neonates need more finesse in dosing of antibiotics

when

what

how: PK

K Allegaert

Erasmus MC Rotterdam, the Netherlands

KU Leuven, Belgium

karel.allegaert@uzleuven.be; k.allegaert@erasmusmc.nl

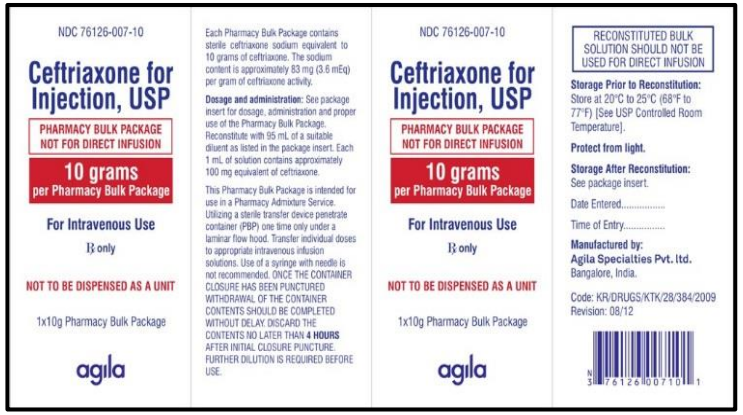
reconsidering history

gray baby syndrome

Life-threatening condition produced by the administration of chloramphenicol to neonates and young children

Many neonatal deaths associated with this syndrome: ontogeny or genetic predisposition?

Can we integrate current knowledge regarding primary paths of drug biotransformation and ontogeny to guide therapy?



when, what (product development) and how ?

antibiotics are very commonly used, practices vary extensively

infections occur, are rather rare, but have impact on outcome

target for antibiotics depend on its mechanism (concepts, no doses)

Penicillins: time about MIC (minimal inhitory concentration)
Vancomycin: both ?
Aminoglycosides: peak > 8 MIC, and trough relates to toxicity

how to apply to neonates

maturational toxicity to be considered

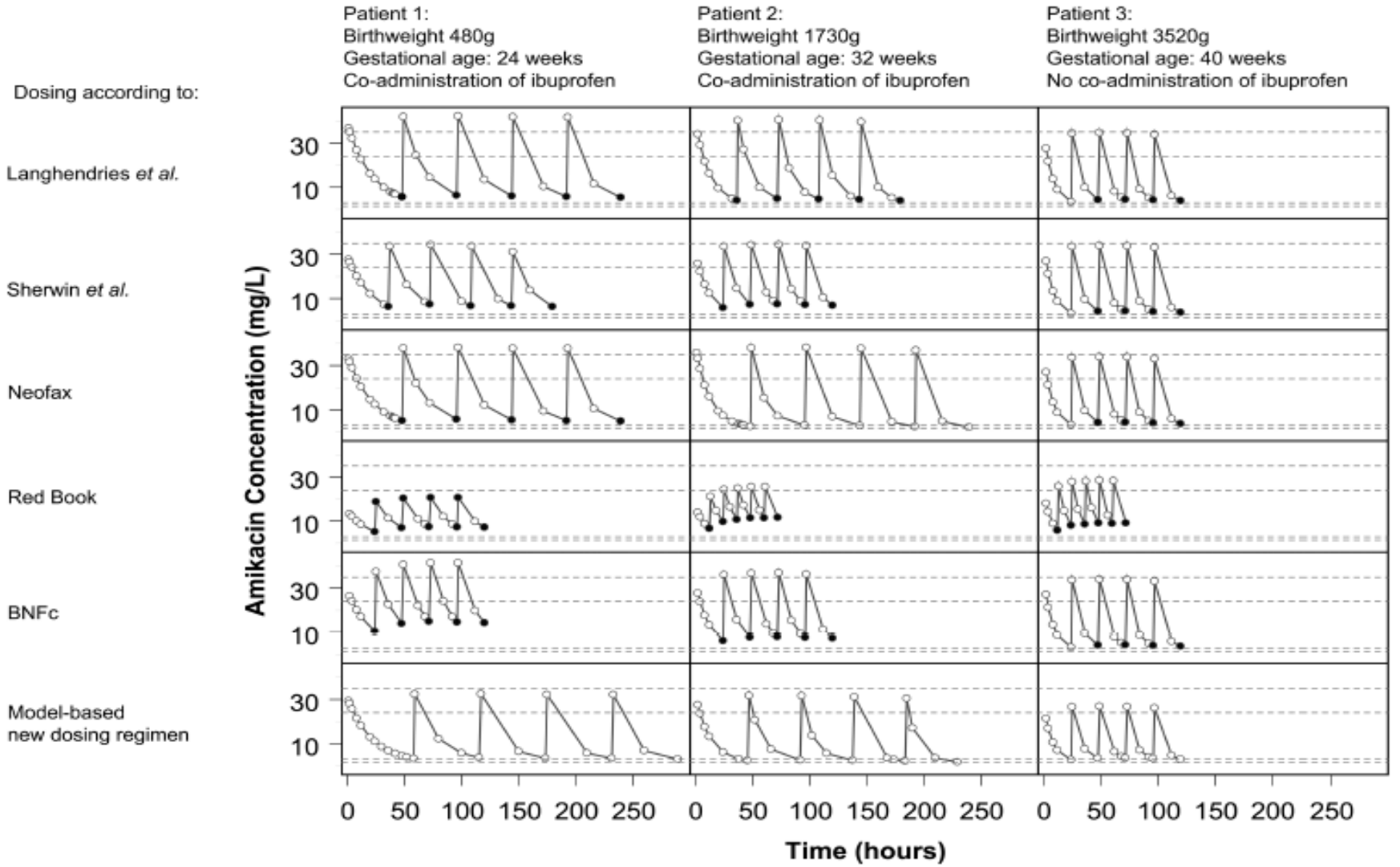
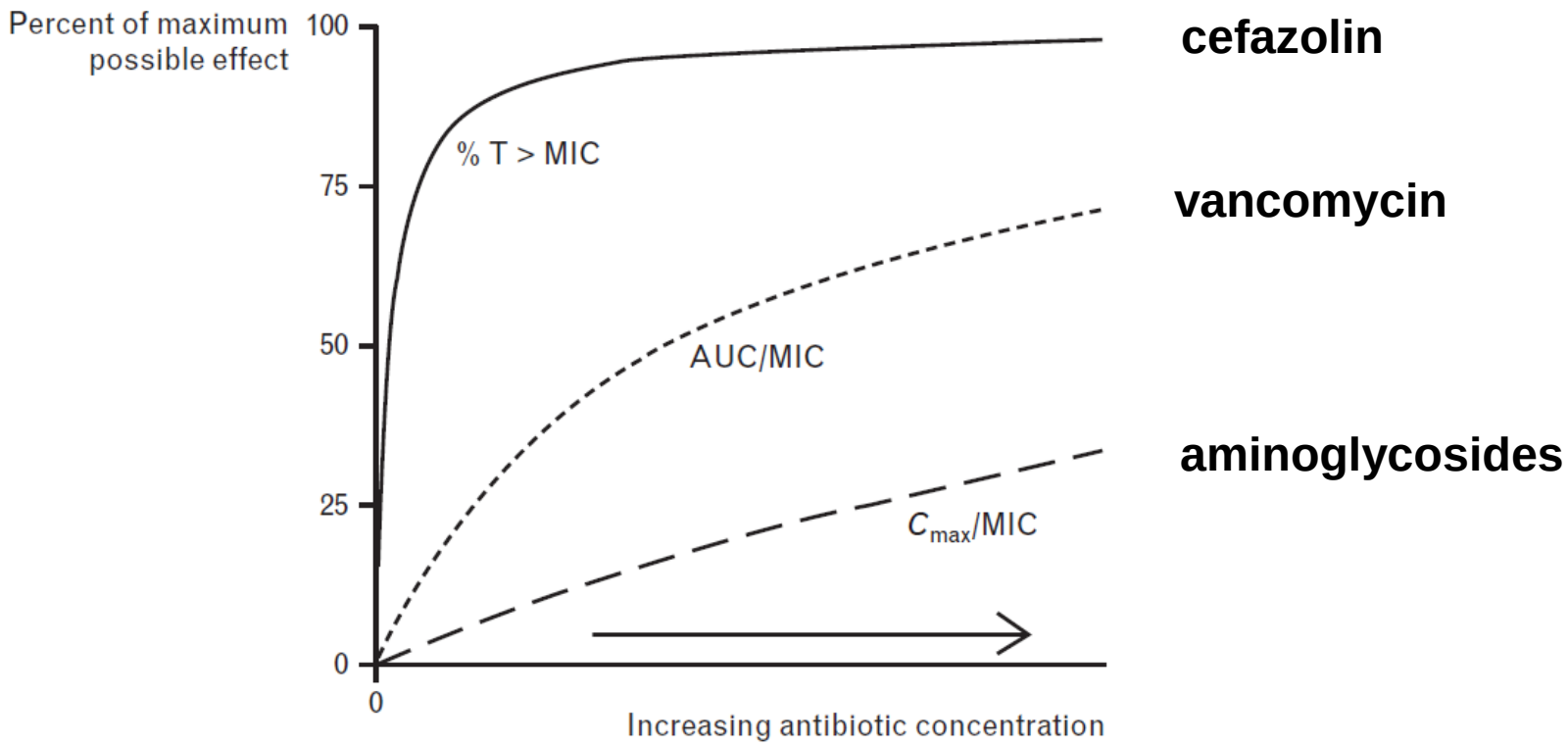


Figure 2 Model-based predicted concentration-time profiles of amikacin for three typical neonates, using five different currently used dosing guidelines[19 34–37] and according to the new model-based dosing regimen. Open dots: concentrations within target range, black filled dots: C_{max} over target C_{max}, grey filled dots: C_{min} under target C_{min}. C_{max}=maximum concentration; C_{min}=minimum concentration. Long dash line, Limit of target C_{max} range; Short dash line, limit of target C_{trough} range. Adapted from De Cock RFW *et al.* Maturation of the glomerular filtration rate in neonates, as reflected by amikacin clearance. Reproduced from Cock R. F. W. De *et al.* Maturation of the glomerular filtration rate in neonates, as reflected by amikacin clearance. *Clinical pharmacokinetics* 2012;51:105–17 with permission from Adis (© Springer International Publishing AG 2012. All rights reserved.)

