

Seminario DOSIFICACIÓN DE PRECISIÓN

6 de Marzo
14:00 - 17:30
7 de Marzo
14:00 - 17:00

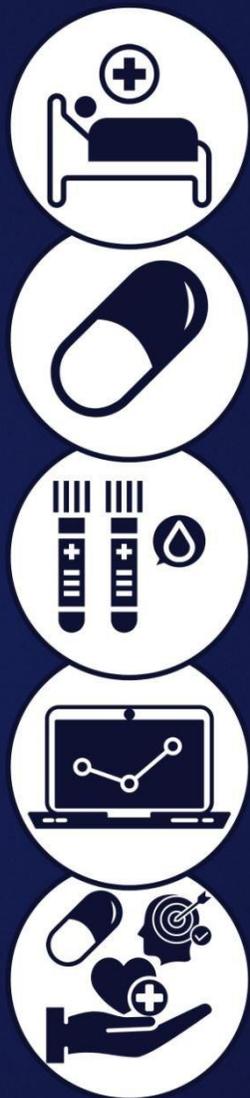
Modalidad híbrida
Hospital de Clínicas
Piso 19
Salón de actos

Inscripción gratuita
Cupos presenciales limitados

Contacto: gidp@fing.edu.uy



¡INSCRIBITE!



GIDP INVITA A PARTICIPAR EN EL SEMINARIO DE DOSIFICACIÓN DE PRECISIÓN

Dosificación de Precisión Informada por Modelos



Imagen adaptada de Kluge et al. (2021), Perspectives on Model-informed Precision Dosing in the Digital Health Era: Challenges, Opportunities, and Recommendations.

¿Quiénes somos?

El grupo interdisciplinario en dosificación de precisión (GIDP) se origina a partir del programa de Semilleros de Iniciativas Interdisciplinarias de la UdelaR. El mismo tiene por objetivo combinar las capacidades existentes en Uruguay para consolidar un marco de trabajo basado en aportes interdisciplinarios que caracterice desafíos y oportunidades para la implementación del paradigma "toma de decisiones informada por modelos" en el ámbito asistencial humano y veterinario. Este grupo ha contado con la participación de las Facultades de Química, Ingeniería, Medicina, Veterinaria y Ciencias Económicas y de Administración.

TEMÁTICAS DEL SEMINARIO

Optimización de terapias



Farmacología individualizada



Poblaciones especiales





Enfermedad renal

Tratamientos de sustitución

Prof. Dr. Oscar Noboa
Centro de Nefrología
Hospital de Clínicas
Facultad de Medicina Udelar

Hoja de ruta:

- Prevalencia de enfermedad renal crónica según grupos etarios
- Precisión en la evaluación del filtrado glomerular.
 - Filtrado glomerular por aclaramiento de iohexol
- Dosificación de fármacos en sustitución de la función renal ,
 - el caso de la vancomicina
- Inmunosupresión en trasplante
 - Tacrolimus modelos predictivos y farmacogenéticos (QF Martín Umpierrez)
- Preservación de la función renal y tratamiento oncológico
 - El caso del Cisplatino

Prevalencia de enfermedad renal crónica según grupos etarios

Artículo original

*Importancia del examen médico preventivo para el diagnóstico precoz de enfermedad renal en Uruguay.
Programa Nacional de Salud Renal*

Importance of preventive medical examination for early diagnosis of renal disease in Uruguay - The National Renal Health Program

FG (CKD-EPI) menor 60 ml/min
según grupos etarios

Chequeo de personas laboralmente activas o deportistas (n11.159)

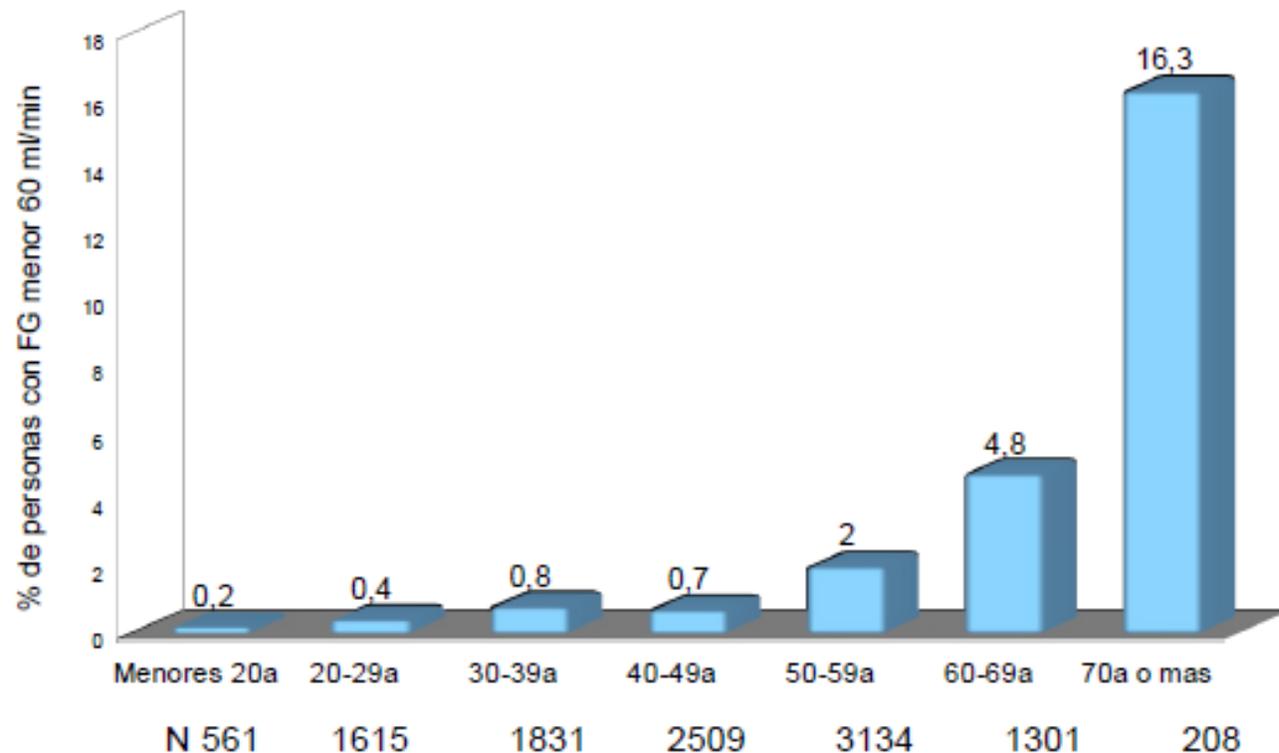


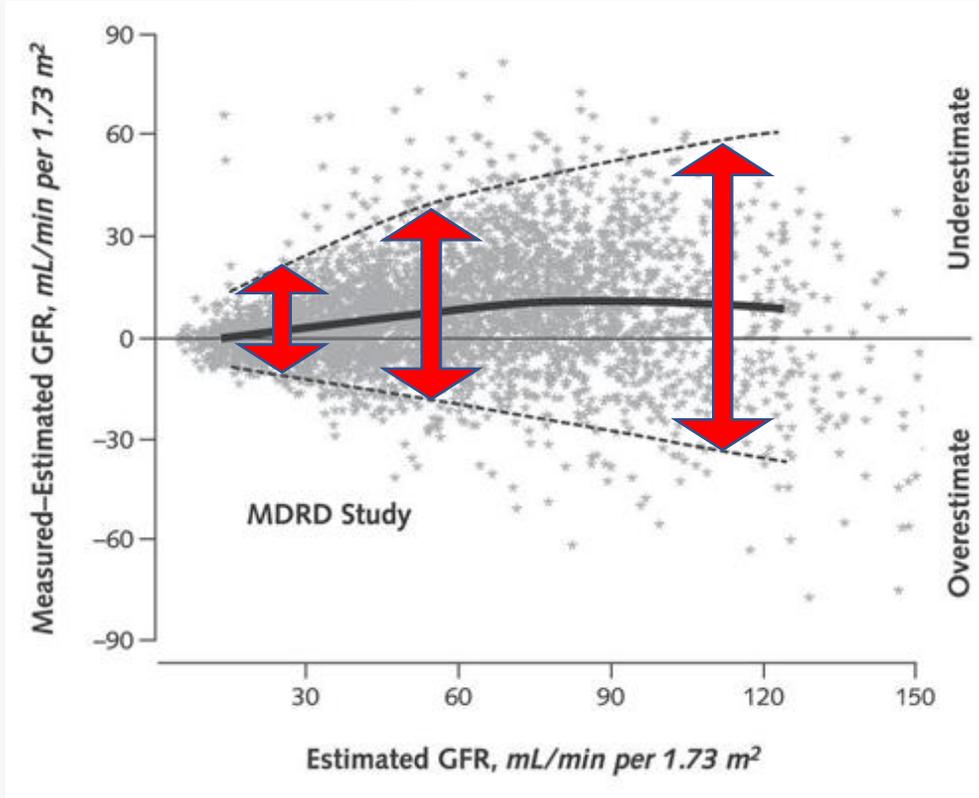
TABLA 1-8. TASA DE INCIDENCIA DE ERC G5D POR GRUPOS DE EDAD (pmp)

