

Actualización en patología renal crónica (ERC) y tratamiento con hormona de crecimiento (rhGH) ¿Cómo nos va?

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Por un niño sano
en un mundo mejor



Hospital de Pediatría
Garrahan

INTRODUCCION

El retardo de crecimiento es una importante complicación en pacientes con ERC comprometiendo la morbilidad y la calidad de vida de estos niños.

A partir de los años setenta cuando se inicia la terapia de remplazo renal en paciente pediátricos, la sobrevida de estos niños mejora progresivamente , comenzando un importante desafío :

mejorar la talla adulta en niños con ERC.

INTRODUCCION

Improvement of growth and food utilization by human recombinant growth hormone in uremia

OTTO MEHLS, EBERHARD RITZ, ERNST-B. HUNZIKER, PETER EGGLE, UDO HEINRICH, and JÜRGEN ZAPF

Departments of Pediatrics and Internal Medicine, University of Heidelberg, Heidelberg, Federal Republic of Germany; and Anatomical Institute, University of Bern, Bern, and Department Internal Medicine, University of Zürich, Zürich, Switzerland

ACTA PÆDIATRICA
PROMOTING CHILD HEALTH

Acta Paediatrica ISSN 0803-5253

REVIEW ARTICLE

Growth hormone treatment in short children with chronic kidney disease

O Mehls (Otto.Mehls@med.uni-heidelberg.de)¹, E Wühl¹, B Tönshoff¹, F Schaefer¹, R Nisse², D Haffner²

¹Division of Pediatric Nephrology, University Hospital of Pediatric and Adolescent Medicine, Heidelberg, Germany

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Pediatr Nephrol (2005) 20:404–408
DOI 10.1007/s00467-004-1688-5

ORIGINAL ARTICLE

Richard N. Fine · Donald Stablein

Long-term use of recombinant human growth hormone in pediatric allograft recipients: a report of the NAPRTCS Transplant Registry

Received: 26 April 2004 / Revised: 8 September 2004 / Accepted: 14 September 2004 / Published online: 29 January 2005

EFFECT OF GROWTH HORMONE TREATMENT ON THE ADULT HEIGHT OF CHILDREN WITH CHRONIC RENAL FAILURE

EFFECT OF GROWTH HORMONE TREATMENT ON THE ADULT HEIGHT OF CHILDREN WITH CHRONIC RENAL FAILURE

DIETER HAFFNER, M.D., FRANZ SCHAEFER, M.D., RICHARD NISSEL, M.D., ELKE WÜHL, M.D., BURKHARD TÖNSHOFF, M.D., AND OTTO MEHLS, M.D., FOR THE GERMAN STUDY GROUP FOR GROWTH HORMONE TREATMENT IN CHRONIC RENAL FAILURE*

Nephrol Dial Transplant (1996) 11: 1747–1750

Progress in Paediatric Nephrology

Growth hormone treatment of short children with chronic renal failure before and after renal transplantation: rationale and recent results

O. Mehls, E. Wühl, D. Haffner, F. Schaefer and B. Tönshoff

Division of Pediatric Nephrology, University Children's Hospital of Heidelberg, Germany

Pediatr Nephrol (2010) 25:1125–1130

DOI 10.1007/s00467-010-1450-0

ORIGINAL ARTICLE

First-year response to rhGH therapy in children with CKD: a National Cooperative Growth Study Report

John D. Mahan · Bradley A. Warady · James Frane · Ron G. Rosenfeld · Rita D. Swinford · Barbara Lippe · D. Aaron Davis

ORIGINAL ARTICLE

Growth and maturation improvement in children on renal replacement therapy over the past 20 years

Doris Franke · Stella Winkel · Jutta Gellermann · Uwe Querfeld · Lars Pape · Jochen H. H. Ehrich · Dieter Haffner · Leo Pavičić · Miroslav Živičnjak

Eurasian J Med 2015; 47: 62-5 The Eurasian Journal of Medicine Review

Growth Hormone Therapy in Children with Chronic Renal Failure

Kronik Böbrek Yetmezliği olan Çocuklarda Büyüme Hormonu Tedavisi

Atilla Cayir¹, Celalettin Kosan²

¹Department of Pediatric Endocrinology, Regional Training and Research Hospital, Erzurum, Turkey

²Department of Pediatric Nephrology, Ataturk University Faculty of Medicine, Erzurum, Turkey



