Monitorización Terapéutica de Antimicrobianos en Neonatología. Optimización de Dosis.

QF. Gustavo Tripailaf

Introducción

- Paciente ingresados a cuidados intensivos son expuestos polifarmacia
- Neonatos de bajo peso al nacer: 25 % de sus fármacos corresponde a un ATB
- Fisiología única afecta la Farmacocinética de los Medicamento eso sumados a sus comorbilidades y medicamentos concomitantes

Future Microbiol. (2017) 12(11), 1001–1016

“infants are not just small children”

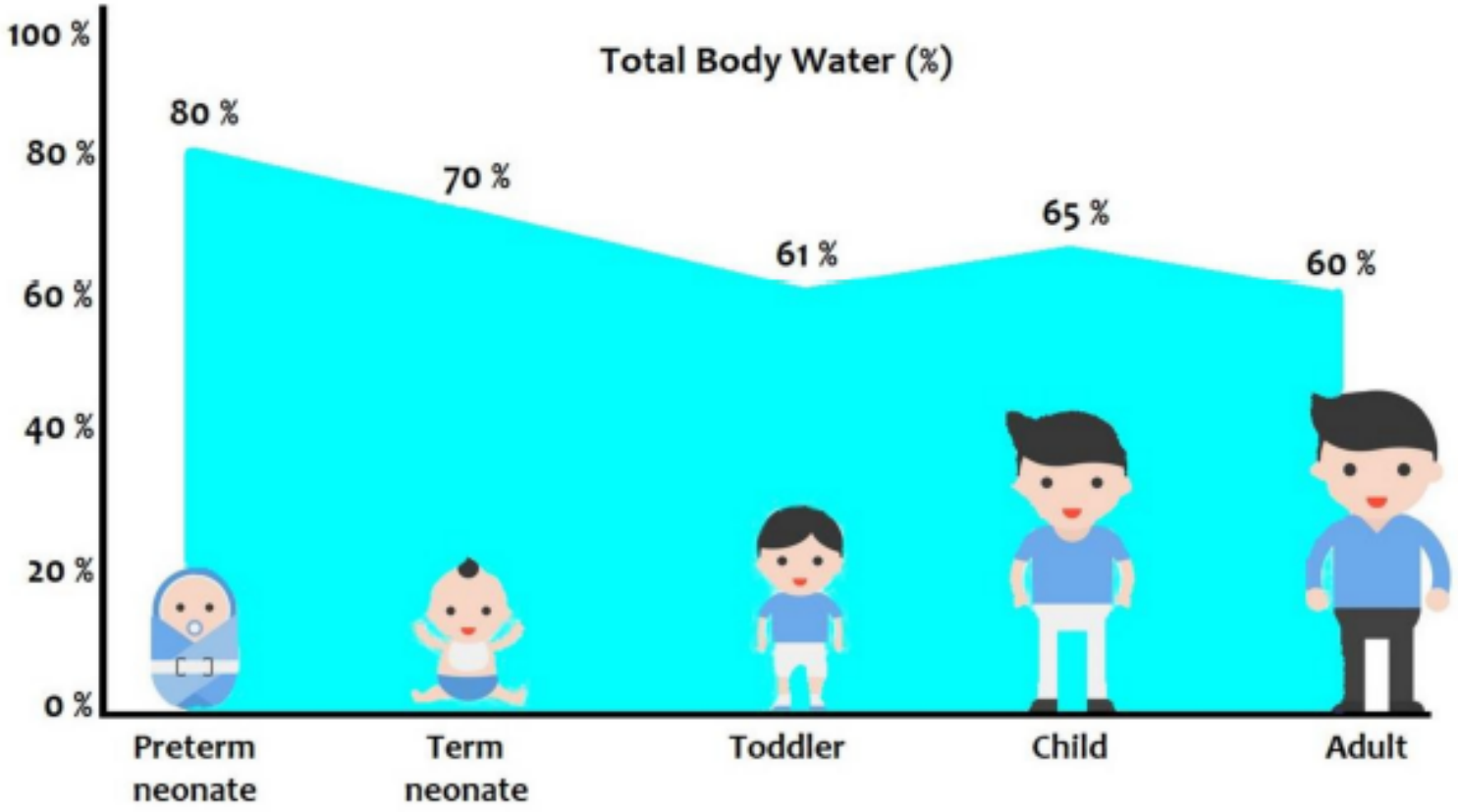


Figure 1. Body composition (total body water) and growth. Modified from Rodieux et al. [11].

Int. J. Mol. Sci. 2020, 21, 5898

Table 1 Effects on drug pharmacokinetics related to organ maturation and development in children

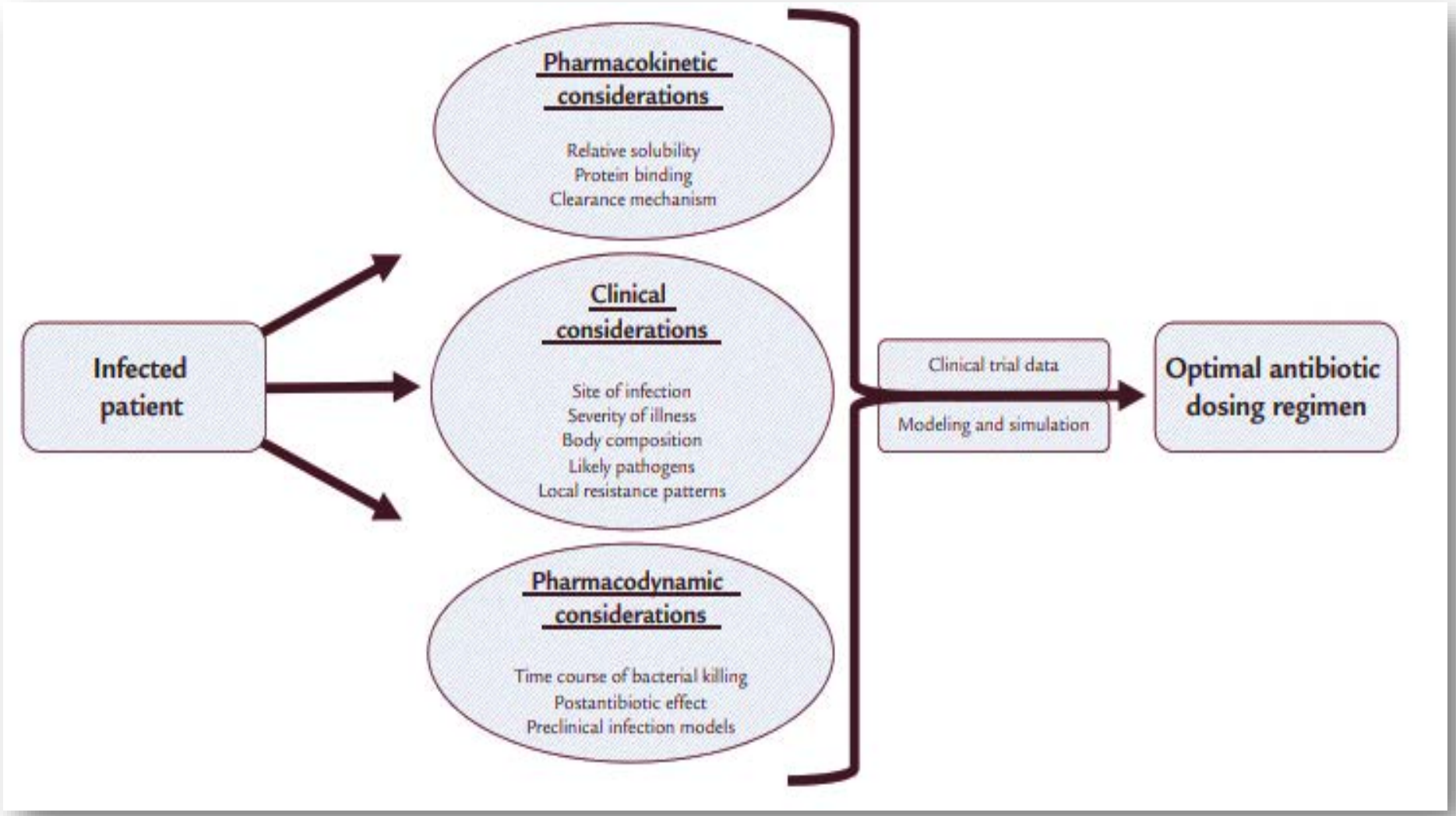
	Neonate/infant	Effect on drug pharmacokinetics
Absorption	↑ Gastric pH	Variable effect on rate and extent of absorption
	↑ Gastric emptying	
	↑ GI transit time	
	↓ Gastric enzyme activity	
	↓ Bile salt	↓ Absorption of some drugs
	Changes in intestinal flora	↑ Absorption of some drugs
	Skin permeability	↑ Absorption of some drugs
Distribution	↑ TBW	↑ Apparent V_d for water-soluble drugs
	↑ ECW	↓ Apparent V_d for drugs that bind to muscle and/or fat
	↓ Body fat	
	↓ Muscle mass	
	↓ Albumin levels	↓ Fraction bound for drugs highly bound to albumin
	↓ α1-acid glycoprotein	↓ Fraction bound for drugs highly bound to α1-acid glycoprotein, resulting in an increased apparent Vd and/or increased toxicity
Metabolism	↓ Oxidative enzyme activity (CYP)[a]	↓ Drug metabolism, plasma clearance with ↑ in apparent half-life in neonates and young infants
	↓ Glucuronidation (UGT)[a]	
		↑ Plasma drug clearance and ↓ in half-life of specific drugs
Elimination	↓ Kidney function (filtration, reabsorption, secretion)	↓ Clearance and accumulation of renally excreted drugs