De Cock et al. Clin Pharmacokinet 2012

Concentration-response relationships and how they relate to common antimicrobial PK/PD indices

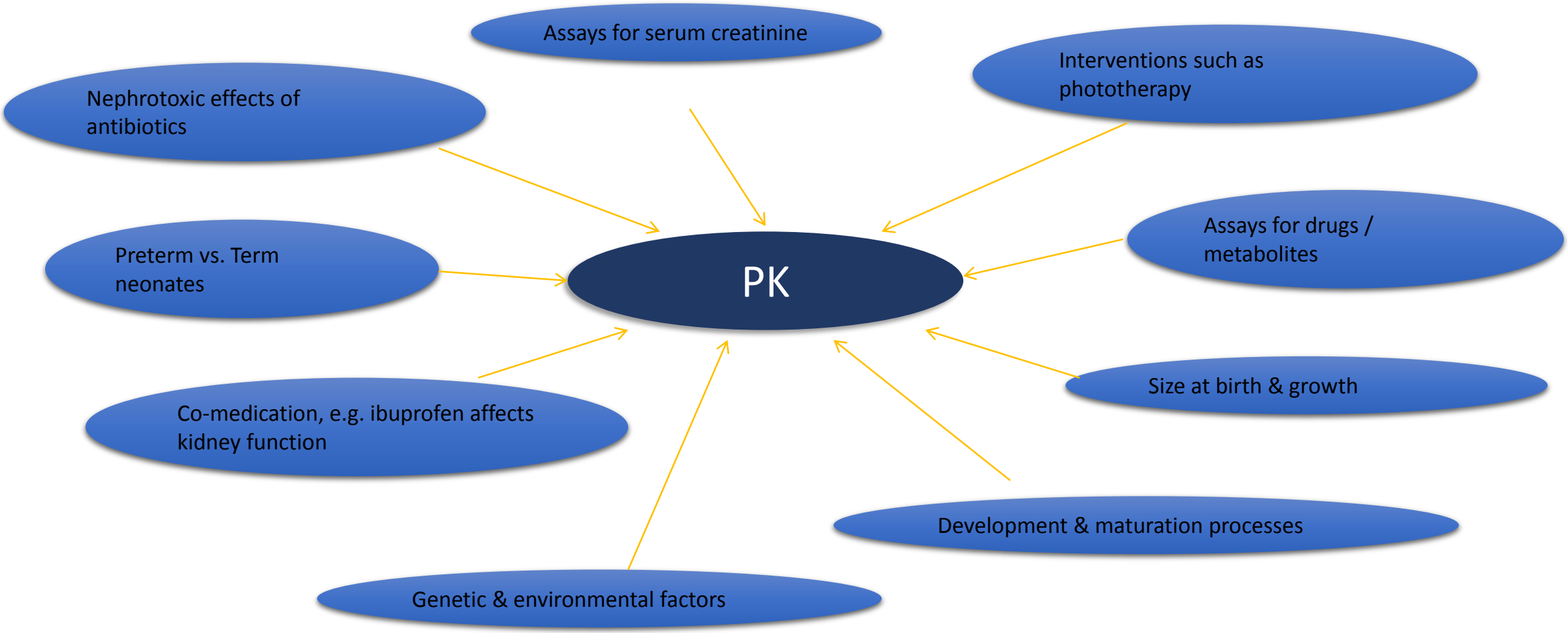


Barker et al. Curr Opin Infect Dis 2012

topics to be discussed

- Antibiotics are very commonly used and practices vary
- Infections occur, are rather rare, but have impact on outcome
- Target for antibiotics depend on its mechanism
  - Penicillins: time about MIC (minimal inhitory concentration)
  - Vancomycin: both ?
  - Aminoglycosides: peak > 8 MIC, and trough relates to toxicity
- **How to apply to neonates (blood compartment only ?)**
- Specific toxicity to be considered

need to understand sources of PK variability in neonates



distribution volume and clearance are sometimes ‘contradicting’ in early life

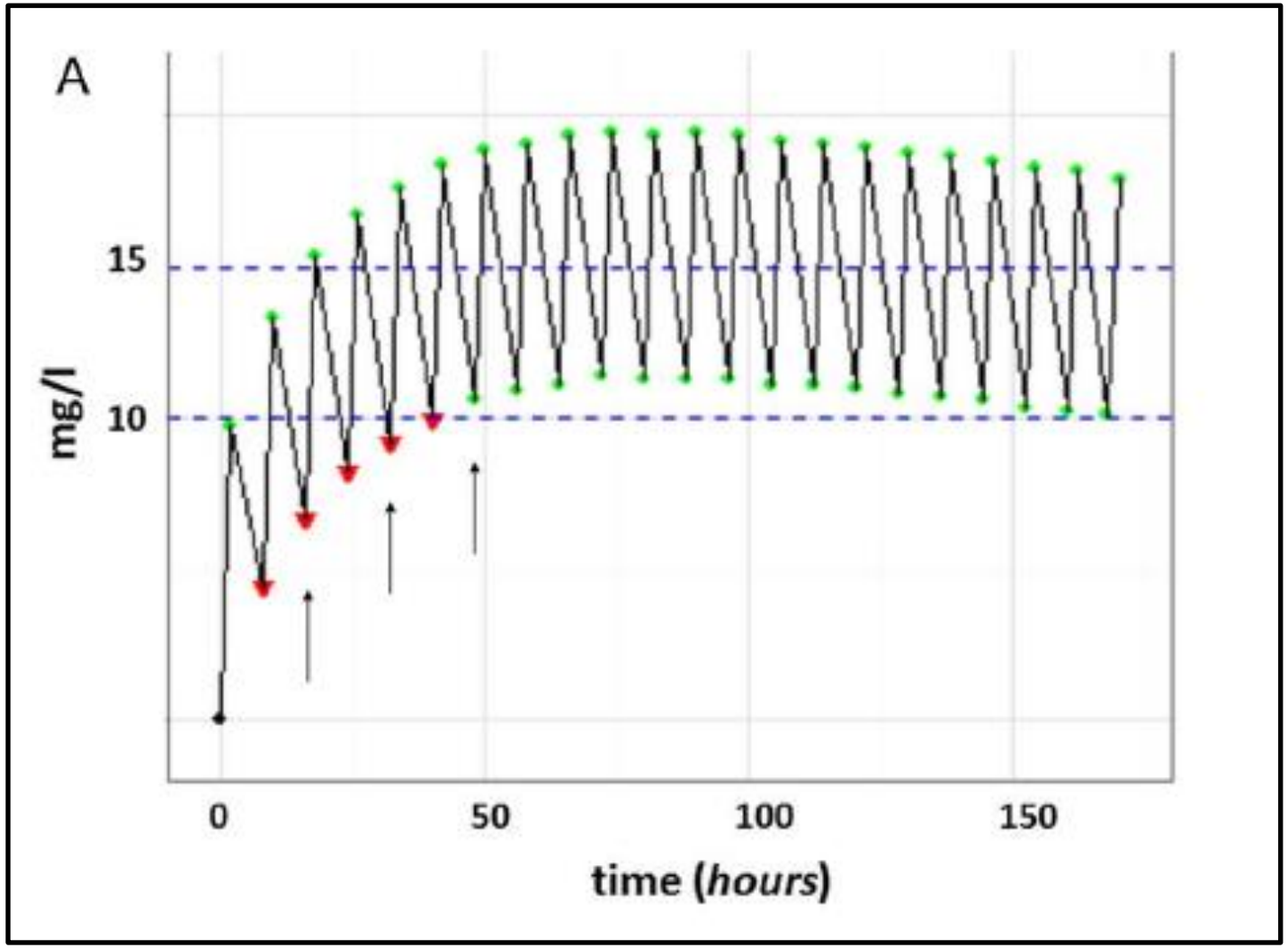
body water content changes with age

Fig. 1. Changes occurring in percentages of body fat and water stores along the continuum of age [16].