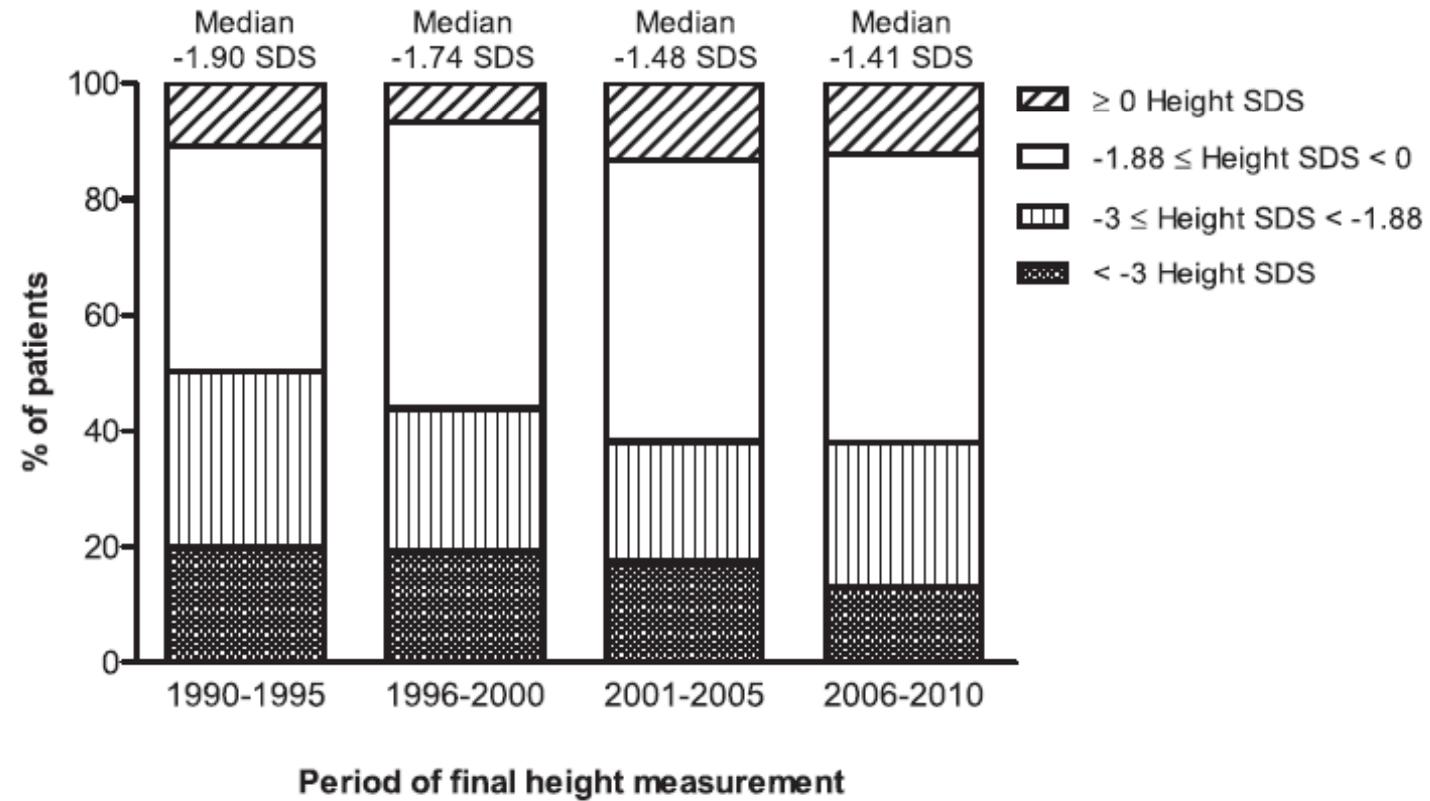
**Cochrane
Library**

Cochrane Database of Systematic Reviews

REVIEW 2006 14 studies (720 enrolled children)			UPDATE 2011 2 studies (60 enrolled children)		
Interventions (studies; children)			Interventions (studies; children)		
rhGH vs placebo	3	152	rhGH vs placebo	0	0
rhGH vs no treatment	6	392	rhGH vs no treatment	1	16
rhGH dose (28 IU ² /m ² /wk vs 14 IU ² /m ² /wk)	4	187	rhGH dose (28 IU ² /m ² /wk vs 14 IU ² /m ² /wk)	1	44
rhGH dose (28 IU ² /m ² /wk vs 56 IU ² /m ² /wk)	1	16	rhGH dose (28 IU ² /m ² /wk vs 56 IU ² /m ² /wk)	0	0
Outcomes reported			Outcomes reported		
Height SDS	3	84	Height SDS	0	0
Height velocity	6	193	Height velocity	2	58
Change in height velocity	2	107	Change in height velocity	0	0
Height velocity SDS	3	49	Height velocity SDS	0	0
Change in height SDS	5	233	Change in height SDS	2	58
Adverse effects	11	619	Adverse effects	2	58

TOTAL (Update 2011) 16 studies (809 enrolled children)		
Interventions (studies; participants)		
rhGH v placebo	3	152
rhGH v no treatment	7	408
rhGH dose (28 IU ² /m ² /wk vs 14 IU ² /m ² /wk)	5	231
rhGH dose (28 IU ² /m ² /wk vs 56 IU ² /m ² /wk)	1	16
Outcomes reported		
Height SDS	3	84
Height velocity	6	251
Change in height velocity	2	107
Height velocity SDS	3	49
Change in height SDS	7	291
Adverse effects	13	677

Crecimiento en ERC y post TxR



Clin J Am Soc Nephrol 9: 92-99, January, 2014

Crecimiento ERC y post TxR

La talla al trasplante renal y la talla adulta ha mejorado

Mejoría de talla relacionada con:

Diagnósticos prenatal con intervenciones terapéuticas tempranas

Mejoría en el manejo del tratamiento nutricional, metabólico, metabolismo óseo y anemia

Mejoría en el manejo dialítico y en la terapia inmunosupresora post-TxR

Edad adecuada de inicio puberal y mejoría del estirón puberal

Uso de hormona de crecimiento

	1987	2007
Talla al Tx renal (SDS)	-2.4	-1.4

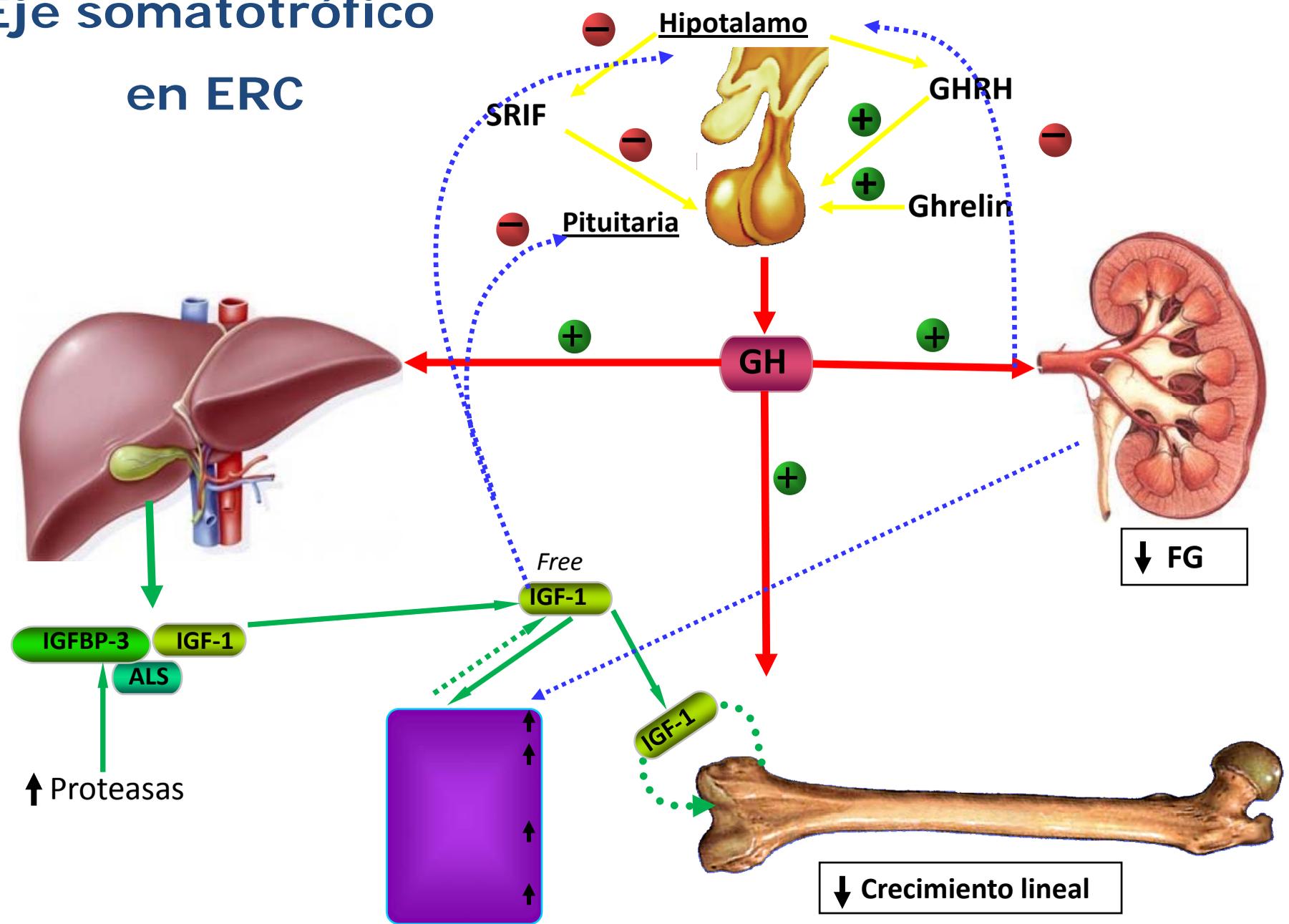
	1987-1991	2005-2013
Talla Adulta (SDS)	-1.77	-0.68

(NAPRTCS /US CKiD)

Cuáles son las alteraciones en el eje somatotrófico que justifican el uso de rhGh en pacientes con ERC ?

