Vancomycin by continuous infusion ... Why and how ?

Hopefully ...

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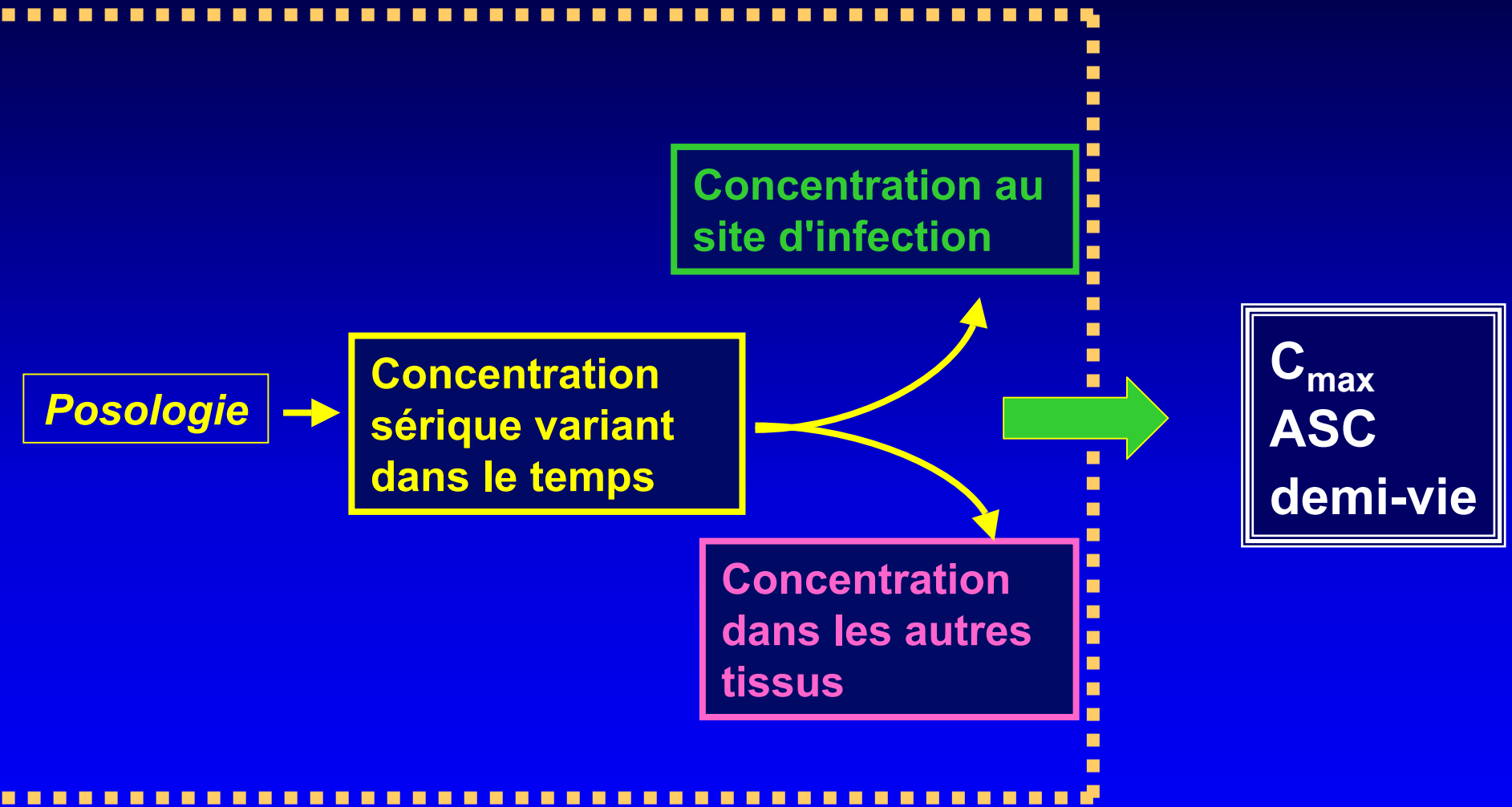
GSK Belgian Symposium -- ECCMID 2004

Principales causes d'échec antibiotique...

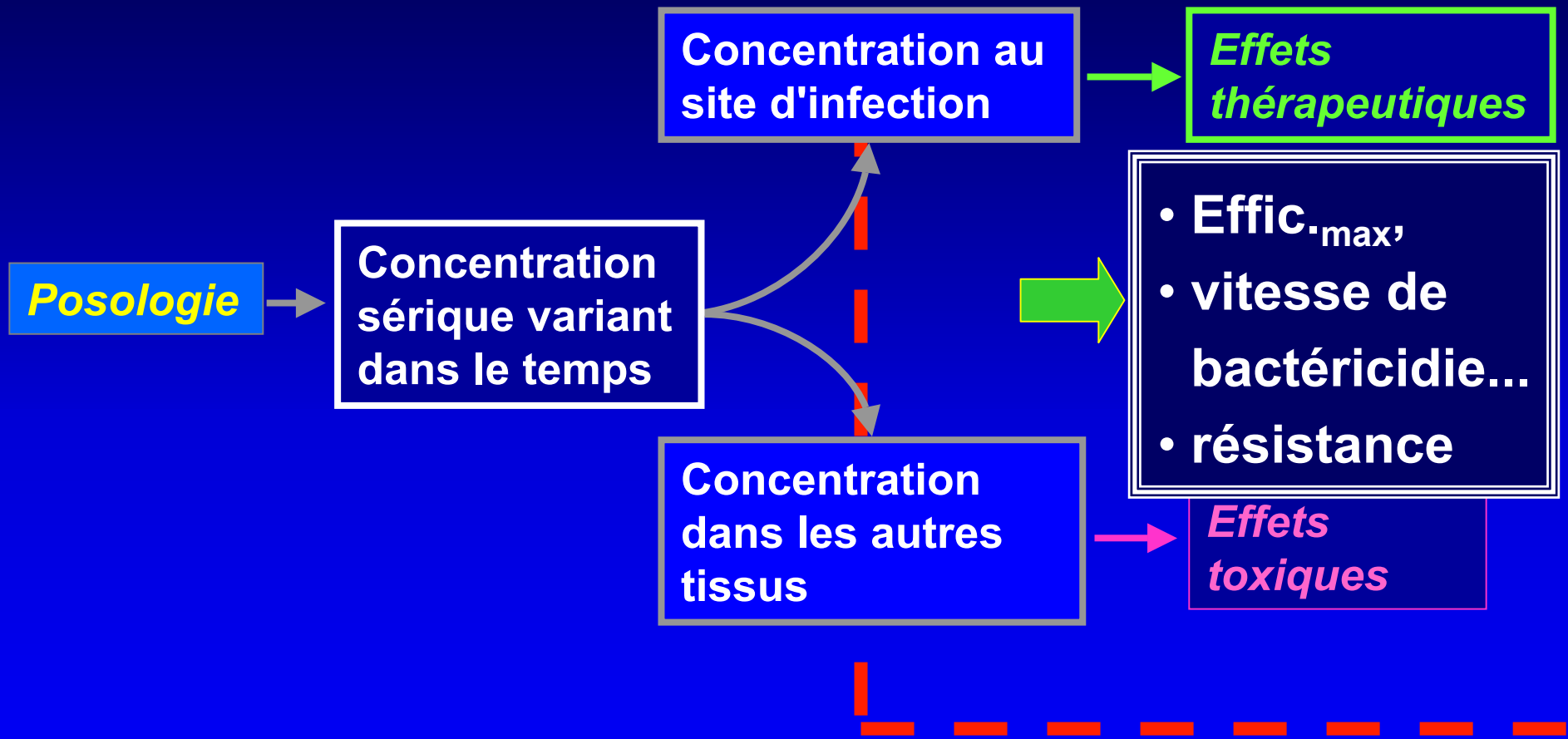
- **Faux échecs**
  - diagnostic erroné
  - maladie sous-jacente non influencée par les antibiotiques
  - manque de patience injustifié
  - inactivation de l'antibiotique
- **Echecs dus au patient**
  - observance insuffisante (au sens large)
  - voie d'administration inadaptée (au sens large
  - sujets immunodéprimés
- **Echecs pharmacologiques**
  - **quantité insuffisante de médicament**
  - **ignorance des paramètres pharmacodynamiques**
  - inactivation *in situ* ou manque de drainage
- **Echecs liés au micro-organisme**
  - erreur sur le pathogène
  - **résistance acquise pendant le traitement**
  - **activité bactéricide insuffisant persistence bactérienne**
  - effet inoculum