GI gastrointestinal, *TBW* total body water, *ECW* extracellular water, V_d volume of distribution, *UGT* uridine diphosphate glucuronosyltransferase, *CYP* cytochrome P450, ↑ indicates increase, ↓ indicates decrease

[a] Apparent increase in activity for selected drug-metabolizing enzymes in older children/adolescents

Clin Pharmacokinet (2015) 54:1183–1204

Antibiótico ideal:
Eficaz y mínimamente toxico.



Clinical Therapeutics/Volume 38, Number 9, 2016

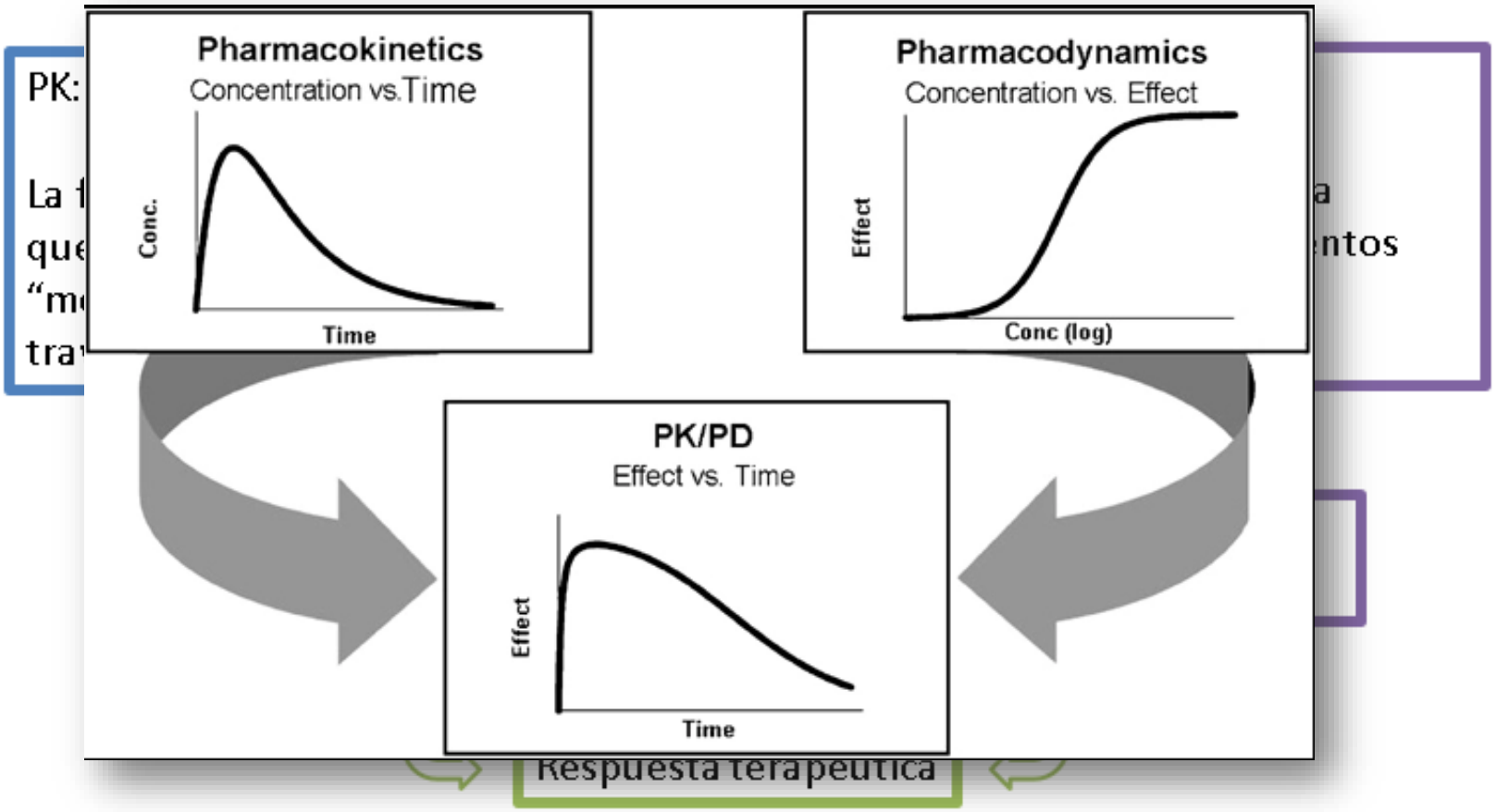
Table 1 The relationship between molecular and pharmacokinetic characteristics of antibiotics

	Hydrophilic antibiotics	Lipophilic antibiotics
PK in healthy conditions	Intracellular penetration: low	Intracellular penetration: good
	Vd: Low	Vd: High
	Cl: >> Renal	Cl: >> Hepatic
PK in critical illness	Vd: increased	Vd: Relatively unchanged
	Cl: increased (e.g., ARC) or decreased (e.g., renal dysfunction)	Cl: Unaffected or decreased depending on hepatic function and blood flow
PK in ECMO	Vd: increased	Vd: Increased or unaffected
	Cl: Unaffected or decreased (in renal function)	Cl: Likely decreased
PK in CRRT	Cl: Increased	Cl: unchanged or only mildly increased
Examples of antibiotic classes	β-Lactams, aminoglycosides, glycopeptides	Macrolides, fluoroquinolones

ARC augmented renal clearance, *Cl* clearance, *CRRT* continuous renal replacement therapy, *ECMO* extracorporeal membrane oxygenation, *PK* pharmacokinetics, *Vd* volume of distribution

Pediatric Drug, 2021 Jan;23(1):39-53

Modelos PK/PD



Parámetros PK/PD

Table 1
Pattern of activity of different antibacterial drugs and their associated pharmacokinetic/pharmacodynamic (PK/PD) targets.[a]

Mechanism of bactericidal effects based on in vitro data	Antibiotic class	PK/PD parameter(s) associated with efficacy	Goal of dosing regimen
Concentration-dependent killing with moderate-to-persistent bactericidal effects	Aminoglycosides Fluoroquinolones Metronidazole Daptomycin Ketolides	C_{max}/MIC AUC_{0-24}/MIC	**Maximise concentration**: increase dose
Time-dependent killing with minimal-to-no persistent bactericidal effects	β-Lactams: Penicillins Cephalosporins Carbapenems Aztreonam Erythromycin	$T_{>MIC}$	**Maximise the duration of exposure**: increase duration of infusion or frequency of administration
Time-dependent killing with moderate-to-prolonged persistent bactericidal effects	Macrolides Tetracyclines Glycopeptides Clindamycin Linezolid[b]	AUC_{0-24}/MIC	**Maximise drug exposure**: increase dose, frequency of administration or duration of infusion

C_{max}, maximum serum concentration; MIC, minimum inhibitory concentration; AUC_{0-24}, area under the concentration–time curve over a 24-h period; $T_{>MIC}$, percentage of the dosing interval above the MIC.

[a] Adapted with permission from Taylor and Francis Group LLC Books [10].

[b] $T_{>MIC}$ has also been reported to be an appropriate PK/PD target for linezolid [9].