Rakhmanina *et al*, 2006

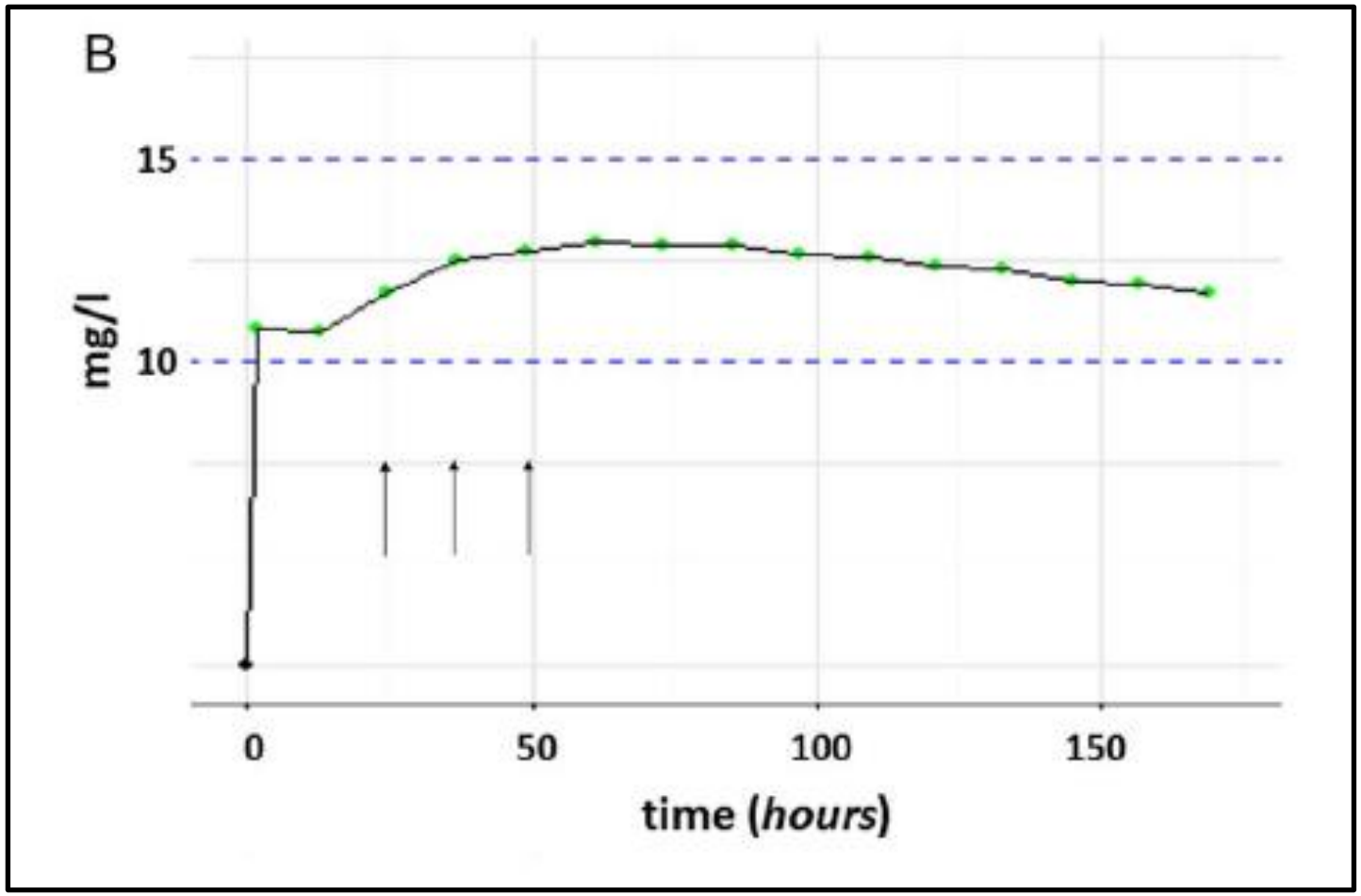

© Murray Sanders

vancomycin, intermittent, target AUC_{400}= 10-15 mg/l ***through***



Pauwels et al. Arch Dis Childh 2016

vancomycin, continuous target AUC_{400}= 15-20 mg/l ***median***



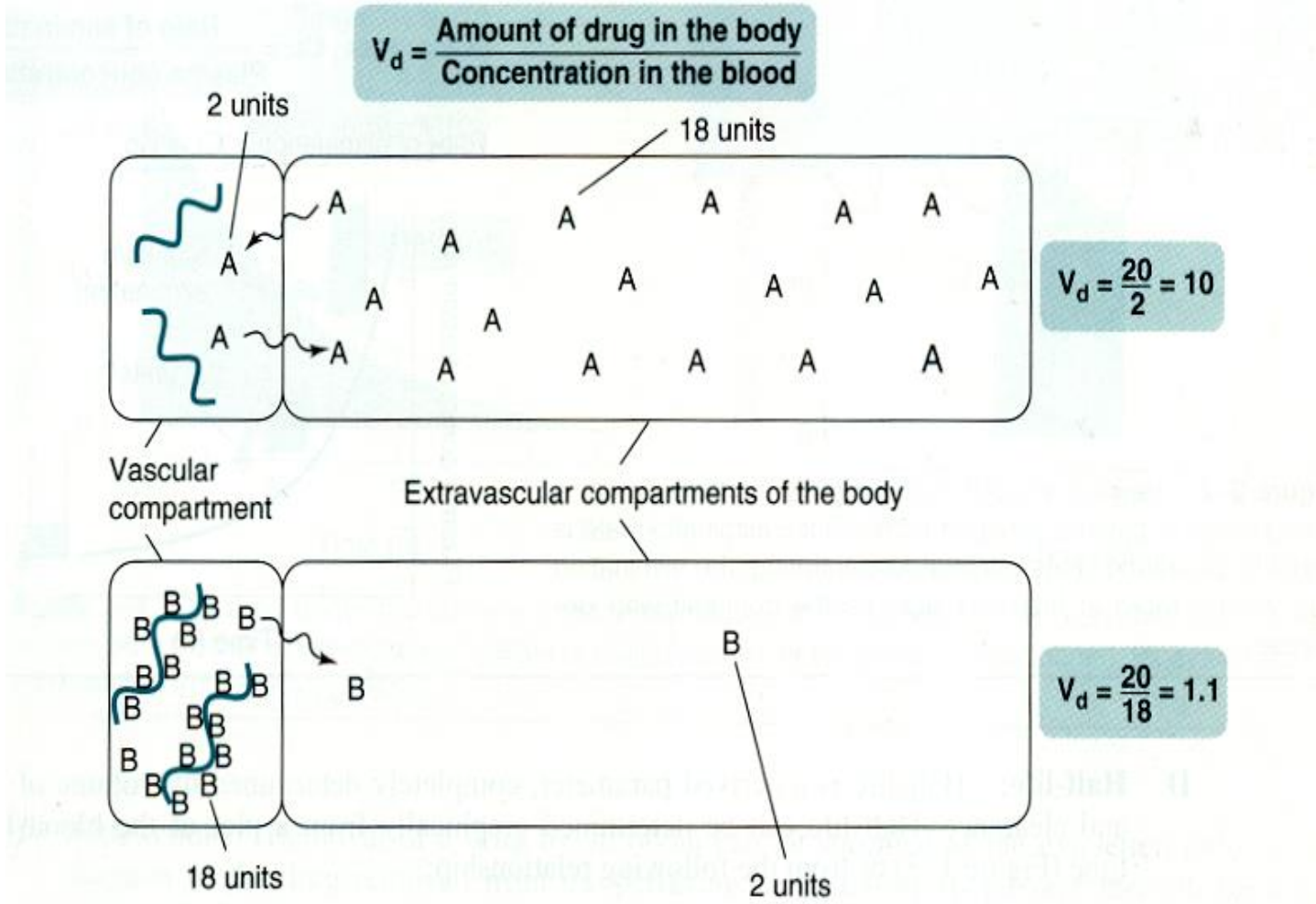
Pauwels et al. Arch Dis Childh 2016

The free (unbound) concentration of the drug at the target site should be used in PK/PD correlations to make prediction for pharmacological activity

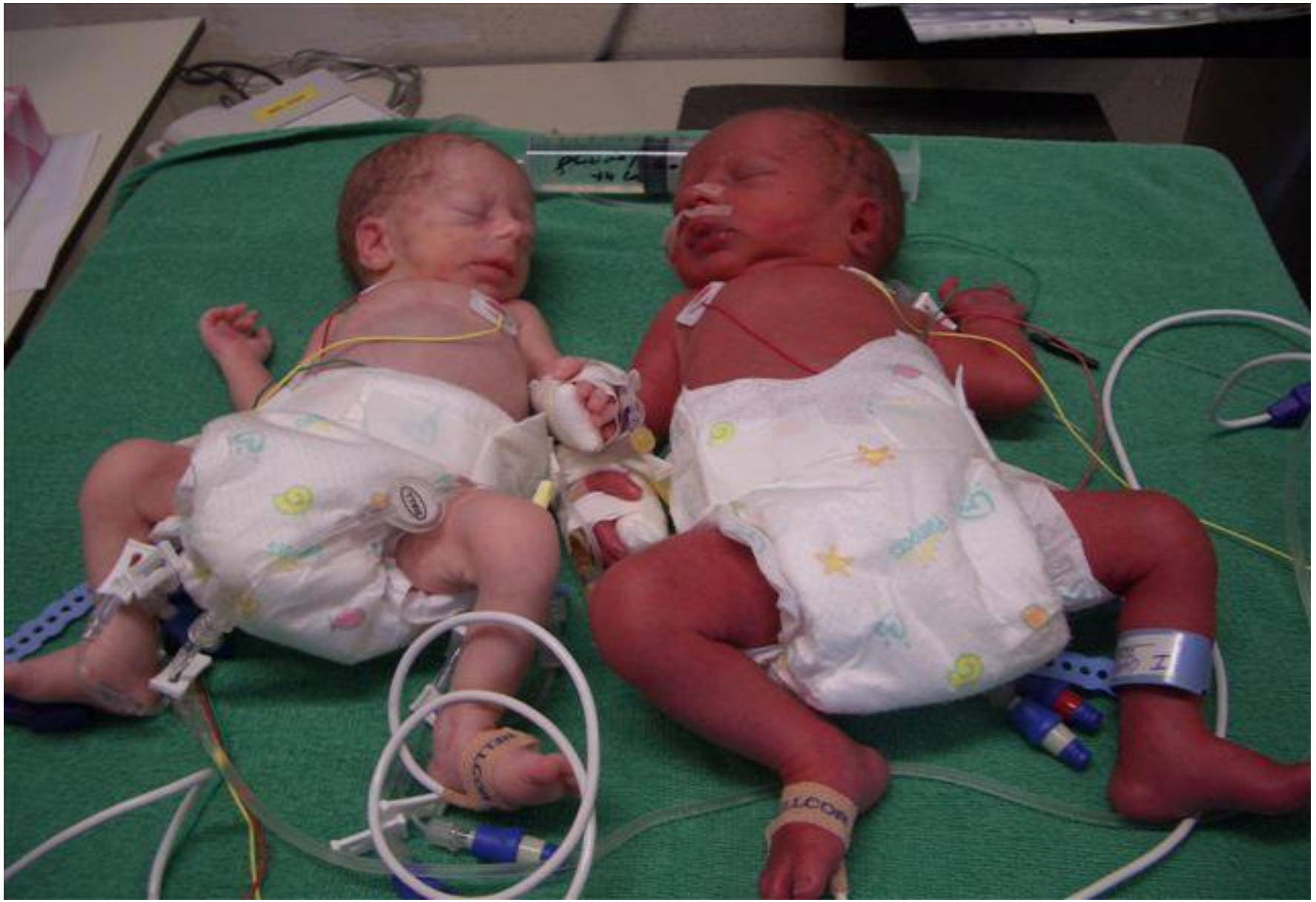
	ICU ADULTS	PEDIATRICS	NEONATES
Samples/patients	51/33	18/11	37/33
albumin (g/l)	28,4	28,9	29,9
vancomycin, total (mg/l)	17,8	10,7	14,2
vancomycin, free (mg/l)	10,9	8,2	13,6
vancomycin, free (%)	61,7	81,3	90

Oyaert et al. Antimicrob Agents Chemother 2015; Smits et al. Eur J Clin Microbiol Inf Dis 2018

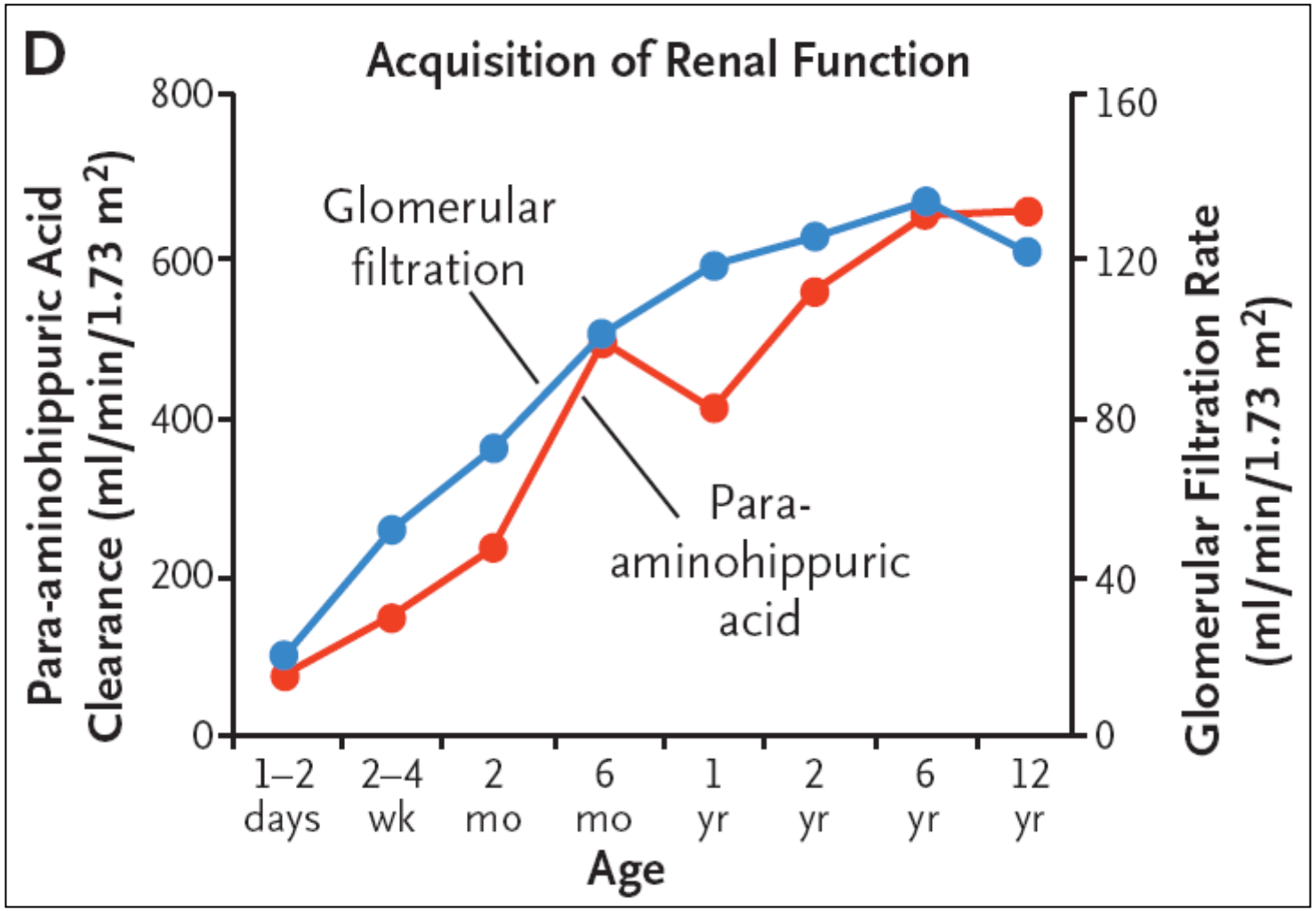
effect of drug binding on volume of distribution
bilirubin



drug clearance: relation to weight/age ?