Adapté de J.C. Pechère (*In* Schorderet e*t coll.*, 1988, 1993, 1998

Pharmacocinétique

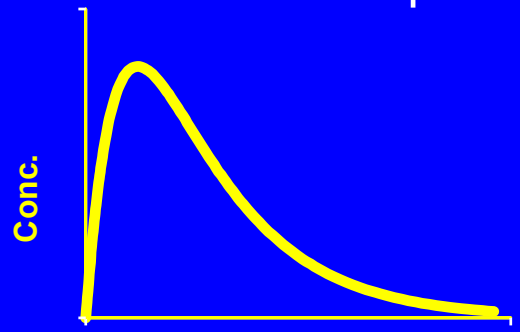


Pharmacodynamie

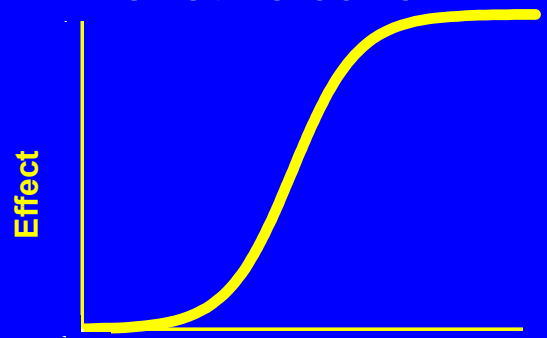


De la pharmacocinétique à la pharmacodynamie ...

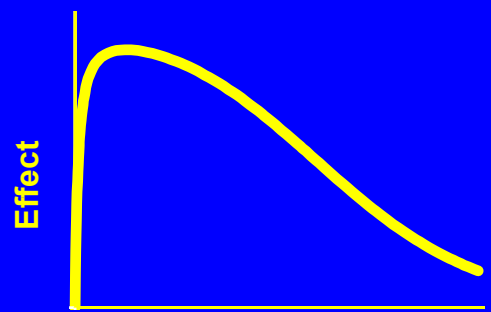
Pharmacocinétique
conc. *vs* temps



Pharmacodynamie
effet *vs* conc.



PK/PD
effet *vs* temps



Adapté de H. Derendorf (2d ISAP Educational Workshop, 2000)

Pharmacokinetics / Pharmacodynamics and resistance to antibiotics ...

"Inadequate dosing of antibiotics is probably an important reason for misuse and subsequent risk of resistance.

A recommendation on proper dosing regimens for different infections would be an important part of a comprehensive strategy.

The possibility to produce such a dose recommendation based on pharmacokinetic and pharmacodynamic considerations will be further investigated in one of the CPMP working parties…"

EMEA discussion paper on Antimicrobial resistance, January 3, 1999 -- EMEA/9880/99

Patterns of antimicrobial activity, PK-PD parameter correlating with efficacy, and goal of therapy **(1 of 3)**

(Craig, Infect. Dis. Clin. N. Amer., 17:479-502, 2003)

1. Time-dependent killing and minimal or no persistent effects

AB	PK-PD param.	goal
• all β-lactams	**Time above MIC**	**Enhance duration of exposure ***

our proposal: * > 50 % in mild infect; 100 % in severe cases

Patterns of antimicrobial activity, PK-PD parameter correlating with efficacy, and goal of therapy **(1 of 3)**

(Craig, Infect. Dis. Clin. N. Amer., 17:479-502, 2003)

2. Concentration dependent killing and prolonged persistent effects

AB	PK-PD param.	goal
• aminoglycosides • daptomycin • oritavancin • ketolides • fluoroquinolones	24h AUC / MIC and peak/MIC	AUC/MIC * and peak/MIC **

our proposal: * > 100 for efficac.; ** > 10 for resist.

Patterns of antimicrobial activity, PK-PD parameter correlating with efficacy, and goal of therapy **(1 of 3)**

(Craig, Infect. Dis. Clin. N. Amer., 17:479-502, 2003)

3. Time-dependent killing but moderate to prolonged persistant effects

AB	PK-PD param.	goal
• conventional glycopeptides • linezolid • macrolides • tetracyclines	**24h AUC / MIC**	**Enhance amount of drug ***

* reminder: AUC = $dose_{24h}$ / clearance

Why do we say that glycopeptides are AUC/MIC-dependent ?

Dose fractionation studies in neutropenic animals

➔ AUC !

- Ebert et al., ICAAC 1987 p. 173
- Dudley et al., ICAAC 1999 p. 49

Rabbit endocarditis model

➔ no effect of concentration !