International Journal of Antimicrobial Agents 43 (2014) 223–230

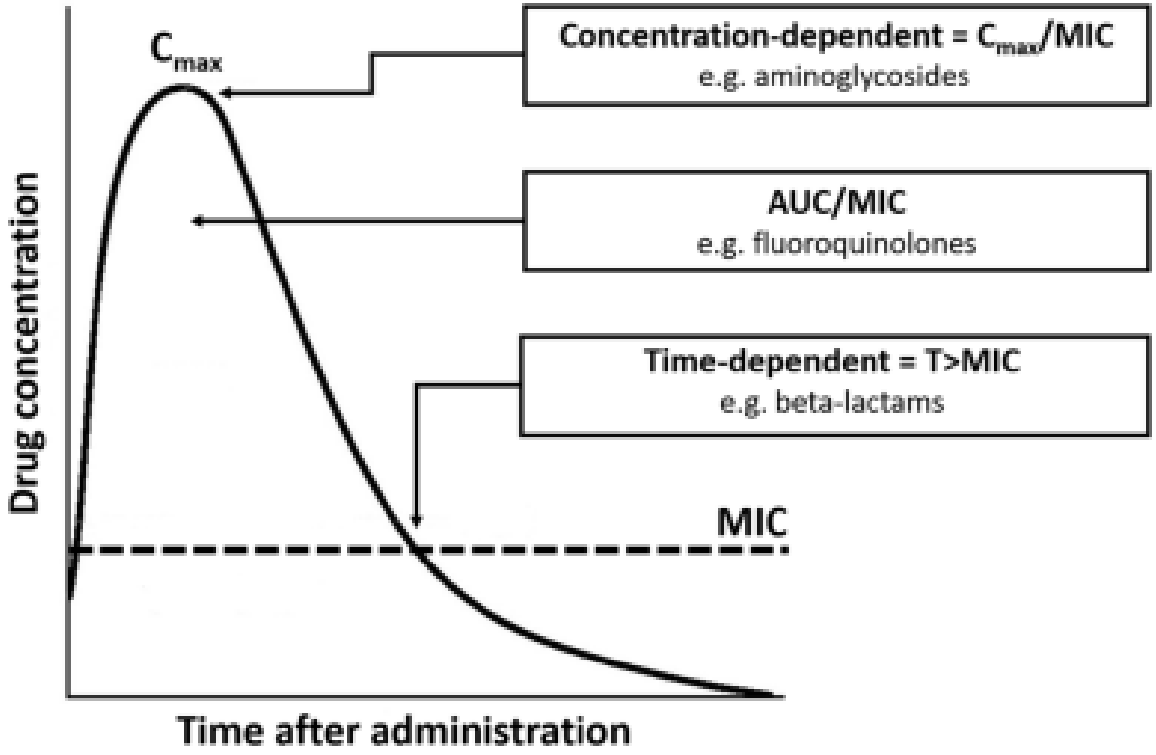


Fig. 2 Pharmacokinetic/pharmacodynamic parameters of antibiotics. *AUC* area under the curve, C_{max} peak drug concentration, *MIC* minimum inhibitory concentration, *T* time

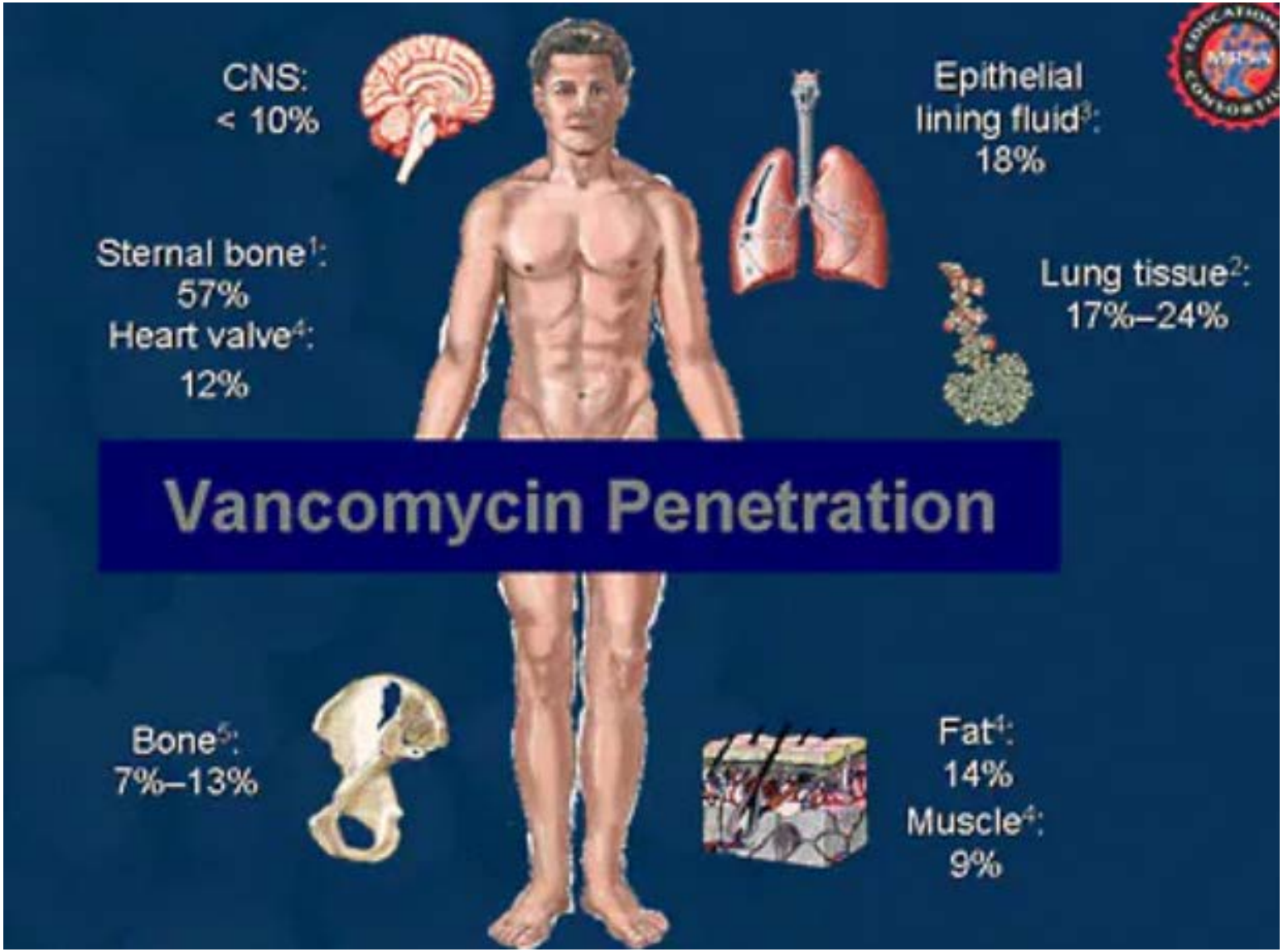
Pediatric Drug, 2021 Jan;23(1):39-53

Optimización de dosis de Vancomicina

- Glycopeptido
- Excreción renal (80-90%).
- Vida media: Premature infants, 8.7 to 11.3 hrs

Hidrofílico

- RAM: Nefrotoxicidad (interacción con otros nefrotóxicos)



Alpesh Amin, MD, MBA, FACP: Let's get started with our discussion on methicillin-resistant *Staphylococcus aureus* (MRSA) in the hospital and community. consultado en: https://www.medscape.org/

Therapeutic monitoring of vancomycin for serious methicillin-resistant *Staphylococcus aureus* infections: A revised consensus guideline and review by the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the Society of Infectious Diseases Pharmacists

AJHP VOICES

An audio interview that supplements the information in this article is available on AJHP's website at www.ajhpvoices.org.

Am J Health-Syst Pharm. 2020;77:835-864

The first consensus guideline for therapeutic monitoring of vancomycin in adult patients was published in 2009. A committee representing 3 organizations (the American Society for Health-System Pharmacists [ASHP], Infectious

Staphylococcus aureus (MRSA) infections. It should be noted, however, that when the recommendations were originally published, there were important issues not addressed and gaps in knowledge that could not be covered ade-

Am J Health-Syst Pharm. 2020;77:835-864

Recomendaciones:

Table 2. Primary Recommendations for Vancomycin Dosing and Therapeutic Drug Monitoring

A. ADULTS AND PEDIATRIC PATIENTS

1. In patients with suspected or definitive serious MRSA infec
advocated to achieve clinical efficacy while improving patie

2. When transitioning to AUC/MIC monitoring, clinicians should conservatively
a vancomycin MIC_{BMD} of 1 mg/L or less at most institutions. Given the impor
the course of therapy, preferably within the first 24 to 48 hours **(A-II)**. As suc
quire steady-state serum vancomycin concentrations to allow for early assessment of AUC target attainment.