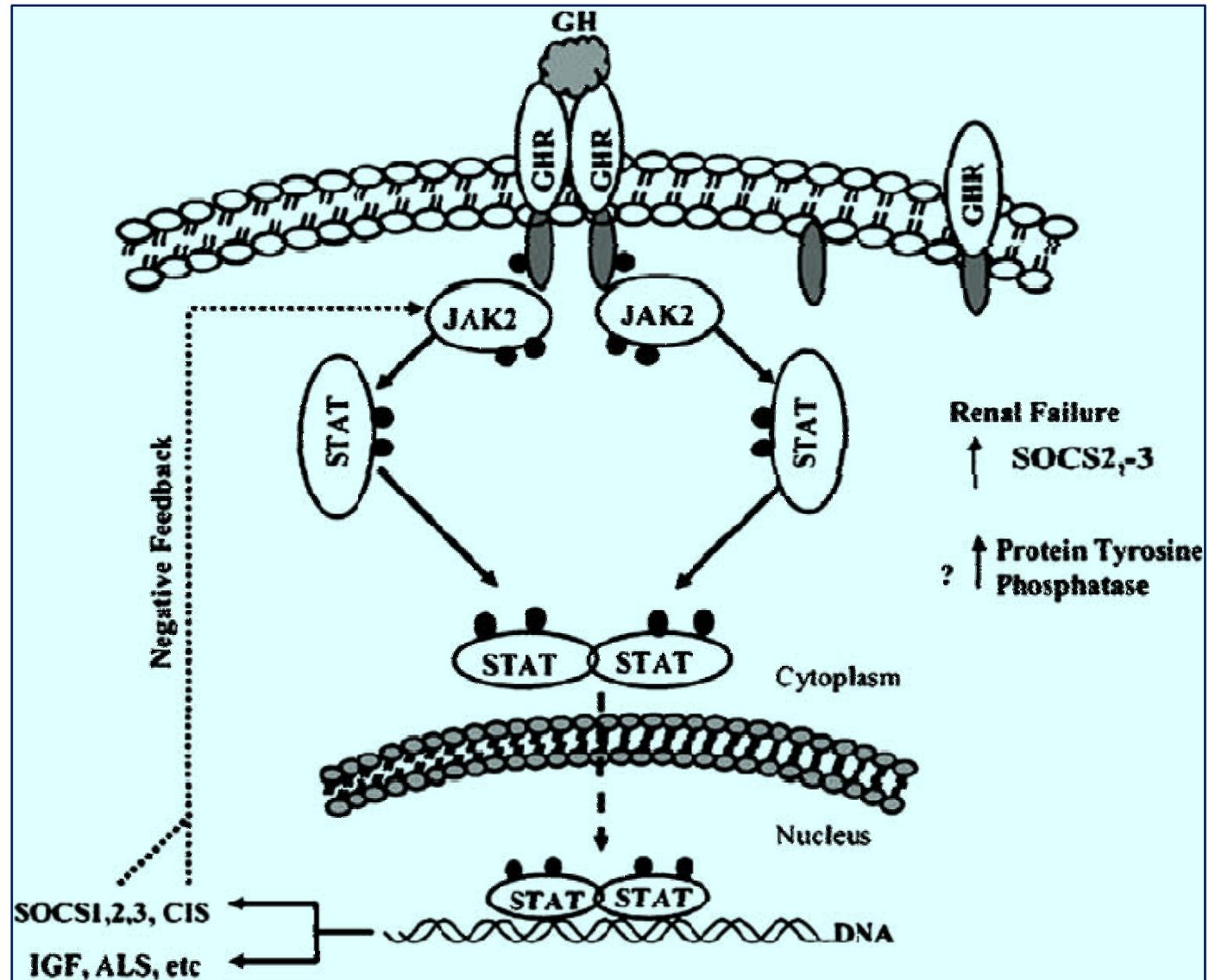


Eje somatotrófico en ERC



Adaptado: Mahan JD, Growth Hormone & IGF Reserch 2006

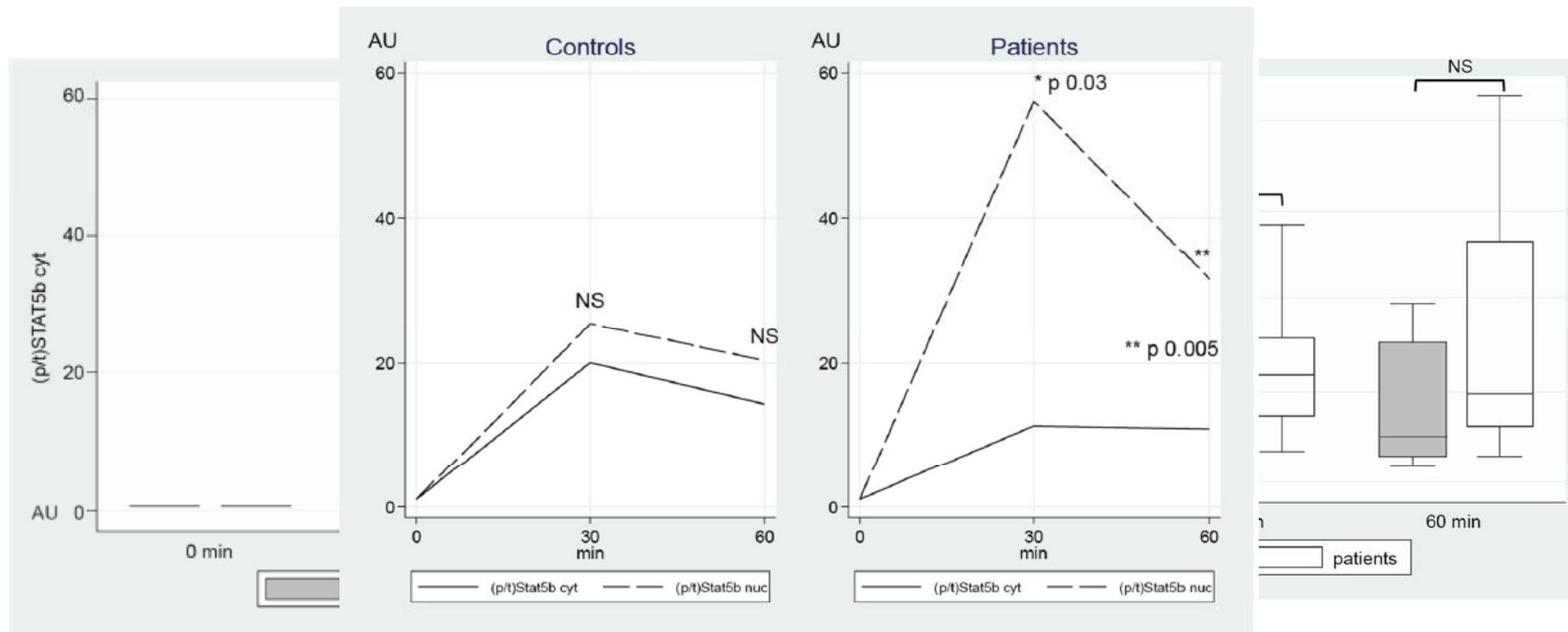
Mecanismo de Acción post-receptor de GH



Growth hormone axis in chronic kidney disease

Impaired phosphorylation of JAK2-STAT5b signaling in fibroblasts from uremic children

