



Subcutaneously delivered antimicrobials: real life, facts and myths

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ESCMID

EUROPEAN SOCIETY
OF CLINICAL MICROBIOLOGY
AND INFECTIOUS DISEASES

Subcutaneously Administered Antibiotics: a National Survey of Current Practice From the French Infectious Diseases (SPILF) and Geriatric Medicine (SFGG) Societies Network

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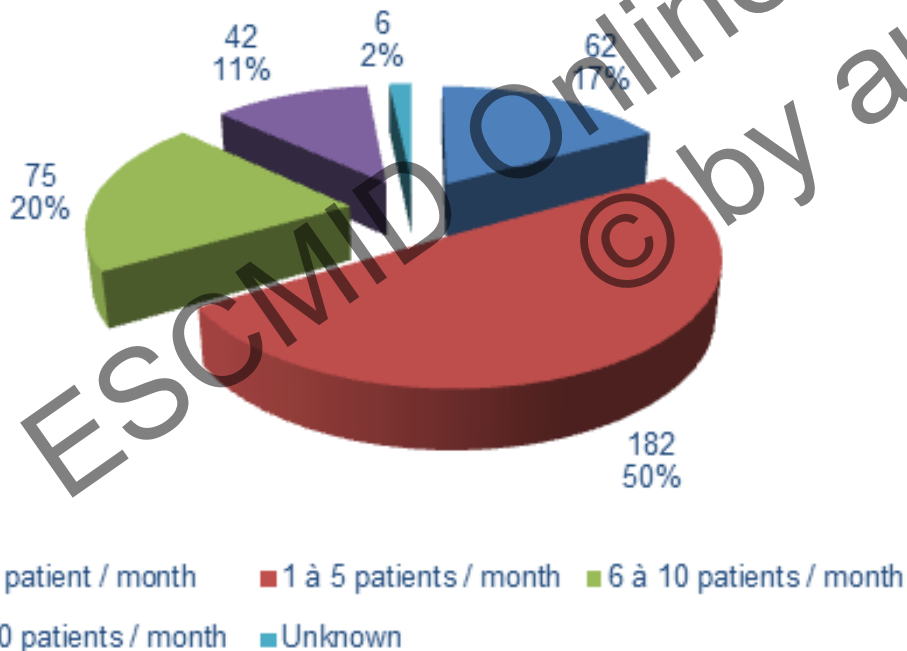
Very sparse data have been published on pharmacokinetic, efficacy, and tolerance of antibiotics (ATB) administered subcutaneously...

... and only ceftriaxone and amikacin are officially approved for SC administration in France.

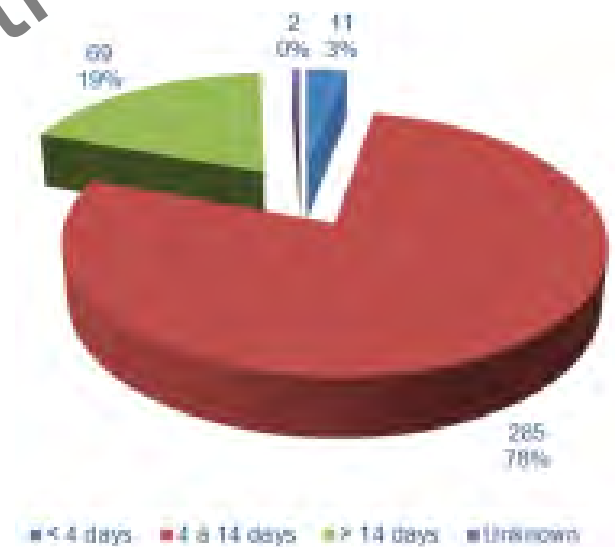
Frequency of prescription of SC antibiotics

96 % of practitioners declare to prescribe SC antibiotics
 (92,5% of ID and 97,5% of geriatricians)

N of patients treated by each practitioner



Length of SC antibiotic treatment



(E. Forestier et al. ECCMID 2014)

Number of practitioners using SC route for each antibiotic cited

	Amoxicillin	Amino-glycosides	Ceftriaxone	Ertapenem	Teicoplanin
ID practitioners N = 86 (%)	8 (9,3)	14 (16,3)	85 (98,9)	61 (70,9)	69 (80,2)
Geriatricians N = 281 (%)	48 (17,1)	115 (40,9)	281 (100)	61 (21,7)	75 (26,7)

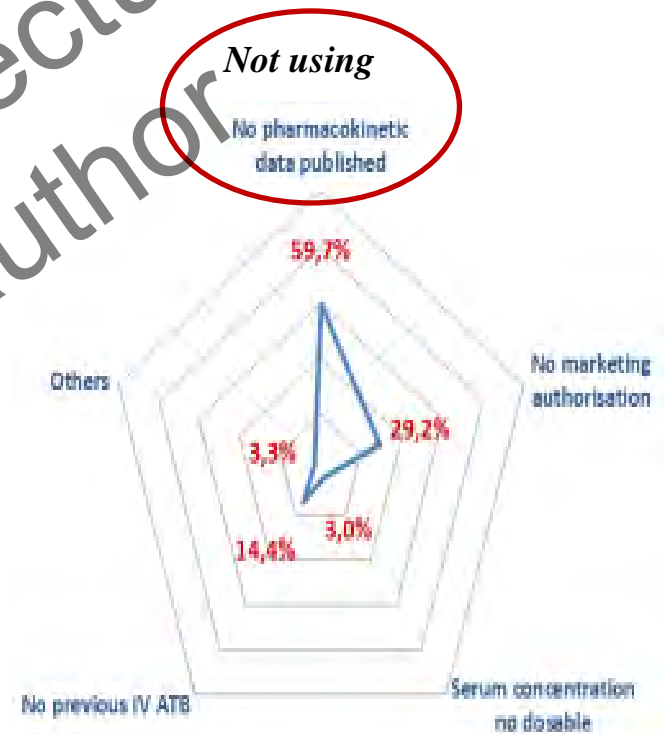
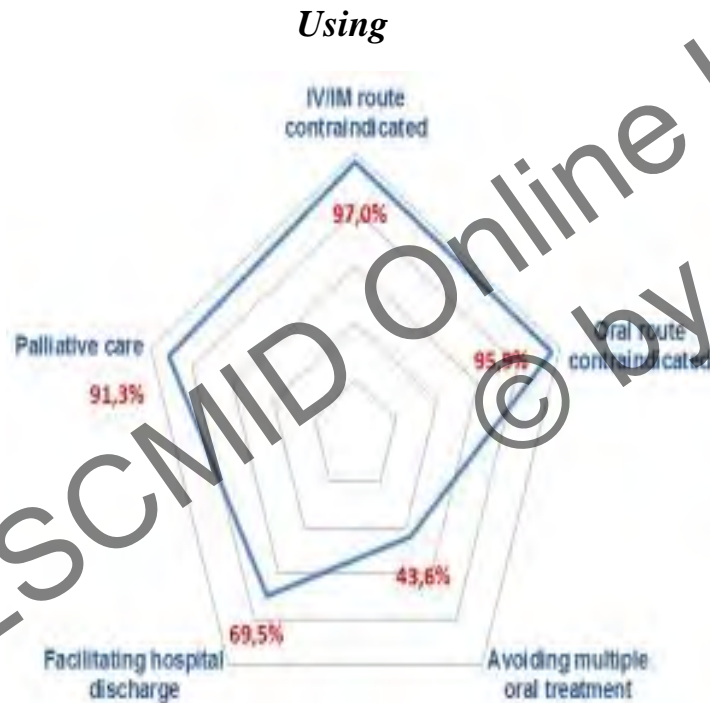
Reported side effects



And on occasion:

Cefepime, imipenem, doripenem, piperacillin/tazobactam, amoxicillin/clavulanic acid

Reason for using or not SC antibiotics



(E. Forestier et al. ECCMID 2014)

