 |
| 8 | 0.00 | 21.16 | 0.00 | 8.13 |

European Journal of Clinical Pharmacology **2020**

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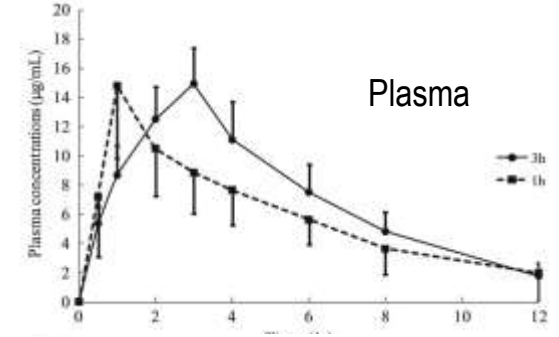


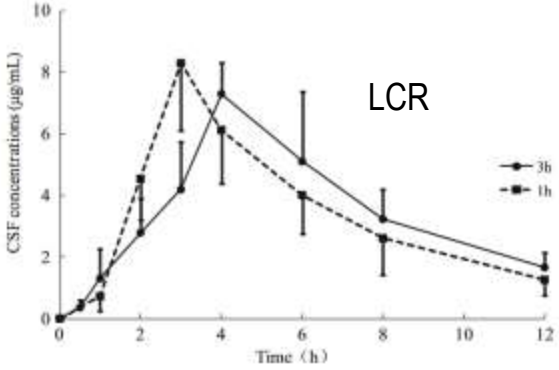


| MIC (μg/mL) | PTA (%) | | | |
|---|---|---|---|---|
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| | $AUC_{0-24\ h}$/MIC | %T > MIC | $AUC_{0-24\ h}$/MIC | %T > MIC |
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European Journal of Clinical Pharmacology **2020**

# Pharmacodynamics of ceftazidime and meropenem in cerebrospinal fluid: results of population pharmacokinetic modelling and Monte Carlo simulation

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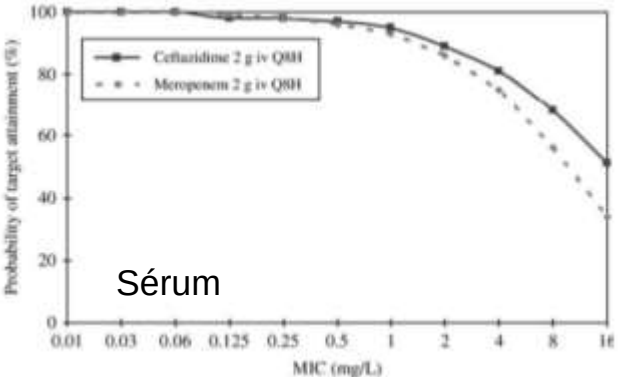


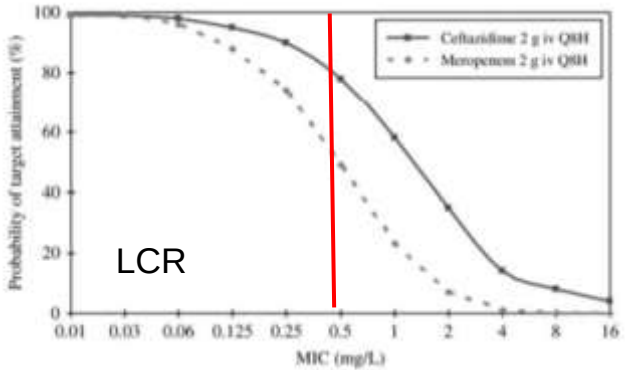


| CRF (%) (cumulative fraction response) | Ceftazidime 2 g intravenously every 8 h | | | Meropenem 2 g intravenously every 8 h | | |
|---|---|---|---|---|---|---|
| | 50% $T_{>MIC}$ (CSF) | 100% $T_{>MIC}$ (CSF) | 60% $fT_{>MIC}$ (serum) | 50% $T_{>MIC}$ (CSF) | 100% $T_{>MIC}$ (CSF) | 40% $fT_{>MIC}$ (serum) |
| *Citrobacter* spp. | 78.7 | 73.3 | 90.3 | 98.2 | 97.0 | 99.6 |
| *E. coli* | 94.1 | 89.0 | 97.3 | 99.8 | 99.4 | 99.9 |
| *Enterobacter* spp. | 71.0 | 65.8 | 83.1 | 98.1 | 95.5 | 99.5 |
| *Klebsiella* spp. | 89.6 | 84.5 | 95.0 | 98.4 | 97.1 | 99.1 |
| *P. mirabilis* | 98.7 | 94.3 | 98.6 | 99.1 | 96.3 | 99.7 |
| *P. aeruginosa* | 33.9 | 27.5 | 77.5 | 53.0 | 44.2 | 87.7 |
| *Serratia* spp. | 94.1 | 87.5 | 97.1 | 98.9 | 96.2 | 99.5 |



*Journal of Antimicrobial Chemotherapy* (2007) **60**, 1038–1044

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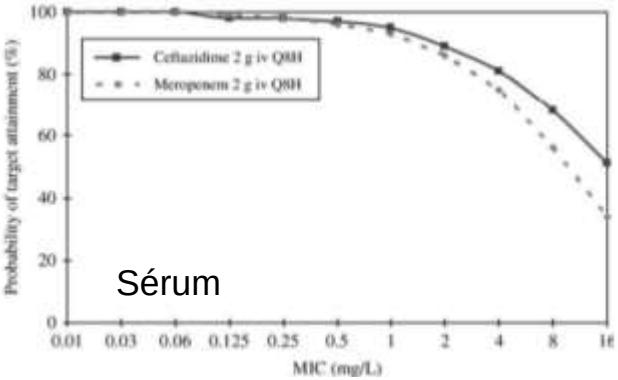


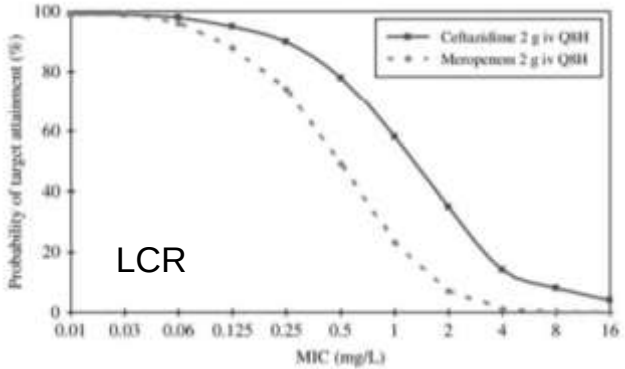


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| *Serratia* spp. | 94.1 | 87.5 | 97.1 | 98.9 | 96.2 | 99.5 |