AÑO	< 15	15 – 44	45-64	65-74	75-84	≥85
1996	9.9	46.5	235.7	502.7	436.2	125.9
1997	7.4	47.5	222.3	496.7	610.1	266.7
1998	7.3	37.9	138.5	328.4	283.6	234.9
1999	13.4	77.3	314.6	650.6	790.2	298.7
2000	6.1	54.2	187.8	410.5	579.8	338.0
2001	3.7	53.0	182.9	522.9	482.0	199.1
2002	12.3	47.7	232.1	469.2	505.3	217.3
2003	9.9	48.7	237.4	496.4	515.2	213.7
2004	1.2	63.0	255.5	515.7	649.7	147.0
2005	10.0	52.2	247.9	530.5	682.5	123.5
2006	6.3	52.9	223.4	459.0	675.9	281.2
2007	7.7	43.8	246.3	464.6	585.3	255.6
2008	6.4	67.2	241.9	584.5	751.4	499.5
2009	3.9	50.6	233.2	545.9	579.2	390.0
2010	7.9	54.3	226.2	448.8	618.6	379.1
2011	10.6	47.0	269.7	554.7	895.6	423.3
2012	8.1	45.9	212.5	526.1	618.0	376.9
2013	9.5	50.3	214.6	572.9	613.6	365.8
2014	6.9	54.0	246.5	492.3	530.1	322.4
2015	5.5	59.1	238.8	459.7	720.6	484.7
2016	8.4	53.5	241.4	662.0	654.3	516.4
2017	7.0	53.9	255.4	691.2	794.6	488.9
2018	5.7	63.7	245.4	538.4	713.0	334.1
2019	4.3	63.6	281.7	624.3	817.7	300.5

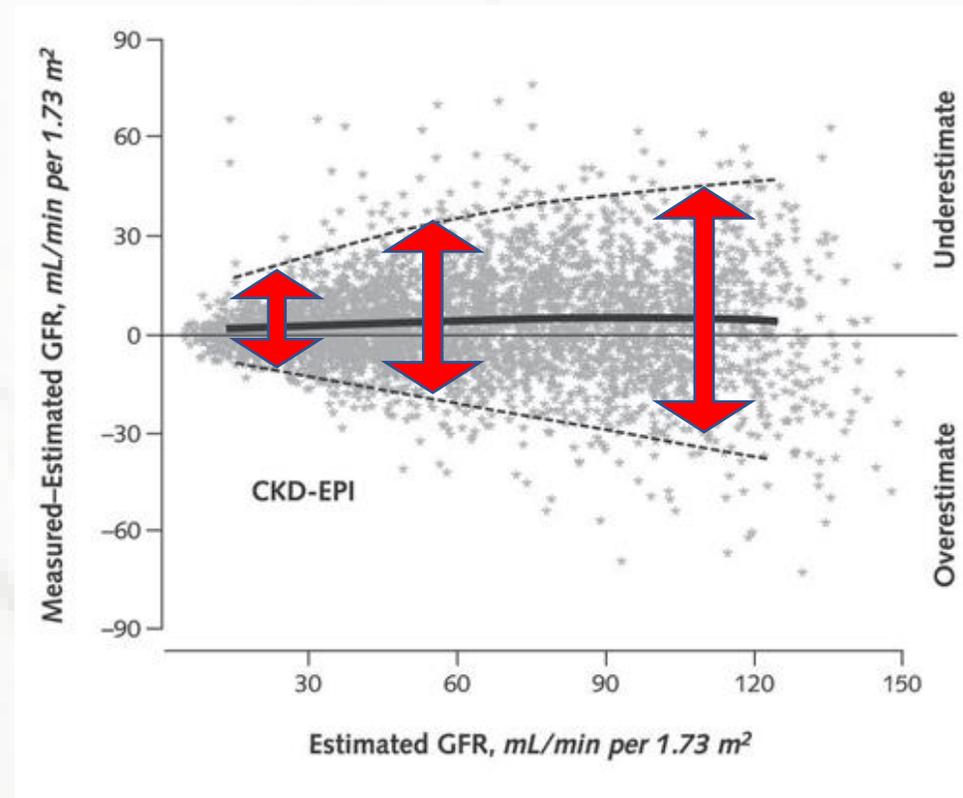
RUD. Informe anual 2019

González-Bedat M C, Luzardo L, Oroza V,
Ceretta M L, Silvariño R y Ferreiro Fuentes A,
Montevideo. Uruguay. Año 2022.

MDRD



CKD-EPI



OPINION

Estimated GFR: time for a critical appraisal

Esteban Porrini, Piero Ruggenenti, Sergio Luis-Lima, Fabiola Carrara, Alejandro Jiménez, Aiko P.J. de Vries, Armando Torres, Flavio Gaspari and Giuseppe Remuzzi

continued to be published, notably the Mayo Clinic Quadratic (MCQ) equation in 2004 (REF.⁷), the CKD Epidemiology Collaboration formula (CKD-EPI) in 2009 (REF.⁸), and an eGFR equation based on normalized values of serum creatinine in 2016 (REF.⁹). In 1985, cystatin C was first proposed as a marker of renal function¹⁵. Since then, more than 15 eGFR formulae based on cystatin C levels have been published (Supplementary Table 1).

In addition, several eGFR formulae have

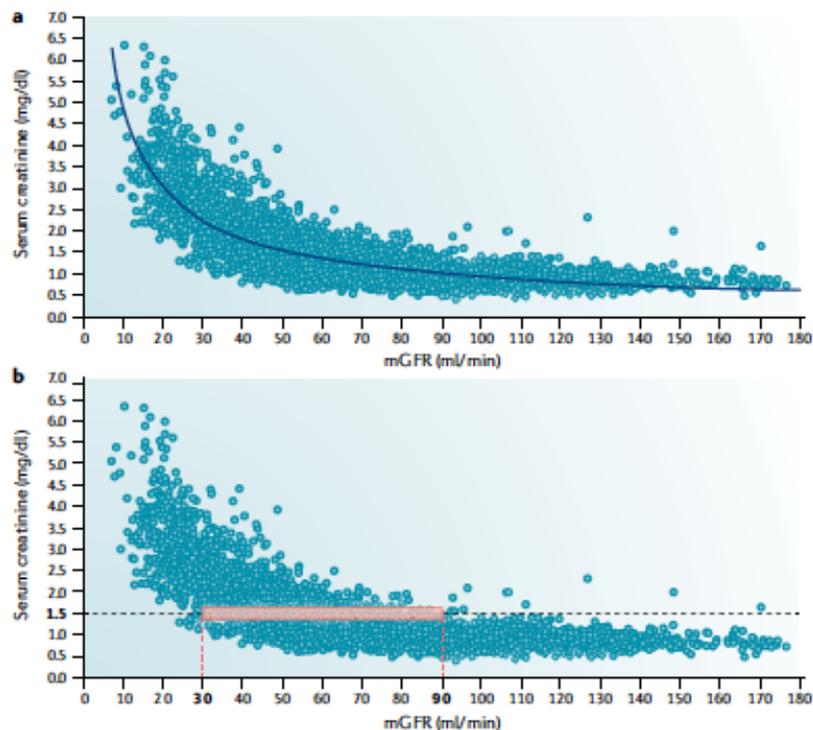


Fig. 1 | Relationship between serum levels of creatinine or serum cystatin C and measured glomerular filtration rate in patients with and without renal disease. The cause of renal impairment in these two cohorts of patients was type 2 diabetes mellitus, renal transplantation, autosomal dominant polycystic kidney disease or chronic kidney disease. Measured glomerular filtration rate (mGFR) was assessed by plasma clearance of iohexol. **a** | The curvilinear relationship between serum creatinine level and mGFR in 3,146 patients with renal impairment. **b** | In these 3,146 patients, serum creatinine 1.5 mg/dl is associated with mGFRs of 30–90 ml/min. **c** | The curvilinear relationship between serum cystatin C level and mGFR in 597 patients with and without renal impairment. **d** | In these 597 patients, serum cystatin C 1.5 mg/l is associated with mGFRs of 30–90 ml/min. Data for this figure were provided by the Laboratory of the Aldo e Cele Daccó Center for Rare Diseases, Mario Negri Institute, Bergamo, Italy and the Laboratory of Renal Function, Hospital Universitario de Canarias, University of La Laguna, Tenerife, Spain.

In 600 patients with T2DM and normalalbuminuria, microalbuminuria, normal renal function or hyperfiltration⁴⁵, 15 creatinine-based eGFR formulae all showed very poor concordance with mGFR

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¹NEFROLOGÍA. HOSPITAL UNIVERSITARIO DE CANARIAS (LA LAGUNA/ESPAÑA), ²NEFROLOGÍA. HOSPITAL UNIVERSITARIO DR NEGRÍN (LAS PALMAS DE GRAN CANARIA/ESPAÑA), ³UNIDAD DE INVESTIGACIÓN. HOSPITAL UNIVERSITARIO DE CANARIAS (LA LAGUNA/ESPAÑA)

La poliquistosis renal autosómica dominante (PQRAD) es la enfermedad renal hereditaria más frecuente. Se caracteriza por un incremento progresivo del número y tamaño de los quistes renales lo que lleva a la pérdida de la función renal. Por consenso se ha definido como progresador rápido la pérdida de función renal ≥ 5 ml/min/1.73m² en un año o ≥ 2.5 ml/min/1.73m²/año durante 5 años o a un aumento del volumen renal $> 5\%$ anual. En la práctica habitual en los pacientes con PQRAD el filtrado glomerular se estima mediante fórmulas. Lamentablemente las fórmulas tienen un error del $\pm 30\%$ de la función renal real. Sin embargo, la magnitud del error de las fórmulas en la PQRAD se desconoce. Estudio de corte transversal donde analizamos el error de 70 fórmulas (creatinina o cistatina) en 70 pacientes con PQRAD a los que se les midió la función renal con el aclaramiento plasmático de iohexol. El acuerdo entre la función renal estimada y la medida se calculó con los siguientes tests: total deviation index (TDI), concordance correlation coefficient (CCC) y coverage probability (cp). La edad media de los pacientes fue 43 ± 13 años, el 37% eran varones. El filtrado medido fue de 78 ml/min: rango: 21-136 ml/min. El error medio de cualquier fórmula variaba entre el 30 y el 40% reflejado por un TDI de 31% (aMDRD), 33% (CKD-EPI creatinina), 30% (CKD-EPI cistatina), 40% (CKD-EPI crea-cist). Los valores de CCC y cp reflejaron un grado bajo de acuerdo entre la función renal medida y la estimada (datos no mostrados). Se adjunta una tabla con los casos más característicos. En conclusión: las fórmulas

Tabla 1.