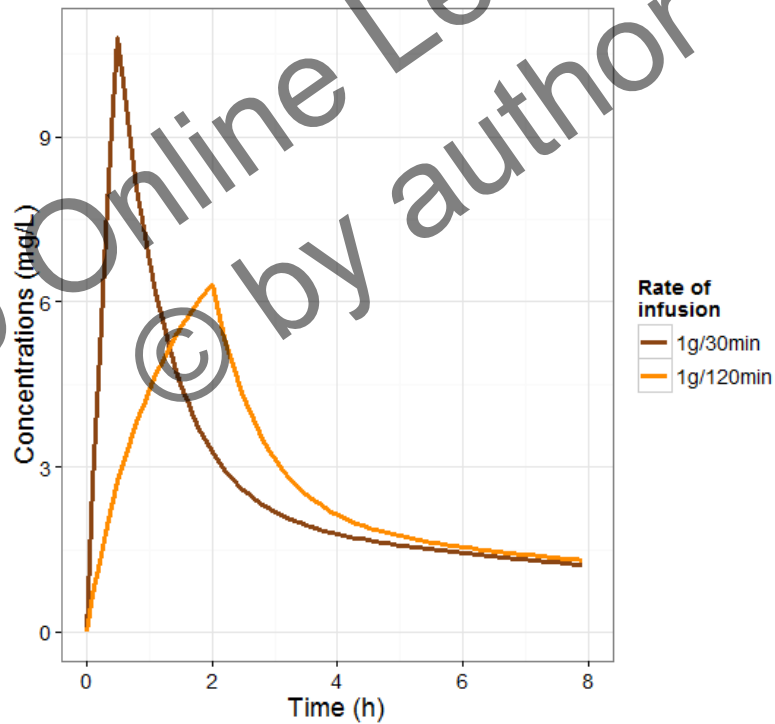


1 - Effect of SC administration on antibiotics PK

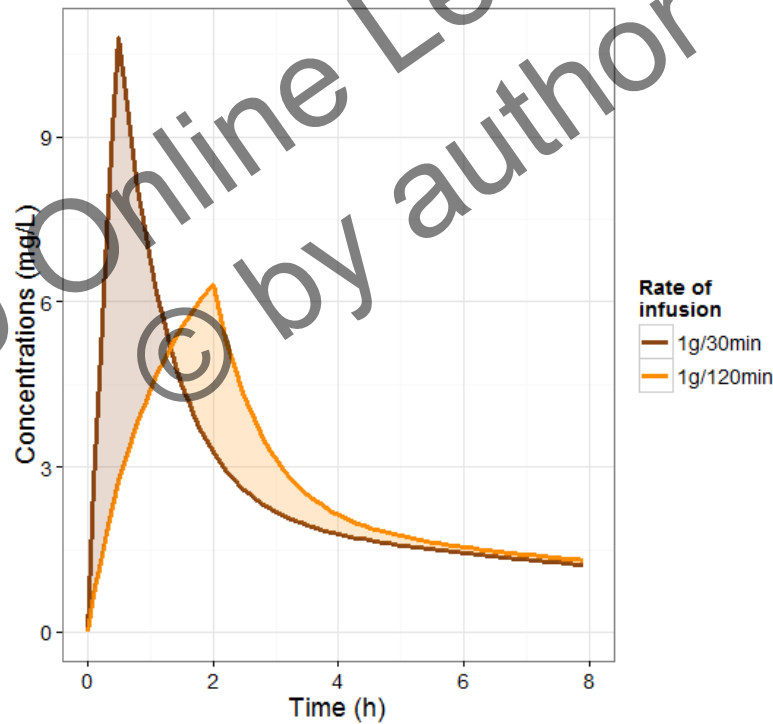
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- **A quantitative aspect: amount bioavailable**
 - Determines AUC and characterized by F ($0 < F < 1$)
- **A qualitative aspect: rate of absorption**
 - Determines peak characteristics: peak plasma concentration (C_{max}) and time to peak (t_{max}).

Altered rate but not extent of absorption after SC infusion



Altered rate but not extent of absorption after SC infusion



After SC infusion: what is the absorption rate limiting step?



Infusion rate $>$ Absorption rate \rightarrow **Absorption rate limited**

Infusion rate $<$ Absorption rate \rightarrow **Infusion rate limited**



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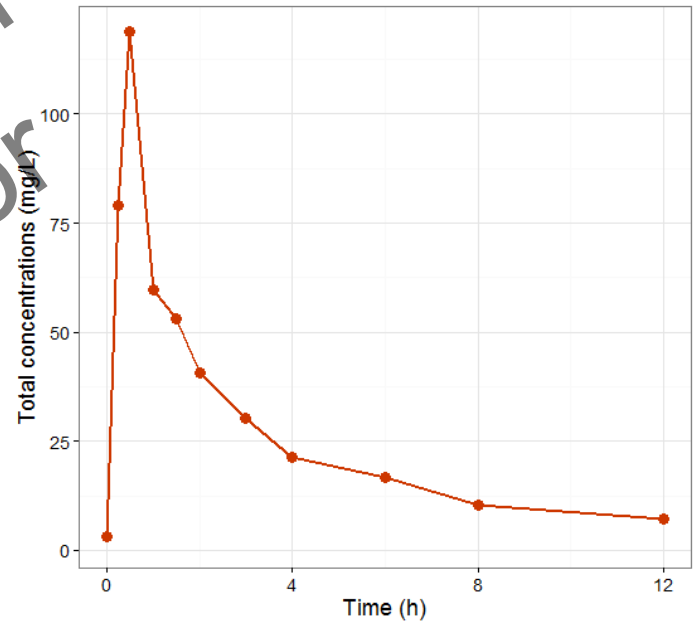
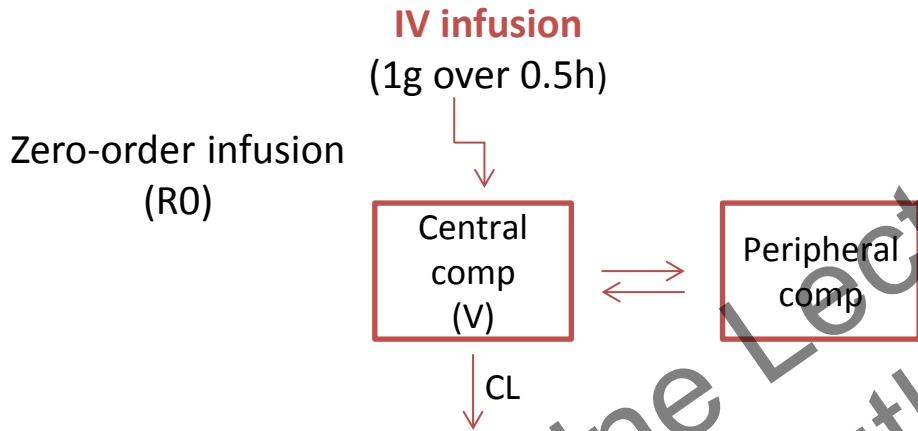
Pharmacokinetics of Ertapenem following Intravenous and Subcutaneous Infusions in Patients^V

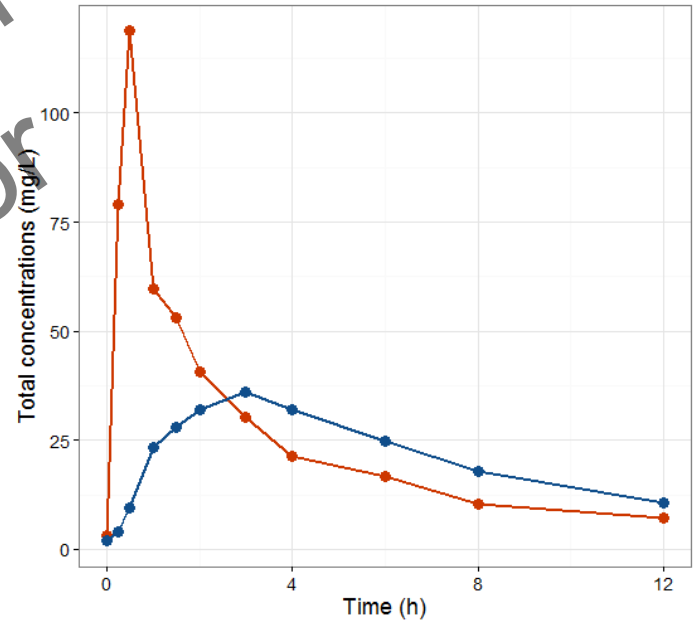
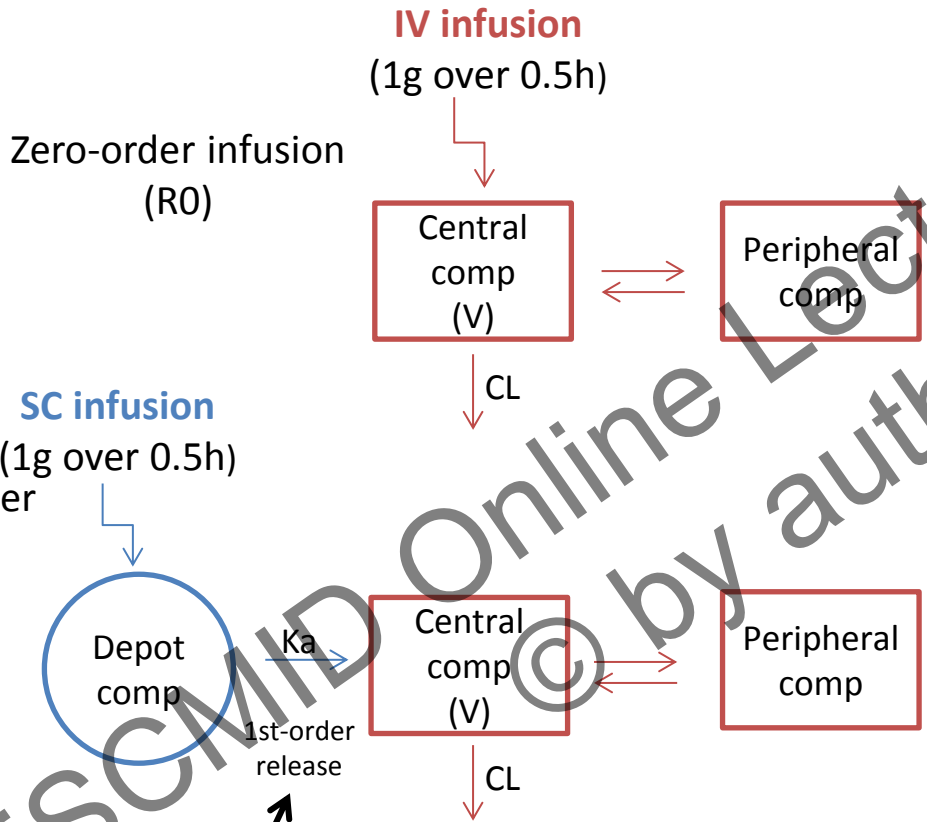
Denis Frasca,^{1,3} Sandrine Marchand,^{1,2,3} Franck Petitpas,^{1,3} Claire Dahyot-Fizelier,^{1,2,3}
William Couet,^{1,2,3*} and Olivier Mimoz^{1,2,3}