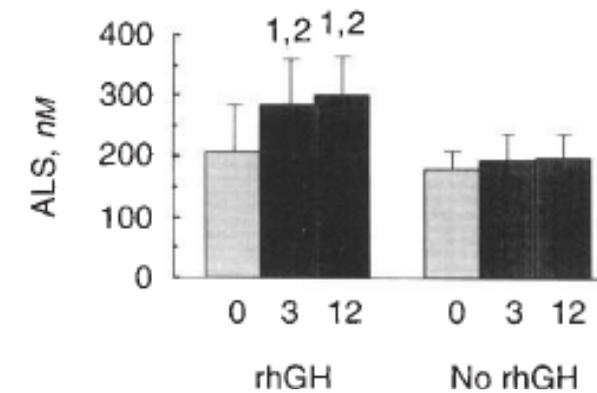
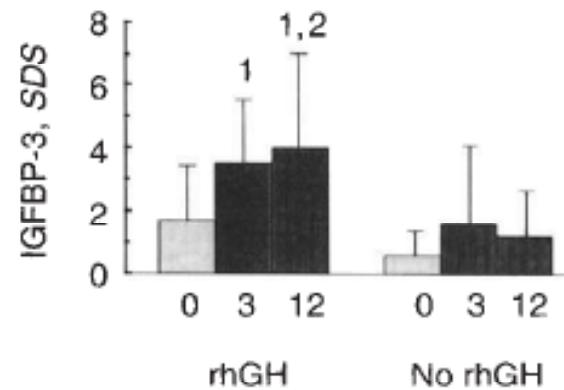
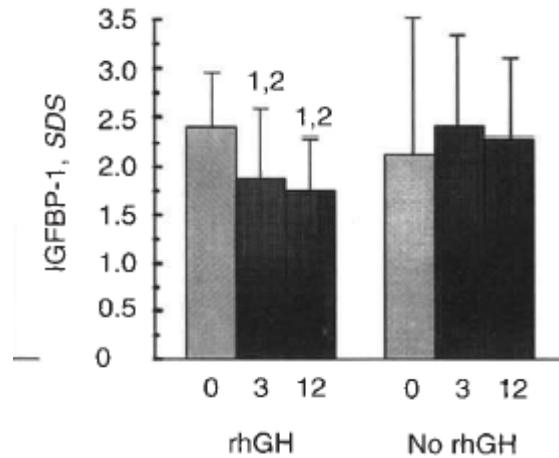
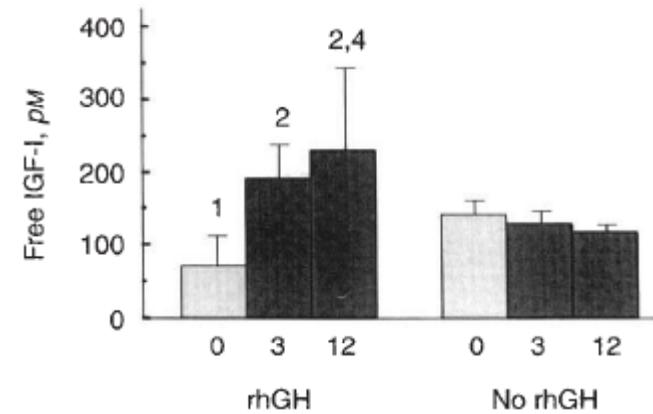
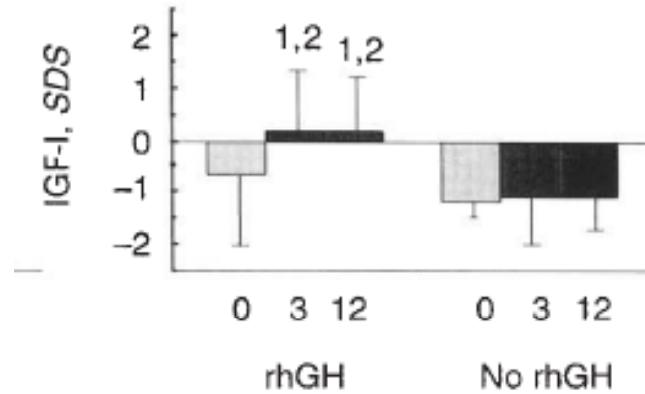
Francisca Ugarte¹ · Carlos Irrazabal¹ · Jun Oh² · Anne Dettmar² ·
María L. Ceballos³ · Angélica Rojo³ · M. José Ibacache³ · Cristián Suazo¹ ·
Mauricio Lozano¹ · Iris Delgado⁴ · Gabriel Cavada¹ · Marta Azocar³ ·
Angela Delucchi³ · Francisco Cano³



(NS: not significant)

(NS: not significant, * p 0,03 , ** p 0,05)

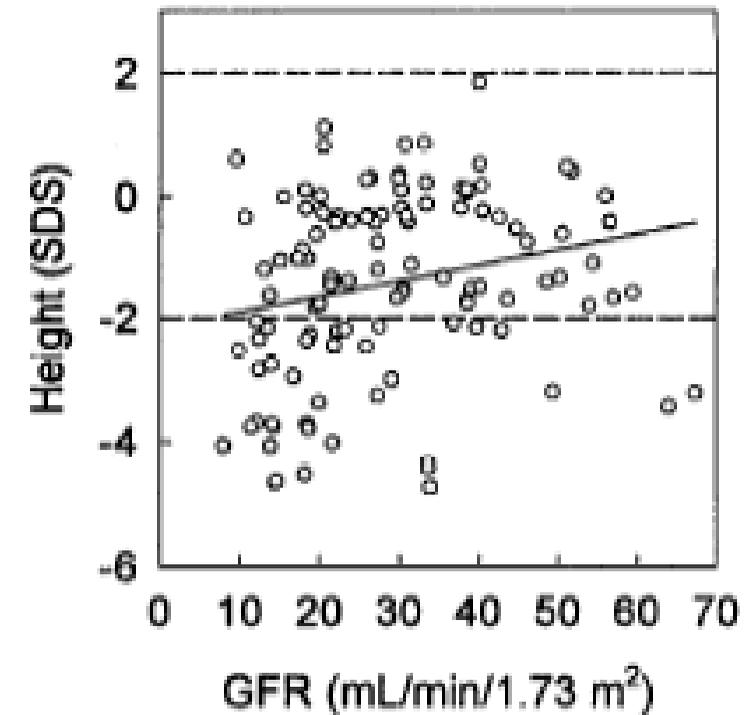
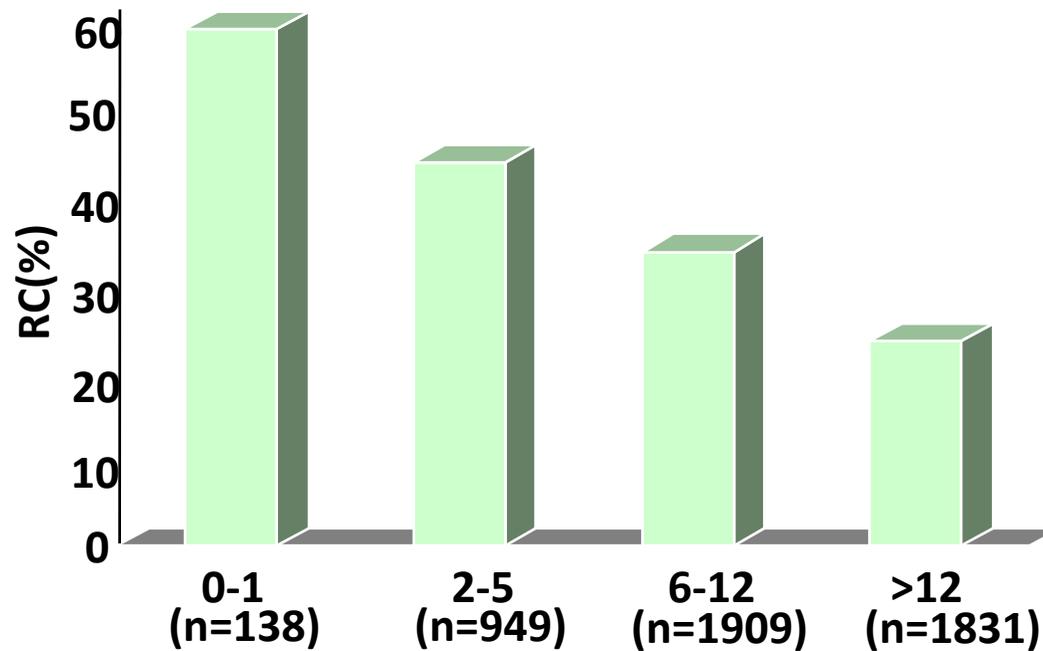
Modificación de IGF1, BP3, ALS en pacientes con ERC tratados con rhGh





**Ha sido el tratamiento
con rhGh un factor
determinante de la
mejoría en la talla
en estos pacientes?**

Factores determinantes no modificables de retardo del crecimiento



Porcentaje de Baja Talla según Edad de Inicio de ERC

(NAPRTCS 2005)