Caso	GFR	aMDRD	Creatinina		Cistatin-C		Crea+Cis-C	
			MCQ	CKD-EPI-cr	CKD-EPI-cy	Stevens	CKD-EPI-crcy	
INFRAESTIMACIÓN								
1	37	32	32	31	34	33	32	
2	68	49	58	53	62	55	57	
3	21	18	19	19	18	18	17	
4	44	36	46	40	39	38	38	
5	24	17	18	18	19	18	17	
6	45	33	41	35	43	38	38	
7	39	35	34	36	43	39	38	
SOBRESTIMACIÓN								
8	36	40	44	43	43	42	42	
9	99	114	140	117	117	117	118	
10	79	94	134	106	100	100	102	
11	60	72	95	80	92	82	86	
12	110	93	134	109	108	102	107	
13	30	37	38	36	28	34	31	
14	69	69	105	80	86	78	82	

las de estimación, ya sea basadas en la creatinina y/o la cistatina, no son fiables y por lo tanto su uso debería reconsiderarse en la PQRAD.

Situaciones especiales donde se requiere una estimación mas precisa de filtrado glomerular

- Diagnóstico de enfermedad renal crónica
- **Añosos**
- Selección de donante vivo
- Obesos Mórbidos
- **Pacientes oncológicos**
- Ajuste de drogas.
- Parapléjicos, amputados
- **Diabéticos**

CLEARANCE DE IOHEXOL

Abstract

While the gold standard for measuring glomerular filtration rate (GFR) is inulin clearance, this method is less accurate and more cumbersome than other methods. Iohexol is a competitive marker with a low extracellular volume, virtually no protein binding, and is excreted both by glomerular filtration and tubular secretion. It is approved by the European Union for the measurement of GFR. The procedure is simple and the procedure is dominated by glomerular filtration. It can be included in the same protocol as other procedures. The conclusion is that iohexol is a good alternative to inulin for the measurement of GFR.

Key words

Considerado “Gold Standar” para la medición del Filtrado Glomerular:

- Estable en plasma
- No es secretado por el riñón
- No es reabsorbido por el riñón
- No es metabolizado por el riñón
- Unión a proteínas <1%
- Excreción extra-renal es anecdótica

In certain situations, there is a need for a urinary (or renal) marker and protocols for its use. Iohexol is a good alternative to inulin as the marker in terms of accuracy. In addition, iohexol is a simple and safe procedure. It can be separated in a simple procedure. The procedure is simple and the procedure is dominated by glomerular filtration. It can be included in the same protocol as other procedures. The conclusion is that iohexol is a good alternative to inulin for the measurement of GFR.



CLEARANCE DE IOHEXOL

PROYECTO DE INVESTIGACIÓN:

“EVALUACIÓN DE TÉCNICAS DE MEDICIÓN DEL FILTRADO GLOMERULAR EN LA SELECCIÓN DE “DONANTE VIVO” PARA TRASPLANTE RENAL”

Tutores: Dra. Alicia Olascoaga / Dr. José Boggia

Junio 2017: postulación para financiación **CSIC-Iniciación a la Investigación**.

Diciembre 2017: financiación aprobada por 24 meses

Abril 2018: Comienzo del Proyecto

Unidad de Monitoreo de Drogas:

Técnica de medición de Iohexol: **HPLC**

QF. Marta Vázquez

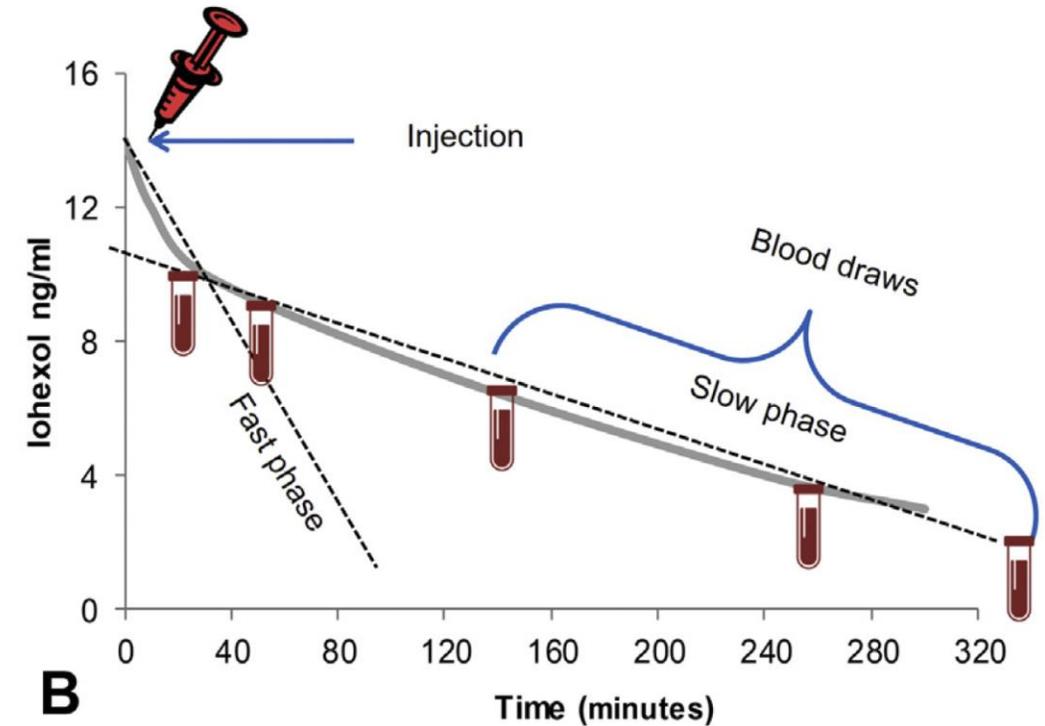
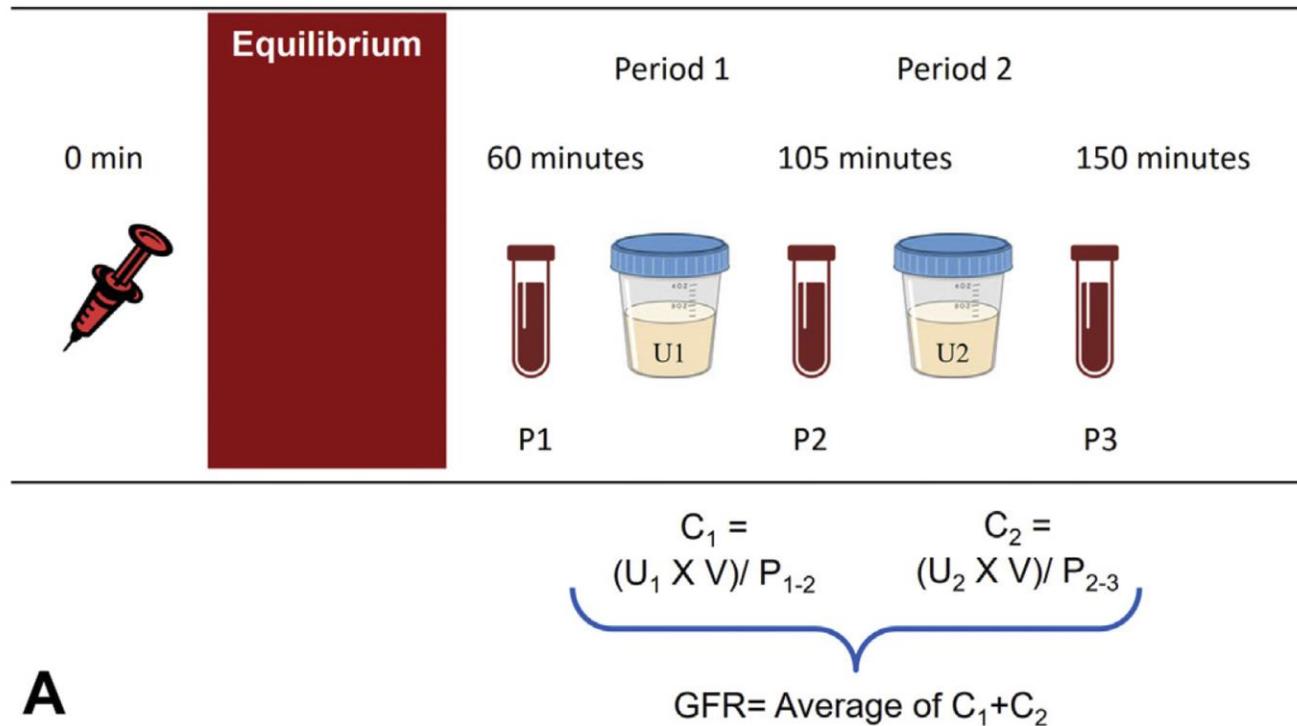
QF. Cecilia Maldonado

QF. Natalia Guevara

Precisión en la evaluación del filtrado glomerular.

Filtrado glomerular por aclaramiento de iohexol .