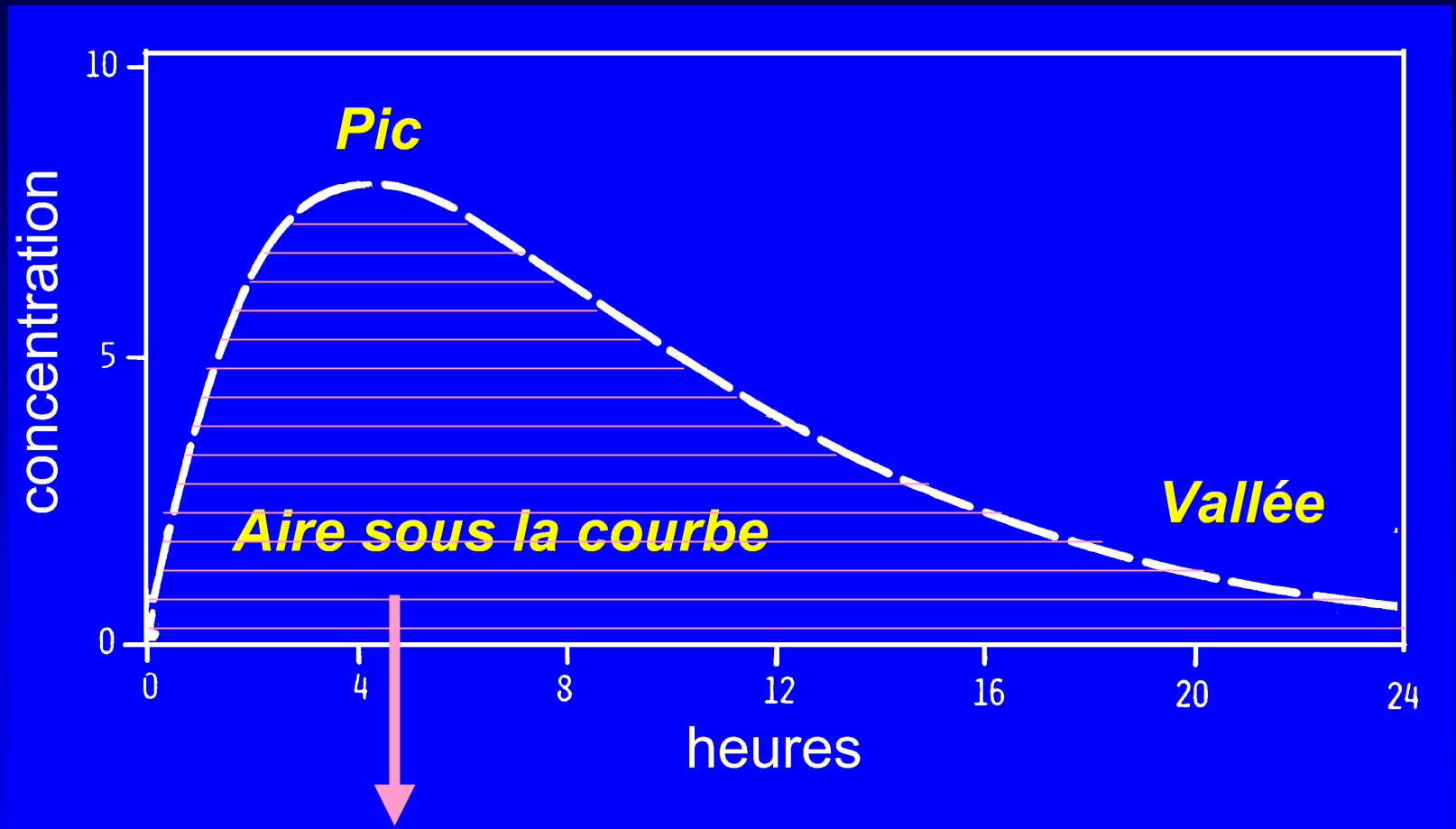
- Chambers et al., AAC 35:510-4, 1990 (interpretation !)
- Houlihan et al., AAC 41:2497-501, 1997

Dynamic *S. aureus* in vitro model:

➔ no effect of concentration if above the MIC !

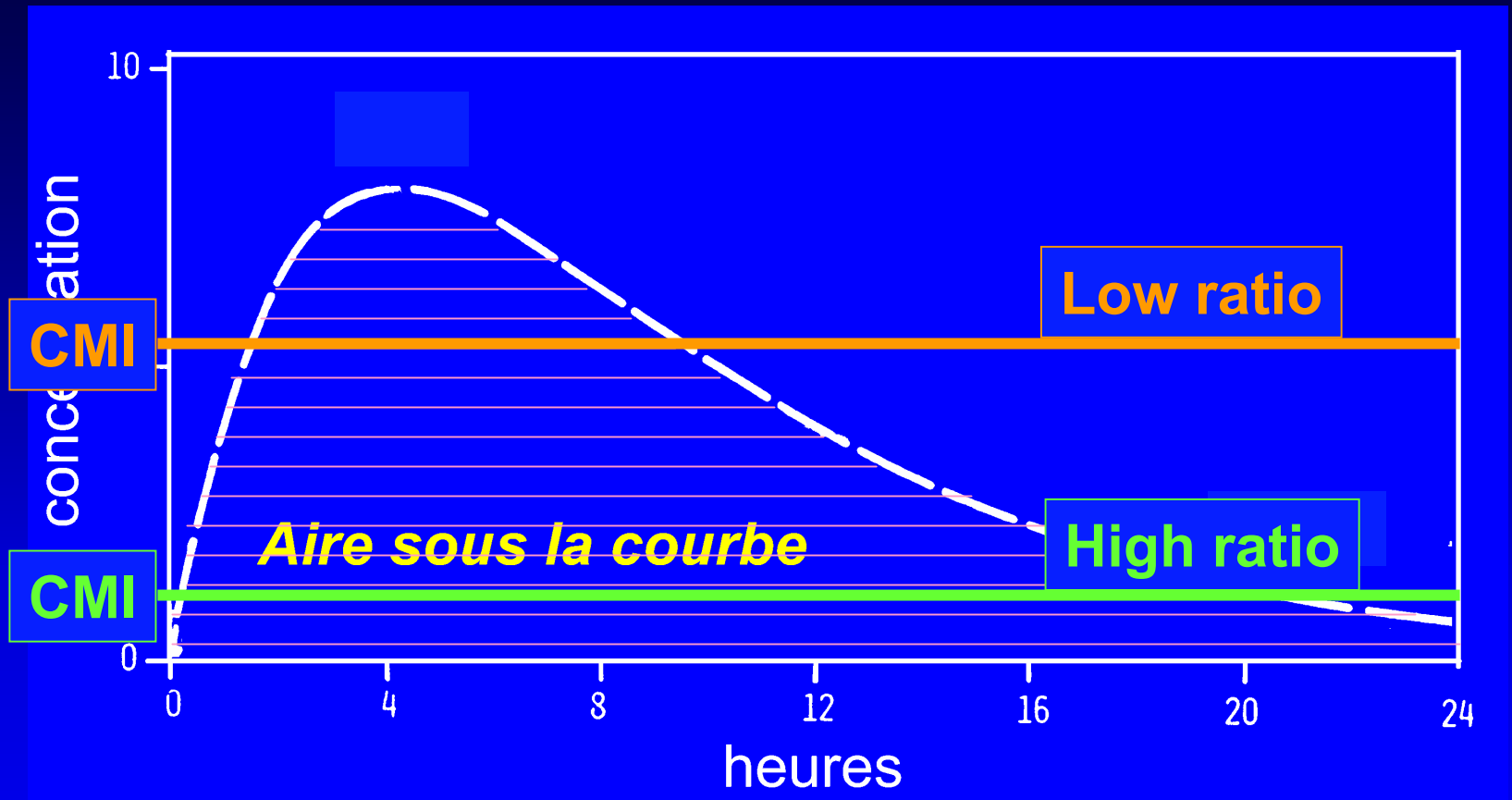
- Duffull et al., AAC 38:2480-2, 1994
- Larson et al. JAC 38:589-597, 1996

What is an AUC_{24h} ?