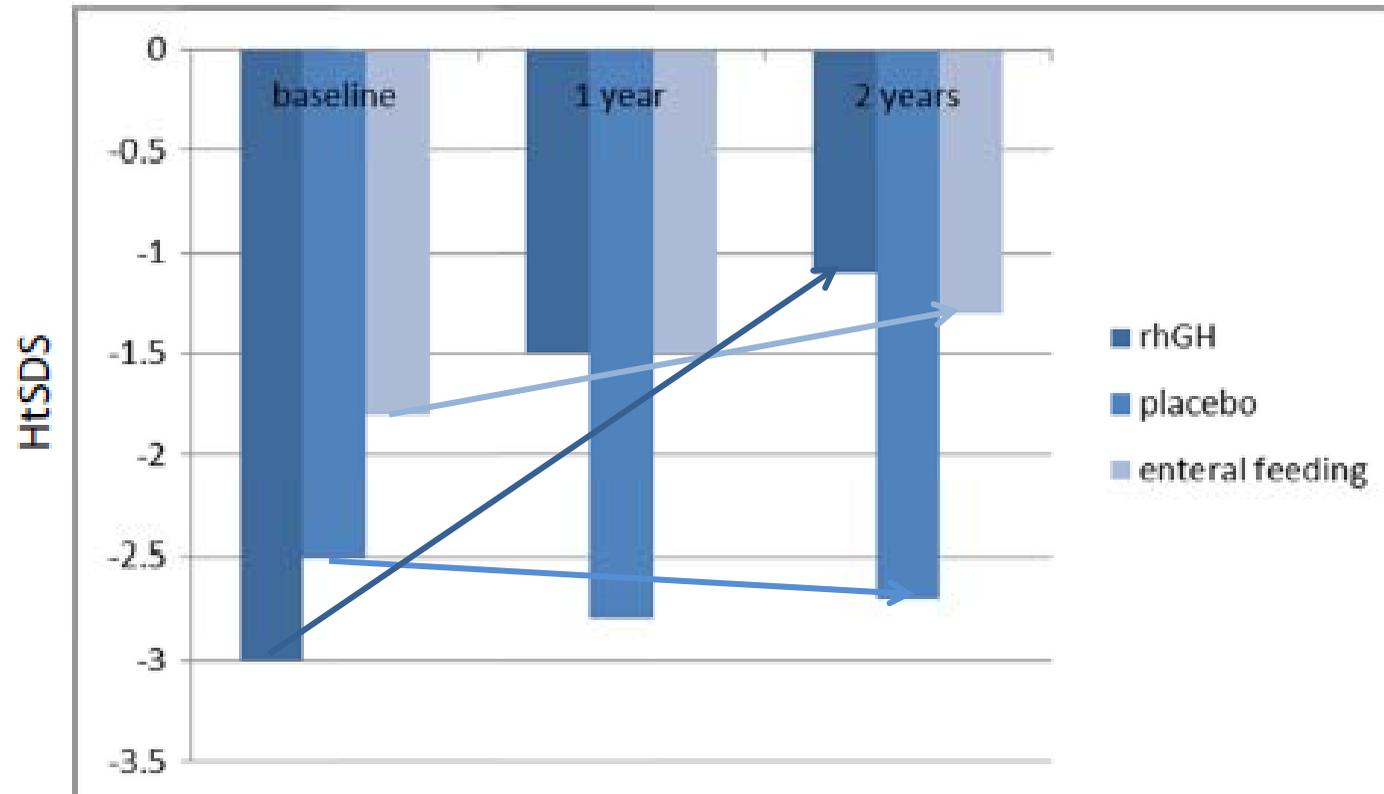
RC: Retardo de Crecimiento

J.C.E.M. Thonshoff y col, 1999

Tratamiento con rhGh en niños con ERC menores de 2 años

	rhGh (n)	C (n)	rhGh FG (ml/min/m ²)	C FG (ml/min/m ²)	rhGh Δ T SDS 1 ^{er} año	C Δ T SDS 1 ^{er} año	rhGh Δ T SDS 2 ^{do} año	C Δ T SDS 2 ^{do} año	p
Santos F Clin J Am Soc Nephrol (2010)	7	7	28	23	+1.4	-0.1	-	-	<0.05
Fine RN Pediatr Nephrol (1995)	19	11	29	23	+1.5	-0.3	+0.4	+0.1	0.025
Mencarelli Pediatr Nephrol (2009)	8	-	17	-	+1.1	-	-	-	-
Maxwell H Arch Dis Child (1996)	12	15	6	20	+0.3	+0.1	+0.8	+0.5	NS

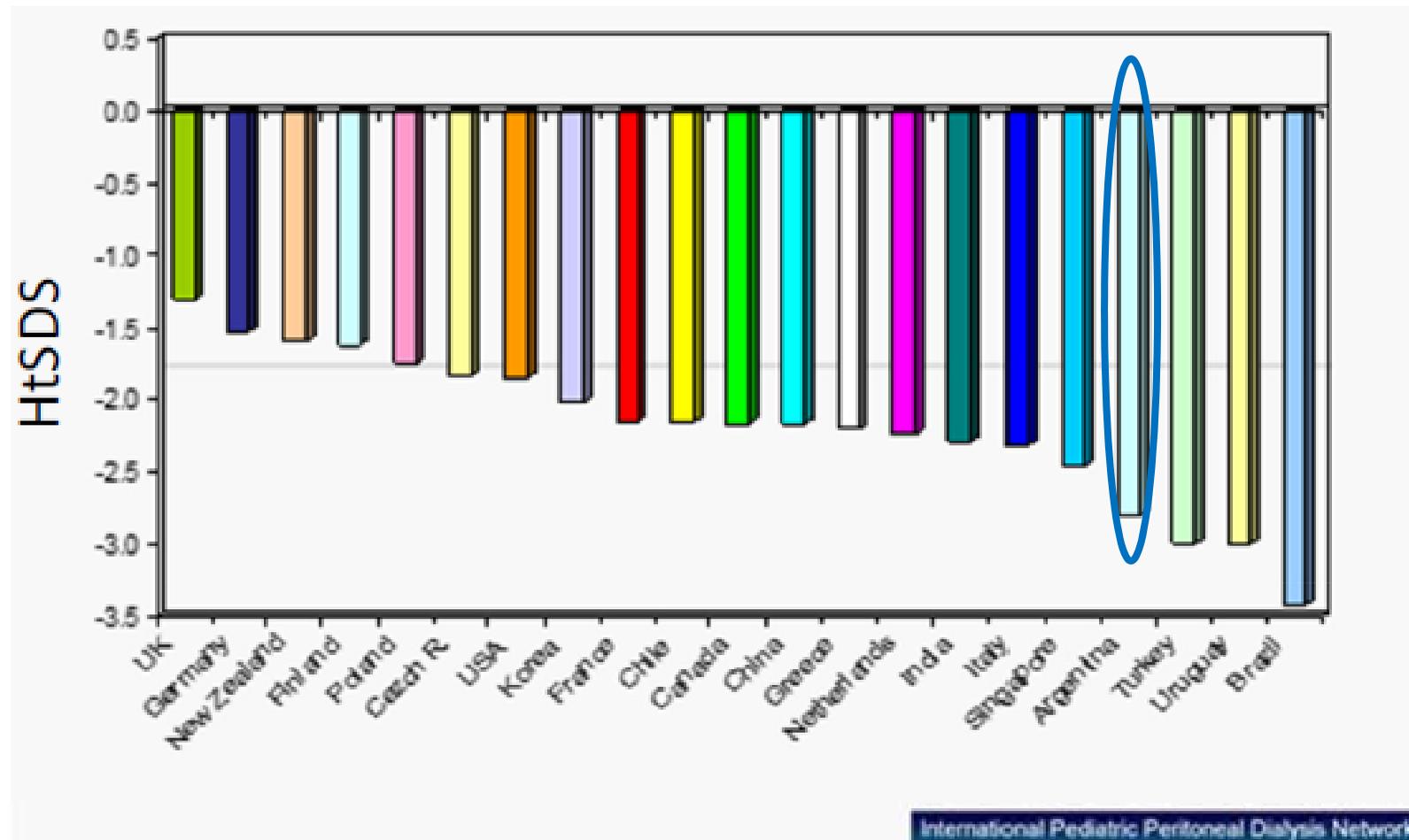
Tratamiento con rhGh en niños con ERC menores de 2 años