Dra. Boragarello Dr. Boggia , Dra. Olascoaga



EXPERIENCIA NACIONAL CON CLEARANCE DE IOHEXOL

POST ANALÍTICA:

Individuals	Gender	Age (years)	CKD EPI mL/min/1.73m ²	Iohexol mL/min/1.73m ²	Iohexol – CKD EPI mL/min/1.73m ²
1	M	60	81.4	103.7	+22.3 (+21%)
2	M	26	102.2	76.8	-25.4 (-33%)
3	F	28	94.6	105.1	+10.5 (+10%)
4	F	41	113.2	114.0	+0.8 (+1%)
5	M	48	79.0	113.9	+34.9 (+31%)
6	F	58	96.4	86.9	-9.5 (-11%)
7	F	50	103.0	109.5	+6.5 (+6%)
8	M	39	13.5	24.2	+10.7 (+44%)
9	F	42	109.5	115.9	+6.4 (+5%)



EXPERIENCIA NACIONAL CON CLEARANCE DE IOHEXOL

Mismos 9 voluntarios se determinó Cl. Iohexol por DBS en España.

	CKD-EPI (ml/min)	Cl. Iohexol (ml/min) Plasma UY	Cl. Iohexol (ml/min) DBS ES	Δ (mL/min) (Plasma UY/DBS ES)	Δ (%) GS(DBS ES)
Paciente 1	81,4	103,67	109,46	5,79	5,3
Paciente 2	102,2	76,78	86,49	9,71	11,2
Paciente 3	94,6	103,56	94,31	9,25	9,8
Paciente 4	113,2	114,01	106,92	7,09	6,6
Paciente 5	79	113,87	110,25	3,62	3,3
Paciente 6	96,4	86,94	104,11	17,17	16,5
Paciente 7	103	109,53	136,87	27,34	19,9
Paciente 8	13,5	24,19	19,29	4,9	25,4
Paciente 9	109,5	115,85	111,04	4,81	4,3

- Limitaciones

- Pacientes estables
- NO podemos predecir como se va a comportar frente a una injuria renal
- Repetir ?

Dosificación de fármacos en sustitución de la función renal , el caso de la vancomicina

- Modalidades de sustitución de la función renal

- Dialisis peritoneal
 - DP intermitente
 - DPCA
- Hemodiálisis
- Hemodiafiltración

- En el paciente critico

- HD/HDF
- SLED
- CRRT

Expansion del LEC (Quemados)
Función residual

Hemodiafiltración en línea como terapia de reemplazo renal crónica. Primera experiencia nacional en el Hospital Universitario

Ricardo Silvariño, Cecilia Baccino, Patricia Larre Borges, Ana Laura Guerisoli, Verónica Miranda, Paula Búcalo, Francisco González-Martínez, Alejandro Ferreiro, Liliana Gadola, Oscar Noboa

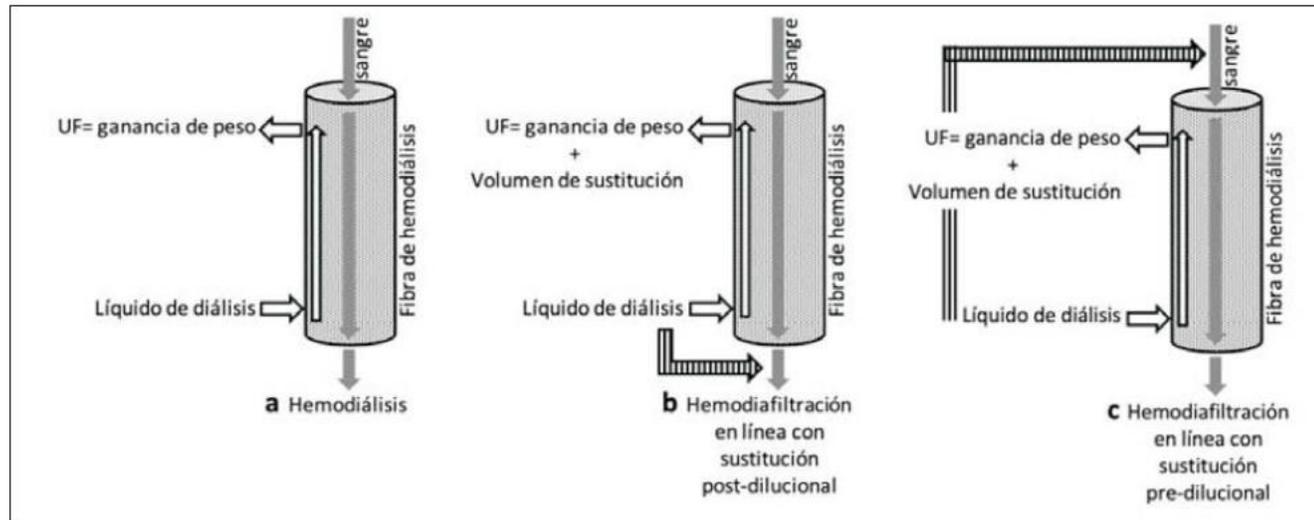


Figura 2. Hemodiálisis (a), la ultrafiltración (UF) se programa en cada sesión según la ganancia de peso del paciente y la valoración del estado de hidratación. Hemodiafiltración en línea con reposición posdilucional (b) y predilucional (c), a la ultrafiltración planificada según peso y valoración del paciente se deben agregar los litros de sustitución infundidos. Modificado de ⁽⁶⁾.



Grupo HDF

- 7 pacientes: 5 hombres/2 mujeres
- Edad 59.4±12 años
- Tiempo HD 50,1±34.6 meses
- HDF-OL 7±4.6 meses.
- Volumen de reposición > 24 l/sesión
- Fibra polisulfona 2.1 m².

Grupo (control) HD

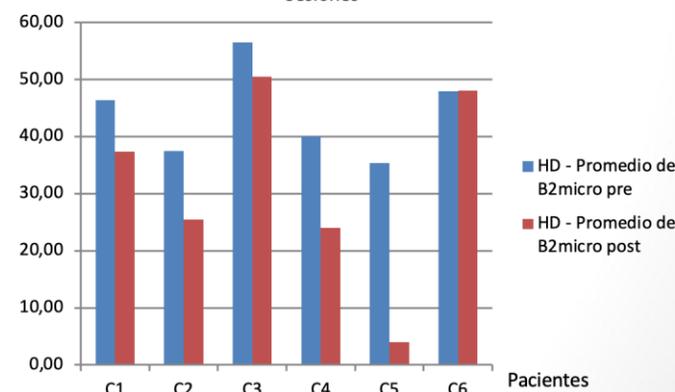
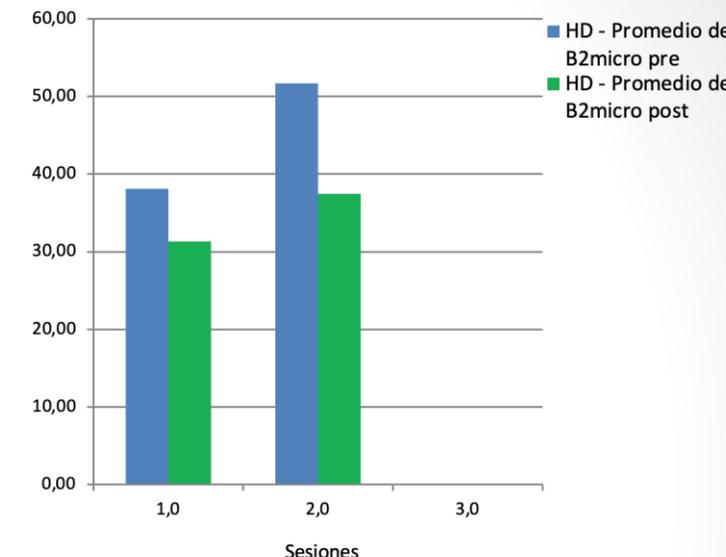
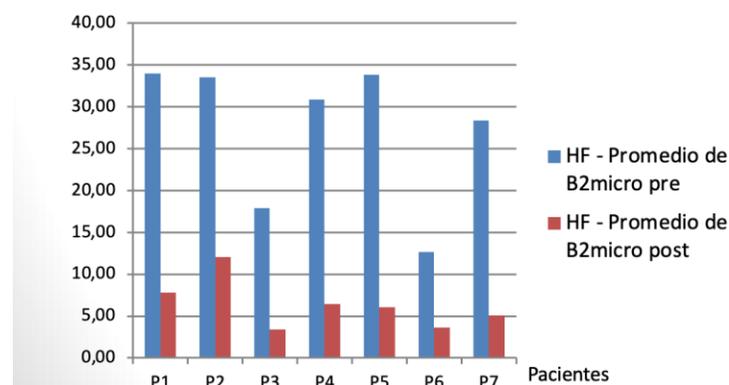
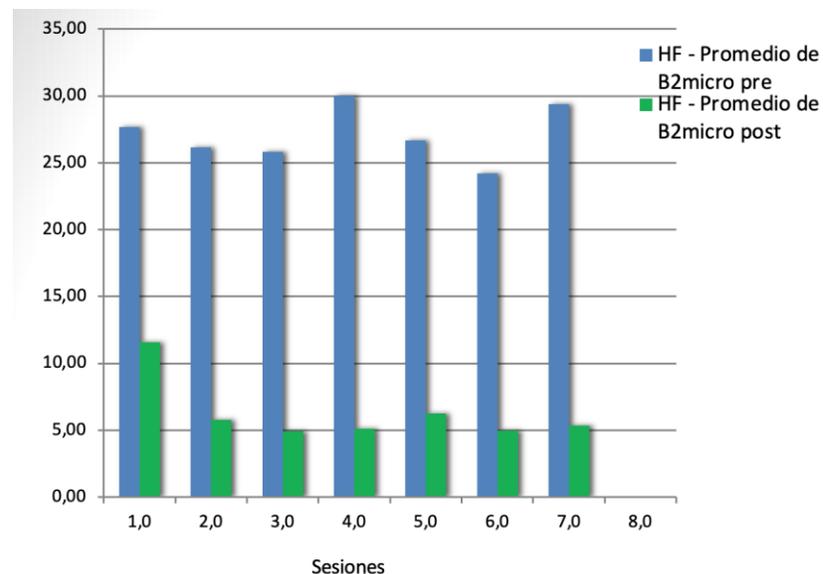
- N 6 pacientes: 3 hombres/3 mujeres
- Edad 50.3±11.4 años
- Tiempo HD 54.5 meses.