AUC_{24h} = $dose_{24h}$ / clearancee
(units: mg x h x ml^{-1})

What does a AUC/MIC ratio mean ?

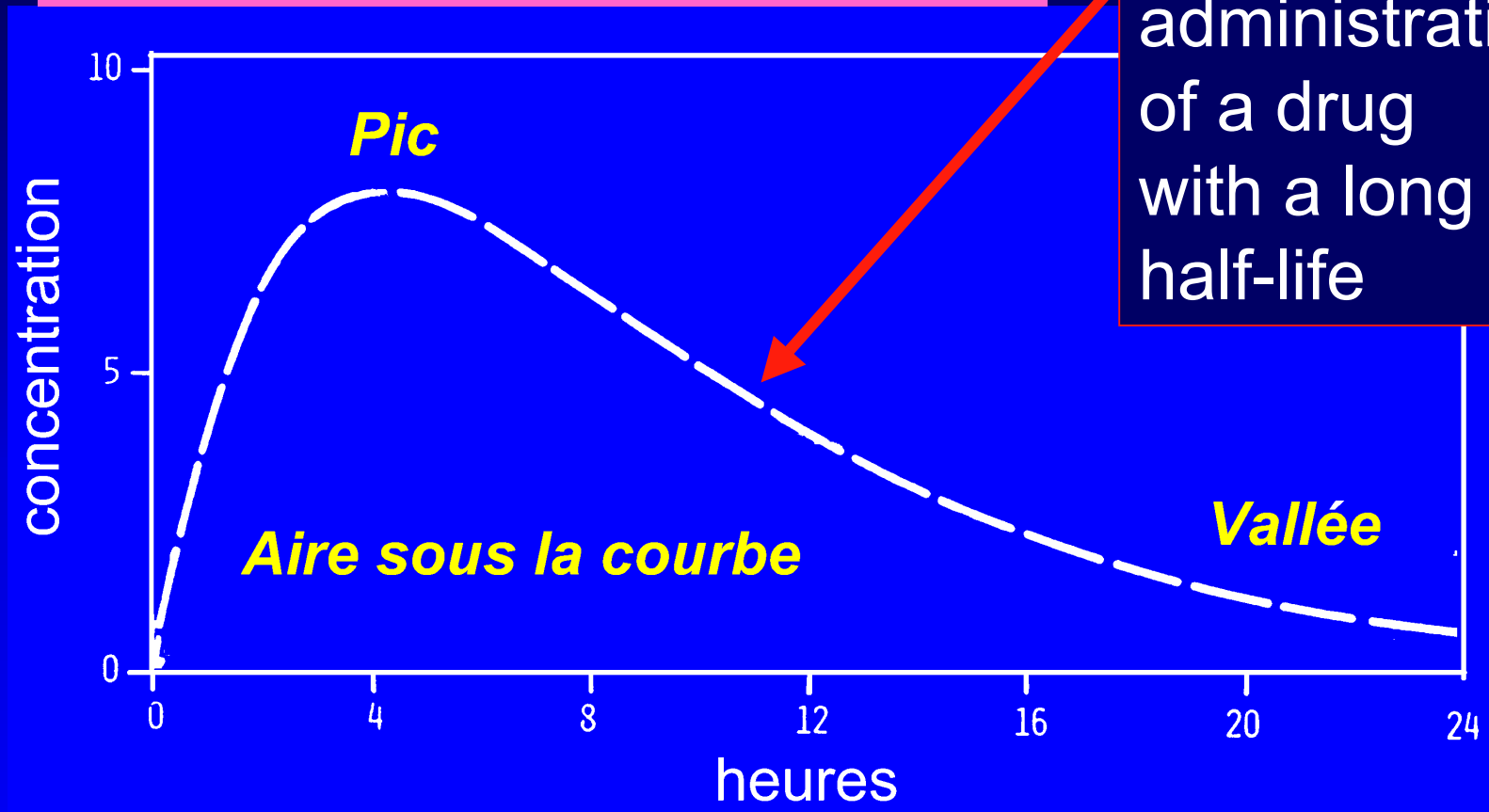


AUC_{24h} / MIC = 125 ⇒ 5 x MIC over 24h

(units : mg x h x ml^{-1} x mg^{-1} x ml = h

Now, the beauty of AUC ...