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Received 22 June 2009/Returned for modification 28 July 2009/Accepted 18 November 2009

Steady-state pharmacokinetics of ertapenem were compared in patients after 1-g intravenous and subcutaneous (s.c.) infusions. Bioavailability was 99% ± 18% after s.c. administration, but peaks were reduced by about 1/2 (43 ± 29 versus 115 ± 28 μg/ml) and times to peak were delayed. Simulations based on unbound concentrations show that time over the MIC should always be longer than 30% to 40% of the dosing interval, suggesting that s.c. infusion could be an alternative in patients with reduced vascular access.





What is the rate limiting step ?

What are the factors controlling the rate of absorption from the sub-cutaneous tissue ?

Blood Flow

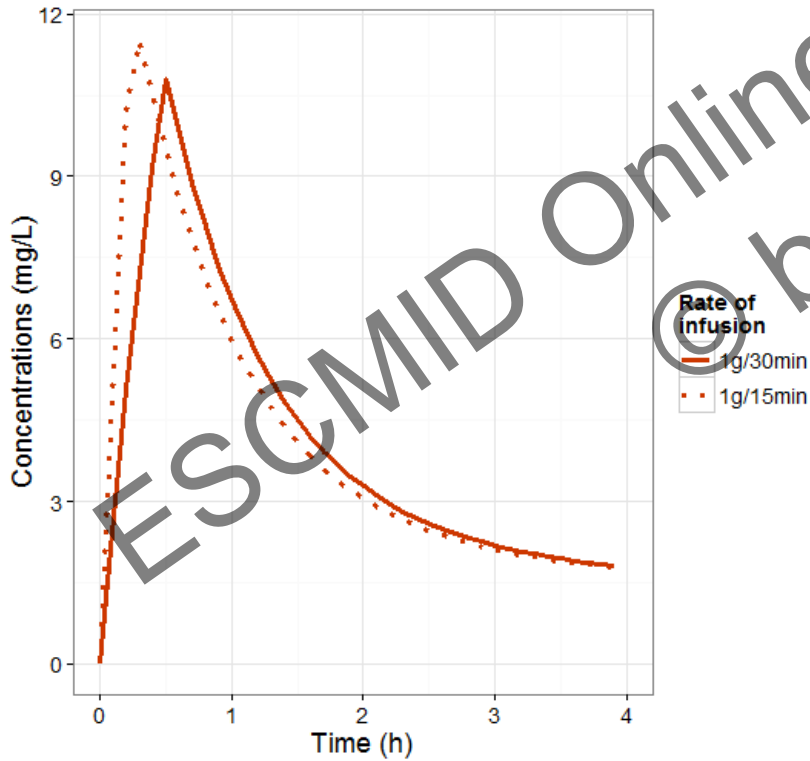
- High permeability drugs
- May be altered by pathology... and aging ?

Drug Permeability

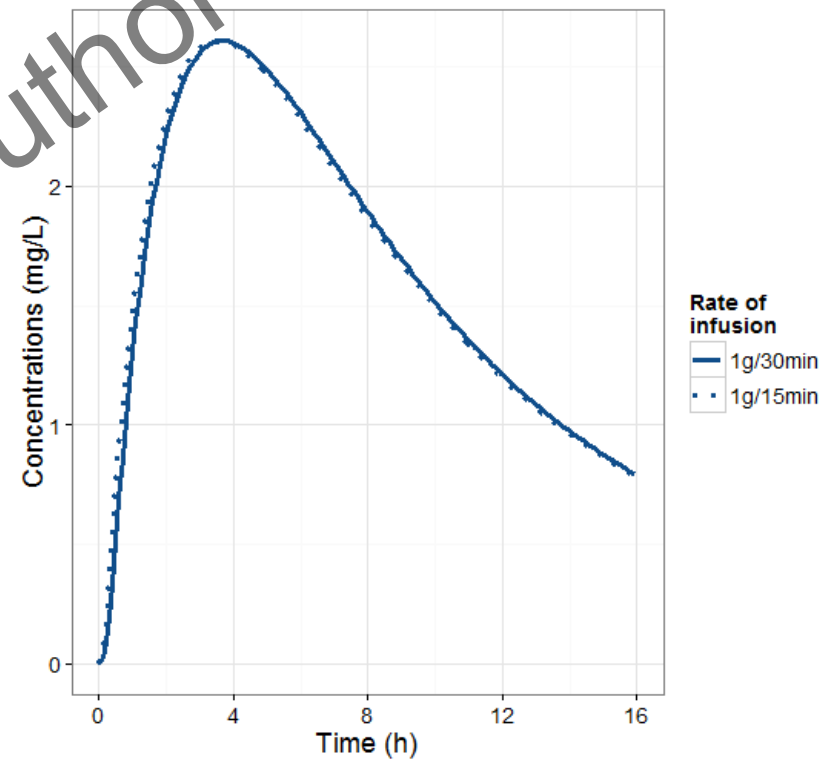
- Low permeability drugs
- Less likely to be altered by pathology or aging
- Hydrophylic antibiotics