- Concentración de urea (60 Da)
- Creatinina (113 Da)
- β_2 -microglobulina (11 800 Da)
- Fósforo
- Calcio
- Albúmina
- Vitamina D
- PCR
- Transferrina en plasma

Inicio de HDL-OF
Ultimas 6 s pre/post sesión

17 AUMENTO DE LA DEPURACIÓN DE MOLECULAS MEDIAS CON HEMODIAFILTRACIÓN ON LINE EN EL PACIENTE CRÓNICO

LarreBorges P, Zulberti C, Villegas N, Sarantes R, Ferrari S, Luzardo L, Garcia F, SanRoman S, Gauronas P, González X, Oyamburo A, Moreno V, Villamil N, López E, Massaro R, Buccalo P, Olascoaga A, Gadola L, Noboa O, Centro de Nefrología, Hospital de Clínicas, Facultad de Medicina UDELAR, Montevideo, Uruguay.





Depuración de moléculas pequeñas y medianas según técnica (HDF-OL vs HD)

Edad (años)	Técnica	Tº TRR (meses)	Tº/técnica (meses)	PAM	Tº proc (minutos)	Fibra (m²)	FB (ml/min)	UF (cc)	Kt/v (mono)	Peso seco (Kg)
78	HD	76	76	86	240	2.1	300	800	1,1	78,6
29	HD	34	34	86.3	240	2.1	350	0	1,7	60
37	HD	16	16	126	240	2.1	350	1200	0,87	101,4
82	HD	70	70	79	240	2.1	350	500	1,31	83
72	HD	105	105	78.7	240	2.1	330	500	1,18	87,9
80	HD	75	75	76.7	240	2.1	300	900	1,86	61,5
76	HD	15	15	76.3	240	2.1	300	100	1,36	76
73	HD	7	7	105	240	2.1	300	0	1,2	97,7
62	HD	5	5	86	240	2.1	300	1300	1,05	111,7
24	HD	34	34	86	240	2.1	340	2200	1,91	53,2
65	HD	48	48	90.7	240	2.1	350	2000	1,73	89
47	HD	74	74	90	240	2.1	330	1200	1,31	64,8

											Reposición	
											Tipo	Volumen (Its)
40	HDF	46	36	114	240	1.7	250	700	2,01	42,9	POS	10,5
48	HDF	45	36	78.3	240	2.1	360	2900	1,26	102,5	POS	21,5
45	HDF	192	62	75.7	240	2.1	350	2400	1,74	62,2	POS	20,5
64	HDF	129	45	92	240	2.1	330	300	1,88	43	POS	22,6
49	HDF	228	53	137	240	2.1	350	700	1,52	50	POS	22,5
45	HDF	168	11	98.3	240	1.7	330	2800	1,42	61,3	POS	19
51	HDF	66	62	88.7	240	2.1	360	1300	1,57	80	POS	19
79	HDF	39	49	60.7	240	2.1	300	1700	1,22	77	PRE	32,5
42	HDF	173	7	115	240	2.1	350	500	1,66	47,3	POS	23
66	HDF	140	75	61.3	240	2.1	360	600	1,96	78	POS	22,9



Depuración de moléculas pequeñas y medianas según técnica (HDF-OL vs HD)

	HD	HDF	<i>p</i>*
Edad (años)	60.4	52.9	<i>0.330</i>
To TRR (mes)	46.5	122.6	<i>0.003</i>
To HDF (mes)	-	43.6	
PAM (mmHg)	88.9	92.1	<i>0.706</i>
To proc (min)	240	240	<i>1</i>
FB (ml/min)	325	334	<i>0.479</i>
UF (cc)	891	1390	<i>0.191</i>
Kt/V M	1.38	1.62	<i>0.086</i>
Peso seco (Kg)	71.9	64.4	<i>0.062</i>
Vol reposición (l)	-	21.4	



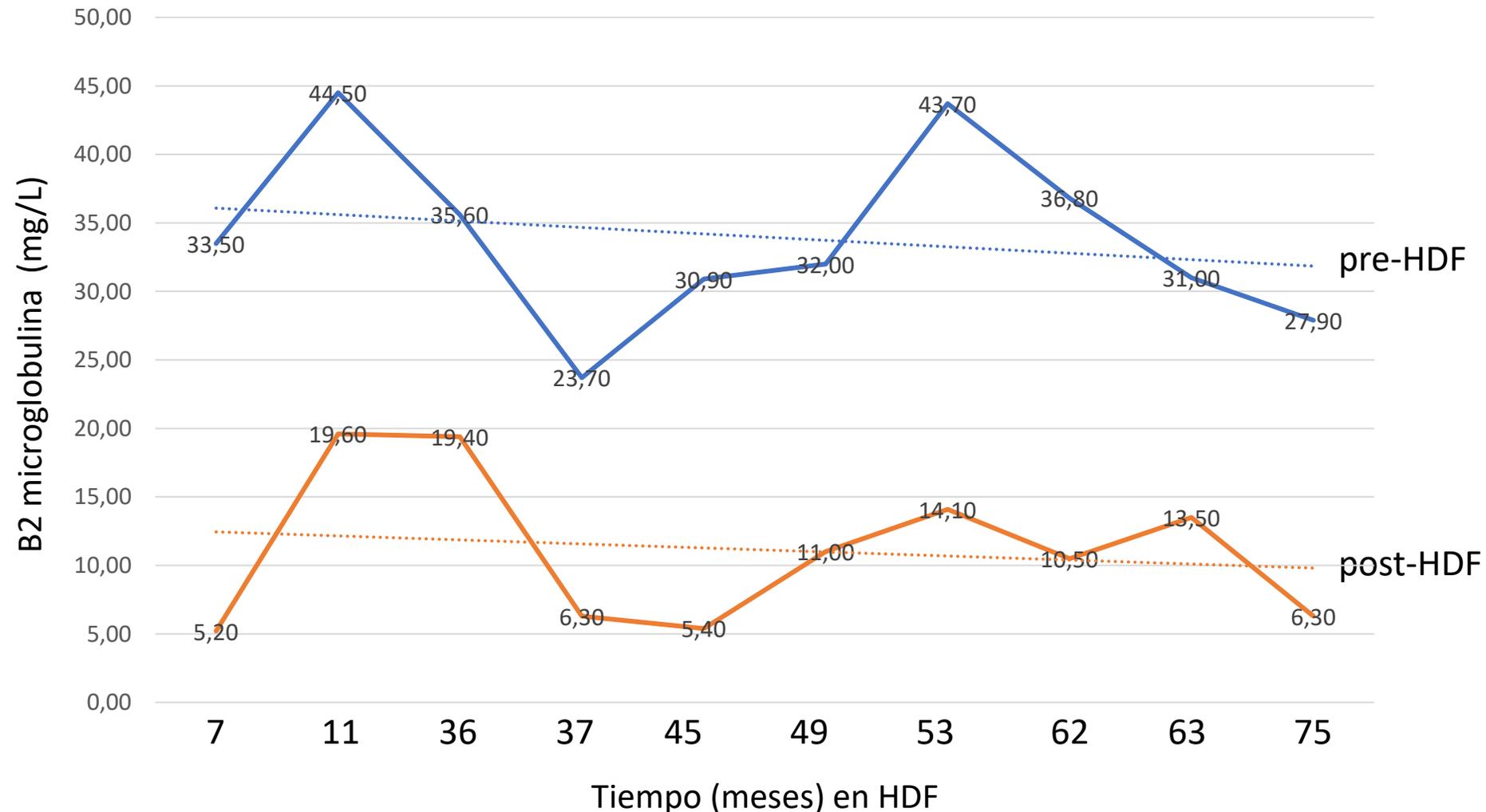
Depuración de moléculas pequeñas y medianas según técnica (HDF-OL vs HD)

	HD	HDF	<i>p</i> *
Cr Pre	9.99 ± 2.82	9.77 ± 2.83	0.853
Cr Post	3.76 ± 1.40	3.27 ± 1.31	0.594
Reducción Cr (%) Pre/Post	62.36	66.53	
Dif Cr Post-pre	- 6,49	- 6,23	0.730
Urea Pre	122.83 ± 40.88	132.60 ± 32.02	0.546
Urea Post	36.75 ± 15.29	33.50 ± 12.25	0.594
Reducción Urea (%) Pre/Post	70.08	74.73	
Dif Urea Post-pre	- 6,49	- 6,23	0.730
Fosforo Pre	5.95 ± 2.78	5.87 ± 2.23	0.936
Fósforo Post	2.44 ± 0.60	2.46 ± 0.63	0.945
Reducción Fósforo (%) Pre/Post	58.99	58.09	
Dif Fosforo Post-pre	- 3,41	- 3,45	0.912
Beta2 Pre	39.10 ± 22.99	74.01 ± 13.46	0.372
Beta2 Post	17.24 ± 12.95	11.13 ± 5.47	0.180
Reducción Beta2 (%) Pre/Post	55.90	84.96	
Dif Beta2 Post-pre	- 21,86	- 62,88	0.039
PCR Pre	8.23 ± 7.69	4.50 ± 4.90	0.202
PCR Post	8.10 ± 8.03	5.40 ± 4.09	0.346
Reducción PCR (%) Pre/Post	1.57	+20	
Dif PCR Post-pre	- 0,9	- 0,12	0.584