Fine RN, *Pediatr Nephrol* (1995)
Mekahli D, *Clin J Am Soc Nephrol* (2010)

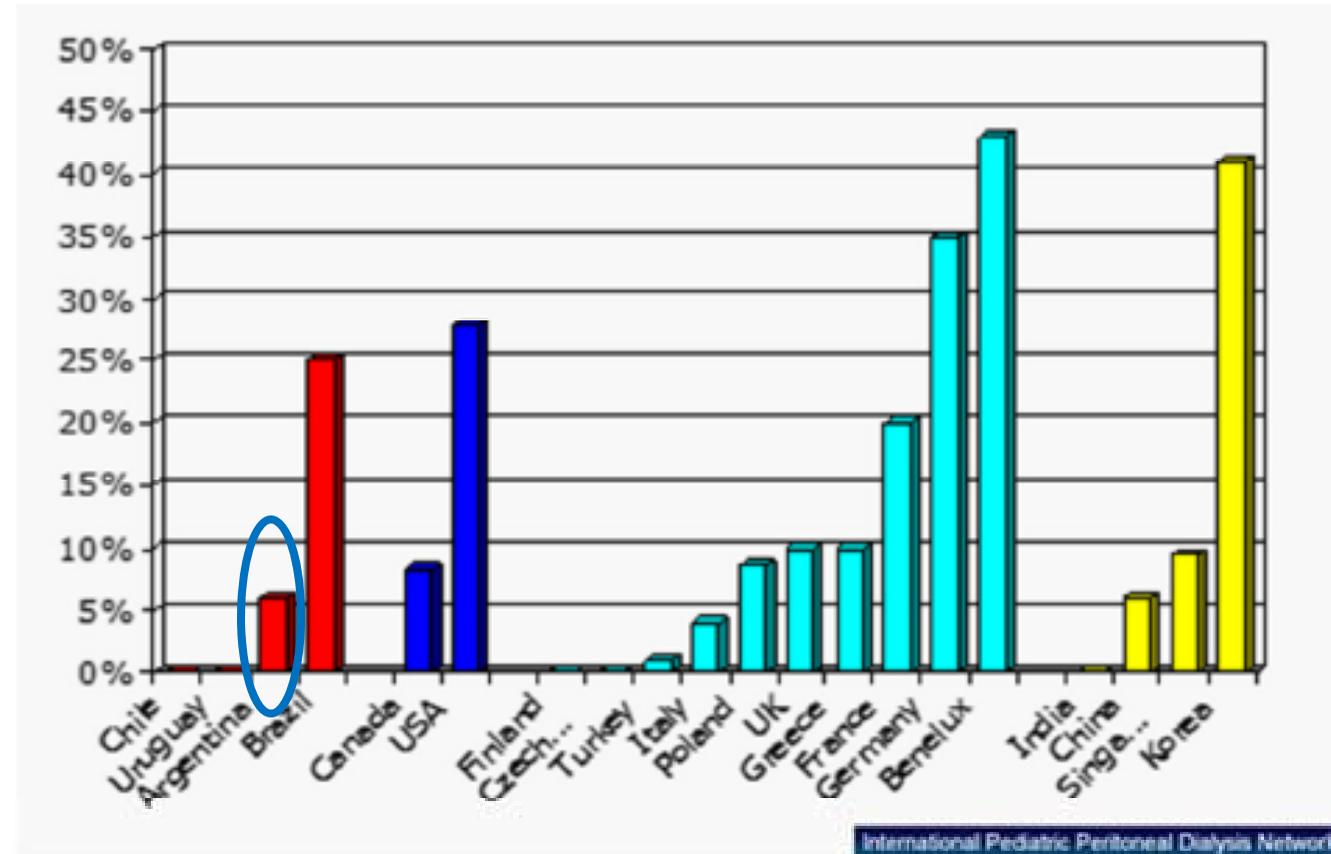
Talla (SDS) en pacientes pediátricos en Diálisis Peritoneal de acuerdo a diferentes países

<http://pedpd.org/>



Uso de rhGh en pacientes pediátricos en Diálisis Peritoneal de acuerdo a diferentes países

<http://pedpd.org/>



Tratamiento con rhGh en niños con ERC y Tx renal mayores de 2 años

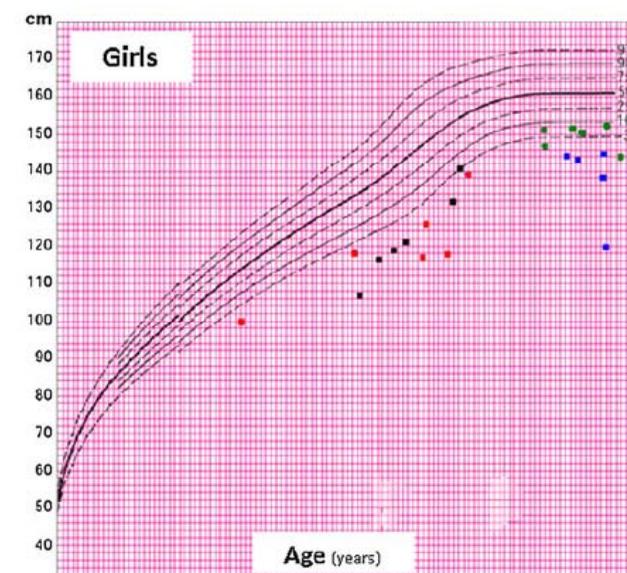
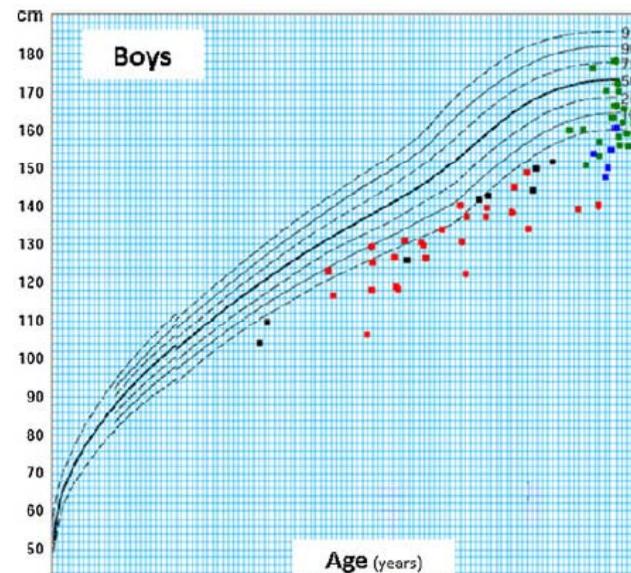
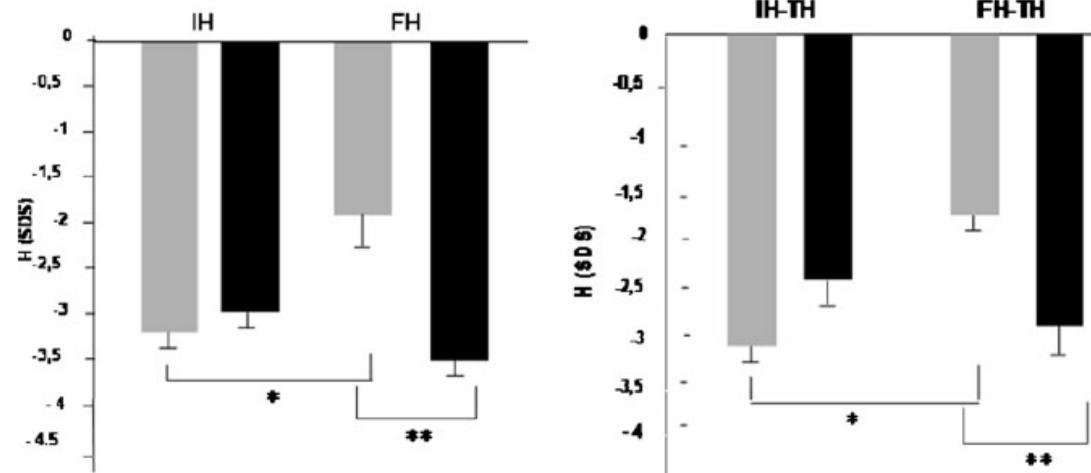
	rhGh (n)	C (n)	rhGh FG (ml/min/m ²)	C FG (ml/min/m ²)	rhGh Δ T SDS 1 ^{er} año	C Δ T SDS 1 ^{er} año	rhGh Δ T SDS 2 ^{do} año	C Δ T SDS 2 ^{do} año
Fine NR J Pediatr (1994)	82	42	28	26	+1	-0.1	+0.3	0
Maxwell H Arch Dis Child (1998)	9	6	51 (Tx pp)	51 (tx)	+0.6	-0.3	+0.4	-
	4	3	48 (Tx p)	48	+0.5	-0.1	+1	-
Broyer m Pediatr Nephrol (1998)	28	30	48 (Tx pp)	48 (tx)	+0.6	+0.1	+0.3	-
	9	11	48 (Tx p)	48	+0.6	-0.1	+0.1	-
Guest G Pediatr Nephrol (1998)	41	44	67	61	+0.3	0		