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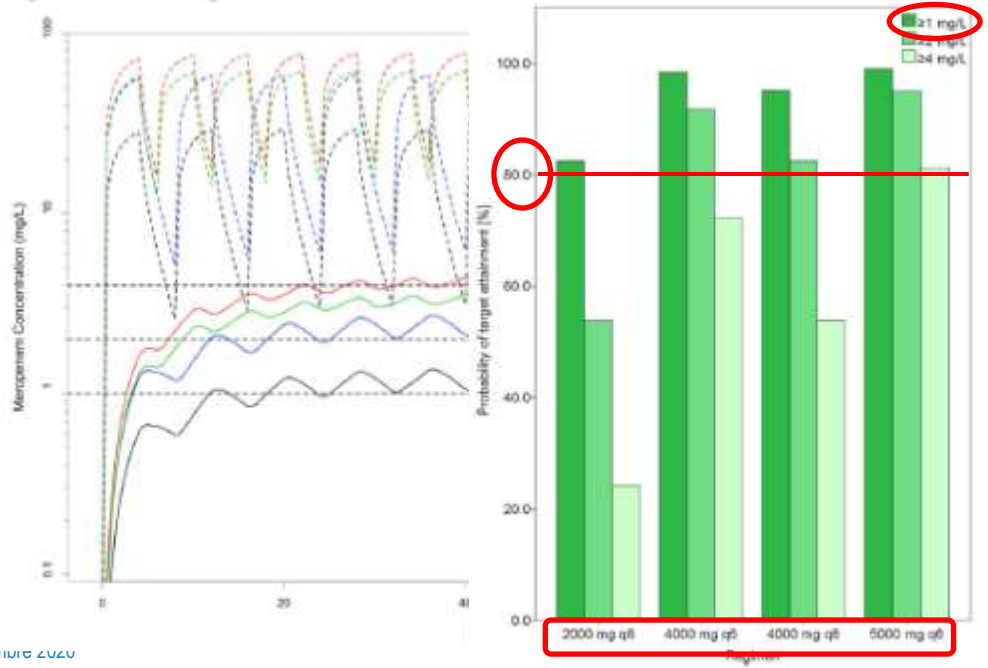
RESEARCH Open Access

# Cerebrospinal fluid penetration of meropenem in neurocritical care patients with proven or suspected ventriculitis: a prospective observational study

Ute Blassmann[1*], Anka C. Roehr[2], Otto R. Frey[2], Cornelia Vetter-Kerkhoff[1], Niklas Thon[3], William Hope[4], Josef Briegel[5] and Volker Huge[5]

N= 21 patients
1000 patients simulés /
4 régimes posologiques

**AUC CSF/pl = 9% [3-16]**




n = 21 patients
209 blood & 199 CSF samples
Meropenem : 2g/8h



Blassmann *et al. Critical Care* (2016) 20:343

RESEARCH Open Access

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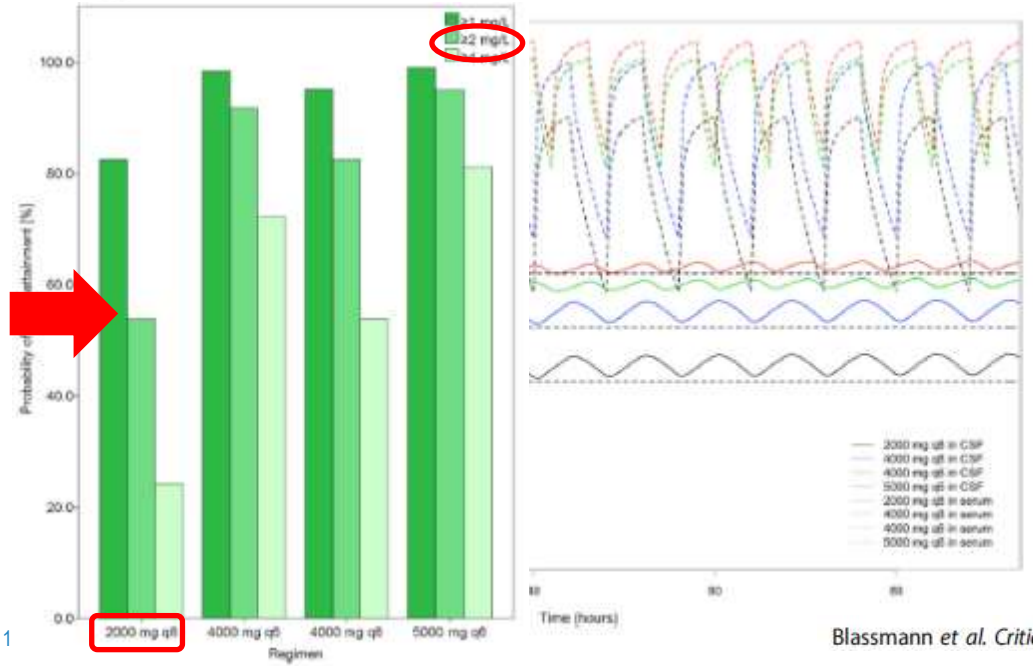
53.8%