Depuración de moléculas pequeñas y medianas según técnica (HDF-OL vs HD)

Depuración de B2-microglobulina en HDF según tiempo en la técnica



Monitoreo de niveles plasmáticos de vancomicina en pacientes en hemodiálisis

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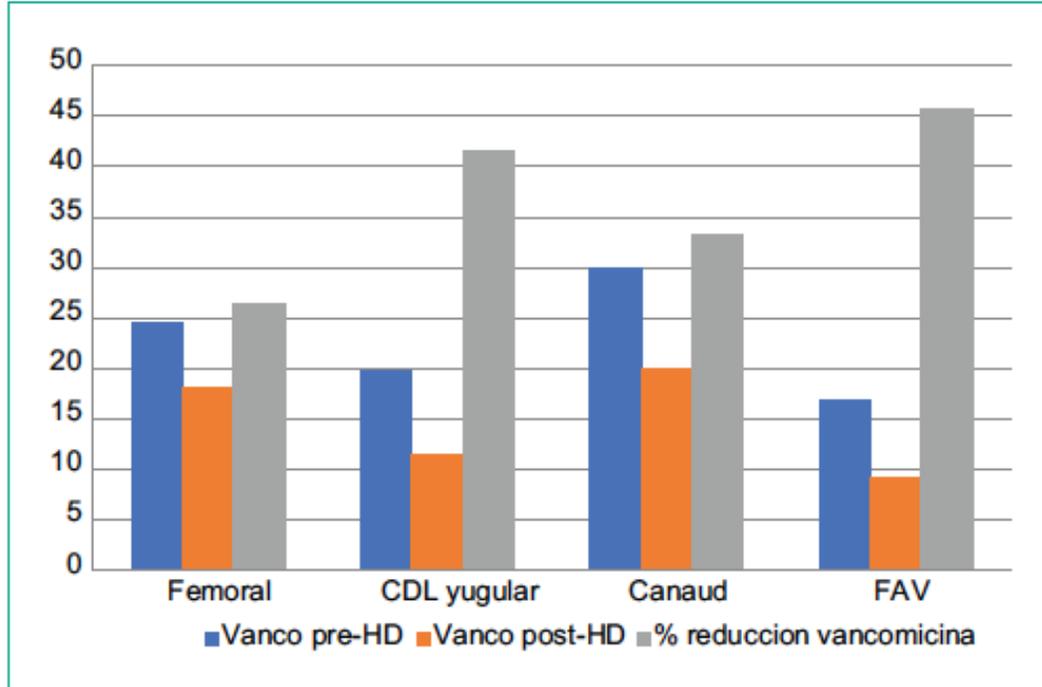


Figura 1. Reducción de vancomicina según acceso vascular (femorales menor reducción vs. resto de accesos, $p = 0.002$).

CDL: catéter doble luz; FAV: fístula arterio-venosa; HD: hemodiálisis; Vanco: vancomicina.

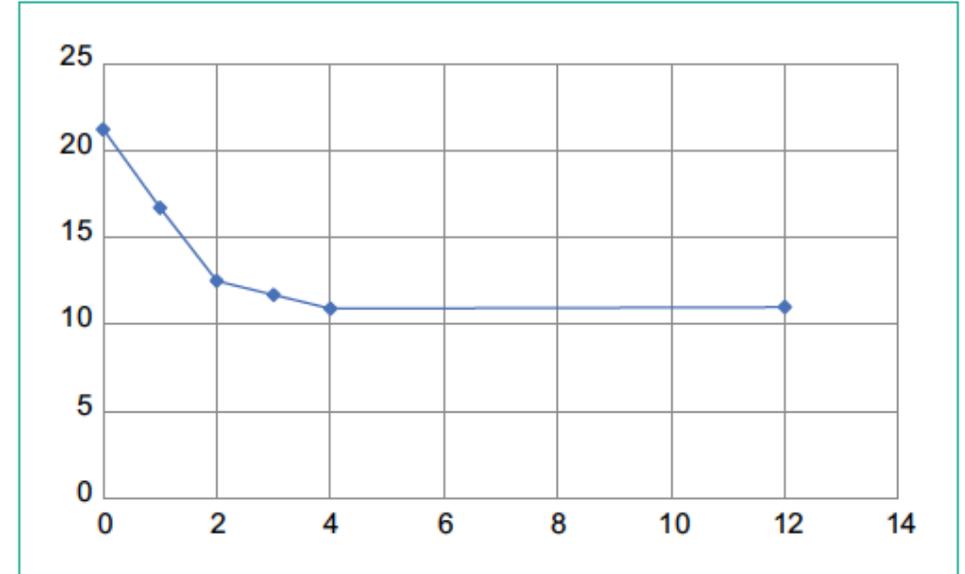


Figura 2. Paciente 11: medición de vancocinemia horaria durante sesión de hemodiálisis y a las 12 h. Se observa la reducción horaria gradual del antibiótico, con estabilidad durante las siguientes horas.

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

Timing and Dialyzer Permeability	Vancomycin Dose, mg/kg ^a
Intradialytic	
Low permeability	Loading: 30 Maint.: 7.5-10 ^b
High permeability	Loading: 35 Maint.: 10-15 ^b

^aFrom references 104, 129, 130, 137, 138, 140, and 147.

^bThrice-weekly dose administration.

Summary and recommendations:

13. The following tabulation outlines recommended vancomycin loading and maintenance doses for patients receiving hemodialysis, with accounting for permeability of the dialyzer and whether the dose is administered intradialytically or after dialysis ends (B-II).

Timing and Dialyzer Permeability	Vancomycin Dose, mg/kg ^a
After dialysis ends	
Low permeability	Loading: 25 Maint.: 7.5 ^b
High permeability	Loading: 25 Maint.: 10 ^b

Summary and recommendations:

1. *In patients with suspected or definitive serious MRSA infections, an individualized target of the AUC/MIC_{BMD} ratio of 400 to 600 (assuming a vancomycin MIC_{BMD} of 1 mg/L) should be advocated to achieve clinical efficacy while improving patient safety (A-II). Doses of 15 to 20 mg/kg (based on actual body weight) administered every 8 to 12 hours as an intermittent infusion are recommended for most patients with normal renal function when assuming a MIC_{BMD} of 1 mg/L (A-II). In patients with normal renal function, these doses may not achieve the therapeutic AUC/MIC target when the MIC is 2 mg/L.*
2. *Given the narrow vancomycin AUC range for therapeutic effect and minimal AKI risk, the most accurate and optimal way to manage vancomycin dosing should be through AUC-guided dosing and monitoring (A-II). We recommend to accomplish this in one of two ways.*
 - a. *One approach relies on the collection of 2 concentrations (obtained near steady-state, postdistributional peak concentration [C_{max}] at 1 to 2 hours after infusion and trough concentration [C_{min}] at the end of the dosing interval), preferably but not required during the same dosing interval (if possible) and utilizing first-order PK equations to estimate the AUC (A-II).*

Hybrid hemodialysis therapies. Contemporary renal replace-

recognizing that these hybrid dialysis therapies efficiently remove vancomycin (B-III). Initial doses should not be delayed to wait for a dialysis treatment to end. Maintenance doses of 15 mg/kg should be given after hybrid hemodialysis ends or during the final 60 to 90 minutes of dialysis, as is done with standard hemodialysis (B-III).¹³⁰ Concentration monitoring should guide further maintenance doses.

New Vancomycin Dosing Guidelines for Hemodialysis Patients: Rationale, Caveats, and Limitations

Susan J. Lewis¹ and Thomas D. Nolin²

KIDNEY360 2: 1313–1315, 2021. doi: <https://doi.org/10.34067/KID.0000192021>

Table 1. Recommendations for patients receiving hemodialysis on the basis of the revised vancomycin consensus guidelines (3)

Dosing Recommendations	Monitoring Recommendations
<ul style="list-style-type: none"> Weight-based initial dosing recommendations with actual body weight should be used. A maximal loading dose of 3000 mg is recommended for patients who are obese. A 30% larger vancomycin dose should be considered if infused intradiallytically. Vancomycin infusion rate should not exceed 1 g/h, even if infused intradiallytically. 	<ul style="list-style-type: none"> TDM should be performed for all patients to individualize maintenance doses. Targeting predialysis concentrations between 15–20 mg/L is likely to attain the efficacy target 24-hour AUC/MIC ratio of 400–600, assuming an MIC of ≤ 1 mg/L.

TDM, therapeutic serum drug concentration monitoring; AUC/MIC, area under the serum concentration-time curve/minimum inhibitory concentration.