Talla adulta (TA) en pacientes con ERC y Tx tratados con rhGh

	Journal	Autores	n	TA rhGh	TA Control
German Study Group	N Engl J Med 2000	Haffner y col	38	-1.7 ± 1.2 (M) -1.3 ± 1.6 (F)	-2.1±1.3 -2.1±1.2
Australian-New Zeland Pediatric Asociation	Nephrology 2004	Crompton	39	-2.3	
NAPRTCS	Pediatr Nephrol 2005	Fine y col	71	-1.83 ± 0.14	-2.6 ± 0.05
Registro KIGS	J.C.EM 2000	Nissel y col	240	-2.3 ± 1.3 (M) -2.8 ± 1.4 (F)	
French Society of Pediatric Nephrology	Pediat Nephrol 2008	Berard y col	102	-2.2 ± 1.2	-3.2 ± 1.1
Hospital Garrahan Argentina	Pediat Nephrol 2012	Gil y col	33	-1.88 ± 1.11	-3.48 ± 1.2
Hospital Garrahan Argentina	Pediat Nephrol 2017	Gil y col	15	-1.86 ± 0.76	-2.87 ± 1

Effectiveness of rhGH treatment on final height of renal-transplant recipients in childhood

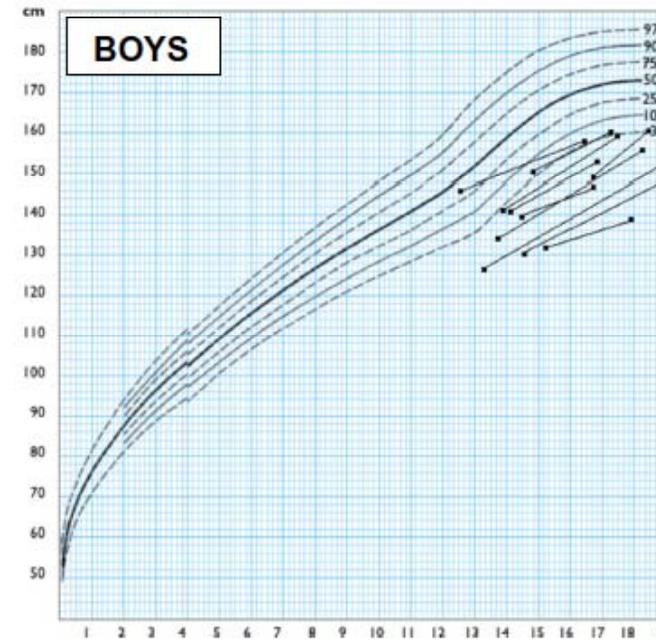
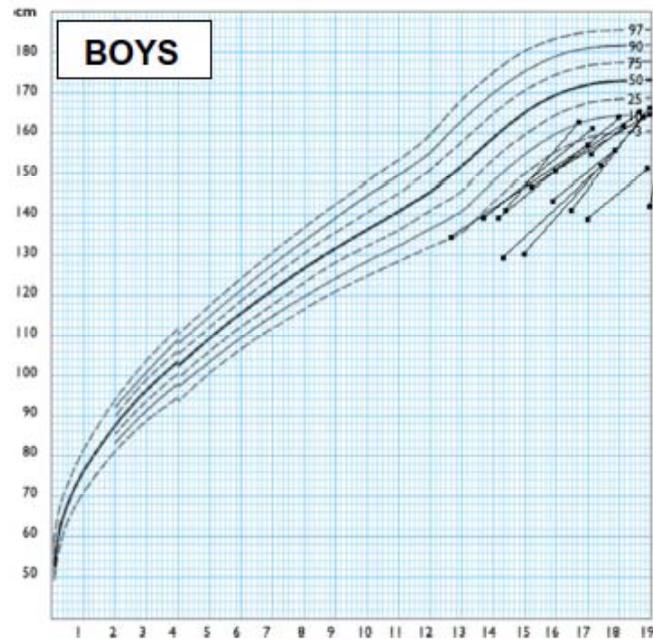
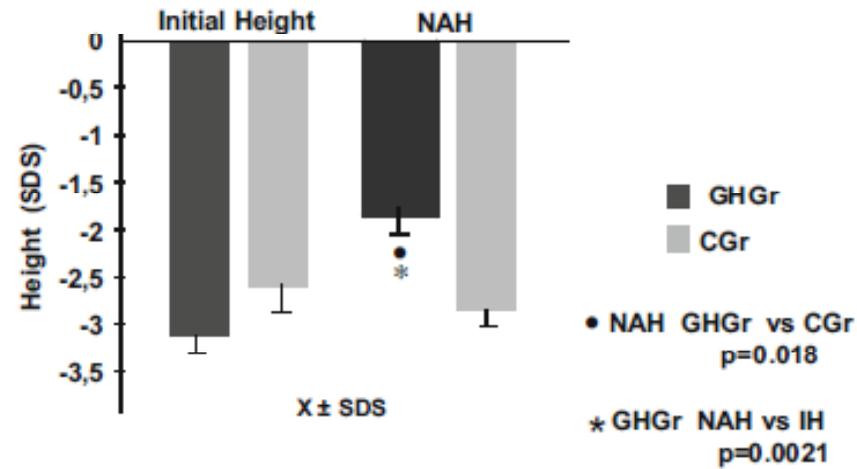
Silvia Gil • Elisa Vaiani • Gabriela Guercio •
Marta Ciaccio • Amalia Turconi • Norma Delgado •
Marco A. Rivarola • Alicia Belgorosky



Near-adult height in male kidney transplant recipients started on growth hormone treatment in late puberty

Silvia Gil¹ • Mariana Aziz¹ • Marta Adragna² • Marta Monteverde² • Alicia Belgorosky^{1,3}