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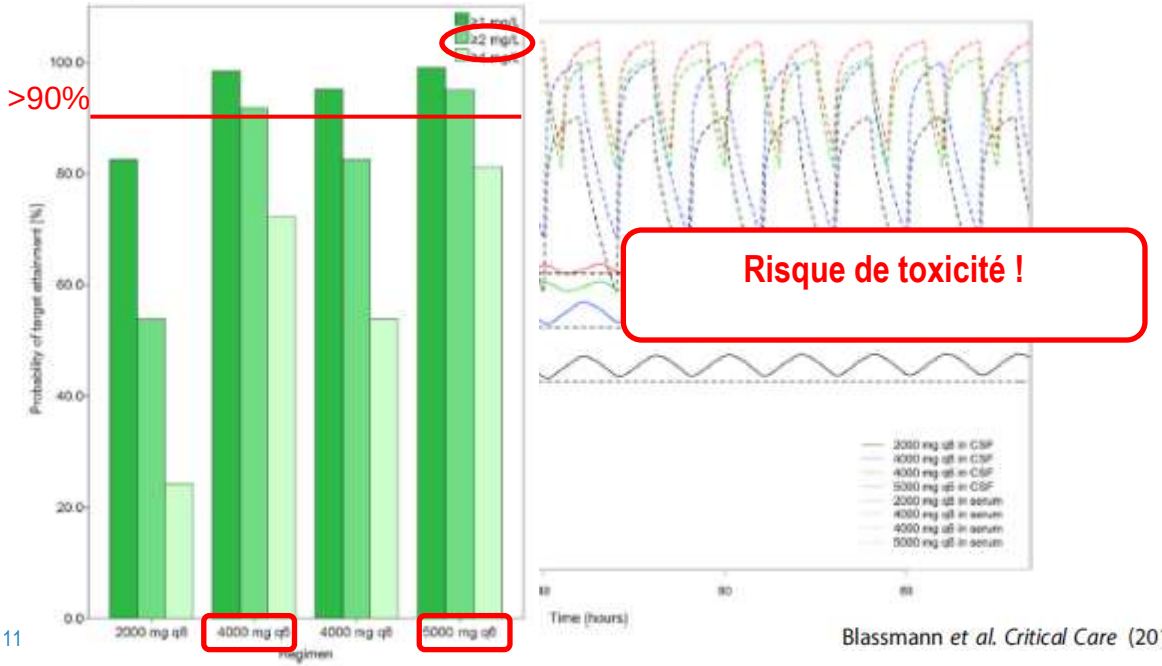


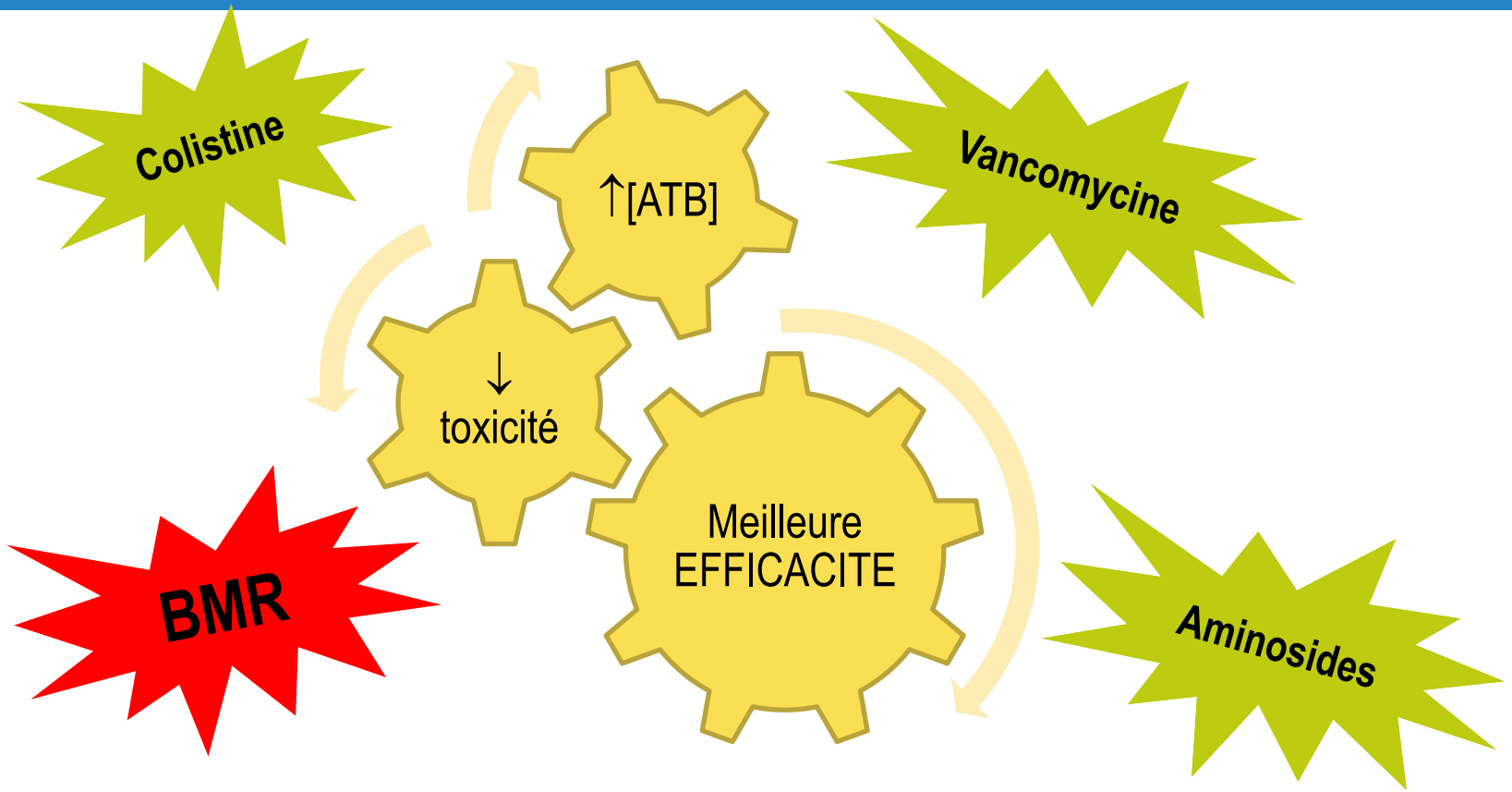

**Risque de toxicité !**



Blassmann *et al. Critical Care* (2016) 20:343

# La voie intra-ventriculaire ?

# Pour les ATB à fenêtre thérapeutique étroite



# Quels objectifs PK-PD en pratique ?

## Practice Guidelines for the Management of Bacterial Meningitis

IDSA GUIDELINES

Allan R. Tunkel,[1] Barry J. Hartman,[2] Sheldon L. Kaplan,[3] Bruce A. Kaufman,[4] Karen L. Roos,[5] W. Michael Scheld,[6] and Richard J. Whitley[7]

Clinical Infectious Diseases 2004; 39:1267–84

**Table 7. Recommended dosages of antimicrobial agents administered by the intraventricular route (A-III).**

| Antimicrobial agent | Daily intraventricular dose, mg |
|---|---|
| Vancomycin | 5–20[a] |
| Gentamicin | 1–8[b] |
| Tobramycin | 5–20 |
| Amikacin | 5–50[c] |
| Polymyxin B | 5[d] |
| Colistin | 10 |
| Quinupristin/dalfopristin | 2–5 |
| Teicoplanin | 5–40[e] |