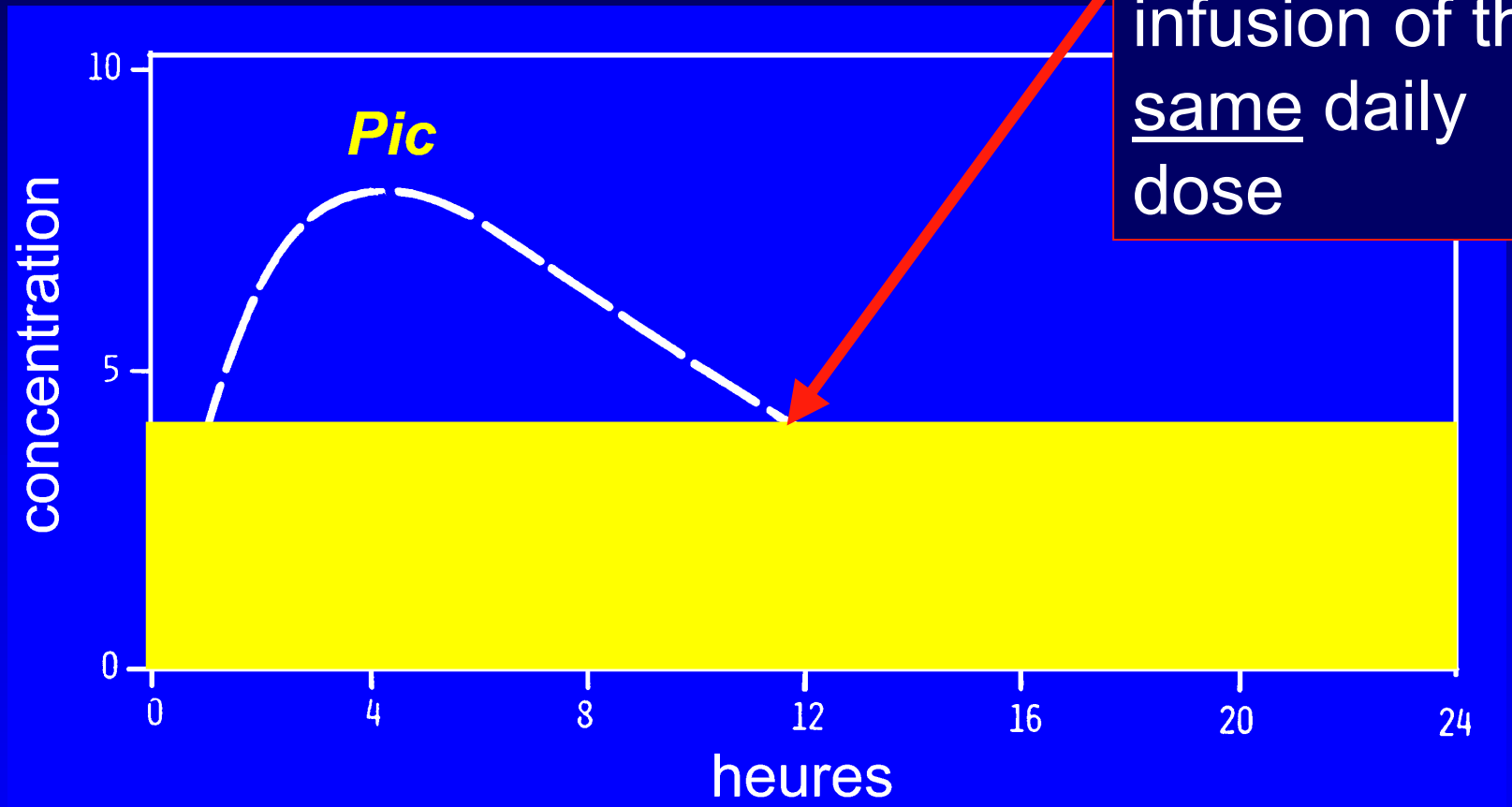
The AUC of this is equivalent to ...



Bolus administration of a drug with a long half-life

Now, the beauty of AUC/MIC ...

To the AUC of that ...



Continuous infusion of the same daily dose

What do we find in the literarture ?

First, A series of French papers ...

- **Brinquin L, Rousseau JM, Boulesteix G, Diraison Y, Bonsignour JP. [Continuous infusion of vancomycin in post-neurosurgical staphylococcal meningitis in adults] Presse Med. 1993 Nov 20;22(36):1815-7. French.**
- **Conil JM, Favarel H, Laguerre J, Brouchet A, Chabanon G, Cazal L, Bodnar M, Rouge D, Virenque C, Costagliola M. [Continuous administration of vancomycin in patients with severe burns] Presse Med. 1994 Nov 5;23(34):1554-8. French.**
- **Borderon JC, Laugier J, Chamboux C, Saliba E, Mathieu A. [Continuous infusion of vancomycin during the neonatal period] Pathol Biol (Paris). 1994 May;42(5):525-9. French.**
- **Jourdan C, Convert J, Peloux A, Boussaid O, Grando J, Tigaud S. [Adequate intrathecal diffusion of teicoplanin after failure of vancomycin, administered in continuous infusion in three cases of shunt associated meningitis] Pathol Biol (Paris). 1996 May;44(5):389-92. French.**

What do we find in the literarture ?

And then, a bit of Italy

- **Di Filippo A, De Gaudio AR, Novelli A, Paternostro E, Pelagatti C, Livi P, Novelli GP. Continuous infusion of vancomycin in methicillin-resistant staphylococcus infection. Chemotherapy. 1998 Jan-Feb;44(1):63-8.**