3. Trough-only monit
(A-II). There is insu
sive MRSA or othe

4. Vancomycin monit
unless it is known to be greater or less than 1 mg/L by BMD). Independent of MRSA infection, vancomycin monitoring is also recommended for all patients at high risk for
nephrotoxicity (
prolonged coun
hemodynamica

5. Based on curre
When the MIC_{BMD} is greater than 1 mg/L, the probability of achieving an AUC/MIC target of 2400 is low with conventional dosing, higher doses may risk unnecessary toxicity, and the decision to change therapy should be based on clinical judgment. In addition, when the MIC_{BMD} is less than 1 mg/L, we do not recommend decreasing the dose to achieve the AUC/MIC target. It is important to note the limitations in automated susceptibility testing methods, including the lack of precision and variability in MIC results depending on the method used **(B-II)**.

6. The pharmacokinetics of continuous infusion suggest that such regimens may be
cannot be achieved **(B-II).**

7. Incompatibility of vancomycin with other drugs commonly coadministere
sidered for continuous infusion **(A-III)**.

Sospecha de infección seria de MRSA. AUC/MIC 400-600

Monitorizar tempranamente 24-48 hrs

No se recomienda solo la monitorización de nivel basal. Basado en la eficacia y nefrotoxicidad.

Frecuencia de monitorización: paciente estable hemodinámicamente 1 vez a la semana,

Infusión continua, puede ser una alternativa

Revisar incompatibilidad con otros fármacos EV

Am J Health-Syst Pharm. 2020;77:835-864

C. PEDIATRIC PATIENTS

17. Based on an AUC target of 400 mg · h/L (but potentially up to 600 mg · hr/L assuming a MIC of ≤1 mg/L) from adult data, the initial recommended vancomycin dosage for children with normal renal function and suspected serious MRSA infections is 60 to 80 mg/kg/day, divided every 6 to 8 hours, for children ages 3 months and older **(A-II)**.

18. The maximum empiric daily dose is usuall… and doses should be adjusted based on o… exceed 2,000 to 3,000 mg/day **(A-III)**. Furt… ance as resolution of their renal function may occur within the first 5 days of therapy.

Ajustar con NPV, target AUC/MIC

19. AUC-guided therapeutic monitoring for vancomycin… mycin CL documented from the newborn to the ad… for adults, including the application of Bayesian est…

Monitorizar guiados por AUC. Preferir estimación bayesiana

Todos los pacientes pediátricos. Cambios en el Clearance (monitorizar función renal)

20. …

Inicio control 24-48 hrs. Dosis inicial ajustado en insuficiencia renal y obesidad o nefrotóxicos concomitantes.

21. Vancomycin exposure may be optimally … of vancomycin above 80 mg/kg/day has … these thresholds **(B-III)**.

AUC < 800; NPV basal <15; evitar dosis > 100 mg/kg/dia

22. Insufficient data exist on which to base a recommendation for a loading dose among the nonobese pediatric population. Loading doses from adult studies may be considered, but further studies are needed to elucidate the appropriate dose for the various pediatric populations, from neonates to adolescents **(C-III)**.

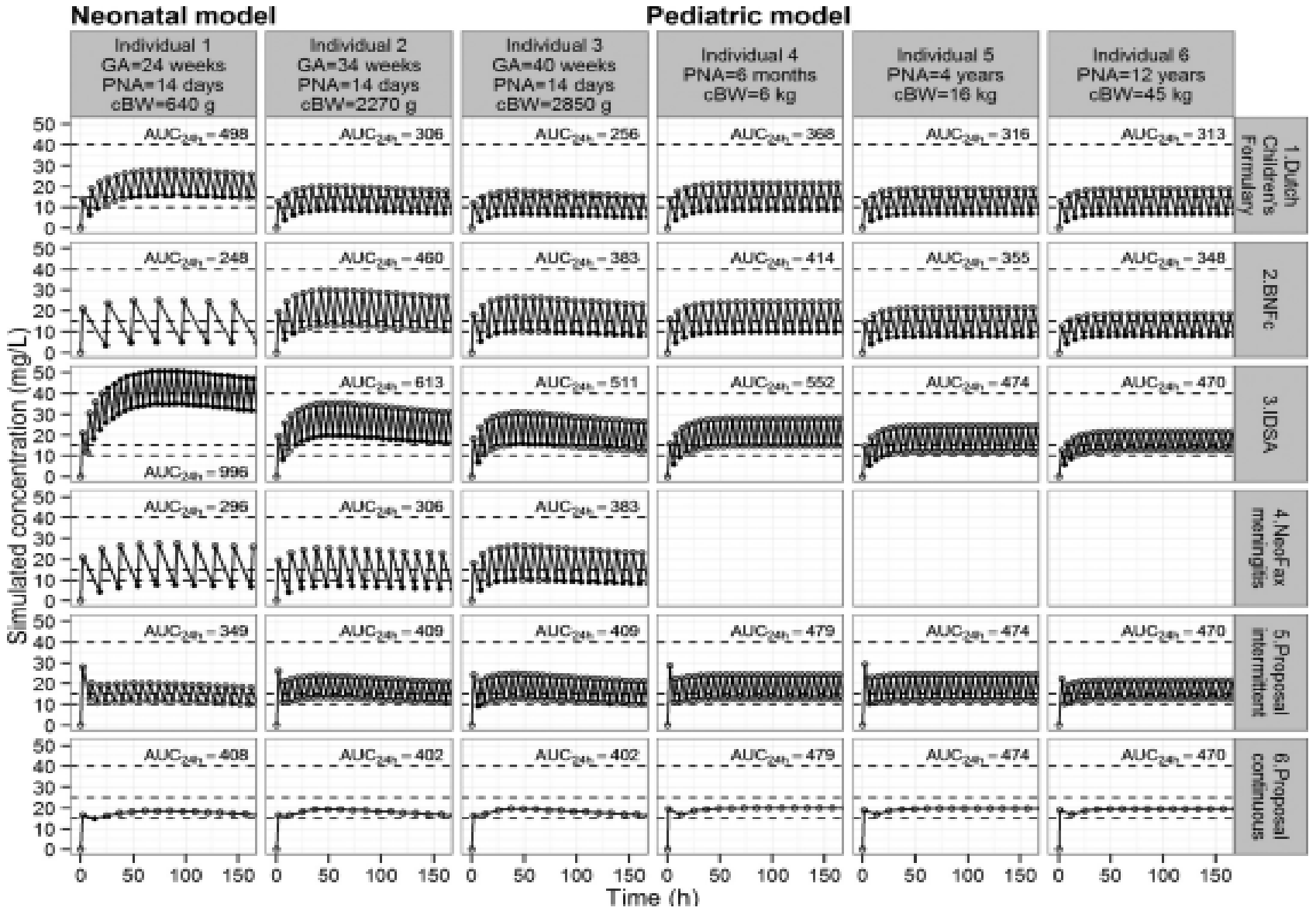
23. *Pediatric Obesity:* Data suggest that obese children are likely to have vancomycin exposures that may be statistically greater than in normal-weight children when doses are calculated on a mg/kg basis, but these differences are not known to be of sufficient clinical importance to suggest different mg/kg empiric vancomycin dosages in obese children at this time. Similar to nonobese children, obese children < 12 years old, compared with those ≥ 12 years, may require higher mg/kg doses **(B-II)**.

24. *Pediatric Obesity:* Therapeutic monitoring is likely to be of particular value in obese children, both for therapeutic response and to minimize the risk of AKI. The specific recommendations for therapeutic monitoring in nonobese children may also apply for obese children **(B-II)**. A loading dose of 20 mg/kg by total body weight is recommended in obese children **(A-III)**.

25. *Neonates:* Dosages recommended to achieve an AUC of 400 mg · hr/L (assuming a MIC of 1 mg/L) in neonates and infants up to 3 months old range from 10 to 20 mg/kg every 8 to 48 hours depending on postmenstrual age, weight, and SCr **(A-II)**.