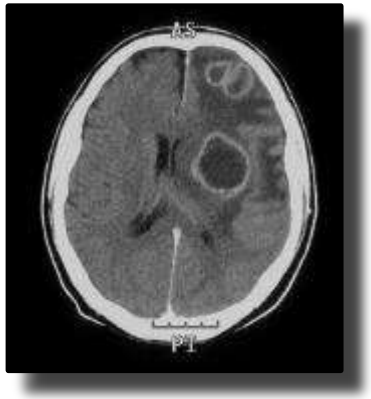
Quotient inhibiteur (QI)

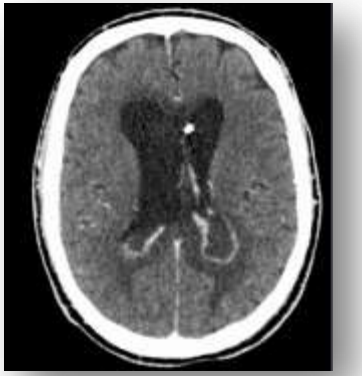
$QI = [ATB]_{CSF} / CMI$

$QI > 10\text{-}20$

**$[ATB]_{CSF} > 10\text{-}20 \times CMI$**

# LCR reflète t-il toutes les cibles du SNC ?





LCR

LEC

BHL

BHE

# Penetration of Drugs through the Blood-Cerebrospinal Fluid/Blood-Brain Barrier for Treatment of Central Nervous System Infections†

Roland Nau,[1,2]* Fritz Sörgel,[3,4] and Helmut Eiffert[5]

| Compound (reference[s] for CSF penetration) | $AUC_{CSF}/AUC_S$[b] | |
|---|---|---|
| | Uninflamed or mildly inflamed meninges | Strong meningeal inflammation |
| Penicillins | **0.02** | **0.2** |
| Penicillin (46, 107, 108, 194, 246) | | |
| Nafcillin (164) | | |
| Cloxacillin (46, 217) | 0.0017 | |
| Amoxicillin (18, 35) | | 0.058 |
| Ampicillin (35, 46, 72) | | |
| Mezlocillin (94) | | |
| Piperacillin (51, 168) | 0.034 | 0.32 |
| β-Lactamase inhibitors | **0.07** | **0.1** |
| Clavulanate (18) | 0.037 | 0.084 |
| Sulbactam (72) | | |
| Tazobactam (168) | 0.104 | |
| Cephalosporins | **0.007–0.1** | **0.15** |
| Cefazolin (111) | | |
| Cephaloridine (46) | | |
| Cefuroxime (112, 229) | | |
| Cefotaxime (96, 175, 194, 195, 230) | 0.12 | 0.04, 0.17 |
| Cefotaxime (96, 175, 194, 195, 230) | 0.12 | 0.04, 0.17 |
| 172, 265) | | |
| Ceftizoxime (165) | | |
| Cefepime (213) | | 0.103 |
| Cefpirome (73, 181, 262) | | 0.145, 0.31 |
| Carbapenems | **0.2** | **0.3** |
| Imipenem (15, 155, 263) | | 0.14 |
| Meropenem (34, 41, 142, 170) | 0.047, 0.21, 0.25 | 0.39 |
| Aminoglycosides | **0.2** | Not available |
| Gentamicin (28, 46) | | |
| Netilmicin (29, 55, 177) | 0.24 | |
| Amikacin (26, 76) | | |
| Fluoroquinolones | **0.3–0.7** | **0.7–0.9** |
| Ciprofloxacin (173, 261) | 0.24, 0.43 | 0.92 |
| Ofloxacin (169) | 0.42 | |
| Levofloxacin (189, 223) | 0.71 | |
| Moxifloxacin (4, 5, 105) | 0.46 | 0.79 (0.71–0.94) |
| Chloramphenicol (46, 74, 270) | 0.6–0.7 | 0.6–0.7 |
| Macrolides (96) | | |
| Clarithromycin (137) | Not available | 0.18 |

| Compound (reference[s] for CSF penetration) | $AUC_{CSF}/AUC_S$[b] | |
|---|---|---|
| | Uninflamed or mildly inflamed meninges | Strong meningeal inflammation |
| Tetracyclines | Ratios of individual CSF and | Ratios of individual CSF and |
| Doxycycline (56, 107, 108, 269) | serum samples suggest AUC ratio ~0.2 | serum samples suggest AUC ratio ~0.2 |
| Fosfomycin (75, 115, 193) | 0.18 (0.09–0.27) | Not available |
| Linezolid (20, 252) | 0.9 (0.8–1) | Not available |
| Metronidazole (93, 101, 258) | Not available | 0.87 |
| 163, 174) | | Not available |
| Trimethoprim and sulfamethoxazole (57, 125, 257) | | |
| Trimethoprim | 0.18 | 0.42–0.51 |
| Sulfamethoxazole | 0.12 | 0.24–0.30 |
| Glycopeptides | | |
| Vancomycin (2, 31, 65, 192, 205) | 0.18, 0.14 | 0.30 (0.29–0.48) |
| Intraventricular therapy | ≫1 | ≫1 |
| Colistin (100, 139, 272) | | |
| Gentamicin (113, 200, 256) | | |
| Netilmicin (55) | | |
| Vancomycin (191, 192, 204) | | |
| Daptomycin (64) | | |
| Amphotericin B (14) | | |

CLINICAL MICROBIOLOGY REVIEWS, Oct. 2010, p. 858–883

Metronidazole and Hydroxymetronidazole Central Nervous System Distribution: 2. Cerebrospinal Fluid Concentration Measurements in Patients with External Ventricular Drain *AAC 2014*

Denis Frasca,[a,b,c] Claire Dahyot-Fizelier,[a,b,c] Christophe Adier,[a,d] Olivier Mimoz,[a,b,c] Bertrand Debaene,[a,b,c] William Couet,[a,b,d] Sandrine Marchand[a,b,d]

Metronidazole and Hydroxymetronidazole Central Nervous System Distribution: 1. Microdialysis Assessment of Brain Extracellular Fluid Concentrations in Patients with Acute Brain Injury *AAC 2014*