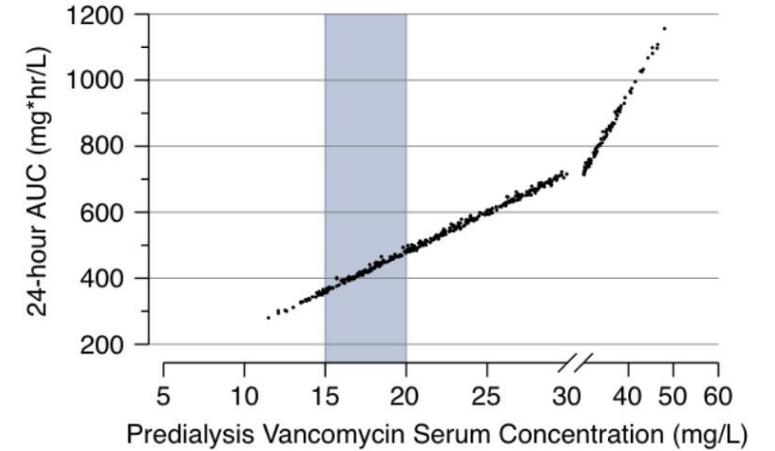


Figure 1. | Target predialysis serum vancomycin concentrations of 15-20 mg/L are predicted to attain the target AUC/MIC ratio in modeled patients on hemodialysis receiving a guideline-recommended dosing regimen (2,8). The model assumed patients with ESKD ($n=500$) weighing 40–139 kg (mean, 76 kg) receiving a 25 mg/kg loading dose, and then 10 mg/kg after each thrice-weekly, high-flux hemodialysis session. Blue vertical lines indicate the target predialysis vancomycin concentrations of 15–20 mg/L that will translate to a 24-hour AUC of <600 mg·h/L, and will likely achieve the target AUC/MIC ratio of 400–600, assuming the MIC is ≤ 1 mg/L. AUC, area under the serum concentration-time curve; AUC/MIC, AUC/minimum inhibitory concentration.

CORRESPONDENCE

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Membrane adsorption in vancomycin treatment is membrane type dependent in CVVHDF: dose correction is crucial

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Keywords: Vancomycin, Doses, PAES membrane, AN69ST membrane

120 min, in the 0.6-m² AN69 filters was significantly greater (10.08 ± 2.26 mg) than in the 0.6-m² polyamide (5.20 ± 1.82 mg) or in the 0.7-m² PS (4.80 ± 2.40 mg) filters [3]. Theoretically, an AN69ST membrane could therefore irreversibly take up almost one third of the initial dose [3]. If proven in vivo, loading and maintenance vancomycin doses would have to be adapted accordingly [3]. Because we routinely apply continuous renal replacement therapy (CRRT) using the AN69 ST, we were able to retrospectively demonstrate that daily vancomycin maintenance doses close to 3,000 mg daily were needed during the first 3 treatment days [4]. Choi demonstrated that, within the first hour after changing the membrane, a striking decline in vancomycin trough concentration occurred, which necessitated a considerable increase in the continuous infusion dose [5].

In conclusion, the clinician should be aware of the specific adsorptive properties of the membrane used and dose accordingly. Both personalization of vancomycin dosing and therapeutic drug monitoring for these patients is essential to guide dose scheduling.

Abbreviations

CVVHDF: Continuous venovenous haemodiafiltration; PAES: Polyarylethersulfone; AN69-ST: Acrylonitrile 69 surface treated; PS: Polysulphone; CRRT: Continuous renal replacement therapy.

Acknowledgements

None.

Kirwan et al. concluded that target attainment with acceptable trough vancomycin concentrations can be achieved early in treatment with a 2000 mg loading dose and maintenance dose of 750 mg 12 hourly for patients on continuous venovenous haemodiafiltration (CVVHDF) [1]. However, the Kirwan study was completed 7 years ago, using a polyarylethersulfone (PAES) which is well known to be a non-adsorptive membrane [1]. In current practice, more than 95% of treatments with the Prismaflex take place with the adsorptive acrylonitrile 69 surface treated (AN69-ST) [2, 3], which also absorbs significant amounts of vancomycin [2]. Accordingly, using a loading dose of 2000 mg and a maintenance dose of 750 mg/12 h in CVVHDF with the present day standard of practice, using a prismaflex with an AN69ST, could risk treatment failure [2]. In a recent study comparing adsorption of vancomycin in AN69ST versus Polysulphone (PS) (with similar specifications to non-adsorptive membranes such as PAES), there was a significant adsorption of roughly 200 mg in 2 h by AN69ST compared to PS [2]. In vitro, Tian studied vancomycin adsorption of AN69, polyamide, and PS membranes in a hemofiltration model [3]. Vancomycin (36 mg) was added to a volume of a blood-crystalloid (target concentration 50 mg/l) [3]. Adsorption, calculated by the fall in concentration over

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Inmunosupresión en trasplante

Tacrolimus modelos predictivos y farmacogenéticos (QF Martín Umpierrez)

- Estabilidad dosificación c/12 hs
- Variante genética CYP3A
- Adherencia médico/ paciente
- Intercurrencias
 - Diarrea
 - Fármacos

Tacrolimus CYP3A Single-Nucleotide Polymorphisms and Preformed T- and B-Cell Alloimmune Memory Improve Current Pretransplant Rejection-Risk Stratification in Kidney Transplantation

Elena Crespo^{1*†}, Anna Vidal-Alabró^{2†}, Thomas Jouve^{1,3,4†}, Pere Fontova², Maik Stein^{5,†}, Sonila Mocka², Maria Meneghini^{1,8}, Anett Seifrin^{5,6,7}, Petra Hrubá⁹, Montserrat Gomà¹⁰, Alba Torija¹, Laura Donadeu¹, Alex Favà¹¹, Josep M. Cruzado¹¹, Edoardo Melilli¹¹, Francesc Moreso⁸, Ondrej Viklický⁹, Frederike Bemelman¹², Petra Reinke^{5,6,7}, Josep Grinyó¹³, Nuria Lloberas^{2‡} and Oriol Bestard^{1,8*†}

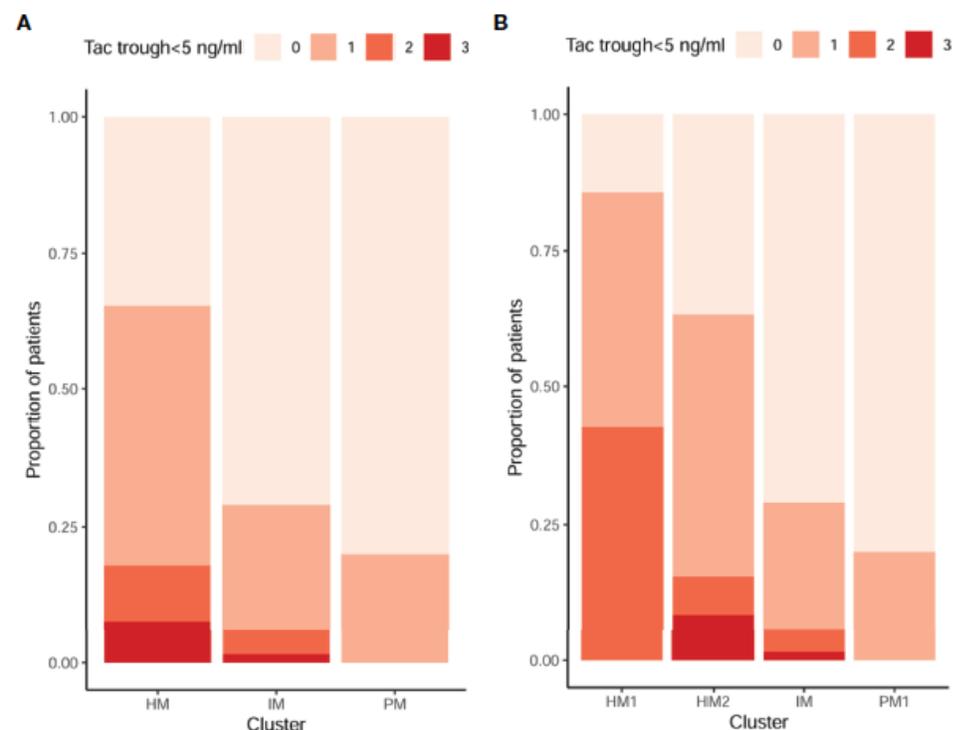
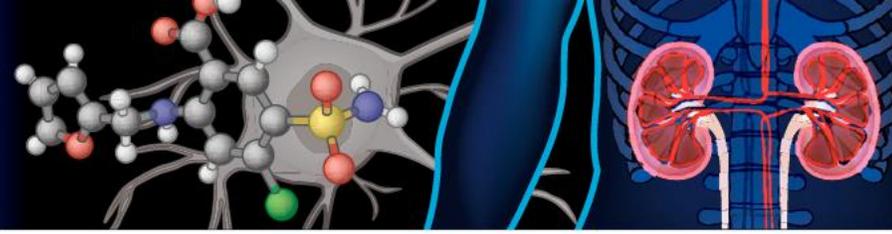


FIGURE 3 | Proportion of TAC underexposure (<5 ng/ml) according to different CYP3A clusters. 0, 1, 2, and 3 in the legend represent the number of times that patients were off target. **(A)** There were a higher proportion of patients with TAC trough levels below 5 ng/ml among HM as compared to IM and PM at mean time of BPAR occurrence or before BPAR. The frequencies of patients with low levels at least once in this follow-up period were 20%, 29%, and 69% in the PM, IM, and HM groups, respectively ($p < 0.001$). **(B)** There were a higher proportion of patients with TAC trough levels below 5 ng/ml among HM1 and HM2 as compared to IM and PM1 at mean time of BPAR occurrence or before BPAR. The frequencies of patients with low levels at least once in this follow-up period were 20%, 29%, 63%, and 86% in the PM, IM, HM2, and HM1 groups, respectively ($p < 0.001$). TAC, tacrolimus; HM, high metabolizers; IM, intermediates; PM, poor metabolizers; BPAR, biopsy-proven acute rejection.