Abbreviations (not defined in body of table): AUC, area under the curve; BMD, broth microdilution; CL, clearance; ICU, intensive care unit; KDIGO, Kidney Disease: Improving Global Outcomes; MIC, minimum inhibitory concentration; MRSA, methicillin-resistant *Staphylococcus aureus*; SCr, serum creatinine; V_d, volume of distribution.

Am J Health-Syst Pharm. 2020;77:835-864



Antimicrob Agents Chemother. 2016, 60:1013–1021.

Dosificación de Vancomicina en Neo

Tabla 11. Recomendación para la dosificación de vancomicina: dosis intermitente

Edad postnatal (días)	Peso nacimiento (gramos)	Dosis de carga (mg/kg)	Dosis de mantención (mg/kg/día)	Intervalo de las dosis (h)
0-7	≤ 700	16	15	8
	701-1.000		21	8
	1.001-1.500		27	8
	1.501-2.500		30	6
	> 2.500		36	6
8-14	≤ 700	20	21	8
	701-1.000		27	8
	1.001-1.500		36	8
	1.501-2.500		40	6
	> 2.500		48	6
15-28*	≤ 700	23	24	8
	701-1.000		42	8
	1.001-1.500		45	8
	1.501-2.500		52	6
	> 2.500		60	6

*Puede dividirse en 21-28 días y utilizarse dosis de carga en este subgrupo de 26 mg/kg. Rivera-Chaparro ND, Cohen-Wolkowiez M y cols.[1]. S Cristea, K Allegaert y cols.[60].

Rev Chilena Infectol 2020; 37 (5): 490-508

Tabla 13. Recomendación para dosificación continua de vancomicina

Creatinina sérica (mg/dL)	Edad gestacional corregida (semanas)	Dosis de carga (mg/kg)	Dosis mantención (mg/kg/día)
< 0,45	≥ 40	15	50
< 0,45	< 40	15	40
0,45-0,68	Todas	15	30
> 0,68	Todas	15	20

Gwee A, Cranswick N y cols.[58].

Css target antes CIV vs IIV
Menos ajustes de dosis
Menos dosis diaria (mg/kg/día)

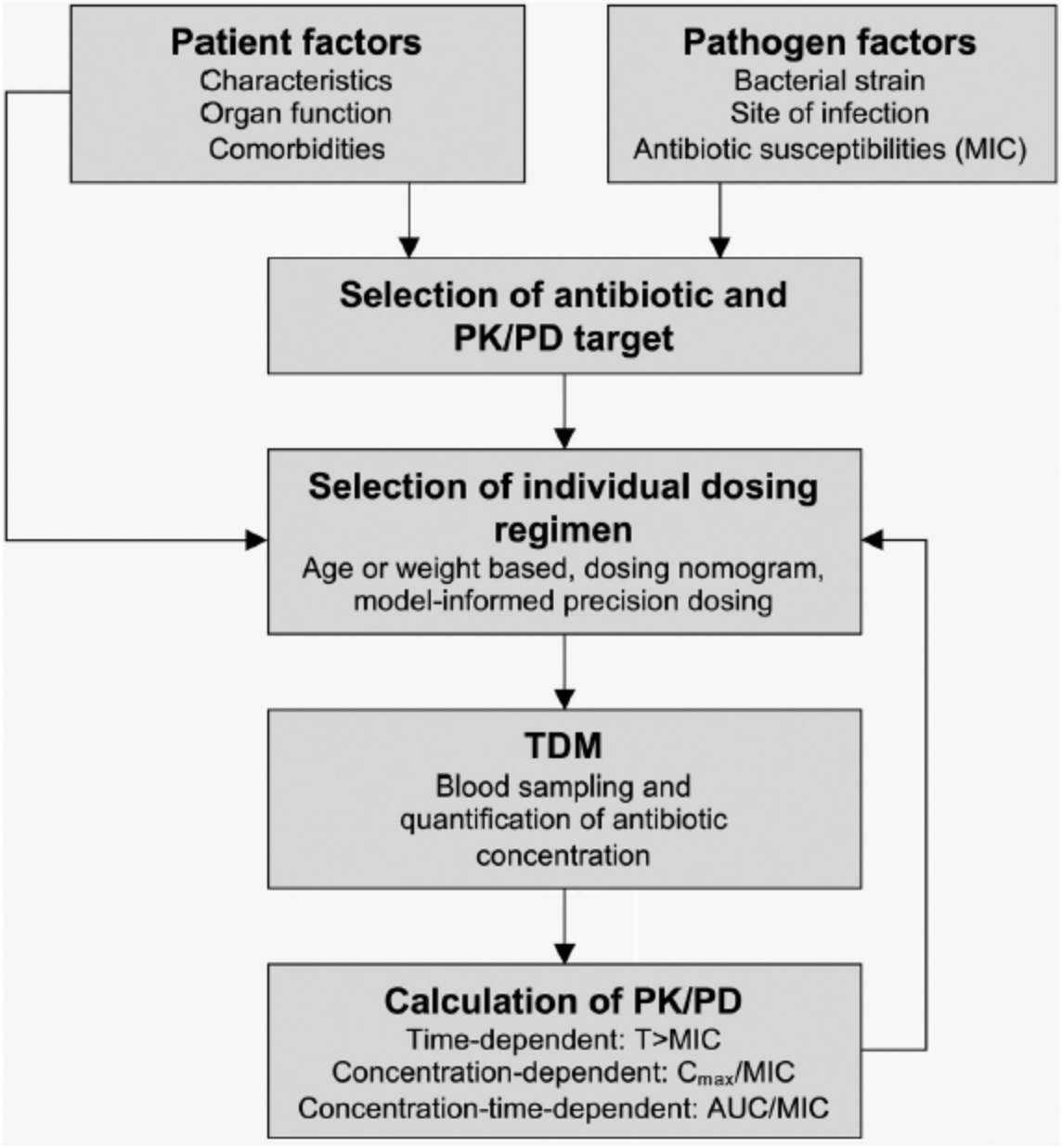
Tabla 14. Ajuste para dosificación c

Adjuste dosis (mg/día): Se calculará por la última dosis de mantenimiento X (concentración target (20 μg/mL)/última concentración de vancomicina).

Gwee A, Cranswick N y cols.[58].

Ojo: compatibilidad EV

Rev Chilena Infectol 2020; 37 (5): 490-508


Patient factors
Characteristics
Organ function
Comorbidities
Pathogen factors
Bacterial strain
Site of infection
Antibiotic susceptibilities (MIC)
Selection of antibiotic and PK/PD target
Selection of individual dosing regimen
Age or weight based, dosing nomogram, model-informed precision dosing
TDM
Blood sampling and quantification of antibiotic concentration
Calculation of PK/PD
Time-dependent: T>MIC
Concentration-dependent: Cmax/MIC
Concentration-time-dependent: AUC/MIC

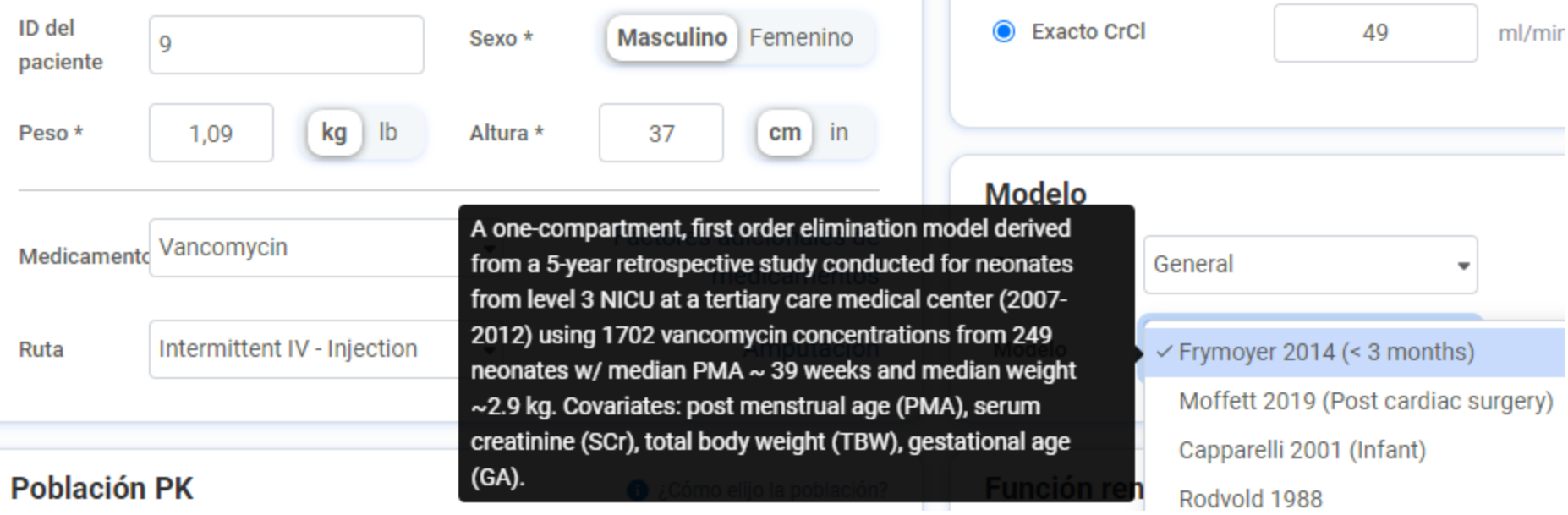
Como podemos calcular el AUC?