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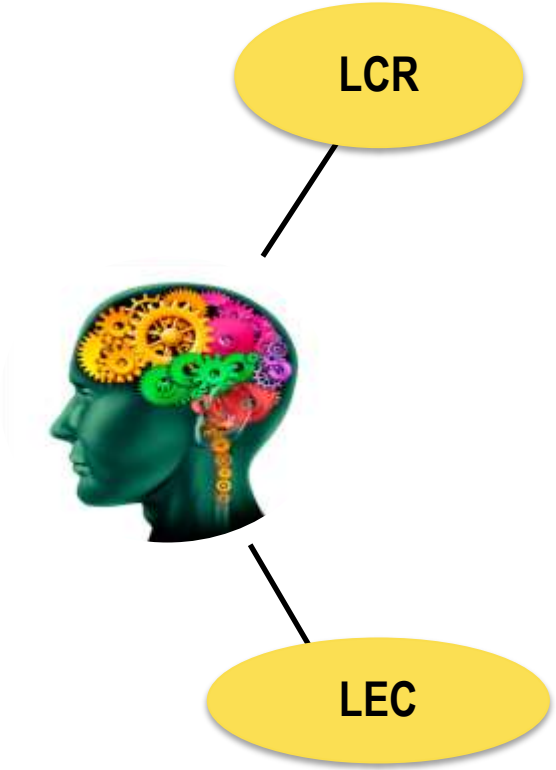
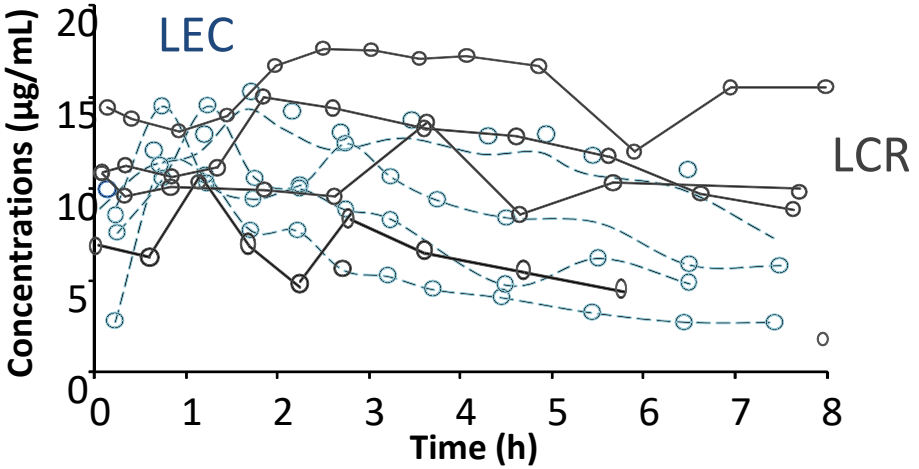
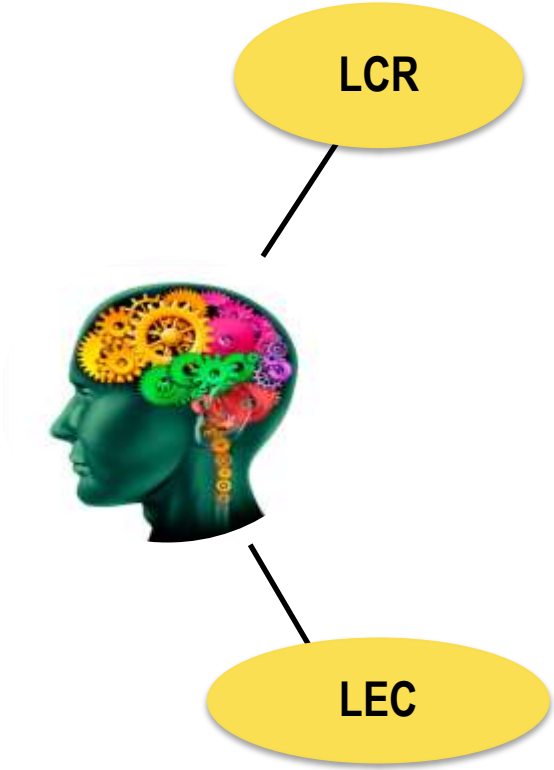
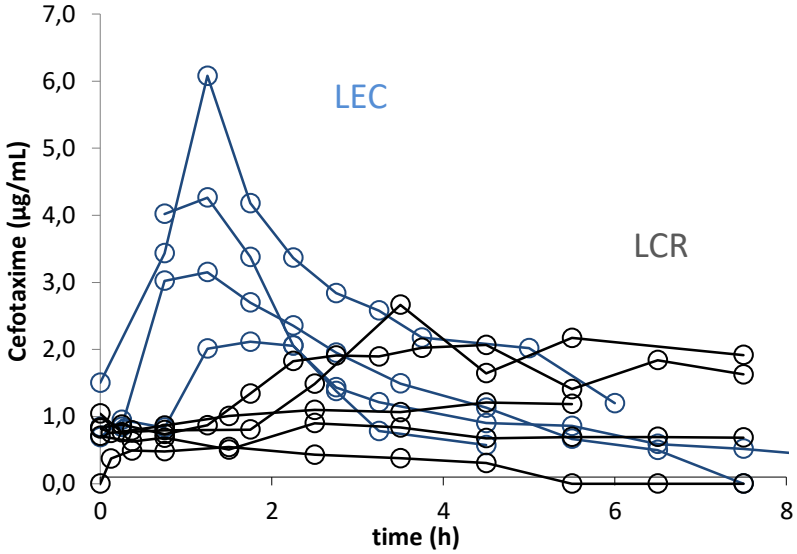