Absorption rate limited: effect of decreasing the duration of infusion

IV infusion



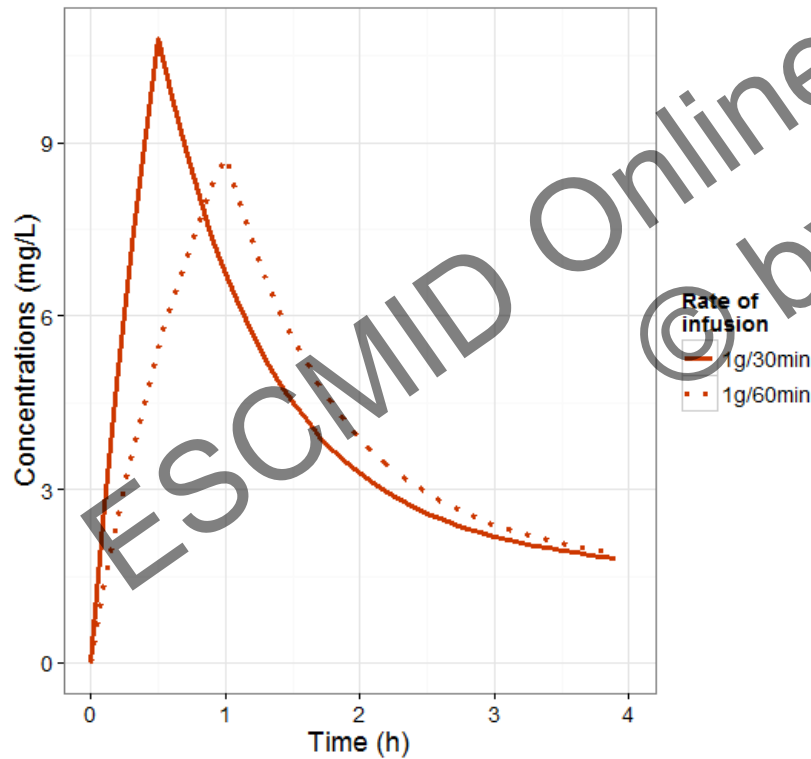
SC infusion



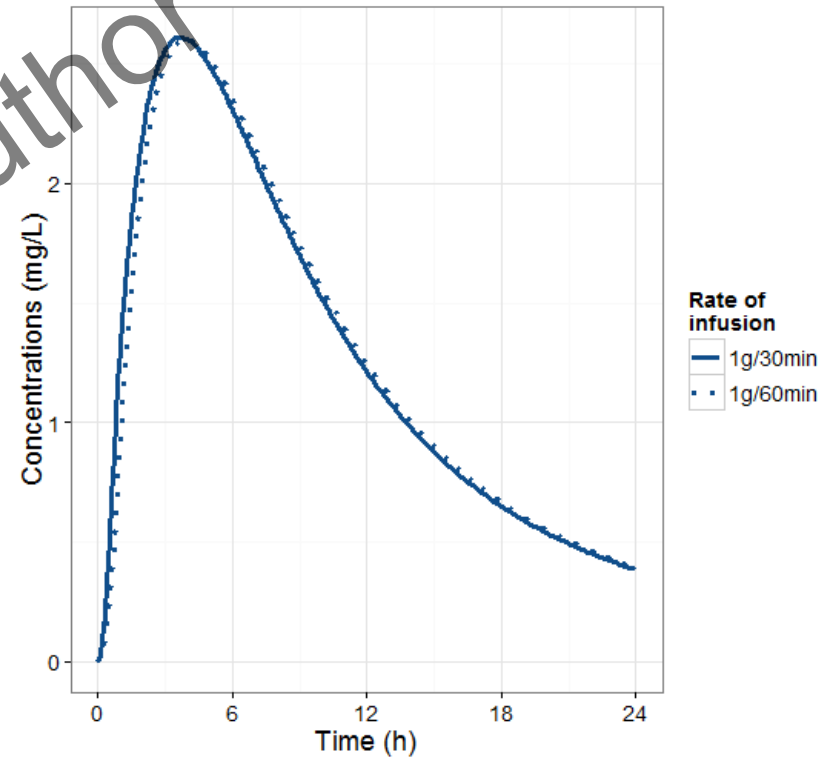
NO EFFECT

Absorption rate limited: effect of increasing the duration of infusion

IV infusion

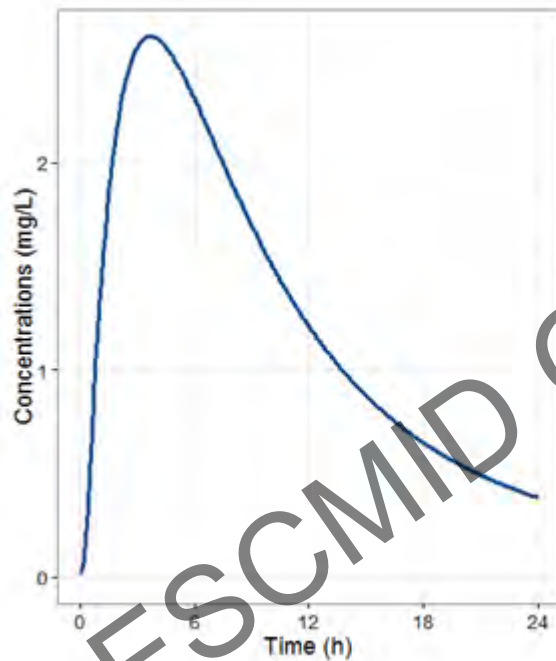


SC infusion

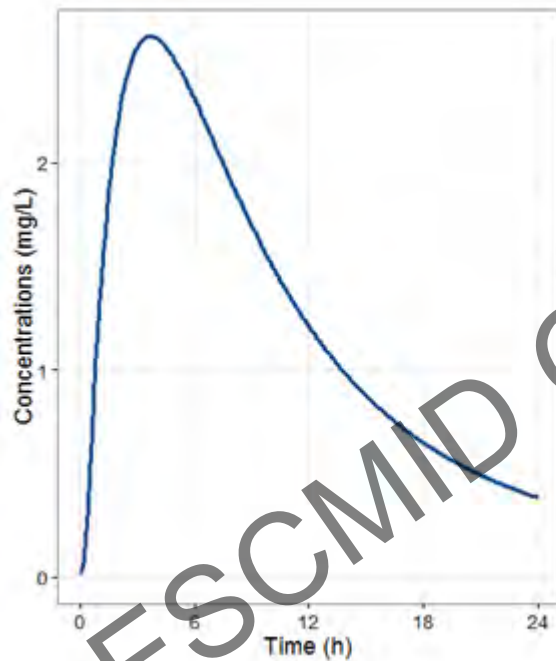


NO EFFECT

Absorption rate limited: increasing the duration of infusion, that is decreasing infusion rate has no effect on C_p vs time profiles....

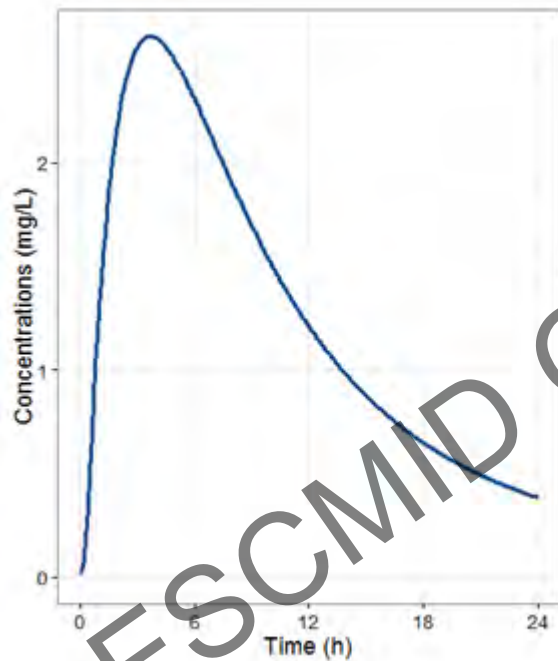


Absorption rate limited: increasing the duration of infusion, that is decreasing infusion rate has no effect on C_p vs time profiles....



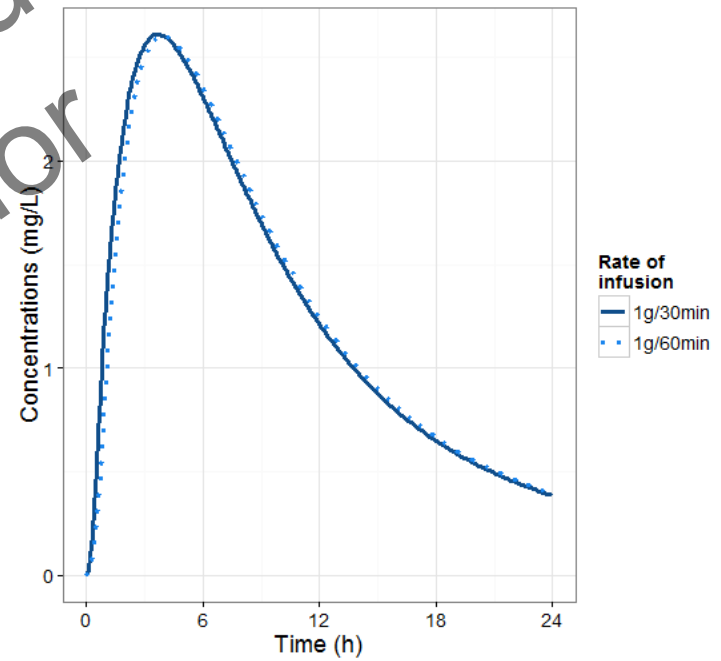
... until infusion rate becomes the rate limiting step

Absorption rate limited: increasing the duration of infusion, that is decreasing infusion rate has no effect on C_p vs time profiles....



Rate of
 infusion
 1g/30min

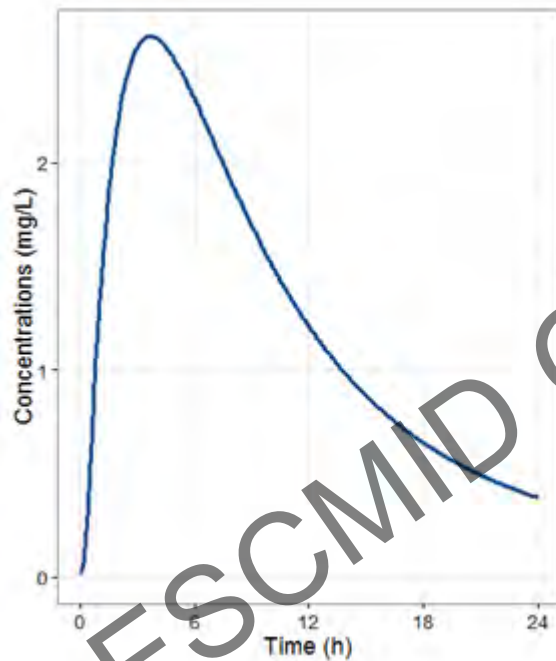
$R_0/2$



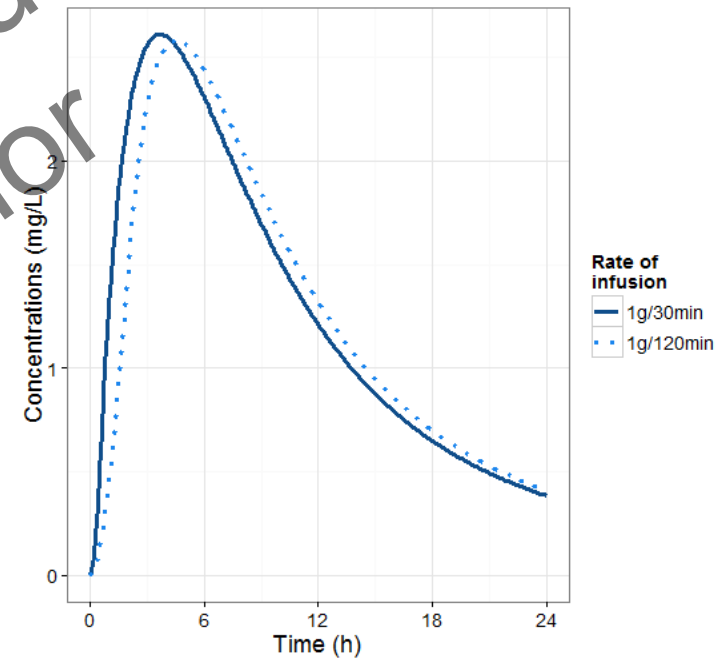
Rate of
 infusion
 — 1g/30min
 ••• 1g/60min

... until infusion rate becomes the rate limiting step

Absorption rate limited: increasing the duration of infusion, that is decreasing infusion rate has no effect on C_p vs time profiles....