1. Método Bayesiano:

- Basado en el teorema de Bayes
- Estima los parámetros farmacocinético usando los datos poblacionales (a priori)
- Revisa la distribución probable usando los datos exactos del paciente mas los datos poblacionales, considerando las características del paciente (a posteriori)
- Requiere la utilización de un Software

2. Método trapezoidal.

- Varios pasos (formulas para calcular PK)
- Requiere dos NPV



Preterm, Term Neonates, and Infants | Frymoyer 2014

- GA < 37 weeks and PNA < 28 days
- GA ≥ 37 weeks and PNA < 28 days
- PNA < 3 months

Infants and Neonates | Capparelli 2001

- PNA ≤ 6 months regardless of Scr levels

Moffett 2019

- Post Cardiac Surgery Neonates and Infants

PK del paciente

	Pob.	Ind.
Vd	0.658	0.650
CL	0.081	
F	100	
k_e	0.123	
$t_{1/2}$	5.63	

Mostrar m

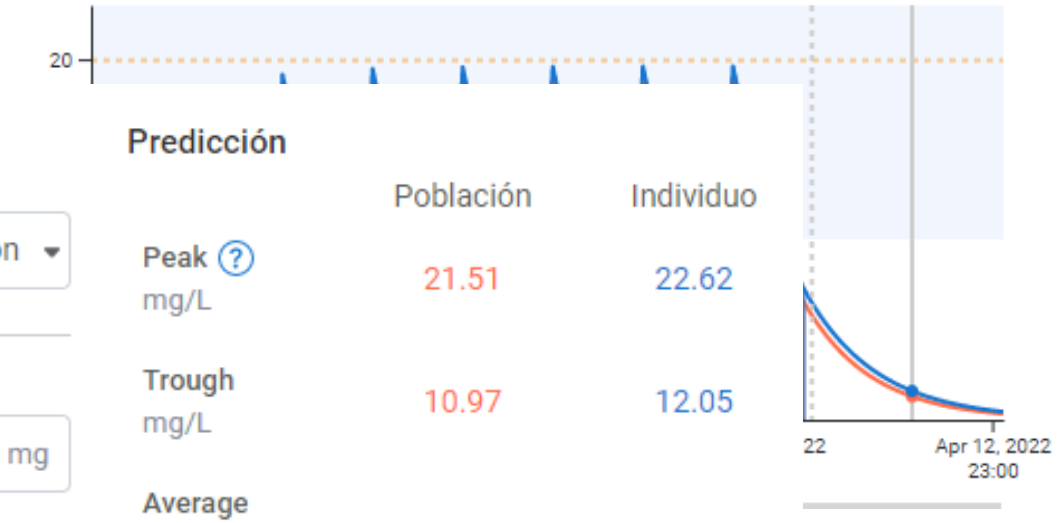
Gráfica del nivel sérico

¿Cómo se interpreta esta gráfica?

Apr 11, 2022 06:34 - Apr 12, 2022 06:19 268.77 287.11 hr*mg/L

Población Individuo Terapéutico Toxicidad Nivel sérico

Nivel sérico (mg/L) Tiempo complet



Entrada

Ruta

Intermittent IV - Injection

Dosis

34 mg

Intervalo

6 hr

Hora de la infusión

2 hr

MIC

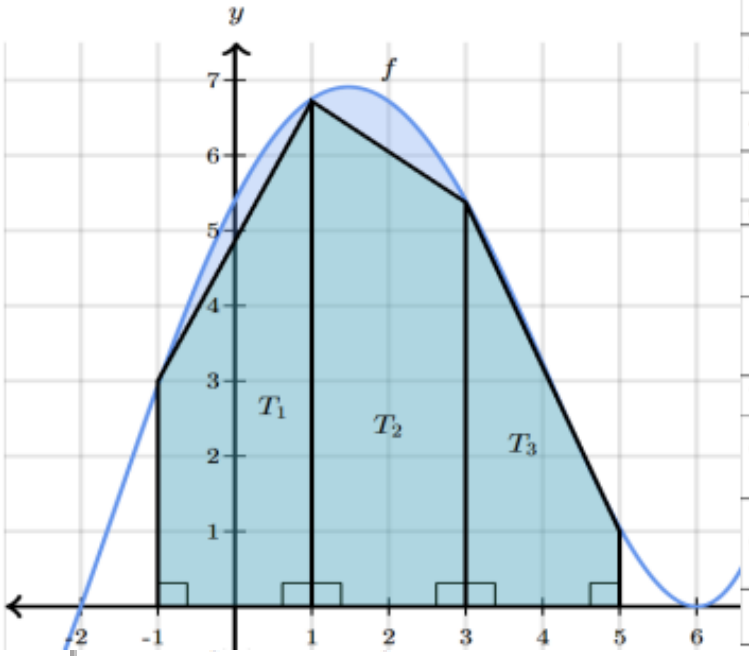
1 mg/L

Predicción

	Población	Individuo
Peak mg/L	21.51	22.62
Trough mg/L	10.97	12.05
Average Concentration mg/L	15.95	17.06
AUC24 hr*mg/L	382.71	409.39
AUC24/MIC	382.71	409.39

Mostrar más

Método trapezoidal



1. Verify that the doses prior to the concentrations were on time and drawn appropriately.	
2. Calculate patient's true k_e from two measured concentrations.	$k_e = \frac{\ln (C_1/C_2)}{(t_2 - t_1)}$
3. Calculate patient's true $t_{1/2}$.	$t_{1/2} = \frac{0.693}{k_e}$
4. Calculate patient's true C_{max}.	$C_{max} = \frac{C_1}{(e^{-k \cdot \Delta T})}$ ΔT=time between end of infusion and time level drawn
5. Calculate patient's true C_{min}. Skip step if only 1 dose received.	$C_{min} = C_{max} * (e^{-k_e * (Tau - t)})$
6. Calculate patient's Vd.	
- If patient has received only 1 dose:	$Vd = \frac{Dose}{t} * \frac{(1 - e^{-kt})}{(k_e * C_{max})}$
- Steady-state condition:	$Vd = \frac{MD}{t} * \frac{(1 - e^{-kt})}{k_e * (C_{max} - [C_{min} * e^{-kt}])}$
7. Calculate actual vancomycin clearance (Cl_{van}).	$Cl_{van} = Vd * k_e$
8. If C_{min} concentration obtained is high, calculate time needed to reach desired range.	$T = \frac{\ln \left({}^{C_{min}}/_{C_{des}} \right)}{k_e}$
9. Calculate the new Tau.	$\text{Tau} = \frac{\ln \left({}^{C_{max,des}}/_{C_{min,des}} \right)}{k_e} + t$
10. Estimate total daily dose (TDD) needed to achieve target AUC_{24}.	$TDD\ (mg) = Cl_{van} * Desired\ AUC_{0-24}$

Hospital Pharmacy Volume 44, Number 9, pp 751–765

Pharmacokinetic Dose Calculator

6.17.2021

Drug	Vancomycin	Steady State/FD	Steady State					
Current Dose	90	mg	Frequency	6	hr	Weight	6	kg
Admin Date	08-10-2021							
Admin Time	12:00							
Current Infusion Duration	3	hr						
Trough (or C2)	8,5	mcg/mL	Time	11:30	Date	08-10-2021		
Peak (or C1)	20	mcg/mL	Time	15:30	Date	08-10-2021		