| $AUC_{ECF}$/ $AUC_{pl}$ | $AUC_{CSF}$/$AUC_{pl}$ |
|---|---|
| 102 ± 19 % | 86 ± 16 % |

# 2- Diffusion passive + Efflux : Céfotaxime




| $AUC_{ECF}$/ $AUC_{pl}$ | $AUC_{CSF}$/$AUC_{pl}$ |
|---|---|
| 26 ± 12 % | 12 ± 6 % |

# Microdialysis Study of Cefotaxime Cerebral Distribution in Patients with Acute Brain Injury

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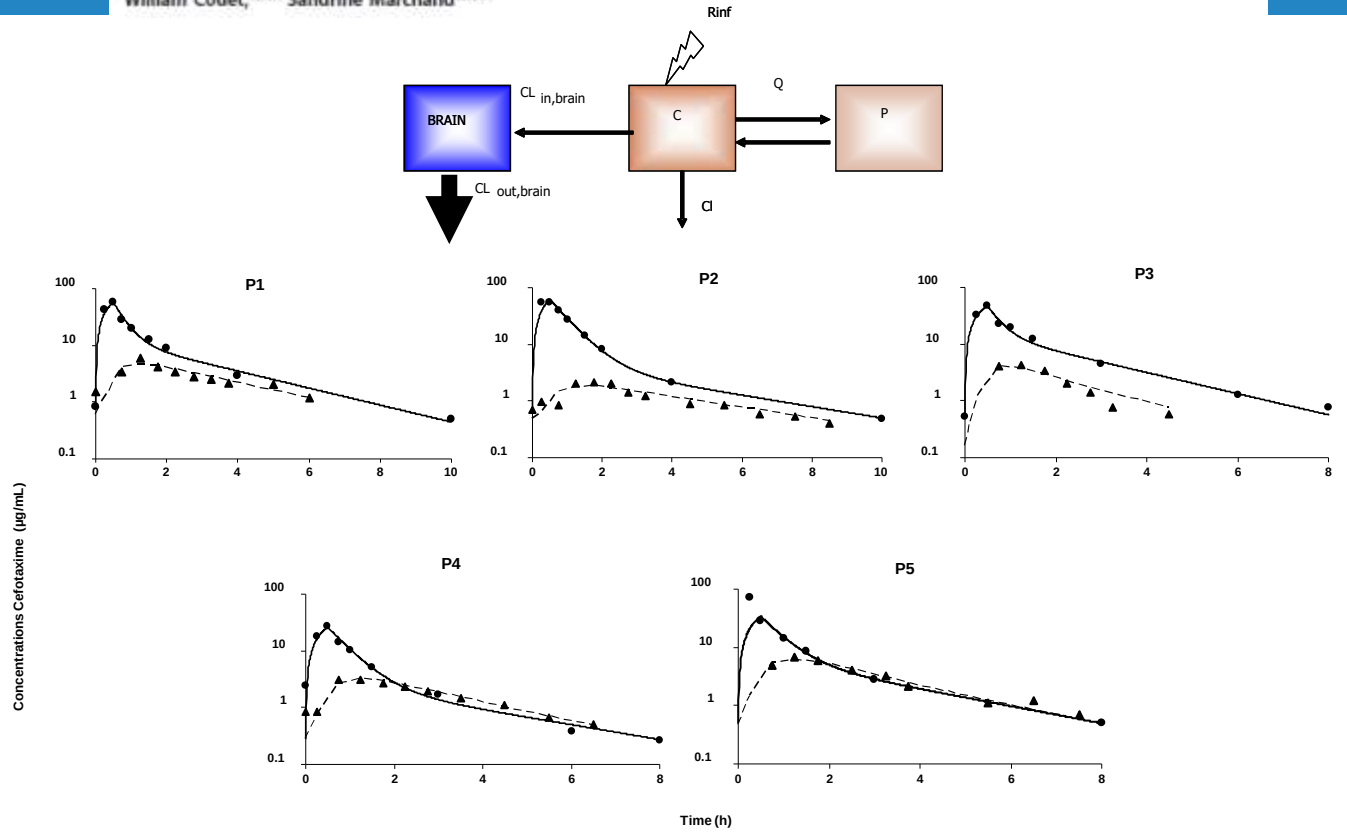


*Antimicrob. Agents Chemother.* 2013, 57(6):2738.

# Microdialysis Study of Cefotaxime Cerebral Distribution in Patients with Acute Brain Injury

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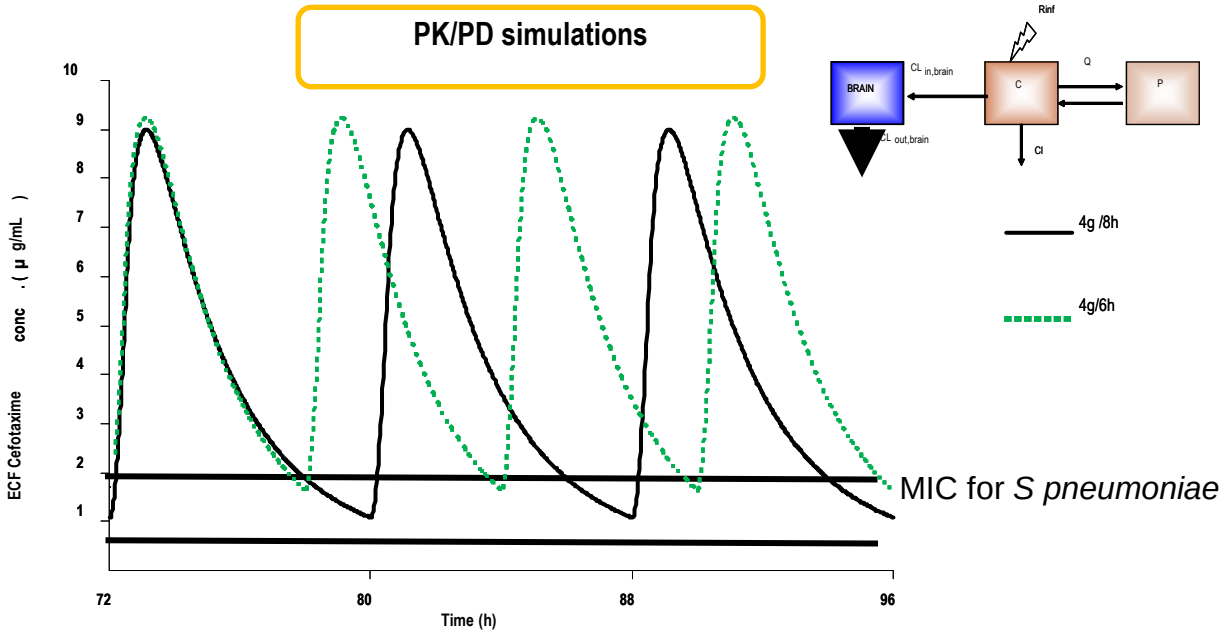



T > MIC : 64 %
4g/8h

T > MIC: 90 %
4g/6h



*Antimicrob. Agents Chemother.* 2013, 57(6):2738.