renal elimination changes with age: not just GFR



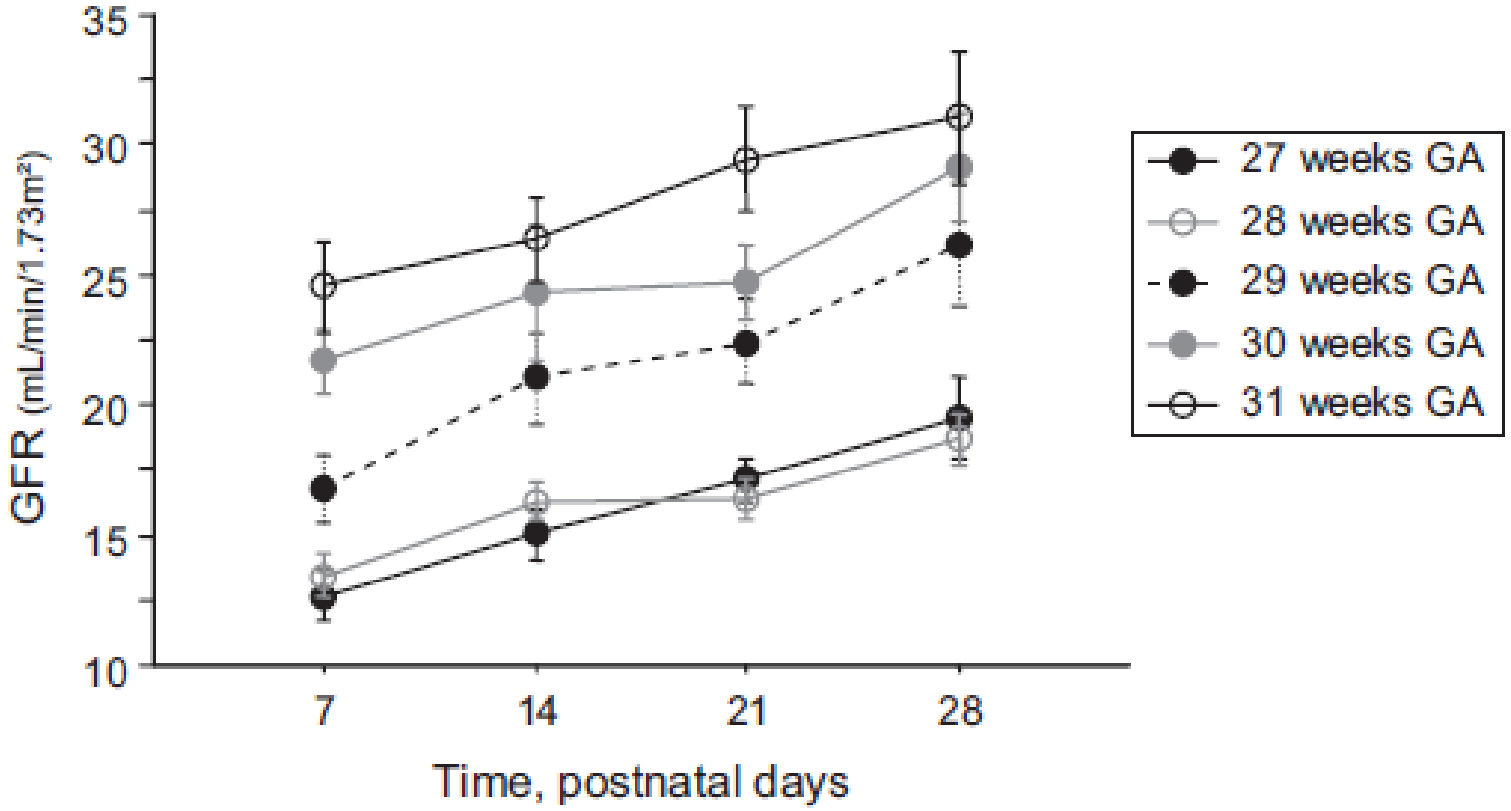


FIGURE 1

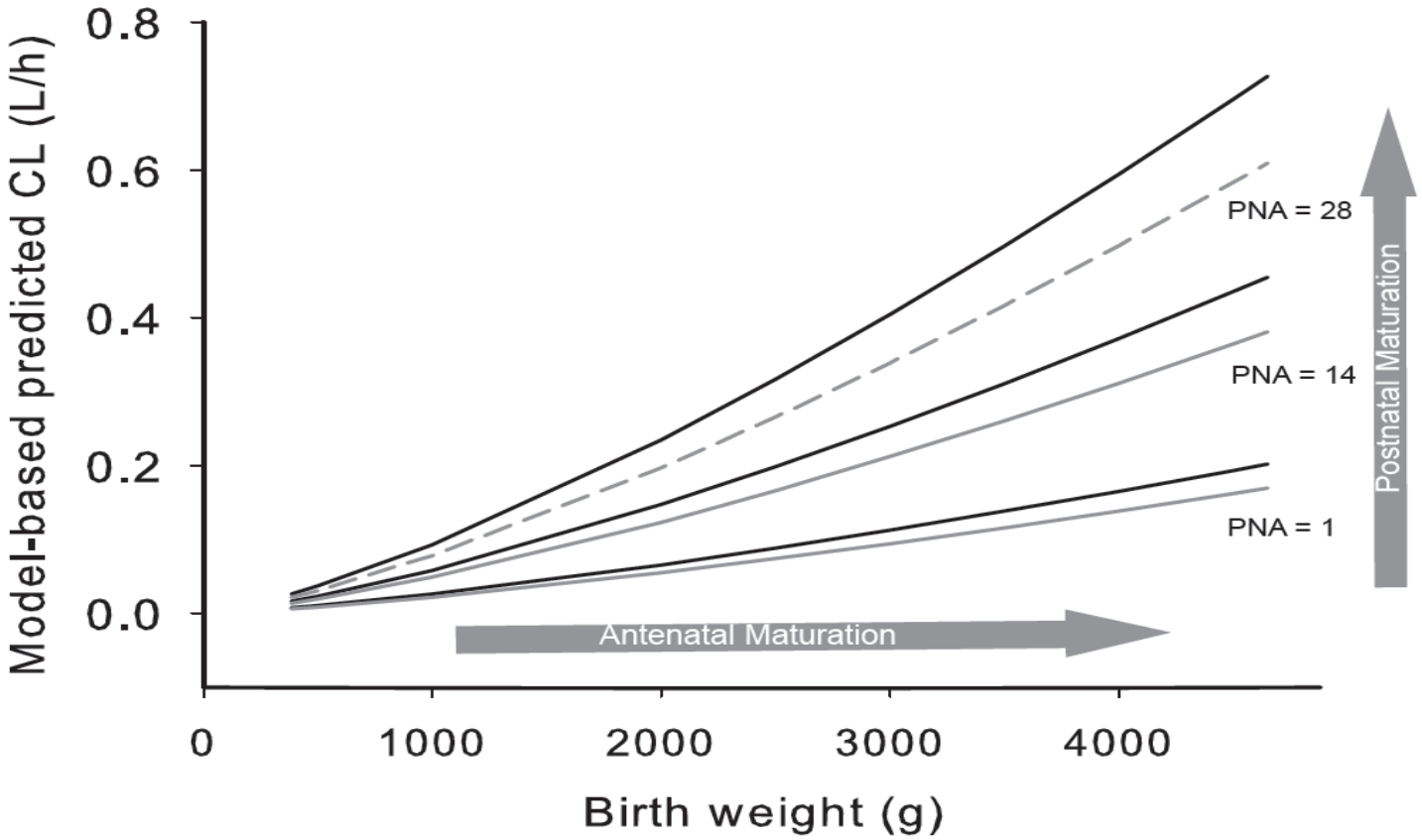
GFR according to GA in the first month of life ($n = 275$). Data are means ± SEM.

Vieux et al. Pediatrics 2014

One dose per day compared to multiple doses per day of gentamicin for treatment of suspected or proven sepsis in neonates (Review)

Rao SC, Srinivasjois R, Hagan R, Ahmed M

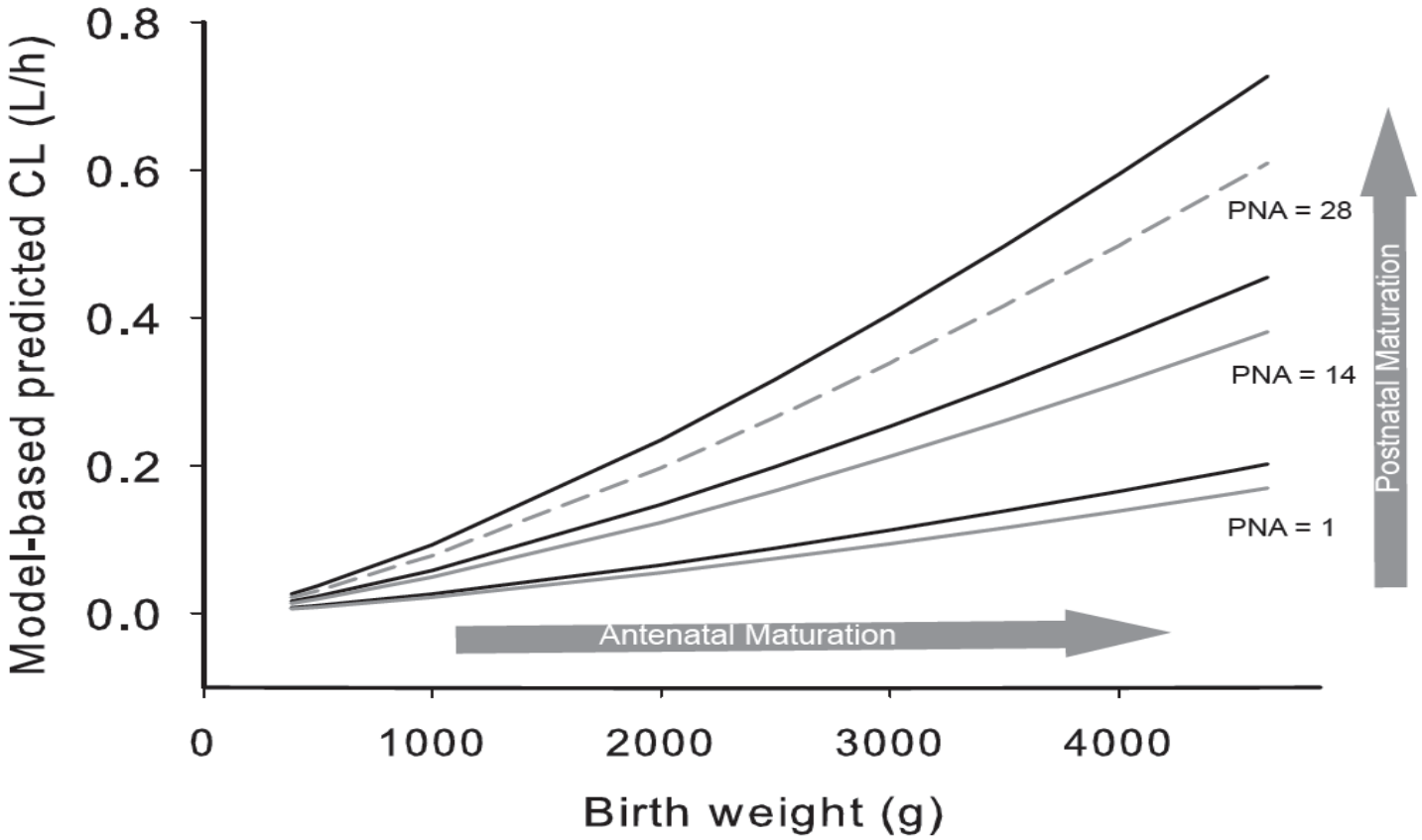
amikacin clearance in neonates: age and weight