Current Trough	6,9	mcg/mL
AUC at Steady State	357,0	mcg*hr/mL
Concentration at time X		mcg/mL
	hours post start of infusion	

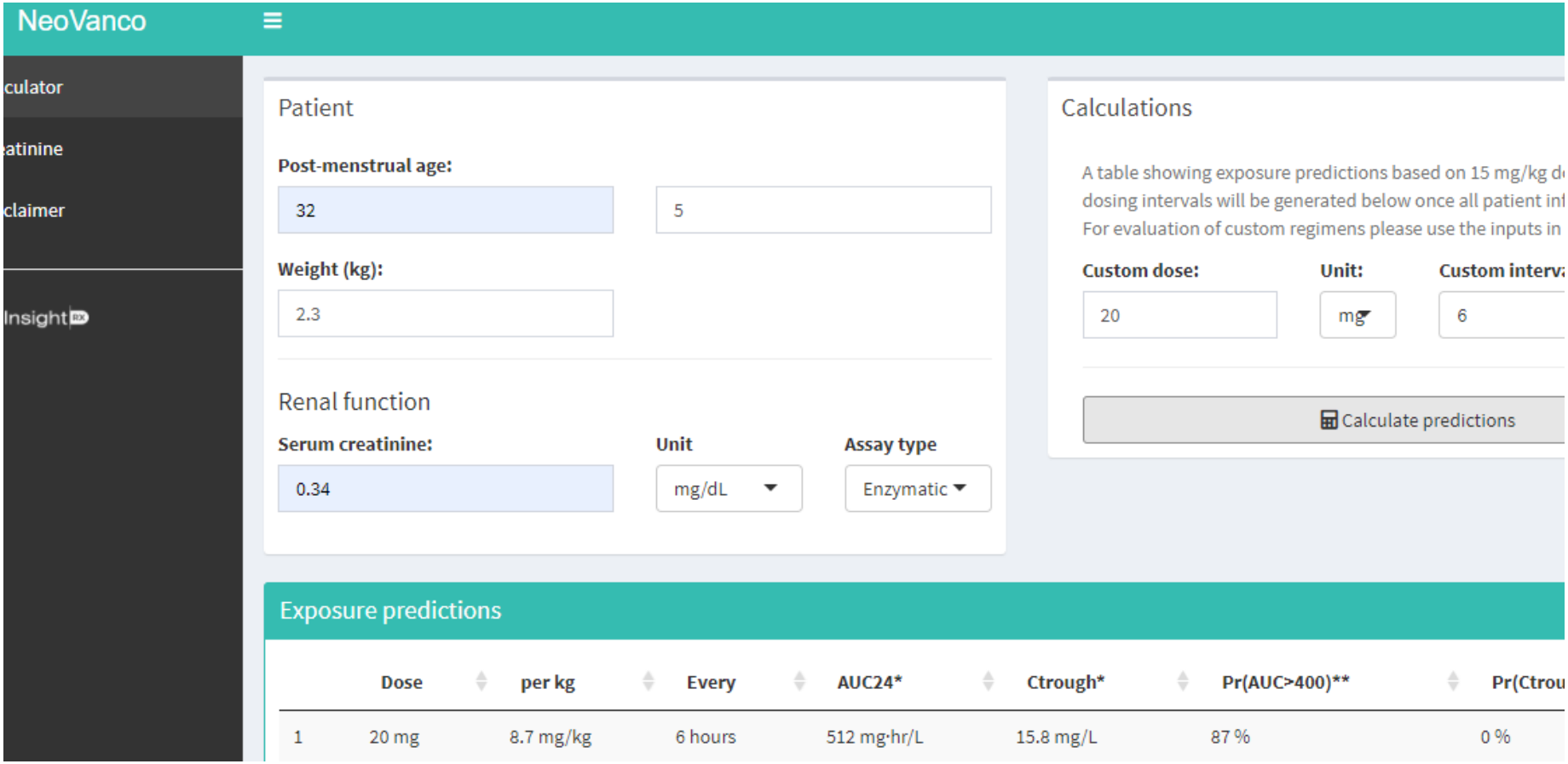
Caution! Calculations may be off, a level was drawn during distribution phase

Ke	0,43	hr-1
$t_{1/2}$	1,6	hr
C_{max}	24,8	mcg/mL
C_{min}	6,9	mcg/mL
Vd	2,2	L
	0,37	L/kg
AUC	357	mcg*hr/mL

AUC 400-600	Frequency (hr)						
	6	8	12	18	24	36	48
Dose low (mg)	95	126	190	285	379	569	759
Dose high (mg)	142	190	285	427	569	854	1138
Recommended (mg)	120	160	240	360	470	710	950
Trough range (mcg/mL)*	7,2 - 10,8	3,9 - 5,9	1 - 1,5	0,1 - 0,2	0 - 0	0 - 0	0 - 0

* based on current infusion duration

https://connect.insight-rx.com/neovanco/



post-menstrual age <52 weeks, NO major congenital heart disease NO congenital kidney disease.

The dosing tool should not be used in patients on ECMO or renal replacement therapy.

Caution is warranted in neonates with poor or worsening kidney function

Frymoyer A et al

Incompatibilidad Vancomicina en sitio Y

Albumin , aminophylline , azathioprine, daptomycin, flucloxacillin, furosemide, ganciclovir, indometacin, ketorolac, methylprednisolone sodium succinate, moxifloxacin, omeprazole, rocuronium, sodium bicarbonate, sodium valproate, urokinase

Vancomycin is incompatible with many beta-lactam antibiotics i.e. penicillins, cephalosporins and carbapenems.1 Precipitation is more likely at higher concentrations of vancomycin. Flush the line well

COMPATIBLE CON ALPAR

Australian Injectable Drugs Handbook – SHPA.2020

Optimización de Dosis de Amikacina

- Aminoglucósido
- Esencialmente eliminada vía excreción renal a través de filtración glomerular y esta eliminación esta determinada por la nefrogenésis, la cual se completa entre las 32 -36 semanas de gestación .
- Hidrofílico
- RAM: nefrotoxicidad (leve, transitoria) y ototoxicidad (es irreversible, bilateral y simétrica. La cantidad de daño es directamente proporcional a la cantidad de exposición)

Dosificación de Amikacina: NEOFAX

Weight	
800 g or less	16
801 to 1200 g	16
1201 to 2000 g	15
2001 to 2800 g	15
2800 g or greater	15
Smits et al, 2017; Rivera-Chaparro et a	

Postnatal Age - Postmenstrual Age D
These regimens were developed by a r
gestational age 36.9 weeks (30.1 to 38
and 2+/-1.7 mg/L, respectively. Target c
[4].

nterquartile
vere 28.5+/
e dose) les

Postmenstrual Age	
29 weeks or less	
30 to 34 weeks	
35 weeks or more	
Hughes, 2017	

Objetivos:
Cp min: 1,5 – 3 ug/mL
Cp max: >24 ug/mL
Resultados
Cp max: 90%
CP min: 71%

Objetivos:
CP max: 20-35 ug/mL
Cp min: > 8 ug/mL
Resultados:
Cp max: 28.5 ± 5.8 mg/L (84%)
CP min : 2.0 ± 1.7 mg/L (98%)