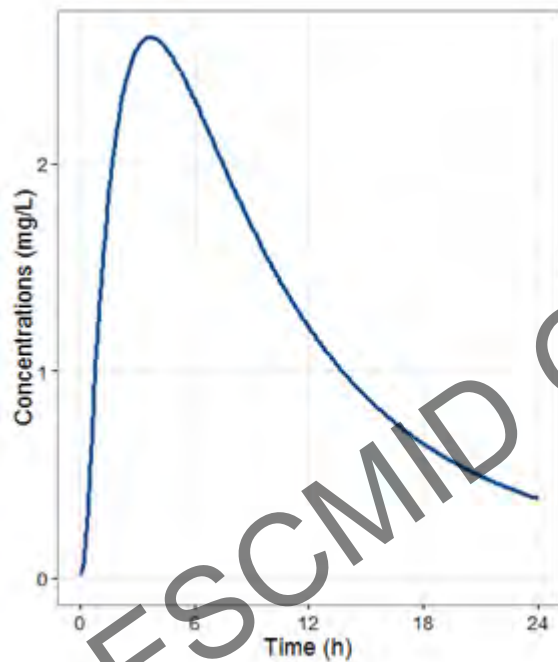


Rate of infusion $R_0/4$ →

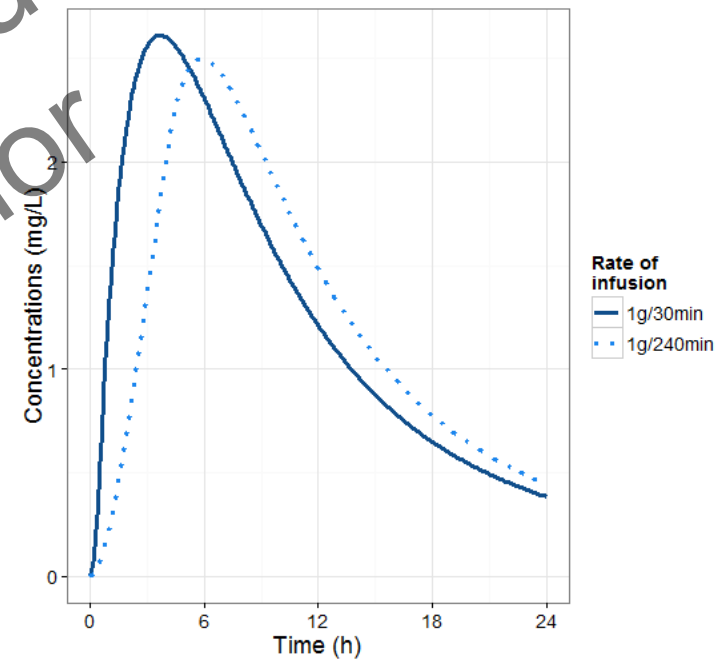


... until infusion rate becomes the rate limiting step

Absorption rate limited: increasing the duration of infusion, that is decreasing infusion rate has no effect on C_p vs time profiles....



Rate of infusion $\xrightarrow{R0/8}$



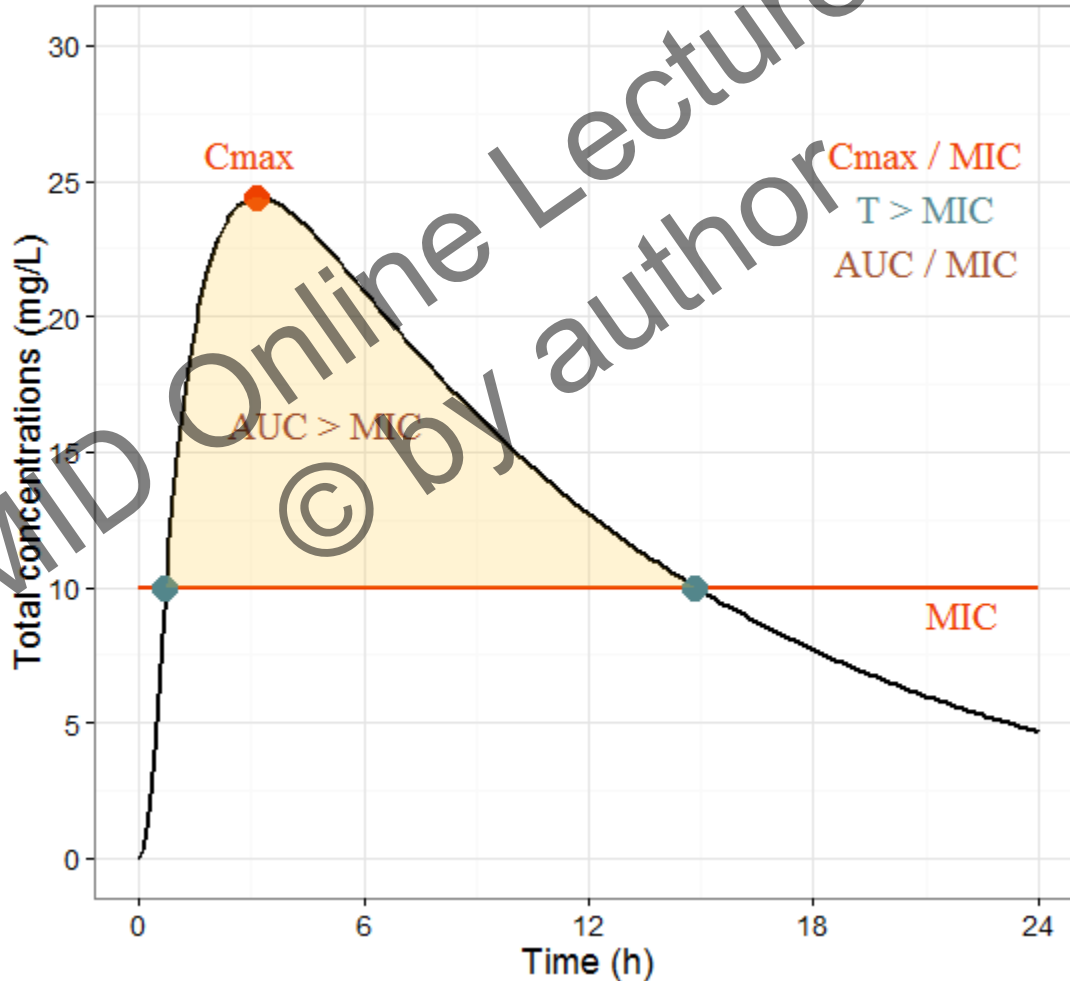
... until infusion rate becomes the rate limiting step



2 - Effect of SC administration on antibiotics PK-PD

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PK-PD index for concentration and time dependent antibiotics