De Cock et al. Clin Pharmacok 2013

*amikacin clearance in neonates: age and weight and **ibuprofen***

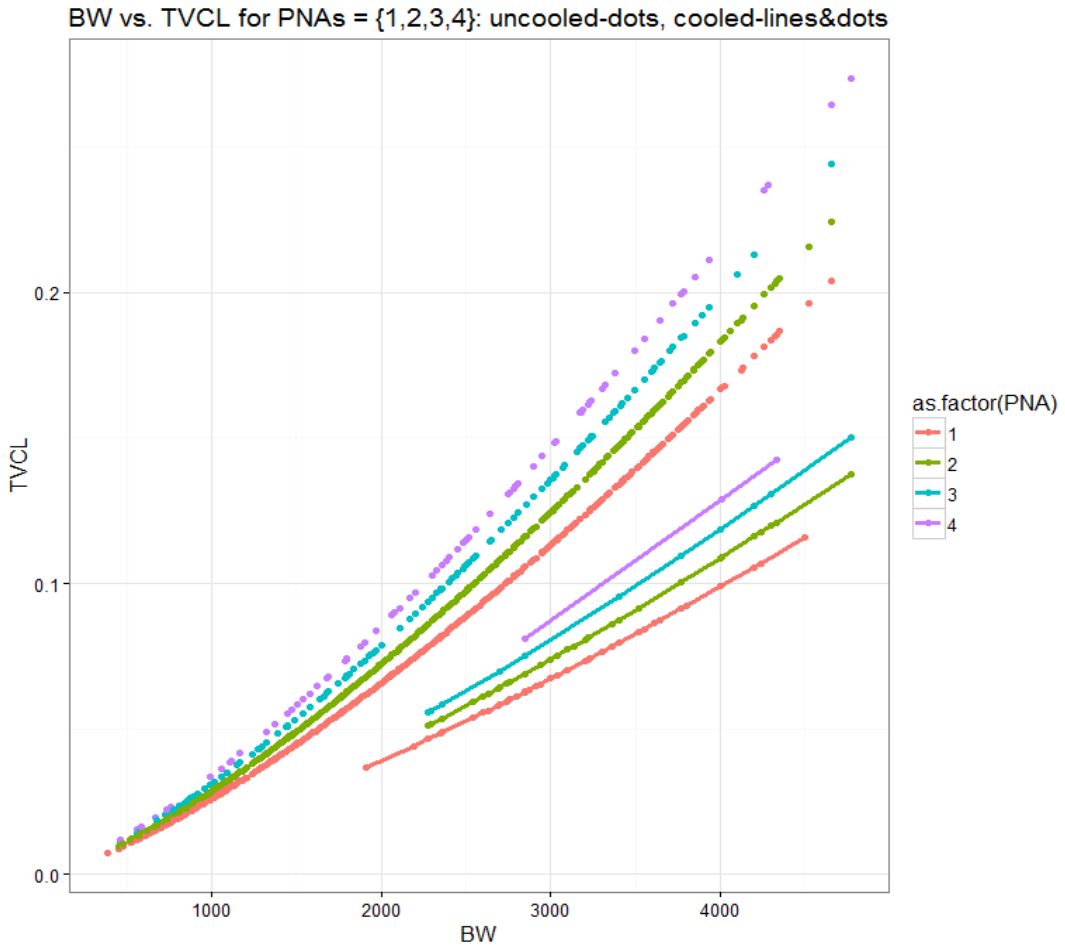
ibuprofen or indomethacin = + 10-12 h of the interval



De Cock et al. Clin Pharmacok 2013

amikacin clearance in neonates: ***whole body cooling +/-***

Whole body cooling/apshyxia = + 10-12 h of the interval



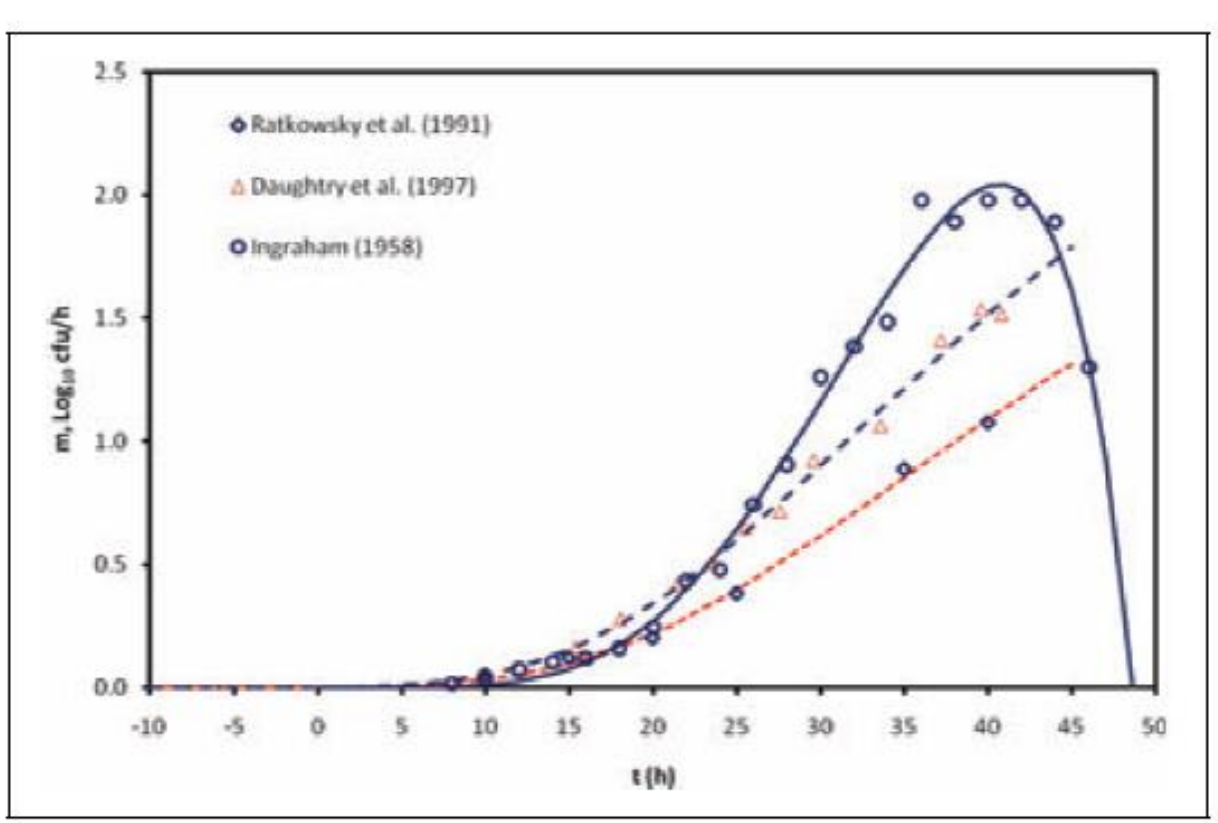


Figure 6–Modeling the effect of temperature on growth rate of *E. coli.*

Cristea et al. Antimicrob Agents Chemother 2017 and Huang et al, J Food Science 2011

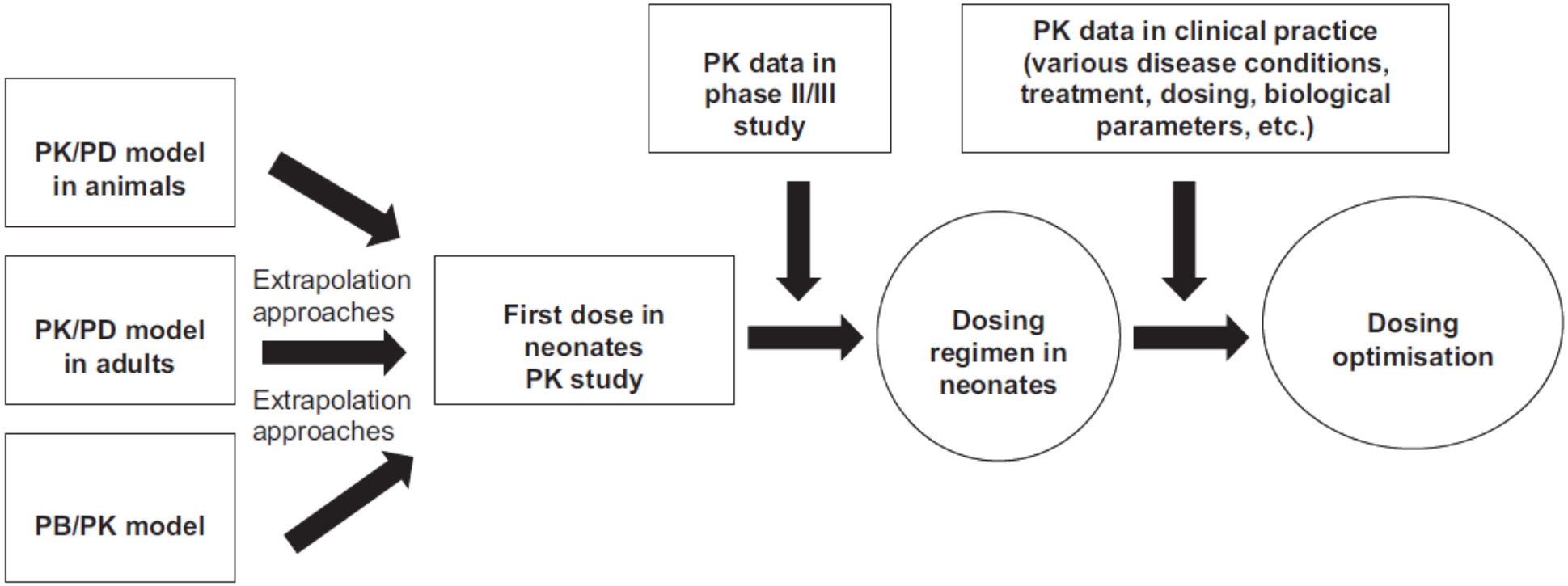
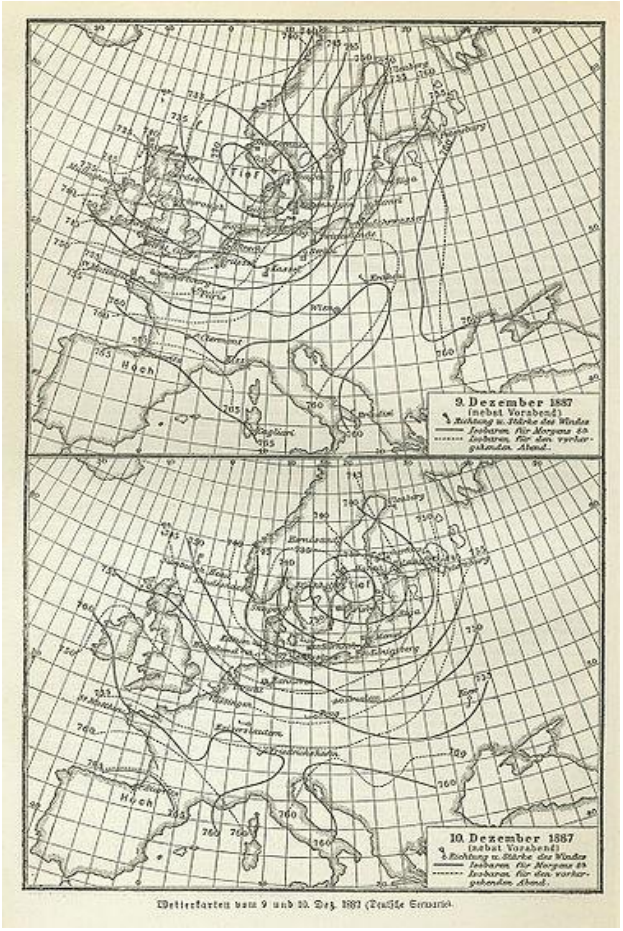


Figure 1. Dosing optimisation of antimicrobial agents in the neonate. PK, pharmacodynamics; PD, pharmacodynamics.