0.5 g x 4/day n=14) vs 2 g/day CI (n=11) in Intensive Care

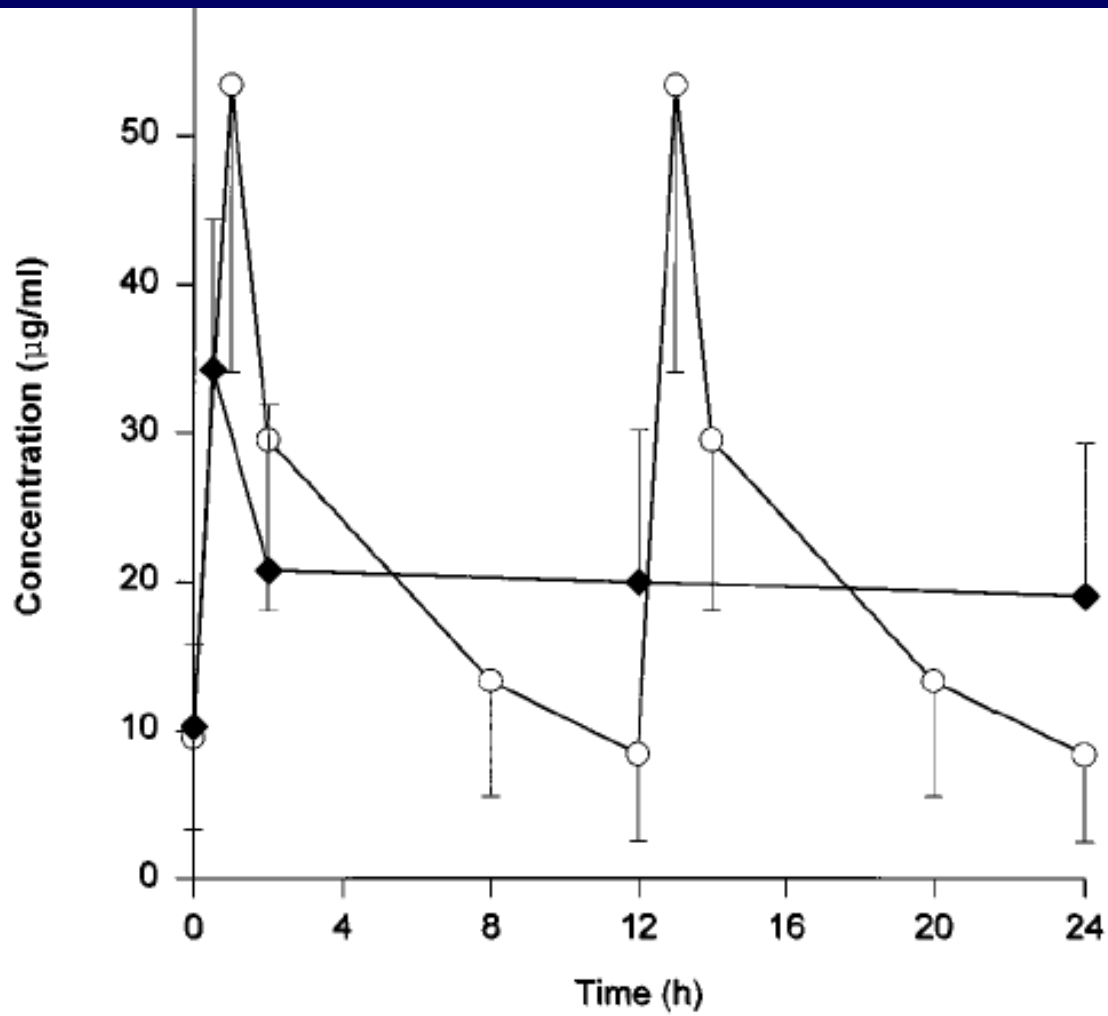
But …

CONCLUSIONS: In critically ill patients suffering from MRSA infection, vancomycin administration in continuous infusions improved organ function and leukocyte response, but did not seem to modify the overall evolution of the disease.

Now, the Americans got the idea from old Europe ...

James J.K. et al. Comparison of Conventional Dosing versus continuous-Infusion Vancomycin Therapy for Patients with Suspected or Documented Gram-Positive Infections. AAC 40:696-700, 1996

1g /12h vs
500 mg loading dose and
2 g CI/24h
(n = 10; cross-over)



And here is another small one from the US ...

- **Klepser ME, Patel KB, Nicolau DP, Quintiliani R, Nightingale CH. Comparison of bactericidal activities of intermittent and continuous infusion dosing of vancomycin against methicillin-resistant Staphylococcus aureus and Enterococcus faecalis. Pharmacotherapy. 1998 Sep-Oct;18(5):1069-74.**

Randomized, open-label, crossover study (n=12) 1g /12 h vs 1 g CI and 2 g CI)

➔ Css of 8.8 +/- 1.6 and 16.9 +/- 1.9 mg/ml vs C_{min} of 5.5 +/- 1.9 mg/ml

CONCLUSIONS: Continuous infusion does not greatly improve the activity of vancomycin and should not be routinely administered. However, it may prove useful against isolates with reduced susceptibility to the agent.

Maar hier zijn de Fransen terug ...

Continuous versus Intermittent Infusion of Vancomycin in Severe Staphylococcal Infections: Prospective Multicenter Randomized Study

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Medico-Surgical Intensive Care Unit[1] and Microbiology,[4] Institut Mutualiste Montsouris, Medico-Surgical Intensive Care Unit, Hôpital Saint-Joseph,[5] Medico-Surgical Intensive Care Unit, Hôpital de Diaconesses,[6] INSERM U13[2] and Infectious Diseases Critical Care Unit,[7] Hôpital Bichat-Claude Bernard, and Respiratory Intensive Care Unit, Hôpital de la Pitié-Salpêtrière,[8] Paris, Medico-Surgical Intensive Care Unit, Hôpital V. Dupouy, Argenteuil,[9] and Medical Intensive Care Unit, Hôpital Louis Mourier, Colombes,[10] France

Received 28 June 2000/Returned for modification 2 January 2001/Accepted 5 June 2001

AAC 45:2460-2467, 2001

En hier is wat ze gedaan en gevonden hebben …

- **119 critically ill patients with MRS infections (bacteremic infections, 35%; pneumonia, 45%).**
- **Microbiological and clinical outcomes,**
- **Safety, pharmacokinetics, ease of treatment adjustment, and cost**

➔ **clinical outcomes and safety were similar.**
➔ **targeted concentrations (20-25 mg/L) reached faster**
➔ **fewer samples required for treatment monitoring**
➔ **lower variability of AUC_{24h}**
➔ **23% lower costs**

☛ **CIV may be a cost-effective alternative to IIV.**

AAC 45:2460-2467, 2001

Mais Bruxelles n'est pas en reste ...

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, June 2003, p. 2015–2017 Vol. 47, No. 6
0066-4804/03/$08.00+0 DOI: 10.1128/AAC.47.6.2015–2017.2003

Vancomycin Penetration of Uninfected Pleural Fluid Exudate after Continuous or Intermittent Infusion

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Blood and pleural exudate samples were obtained from 16 patients receiving intermittent or continuous infusions of vancomycin after lung surgery. The areas under the concentration-time curves for blood and pleural exudates were identical for both administration schedules, while continuous infusion allowed the concentrations in pleural exudates to be more sustained (mean concentration, 12 mg/liter).

15 mg/kg BID vs 30 mg/kg/24h CI

AAC 47:2015-2017, 2003

Et même pas du tout ...

TABLE 1. Blood and pleural fluid vancomycin concentration during intermittent and continuous infusion

Time after administration	Concn (mg/liter)			
	Intermittent infusion		Continuous infusion	
	Blood	Pleural fluid	Blood	Pleural fluid
0	4.1 ± 1.4	5.5 ± 2.0	14.0 ± 3.8	11.8 ± 2.7
30 min		5.8 ± 2.0		
1 h	48.3 ± 14.9	9.4 ± 3.0		
1 h 30 min		15.3 ± 3.7		
2 h	22.4 ± 5.2	19 ± 4.8		
4 h	14.4 ± 4.9	16 ± 4.5	14.0 ± 4.3	12.1 ± 2.9
6 h	10.3 ± 3.8	13 ± 3.6		
8 h	8.6 ± 3.3	9.8 ± 3.0	14.7 ± 4.3	13.0 ± 3.6
12 h	5.6 ± 2.1	6.6 ± 2.3	16.0 ± 4.5	13.7 ± 3.5
AUC_{0-12}	172 ± 40	145 ± 35	178 ± 52	152 ± 37
AUC_{0-12} for pleural fluid/AUC_{0-12} for blood		0.88 ± 0.07		0.86 ± 0.14

AAC 47:2015-2017, 2003

Let us make some calculations ...

Continuous infusion	
Blood	Pleural fluid
14.0 ± 3.8	11.8 ± 2.7
14.0 ± 4.3	12.1 ± 2.9
14.7 ± 4.3	13.0 ± 3.6
16.0 ± 4.5	13.7 ± 3.5
178 ± 52	152 ± 37
	0.86 ± 0.14

AUC 24h after 30 mg/kg CI

For an AUC/MIC of 125, the breakpoint would be 1.4 mg/L !!!

But … what is the ideal AUC/MIC value ?