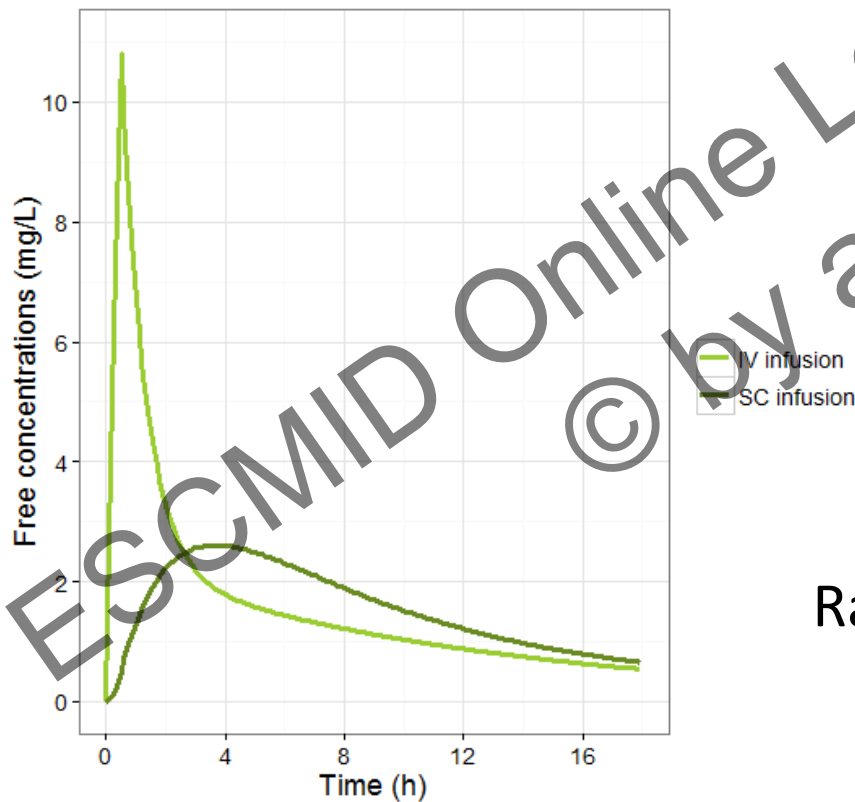




PK parameters values for ongoing PK-PD simulations

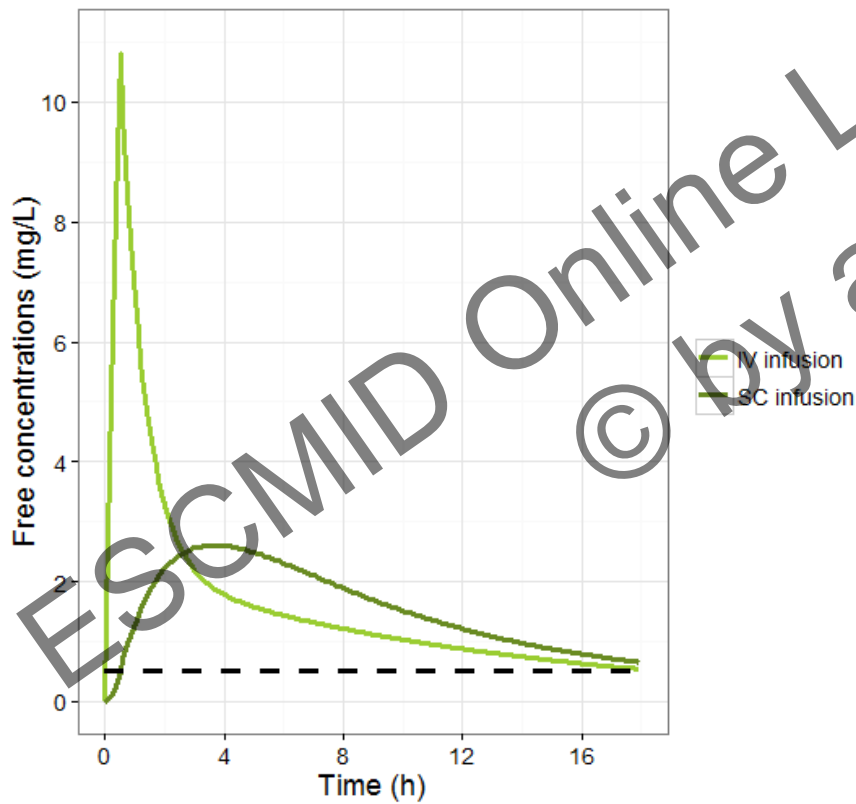
Parameter	Value
Cl (L/h)	2.7
Vd (L)	7.2
$t_{1/2}$ (h)	2
Ka (h^{-1})	0.16

Effect of decreasing absorption rate such as for example after switching from IV to SC infusion on PK-PD



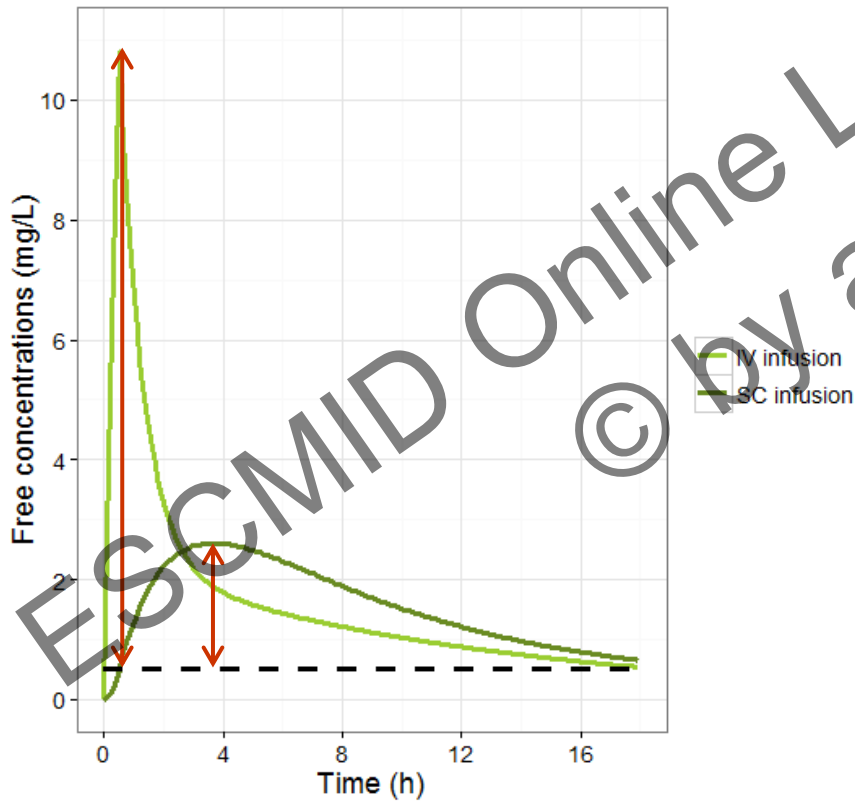
Rabs \searrow \rightarrow Cmax \searrow and tmax \nearrow

Concentration dependent antibiotics



$$\text{Target: } \frac{C_{max}}{MIC} \geq 8$$

Concentration dependent antibiotics

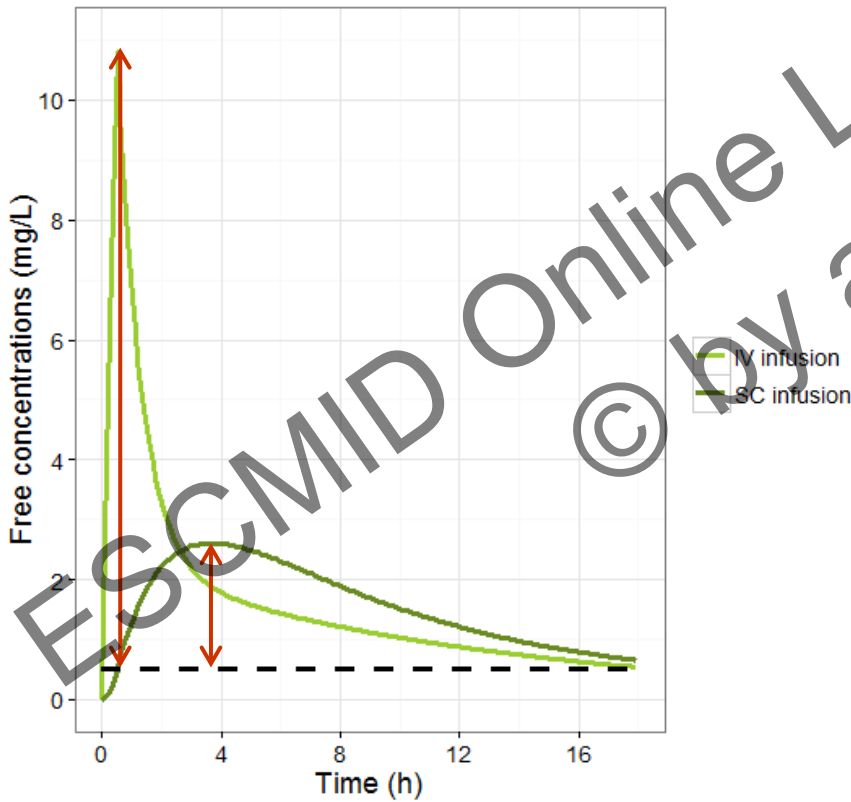


$$\text{Target: } \frac{C_{max}}{MIC} \geq 8$$

$$\frac{C_{max}}{MIC} \searrow \text{ when } R_{abs} \searrow$$

Concentration dependent antibiotics

Target: $\frac{C_{max}}{MIC} \geq 8$



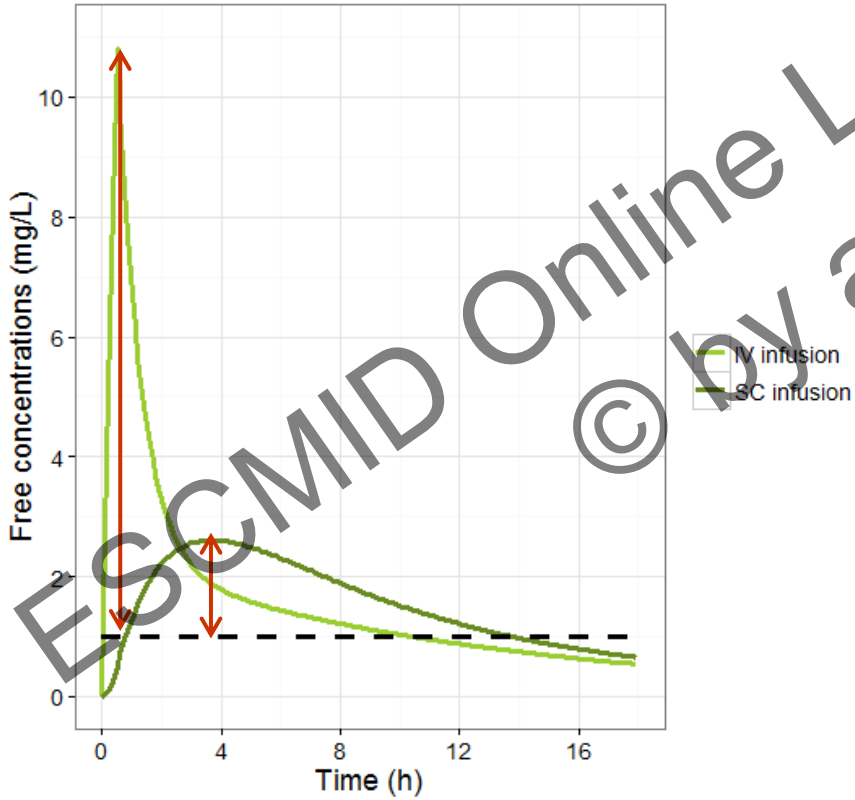
$\frac{C_{max}}{MIC} \searrow$ when Rabs \searrow