Jacqz-Aigrain E et al. Semin Fetal Neonatal Med 2013

models: *let's make things better...*

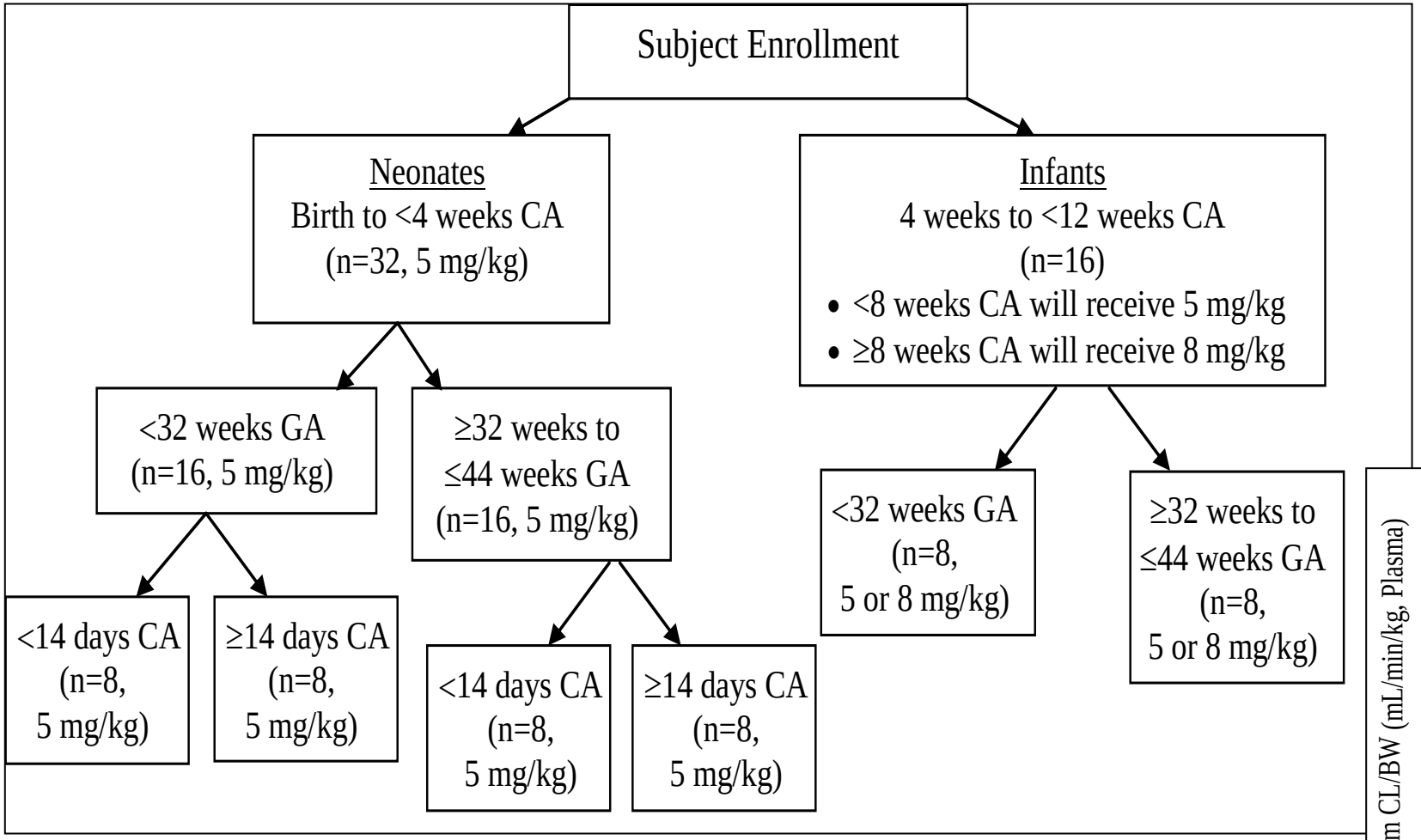


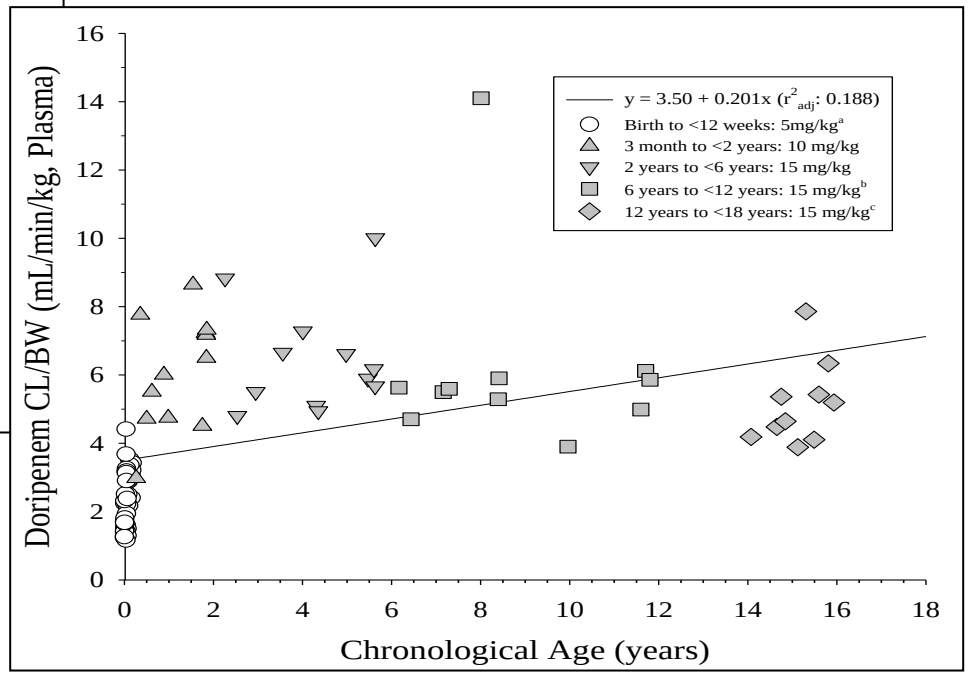
1887

2014

Essentially, all models are wrong, but some are useful.

(George E.P. Box, 1919 - 2013)


Subject Enrollment
Neonates
Birth to <4 weeks CA
(n=32, 5 mg/kg)
Infants
4 weeks to <12 weeks CA
(n=16)
• <8 weeks CA will receive 5 mg/kg
• ≥8 weeks CA will receive 8 mg/kg
<32 weeks GA
(n=16, 5 mg/kg)
≥32 weeks to
≤44 weeks GA
(n=16, 5 mg/kg)
<32 weeks GA
(n=8,
5 or 8 mg/kg)
≥32 weeks to
≤44 weeks GA
(n=8,
5 or 8 mg/kg)
<14 days CA
(n=8,
5 mg/kg)
≥14 days CA
(n=8,
5 mg/kg)
<14 days CA
(n=8,
5 mg/kg)
≥14 days CA
(n=8,
5 mg/kg)

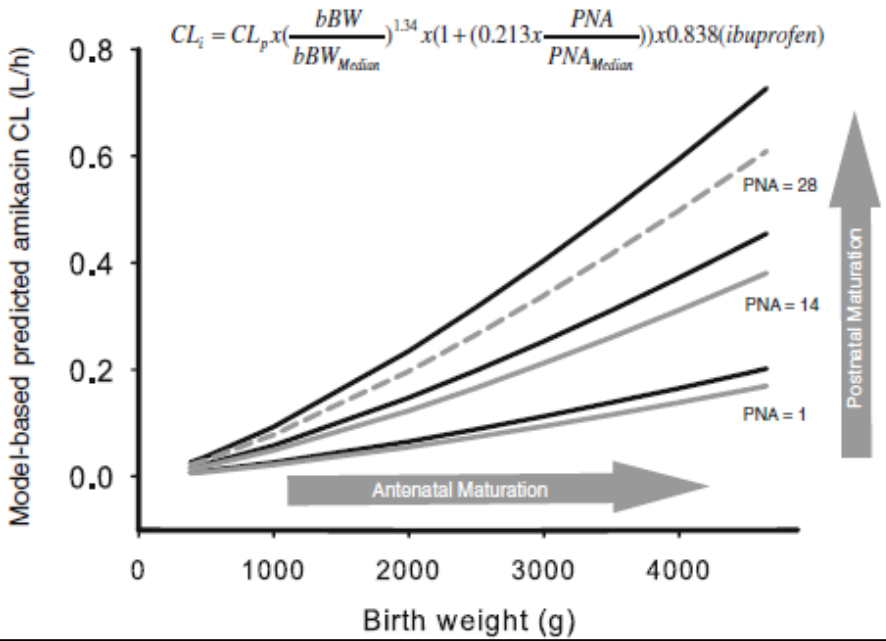

Doripenem CL/BW (mL/min/kg, Plasma)
Chronological Age (years)
y = 3.50 + 0.201x (r2adj: 0.188)
Birth to <12 weeks: 5mg/kg[a]
3 month to <2 years: 10 mg/kg
2 years to <6 years: 15 mg/kg
6 years to <12 years: 15 mg/kg[b]
12 years to <18 years: 15 mg/kg[c]
0
2
4
6
8
10
12
14
16
18

A Neonatal Amikacin Covariate Model Can Be Used to Predict Ontogeny of Other Drugs Eliminated Through Glomerular Filtration in Neonates