AAC 47:2015-2017, 2003

Additional arguments for the continuous infusion of vancomycin

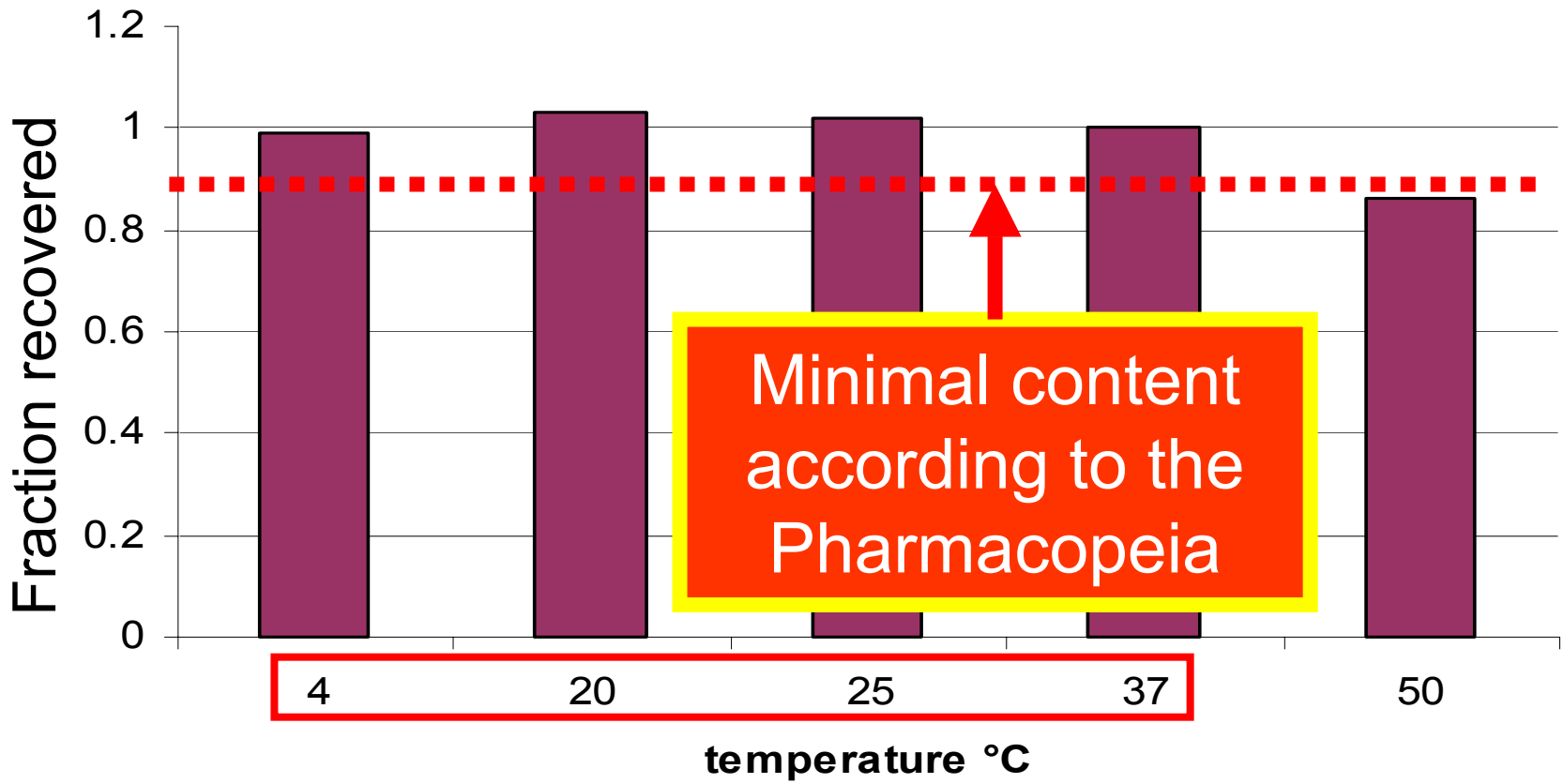
- this drug kills slowly, but maximal kill rates are obtained if the concentration remains above the MIC
- if you know the MIC, you can easily achive this...

But now, is the CI of vancomycin **pharmaceutically** acceptable ?

- Stability ...
- Compatibility ...

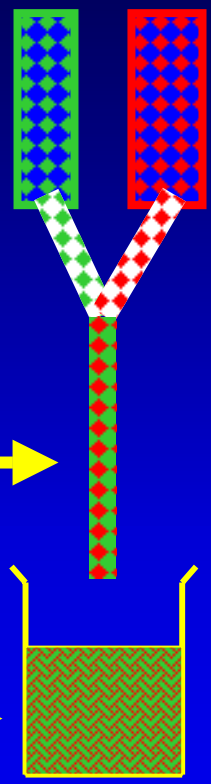
Stability of vancomycin (VANCOCIN ® Lilly) *

4 g vancomycin in 48 ml *aqua pro injectione* maintained at the temperatures indicated for 72h



Compatibiliteitstudies: methodes

Vancomycin 4 g /48 mL



Drug X in the infusion set administered at in the clinics (dose and schedule)

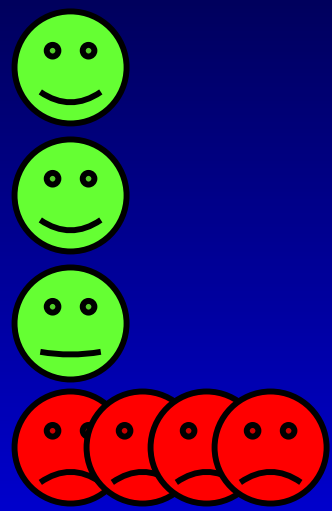
1ste contact aan 37°C en aan hoge concentraties (10 min)

2de contact aan 37°C in meer gedilueerde condities (V= 3 L) voor 1u

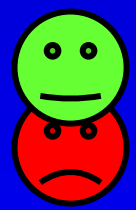
- physical examination (viewer)
- HPLC (chemical compatibility)

Compatbility of vancomycin
(mimicking CI of 4 g /48 ml in 24 h)
with antiinfectives