$MIC = 0.5 \text{ mg/L}$

$\frac{C_{max}}{MIC}$ $\begin{cases} > 8 \text{ for IV infusion} \\ < 8 \text{ for SC infusion} \end{cases}$

Concentration dependent antibiotics

Target: $\frac{C_{max}}{MIC} \geq 8$



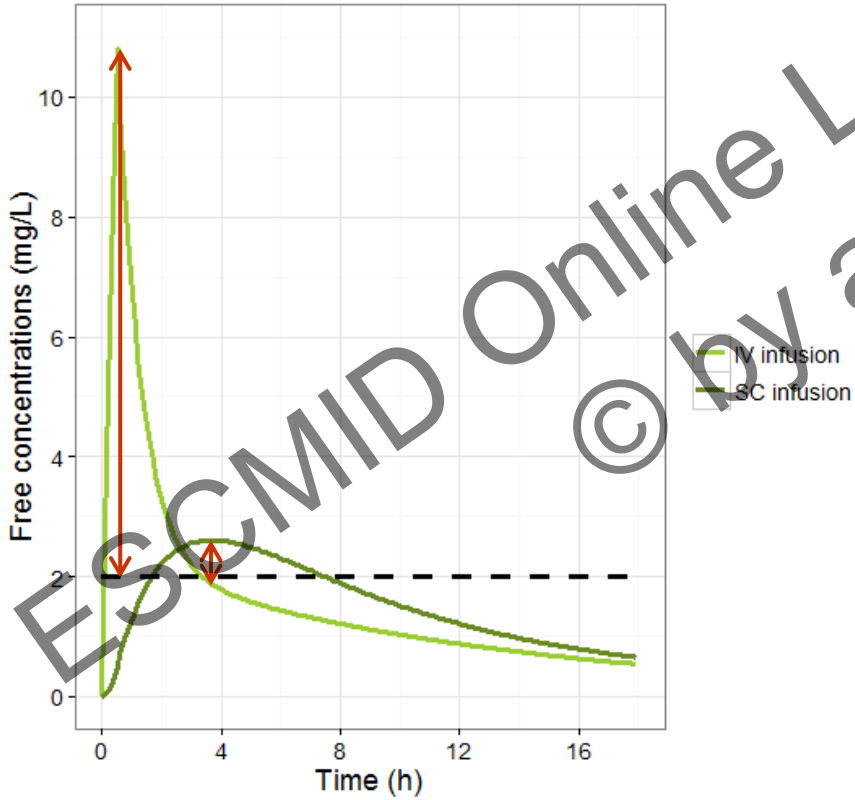
$\frac{C_{max}}{MIC} \searrow$ when Rabs \searrow

$MIC = 1 \text{ mg/L}$

$\frac{C_{max}}{MIC}$ $\begin{cases} > 8 \text{ for IV infusion} \\ < 8 \text{ for SC infusion} \end{cases}$

Concentration dependent antibiotics

Target: $\frac{C_{max}}{MIC} \geq 8$

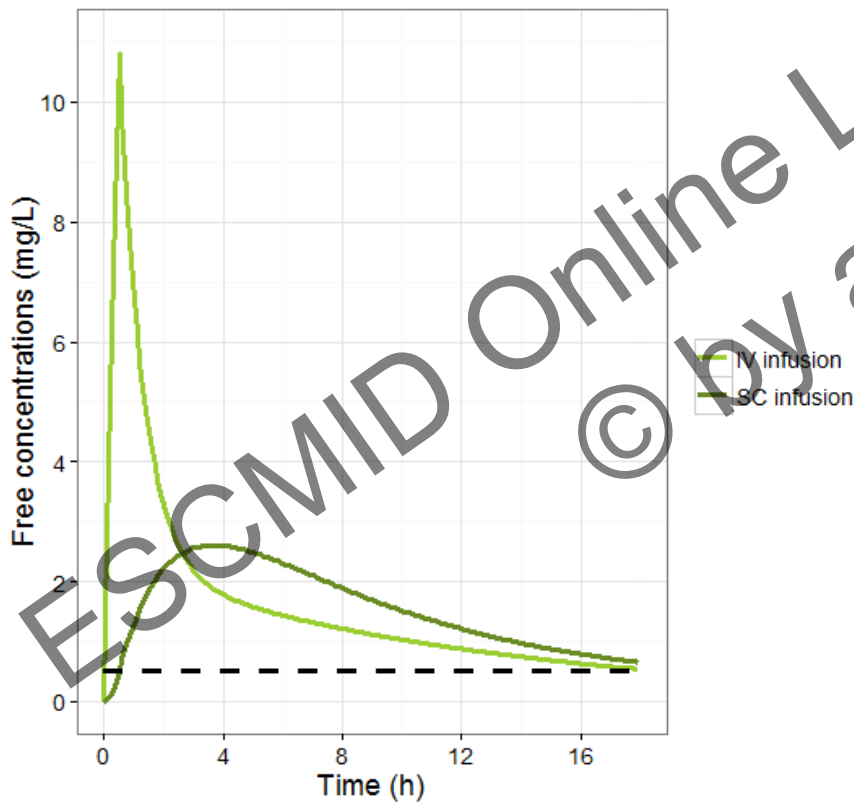


$\frac{C_{max}}{MIC} \searrow$ when Rabs \searrow

$MIC = 2 \text{ mg/L}$

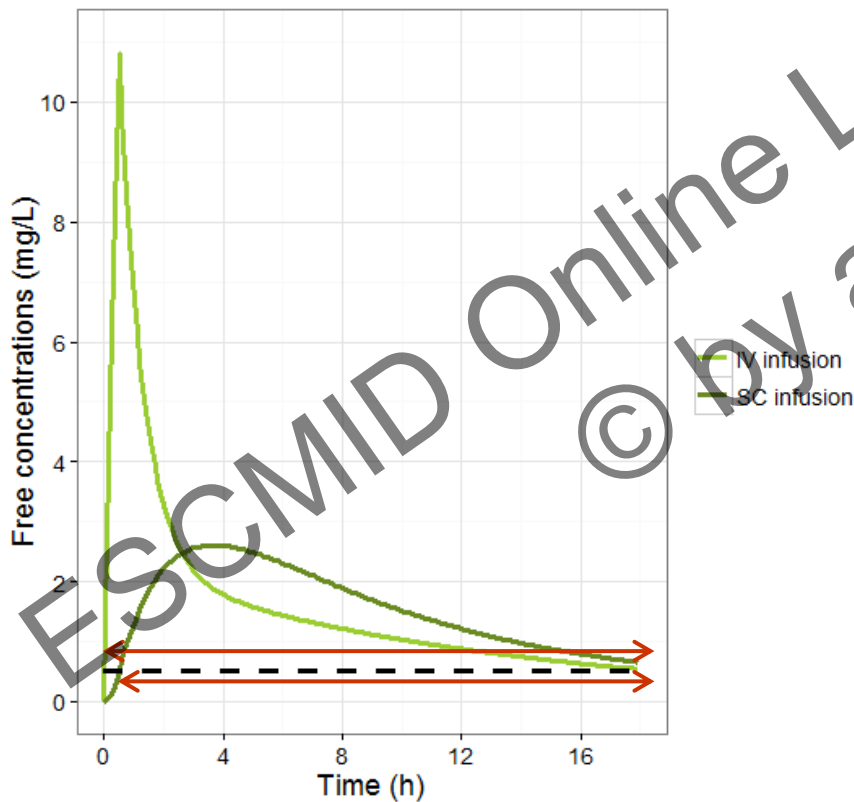
$\frac{C_{max}}{MIC} < 8$ for IV and SC infusion