# Qu'avons-nous appris sur céfotaxime et métronidazole

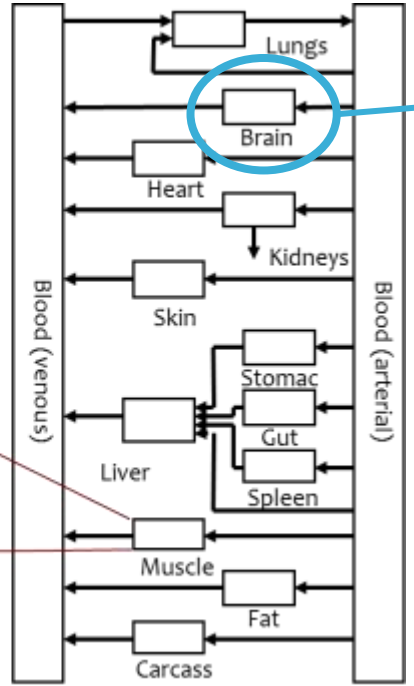
1. Métronidazole : Large distribution dans le LEC & LCR.
2. Céfotaxime : Distribution restreinte dans les deux milieux, deux fois moins bonne dans le LCR que dans le LEC.
3. Profils PK différents dans le LCR et le LEC, profil PK plats dans le LCR…
4. LCR n'est pas un bon substitut du LEC pour tous les antibiotiques.
5. Etudes chez des patients non infectés & cérébro-lésés. Extrapolation fiable ?

# PBPK pour surmonter les limites de ces études PKPD?

# Physiological Based-Pharmacokinetic (PBPK) modeling

Modèles globaux

Modèles partiels

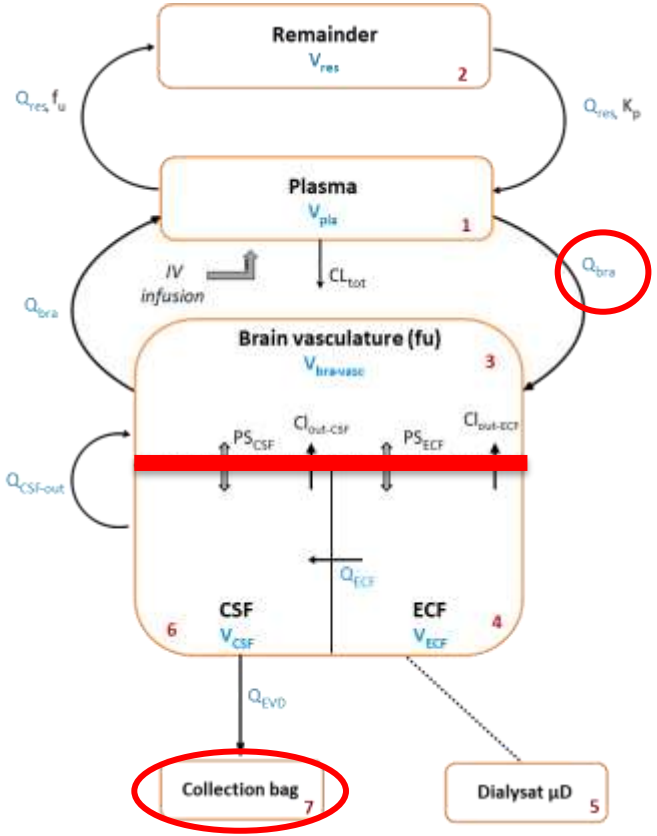



Paramètres physiologiques selon
La littérature

V

Q

# Modèle PBPK partiel



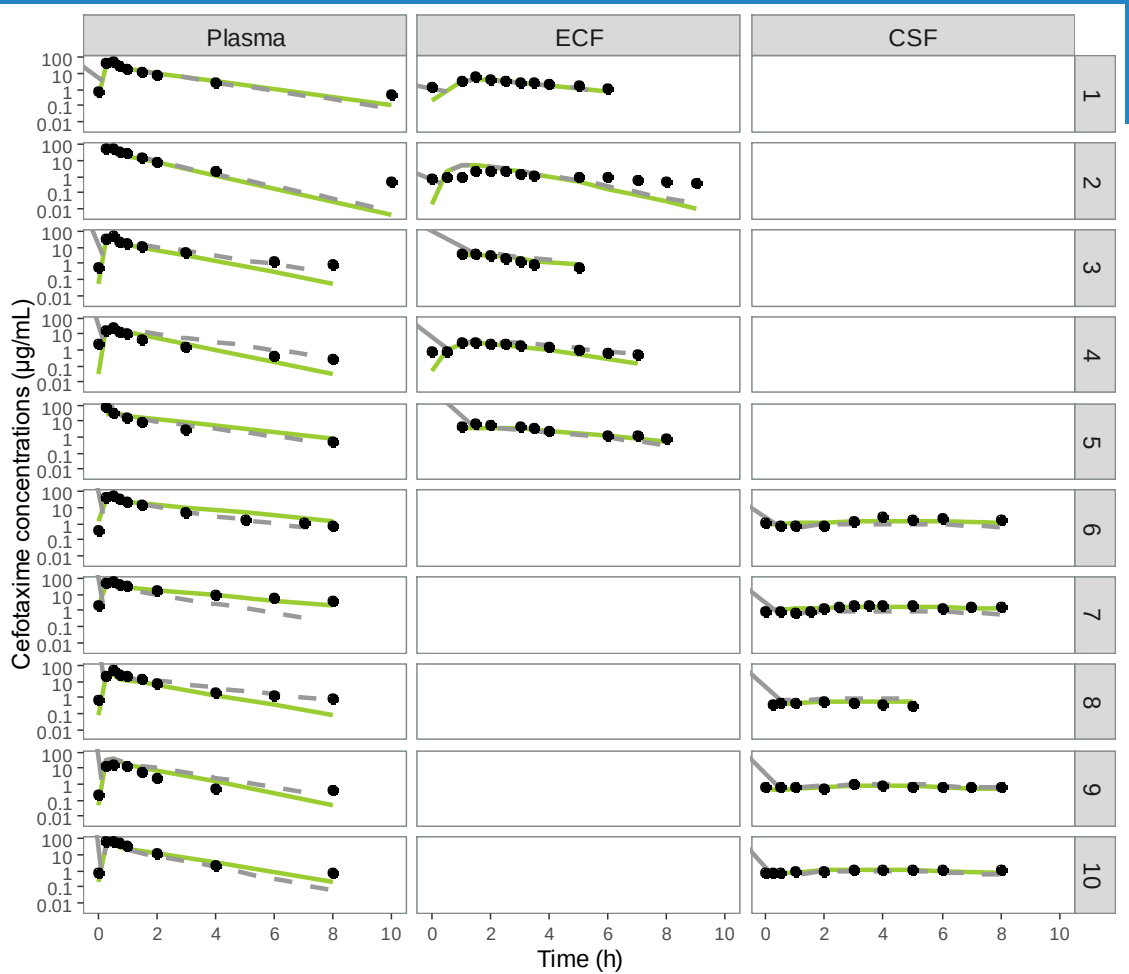

**Objectif = Simuler des situations pathologiques**

- Perméabilité des barrières
- Variations du DSC
- Variation du débit de DVE….