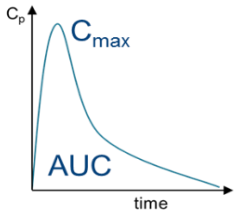
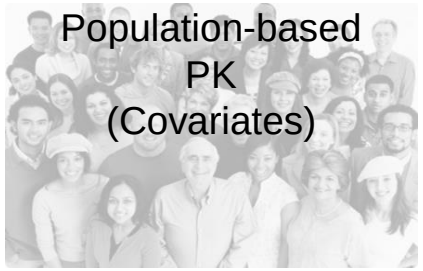
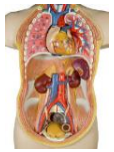
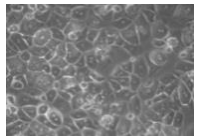
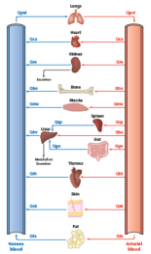
$$CL_i = CL_p \times \left(\frac{bBW}{bBW_{Median}}\right)^{1.34} \times \left(1 + \left(0.213 * \frac{PNA}{PNA_{Median}}\right)\right) \times 0.838_{ibuprofen}$$

Drug specific property

Amikacin covariate model



De Cock et al. Pharm Res 2014

	Data gathering	Modelling	Clinical implications
"TOP DOWN" Clinic to mechanistic (population-based)	Plasma Data 	Population-based PK (Covariates) 	Confirming 
"BOTTOM UP" *In vitro* to *In vivo* (IVIVE)	 Demography Physiology Genetics *In vitro* data  	physiology 	Learning 

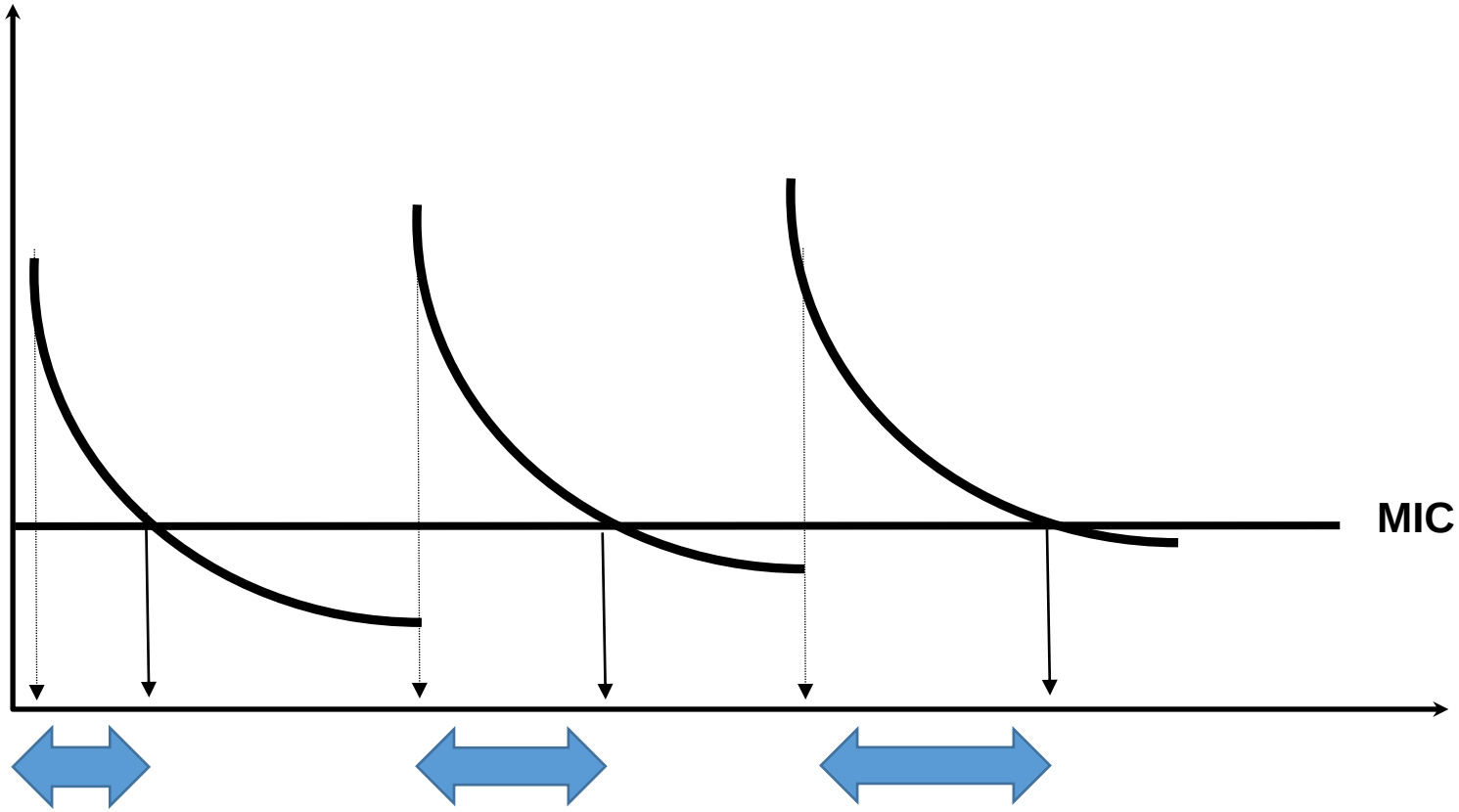
BACK-UP SLIDES

repeated administration, the impact of the frequency of administration despite the same 24 h dose

Time above MIC

Penicillines

(vancomycin)

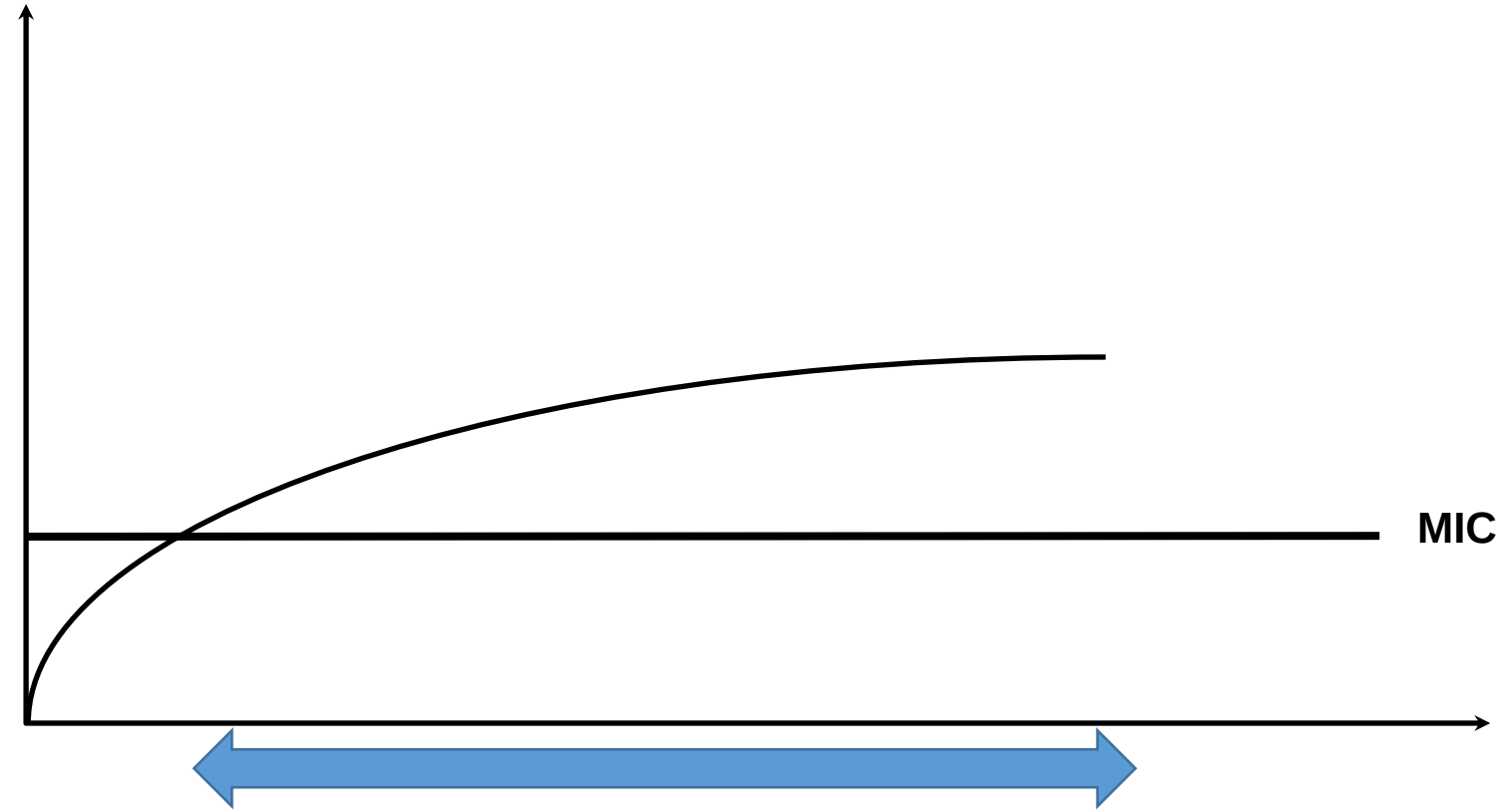


the impact of the continous administration despite the same 24 h dose

Time above MIC

Penicillines

(vancomycin)

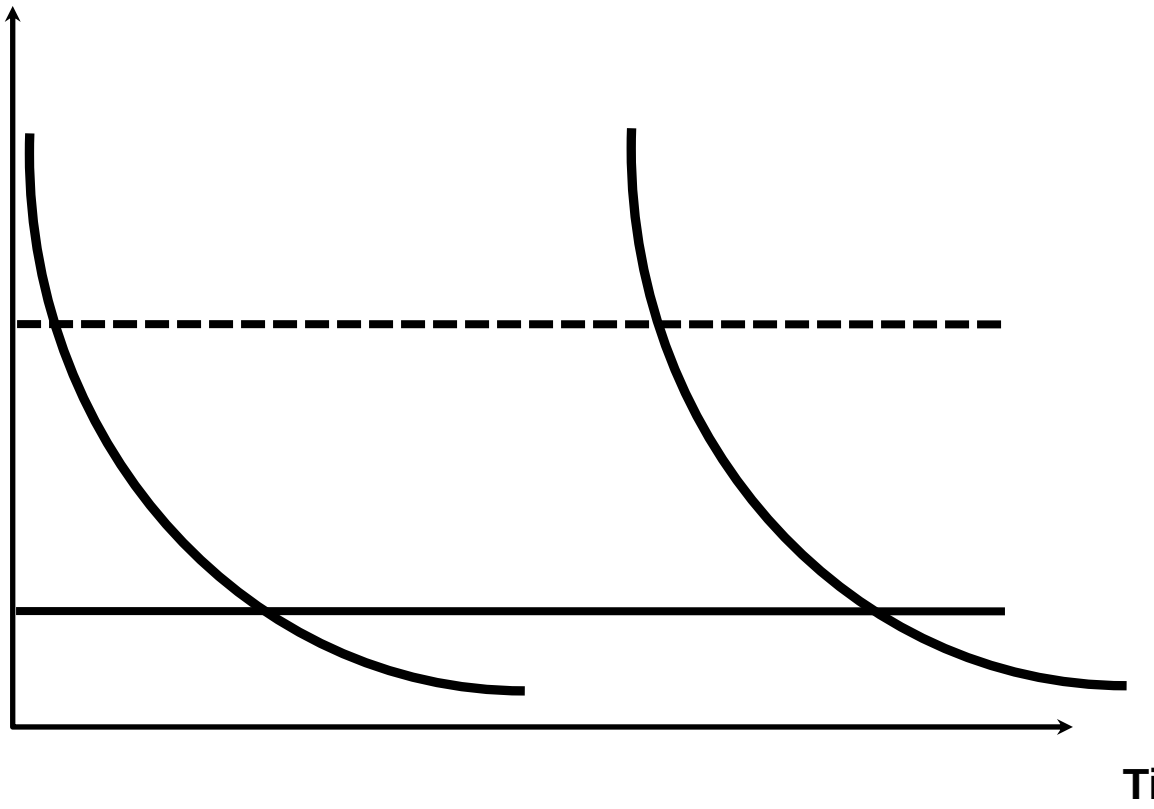


aminoglycosides: aim for a high peak and wait for a low trough level

Peak/MIC > 8

ratio of the peak concentration to MIC

(aminoglycosides)