Time dependent antibiotics



Target: $(t > MIC) \geq 40\%$
of the dosing interval

Time dependent antibiotics



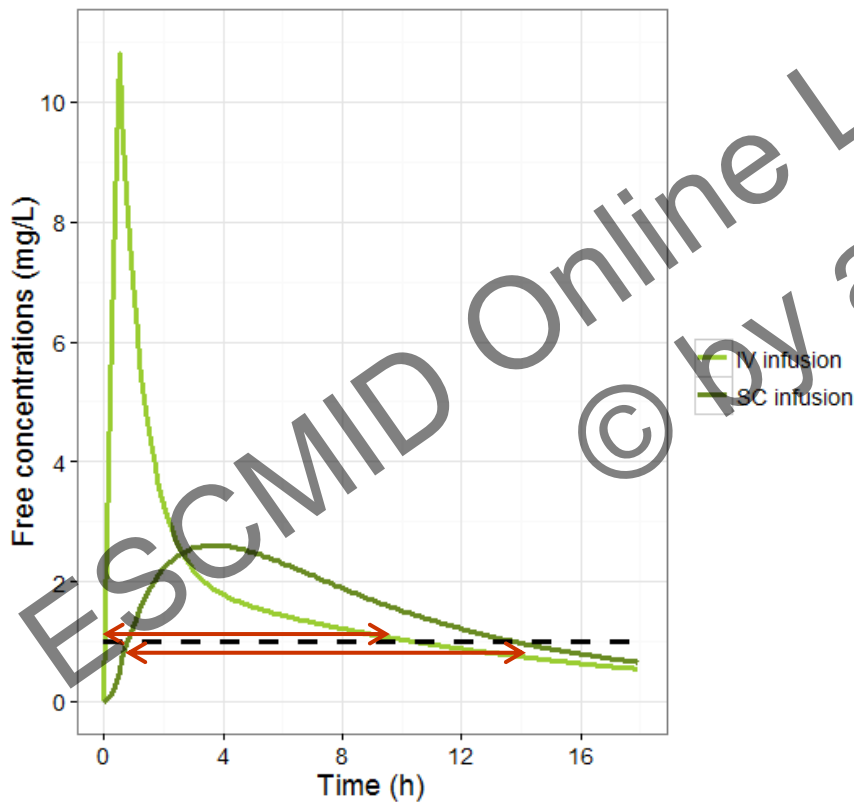
Target: $(t > MIC) \geq 40\%$
 of the dosing interval

$$MIC = 0.5 \text{ mg/L}$$

$(t > MIC) \approx$ when $R_{abs} \searrow$

$(t > MIC) > 40\%$ for IV and SC infusion

Time dependent antibiotics



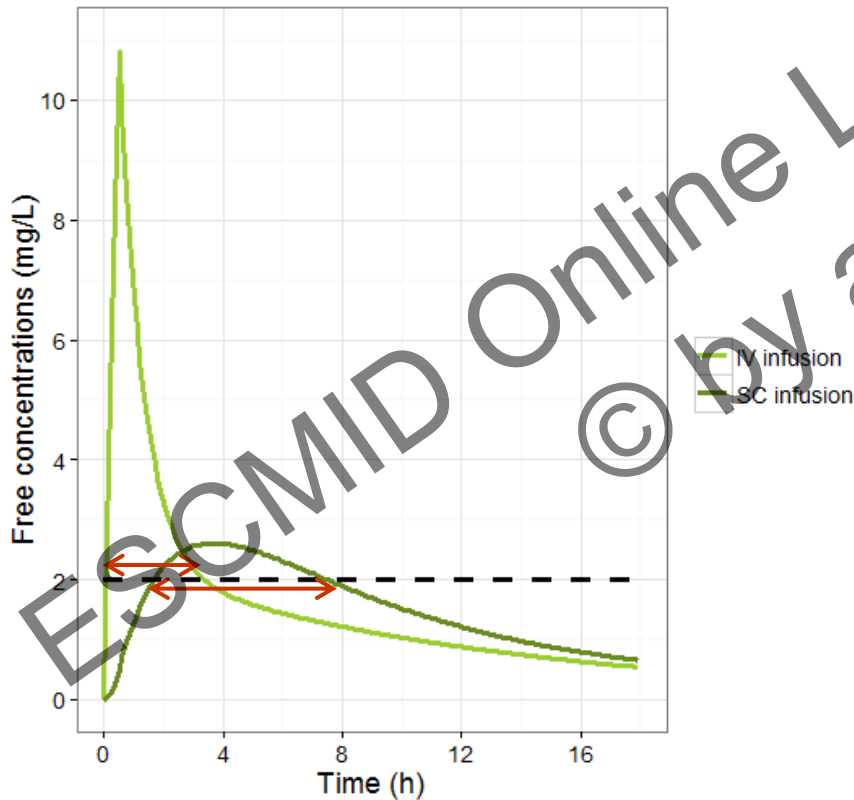
Target: $(t > MIC) \geq 40\%$
of the dosing interval

$$\underline{MIC = 1 \text{ mg/L}}$$

$(t > MIC) \nearrow$ when $R_{abs} \searrow$

$(t > MIC)$ $\begin{cases} < 40\% \text{ for IV infusion} \\ > 40\% \text{ for SC infusion} \end{cases}$

Time dependent antibiotics



Target: $(t > MIC) \geq 40\%$
 of the dosing interval

$$MIC = 2 \text{ mg/L}$$

$(t > MIC) \nearrow$ when Rabs \searrow

$(t > MIC) < 40\%$ for IV and SC infusion

**Effect SC
 infusion on PK
 and PK-PD**

PK

PK-PD

**Infusion rate
 limited**

**Absorption rate
 limited**

Flow rate limited

Permeability rate
 limited

(-)

(+)

(+)

Conc Dep

Time Dep

Conc Dep

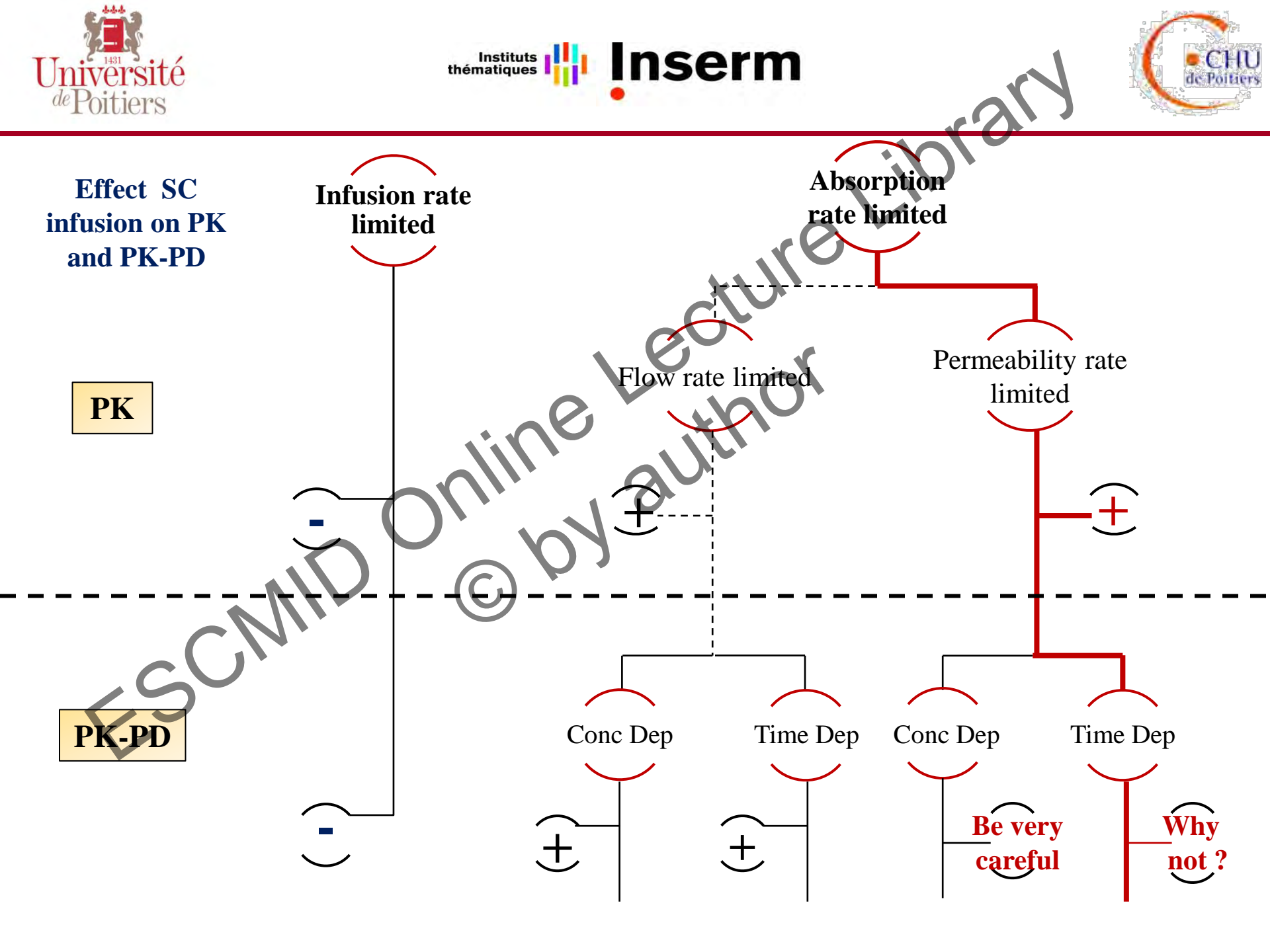
Time Dep

(+)

(+)

**Be very
 careful**

**Why
 not ?**



But facts may differ from predictions





Acknowledgements

**- E. Forestier, C. Roubaud-Baudron, T. Fraisse, M. Paccalin,
L. Pagani, J. Gaillat, G. Gavazzi**

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