*Diapo Alexia Chauzy*

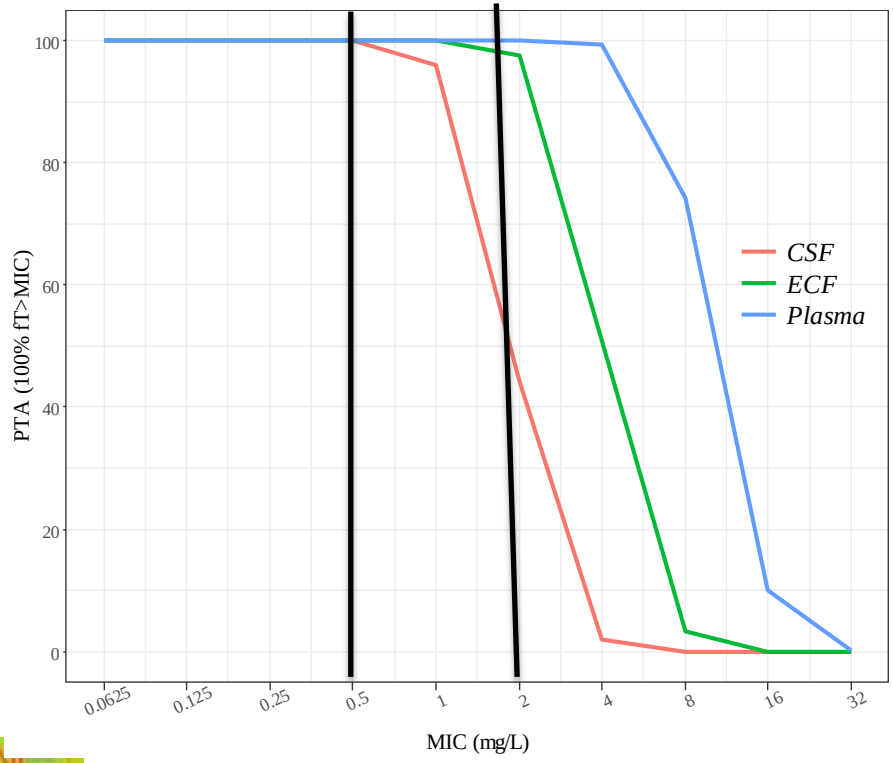
# Céfotaxime



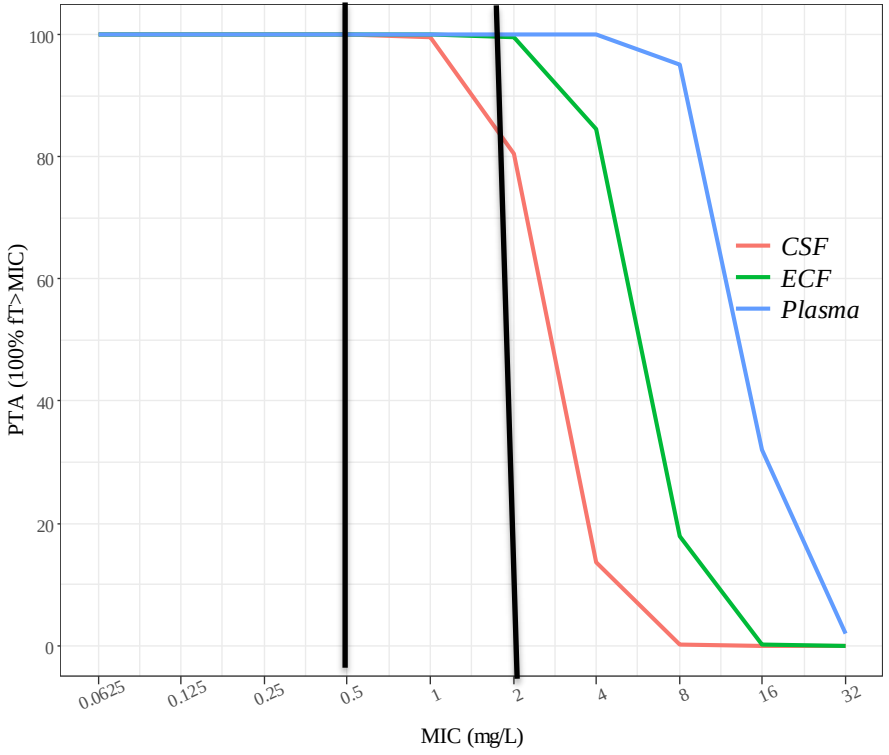



*Diapo Alexia Chauzy*

# Céfotaxime
# 50mg/kg puis 200 mg/kg/j
# IVSE




# Céfotaxime
# 75mg puis 300mg/kg/j
# IVSE






*Diapo Alexia Chauzy*


# Etude multicentrique de PKPD de population de 7 anti-infectieux à large spectre, chez des patients cérébro-lésés porteurs d'une DVE

# Qu'apprenons nous de ces études PKPD ?

- Le LCR n'est pas un bon reflet du LEC
- L'interpretation des résultats doivent prendre en compte les limites des études PKPD
- L'adaptation posologique dépend de la diffusion théorique, du site infectieux, de la virulence bactérienne, des modifications physiopathologiques du patient
- Privilégier des posologies élevées en probabiliste & adapter 2$^{airement}$ à la CMI
- En cas de CMI élevée ou d'échec thérapeutique : le dosage PK aide l'adpatation posologique
- Toujours considérer le risque toxique de l'adaptation posologique et le recours à la voie intra-venticulaire ou thécale associée

# Approche individuelle de l'adaptation posologique

PHAR

# Pharmacology of Antimicrobial Agents

Research group - INSERM U1070

Inserm

Université de Poitiers

CHU de Poitiers

PHAR

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