Preservación de la función renal y tratamiento oncológico

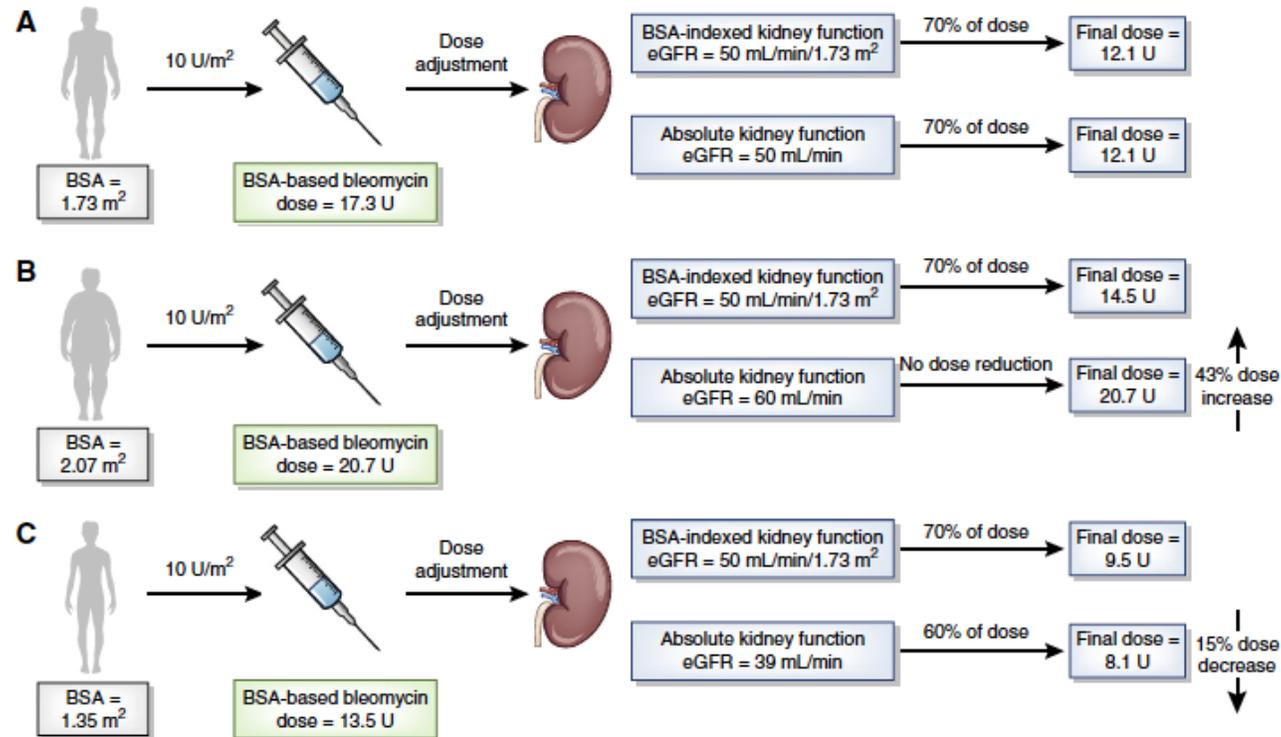
El caso del Cisplatino

- Lograr que el paciente reciba el tratamiento mas eficaz posible.
- Evitar infradosificación que transforme el tratamiento en ineficaz.
- Evitar que la polifarmacia aumente la nefrotoxicidad.
- Disminuir pérdida de función renal.
 - Aguda
 - Crónica
- Preservar función para nuevos tratamiento.
- Máxima capacidad de predicción.



Estimation of Kidney Function in Oncology Implications for Anticancer Drug Selection and Dosing

Morgan A. Casal,¹ Thomas D. Nolin,^{1,2} and Jan H. Beumer^{3,4,5}



Patient - related

Old age (≥ 60 -65 years)

Female sex

Altered pharmacogenetics
- genetic variations in hepatic
CYP450 system and kidney
transporters

Comorbidities: cirrhosis, diabetes,
hypertension, heart failure, sepsis,
metabolic perturbations
(hypokalemia, hypomagnesemia,
hypercalcemia, urine pH
disturbances), active cancers

Kidney - related

Underlying kidney insufficiency with
GFR < 60 mL/min/1.73m²

True or effective volume depletion
(kidney hypoperfusion)

Biotransformation of drugs to
nephrotoxic metabolites and
reactive oxygen species

High metabolic rate of tubular cells
within a hypoxic environment

Proximal tubular uptake of drugs:
apical via endocytosis or
pinocytosis with drug accumulation
or basolateral drug transport via
hOATs or hOCTs

Drug-related

Use of high doses and prolonged
dosing periods

Potent direct nephrotoxic drug
effects

Exposure to multiple nephrotoxic
agents

Pharmacokinetic and / or
pharmacodynamic interactions
between drugs that increase the
free fraction, interfere with
biotransformation or impair the
excretion of drugs and their
metabolites

Cisplatin nephrotoxicity: new insights and therapeutic implications

Chengyuan Tang¹, Man J. Livingston², Robert Safirstein³ and Zheng Dong^{1,2}✉

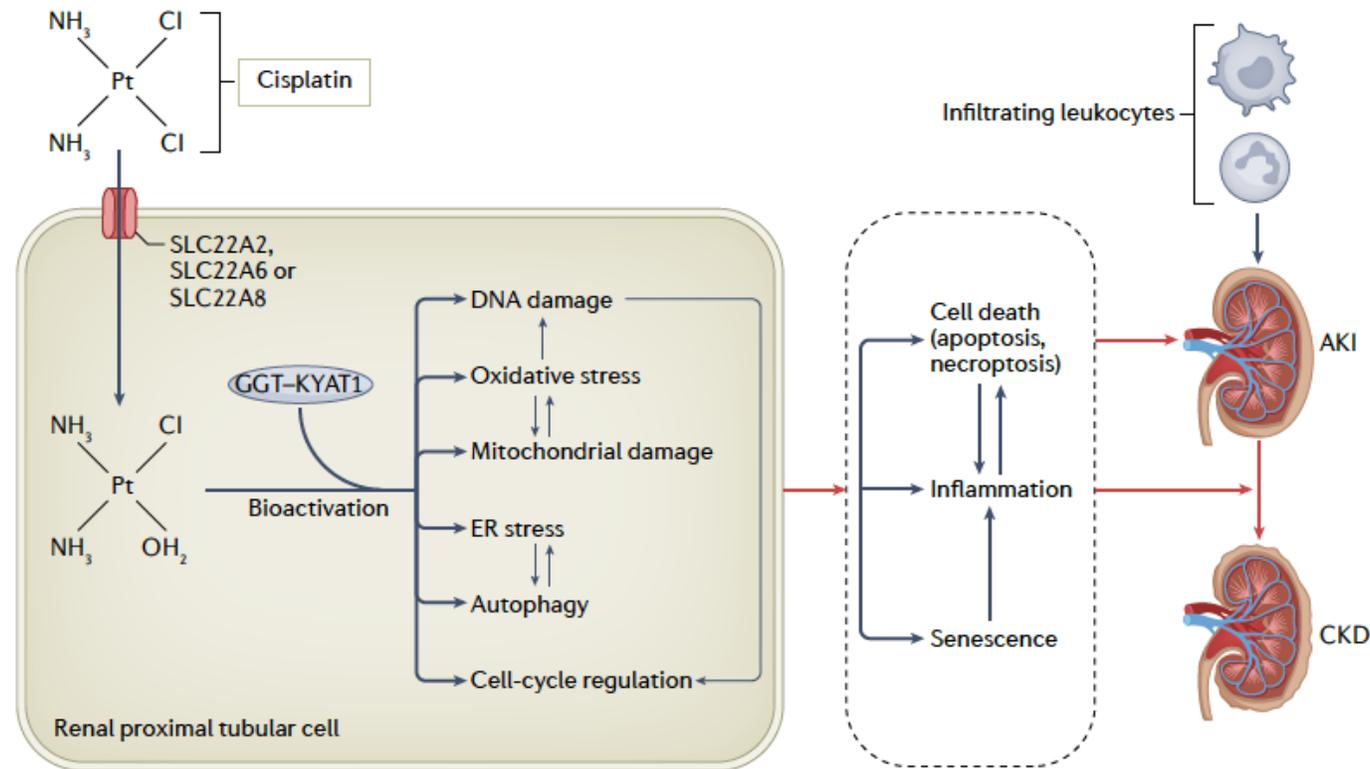


Fig. 1 | The pathophysiology of cisplatin nephrotoxicity. Cisplatin uptake in renal proximal tubular cells is mediated by membrane transporters such as solute carrier family 22 member 2 (SLC22A2), SLC22A6 and SLC22A8. After entering cells, a chloride ion of cisplatin is replaced with a water molecule. Hydrated cisplatin is then metabolically activated to the toxic form by a gamma-glutamyl transpeptidase (GGT) and kynurenine aminotransferase 1 (KYAT1)-dependent pathway. Accumulation of cisplatin in renal proximal tubular cells induces DNA damage, mitochondrial damage, oxidative stress, endoplasmic reticulum (ER) stress, autophagy and cell-cycle regulation. These processes result in renal cell death, inflammation and cell senescence, which lead to acute kidney injury (AKI) and chronic kidney disease (CKD).

Hoja de ruta:

- Prevalencia de enfermedad renal crónica según grupos etarios
- Precisión en la evaluación del filtrado glomerular.
 - Filtrado glomerular por aclaramiento de ioexhol
- Dosificación de fármacos en sustitución de la función renal ,
 - el caso de la vancomicina
- Inmunosupresión en trasplante
 - Tacrolimus modelos predictivos y farmacogenéticos (QF Martín Umpierrez)
- Preservación de la función renal y tratamiento oncológico
 - El caso del Cisplatino

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