Dosificación de Amikacina en Neonatología

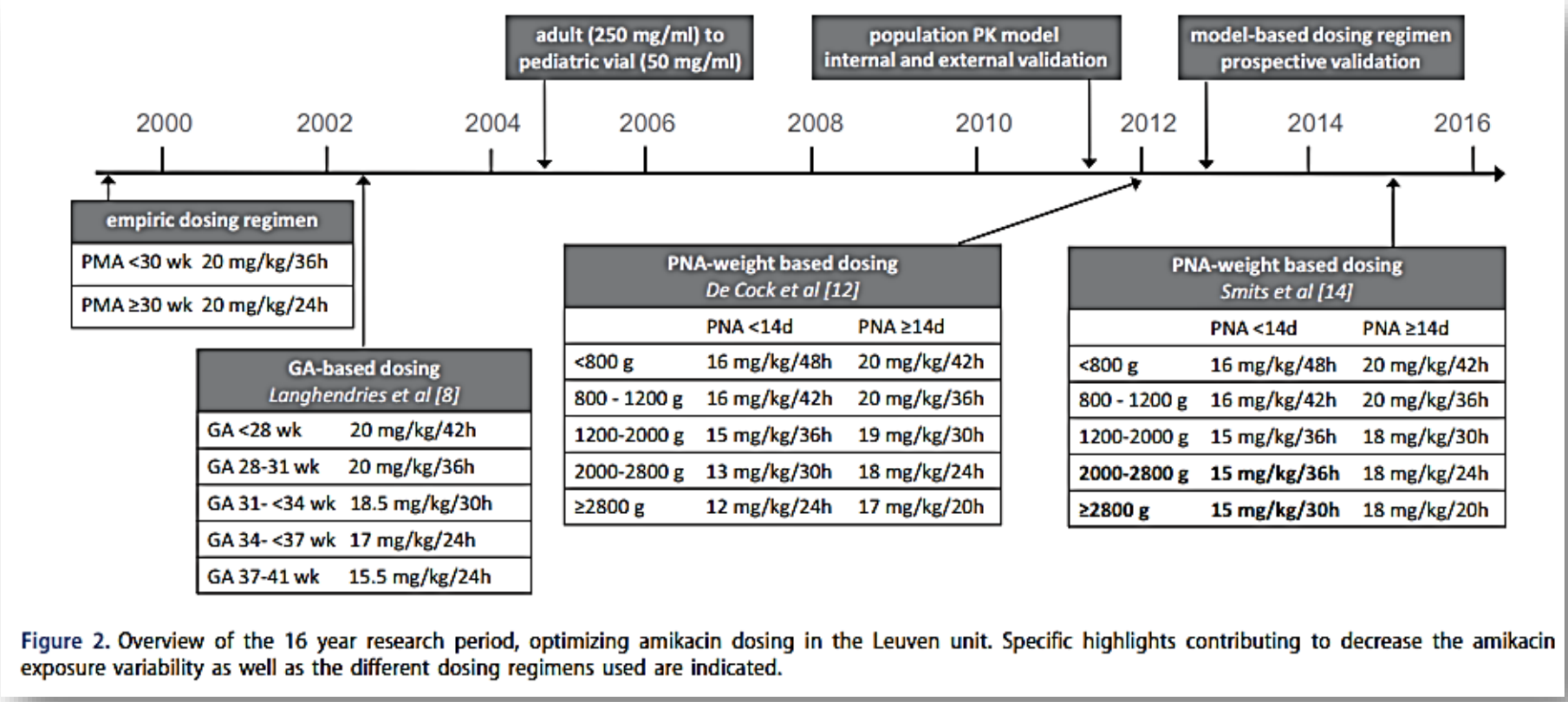
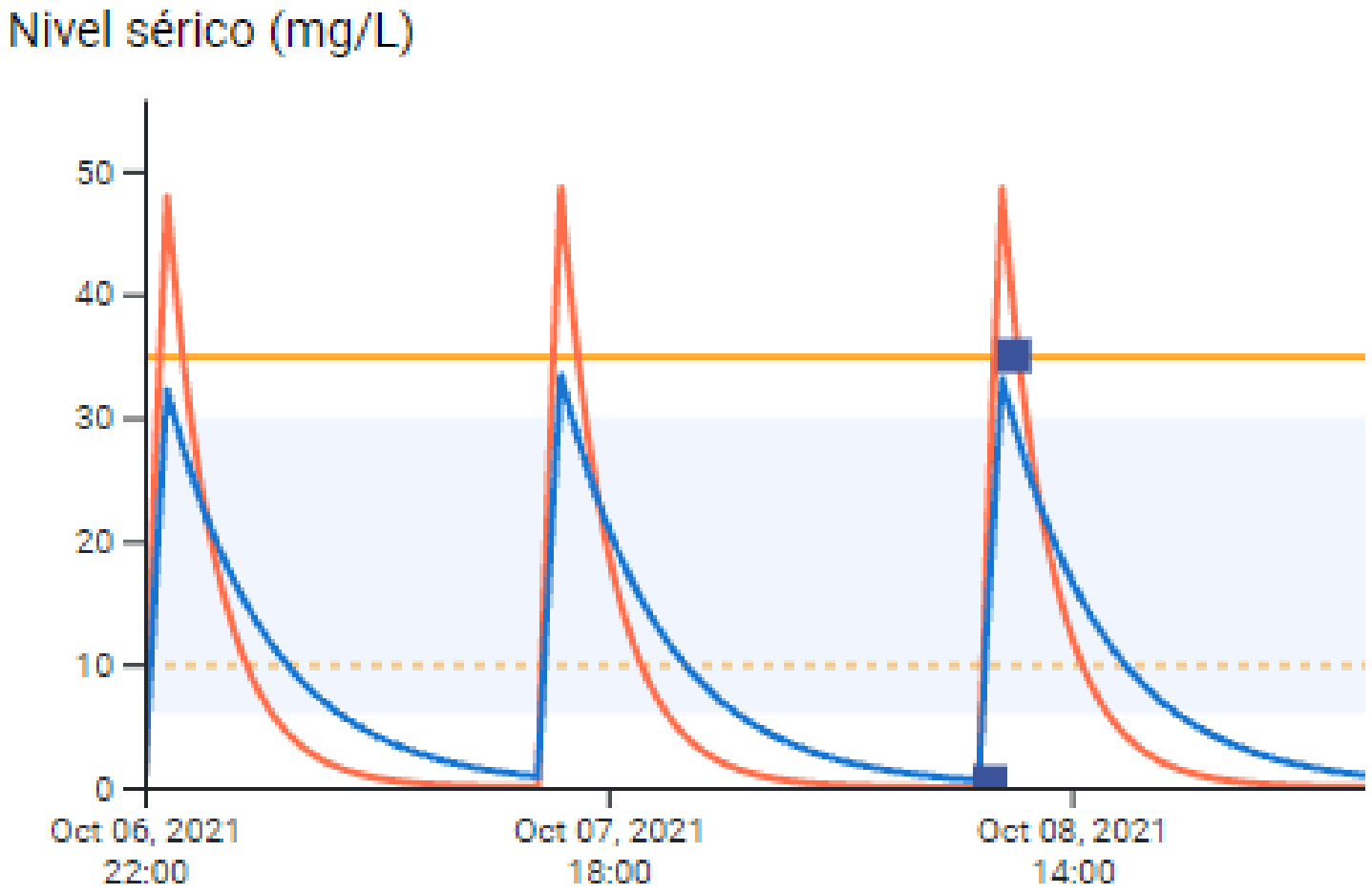


Figure 2. Overview of the 16 year research period, optimizing amikacin dosing in the Leuven unit. Specific highlights contributing to decrease the amikacin exposure variability as well as the different dosing regimens used are indicated.

Ajustar dosis en caso de uso concomitante ibuprofeno, Hipotermia/asfixia, falla renal

EXPERT OPINION ON DRUG METABOLISM & TOXICOLOGY, 2016


Nivel sérico (mg/L)
50
40
30
20
10
0
Oct 06, 2021
22:00
Oct 07, 2021
18:00
Oct 08, 2021
14:00

Incompatibilidad amikacina en sitio Y

Penicillins and cephalosporins, azathioprine, azithromycin, defibrotide, folic acid, ganciclovir, indometacin, propofol , teicoplanin

INCOMPATIBLE CON ALPAR

PRECAUCIÓN CON INTERACCIÓN CON PENCILINAS Y CEFALOSPORINAS: SEPARAR HORARIOS DE ADMINISTRACIÓN

Australian Injectable Drugs Handbook – SHPA.2020

Medicamento	Muestra/ desde cuando se puede tomar la muestra	Concentración plasmática	Target PK/PD
Vancomicina	Predosis	5-20 ug/mL (con este resultado se realiza el cálculo de AUC).	AUC /CIM > 400 < 600
	Previo a 4° dosis. Excepcionalmente el Farmacéutico o infectólogo puede solicitar un nivel antes de la 4° dosis o en horario aleatorio	Precaución con nivel > a 15 ug/mL, dado que en algunos casos da una AUC > 600 (nefrotoxicidad)	
Amikacina	pre y postdosis	POSTDOSIS (efectividad)	Cmax/CIM: 8-10 veces
		20-35 ug/ml infecciones leves con CIM bajas.	
	previo a 2° dosis (y posterior a ella). Excepcionalmente el Farmacéutico o infectologo puede solicitar un nivel en horario aleatorio	45-65 ug/mL infecciones graves con CIM elevadas	
		PREDOSIS (seguridad)	
		< 2 ug/mL o indetectable	