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Drug specific property

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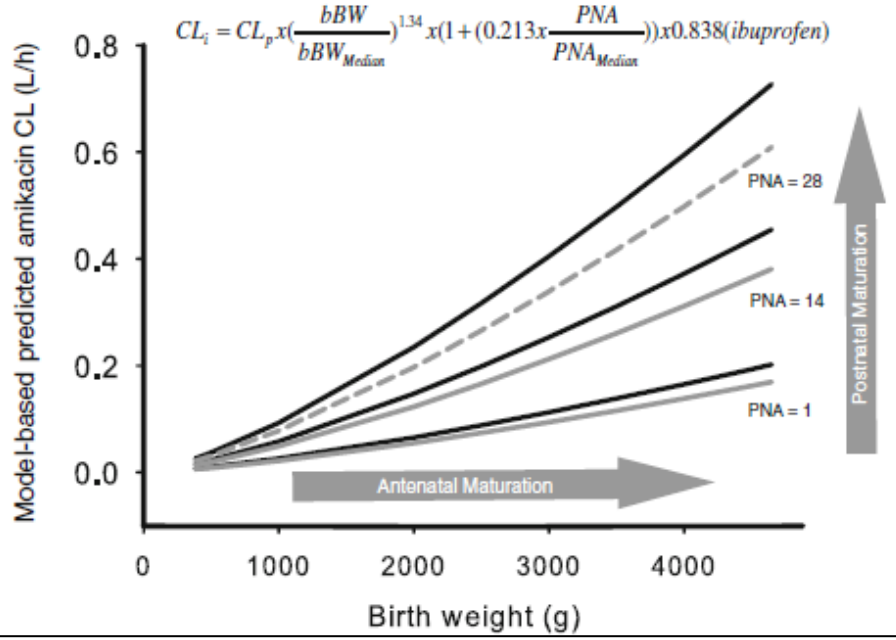
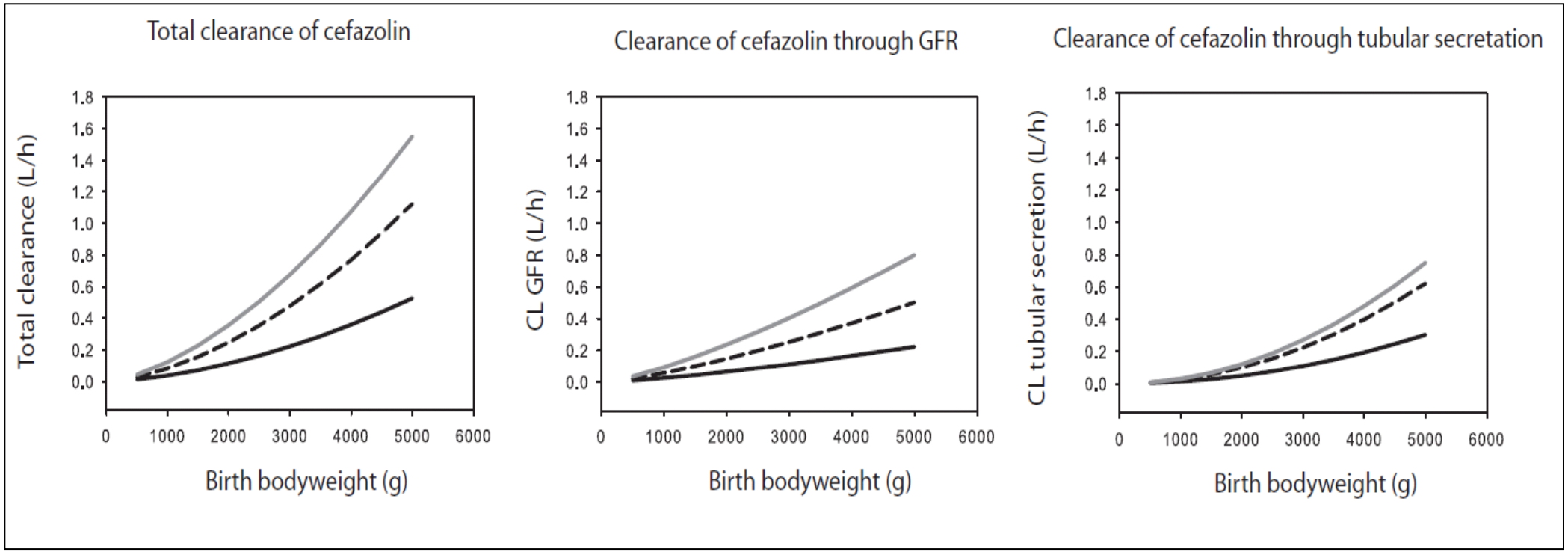


De Cock et al. Pharm Res 2014

$$CL_i = \{ CL_{p\ amikacin} \times (\frac{BWb}{BWb_{Median}})^{1.34} * (1 + (0.213 * \frac{PNA}{PNA_{Median}})) \} + \{ CL_{p\ cefazolin} \times \text{Covariates} \}$$

Developmental changes in GFR based on amikacin clearance

Developmental changes in tubular processes



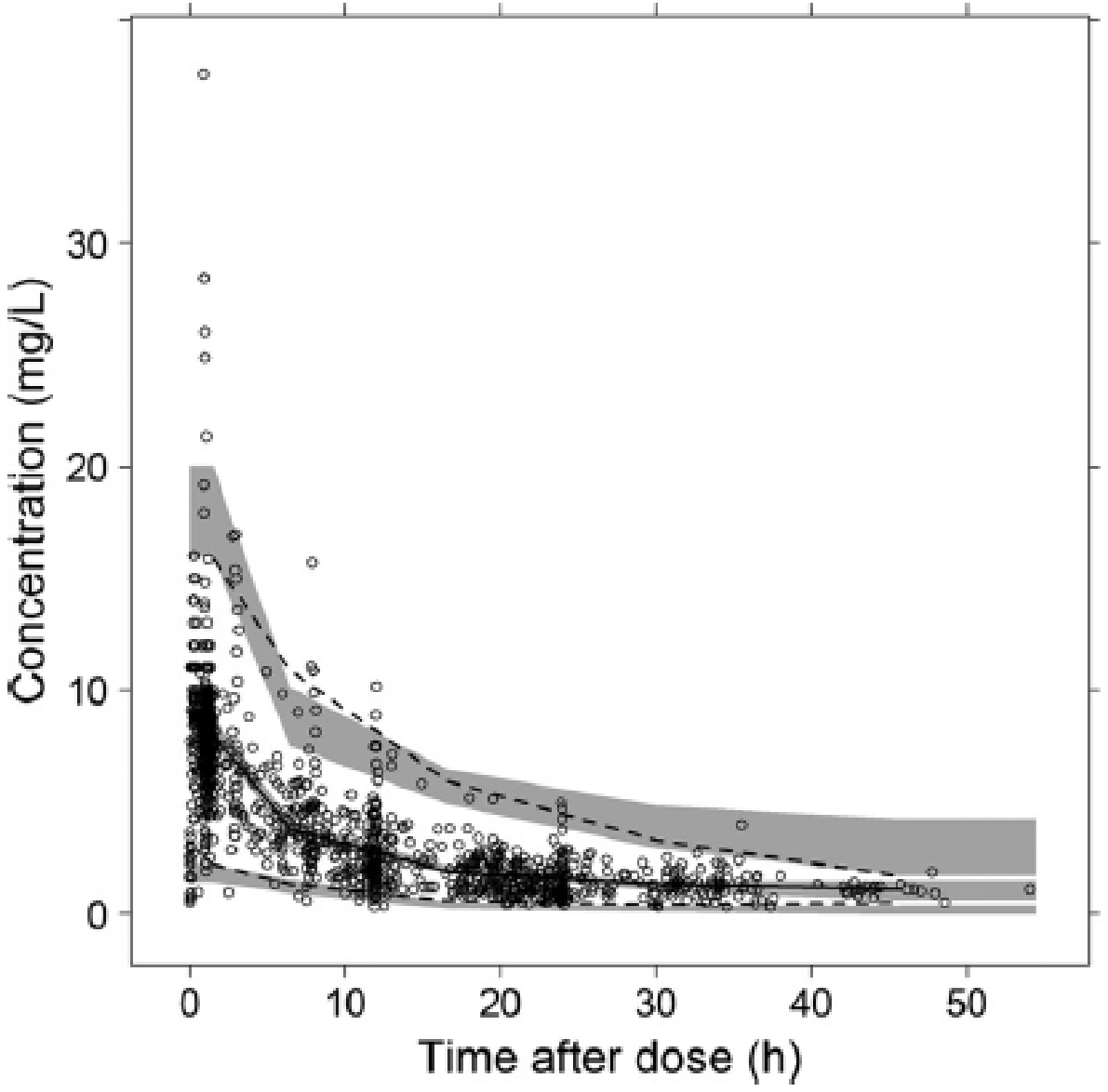
De Cock et al. Int J Antimicrobiol Chemother 2014

AMERICAN SOCIETY FOR MICROBIOLOGY | Anti and

Development That Facilitat Monitoring i Model

Eva Germovsek,[a] Alison
Paul T. Heath,[b] Joseph F. lsen,[e]

CrossMark click for updates



http://www.tdmx.eu

Meropenem

20 mg/kg.q8h

Randomisation
30 minutes, or 4 h infusion

TABLE 3. Impact of Meropenem Therapy on Clinical Outcomes

Characteristics	Conventional Group (n = 51)	Infusion Group (n = 51)	*P*
Neonatal mortality	16 (31)	7 (14)	0.03
Clinical improvement	17 (33)	31 (61)	0.009
Necrotizing enterocolitis	7 (14)	6 (12)	1.0
LOS*	23 (14–33)	27 (13–43)	0.31
Meropenem-related LOS (d)*	25 (15–36)	27 (15–39)	0.2
Duration of respiratory support (d)*	12.5 (5.7–17.2)	4 (0–18)	0.03
Duration of mechanical ventilation (d)*	3 (0–8)	1 (0–10)	0.6
Meropenem-related duration of mechanical ventilation (d)*	2 (0–5)	0 (0–7)	0.8
Meropenem-related duration of inotropes therapy (d)*	0 (0–3.5)	0 (0–4)	0.8
CRP after intervention (mg/L)	72 (6–100)	12 (6–96)	0.01

Data expressed as median (interquartile range) or number (%).
*After exclusion of deceased cases and cases who developed hypersensitivity reaction.
LOS indicates length of hospital stay.

Shabaan et al. Pediatr Infect Dis J 2017

Research sequence: Towards improved drug exposure predictability