- aminoglycosides qD
- macrolides 100-500 mg/20 min
- fluconazole 200 mg/30 min
- beta-lactams (all) [a]
- fluoroquinolones
  - ciprofloxacin (400 mg / 1h)
  - moxifloxacin (400 mg / 1h)



phys *./chem.**

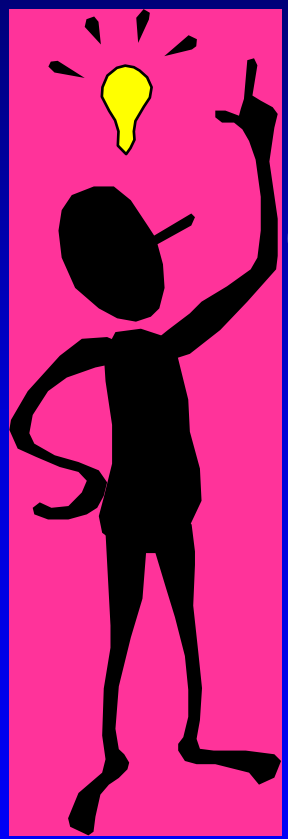


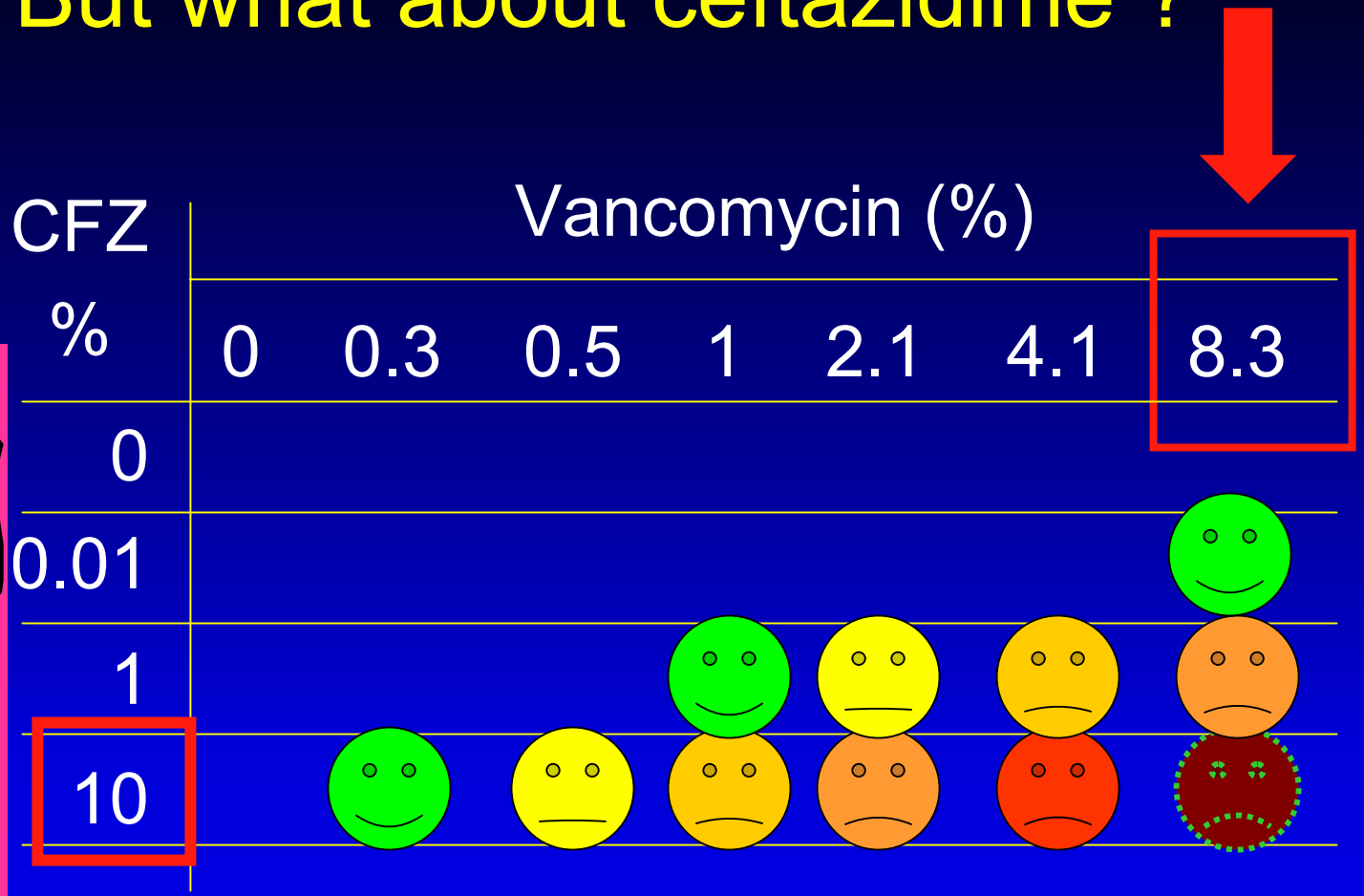
chem.**

* phys: visual evidence;

** chem. : > 10% loss of vanco

But what about ceftazidime ?





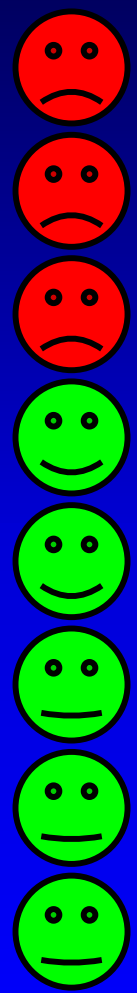
You MUST use dilute solutions …
or no common infusion line ….

Compatibility of vancomycin

(mimicking CI of 4 g /48 ml in 24 h)

with sedatives, anticonvulsivants, analgesics ...

- propofol (300 mg/24h) — phys *
- phenytoin (750 mg/15 min) — phys *
- valproic acid (1.2 g/24h) — phys *
- midazolam (600 mg/24h)
- piritramide (10 mg/1h)
- ketamine (480 mg/24h)
- sufentanil (0.12 mg/24h)
- morphine (5mg/1h)



* phys: visual evidence;

Compatibility of vancomycin

(mimicking CI of 4 g /48 ml in 24 h)

with diuretics , vasodilators and drugs acting on the sympathic system

- furosemide (960 mg/24h)
- nicardipine (120 mg/24h)
- uradipil (2.4 g/24h)
- isosorbide dinitrate (6 mg/1h)
- dopamine (0.4 mg/1min)
- dobutamine (0.84 mg/1 min)
- adrenaline (0.5 mg/20 min)

phys *

* phys: visual evidence;

Shall we have a bright future ?

Do not deny the difficulties....

GlaxoSmithKline

But they are there to help...

But, everything was already said there ....

International Society of Anti-Infective Pharmacology
Founded in 1991

10th ISAP Educational Workshop
An introduction to Pharmacokinetics and Pharmacodynamics
Prague, May 1st, 2004; 14:30-17:30

The defenestration of Prague ...

In cooperation with the
14th European Congress of Clinical Microbiology and Infectious Diseases (ECCMID)

PRAHA
14th ECCMID
14th European Congress of Clinical Microbiology and Infectious Diseases

Scientific organizers: Hartmut Derendorf, PhD (University of Florida, Gainesville, FL, USA) & Johan W. Mouton, MD (Canisius Wilhelmina Hospital, Nijmegen, The Netherlands)

- Goals and Format | Programme
- Registration | Venue | Accomodation
- Useful links | Credits

Do not panic, you'll get all my slides on **www.antiinfectieux.org**