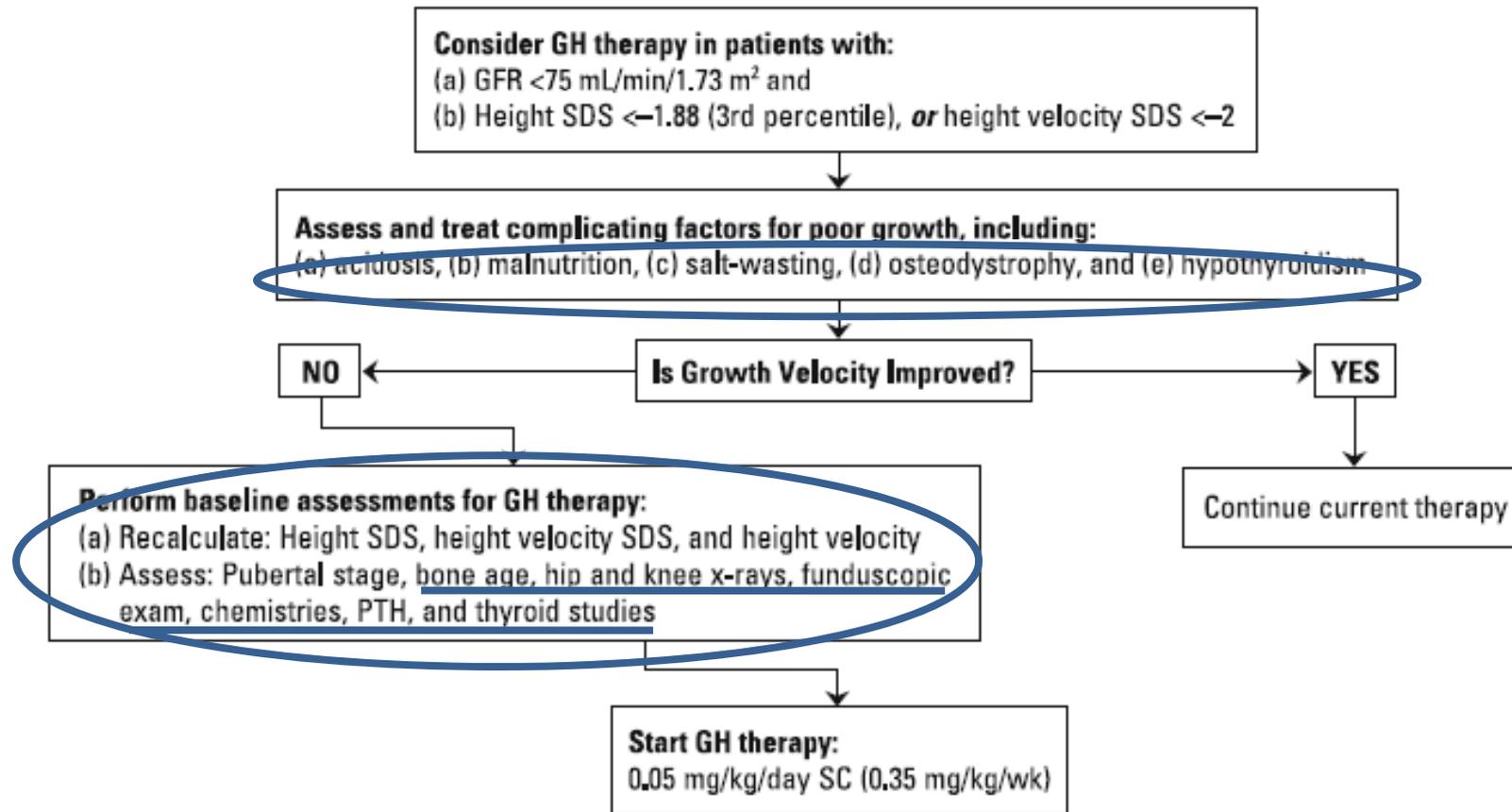
Pediatr Nephrol
August 2017





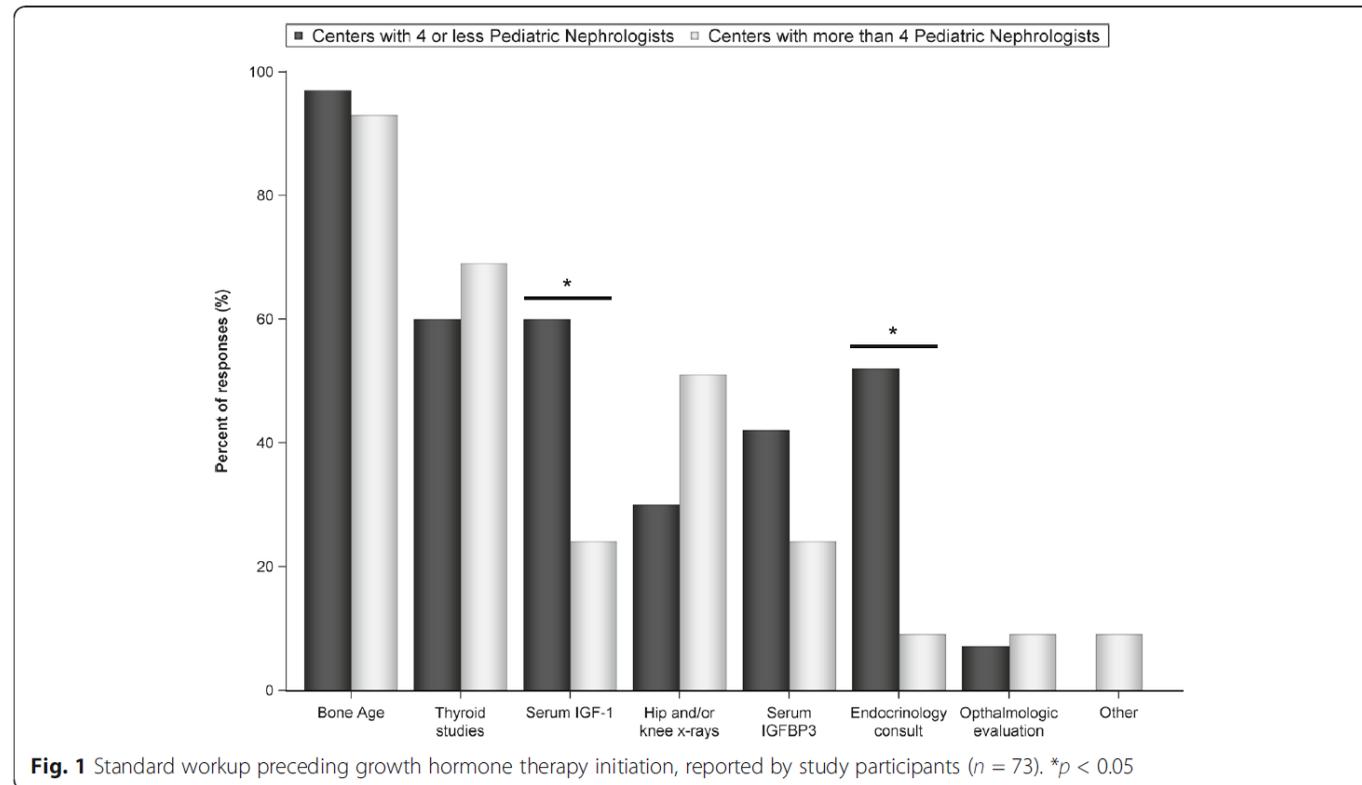
Es el tratamiento con rhGh utilizado como terapéutica habitual y siguiendo las recomendaciones del consenso del 2006 en pacientes con ERC?

Assessment and treatment of short stature in pediatric patients with chronic kidney disease: a consensus statement



Approach to growth hormone therapy in children with chronic kidney disease varies across North America: the Midwest Pediatric Nephrology Consortium report

Oleh M. Akchurin^{1*}, Amy J. Kogon², Juhi Kumar¹, Christine B. Sethna³, Hoda T. Hammad¹, Paul J. Christos¹, John D. Mahan², Larry A. Greenbaum⁴ and Robert Woroniecki⁵



Considerable variations in growth hormone policy and prescription in paediatric end-stage renal disease across European countries—a report from the ESPN/ERA-EDTA registry

M. van Huis¹, M. Bonthuis², E. Sahpazova³, F. Mencarelli⁴, B. Spasojević⁵, G. Reusz⁶, A. Caldas-Afonso⁷, A. Bjerre⁸, S. Baiko⁹, K. Vondrak¹⁰, E.A. Molchanova¹¹, G. Kolvek¹², N. Zaikova¹³, M. Böhm¹⁴, G. Ariceta¹⁵, K.J. Jager², F. Schaefer¹⁶, K.J. van Stralen² and J.W. Groothoff¹

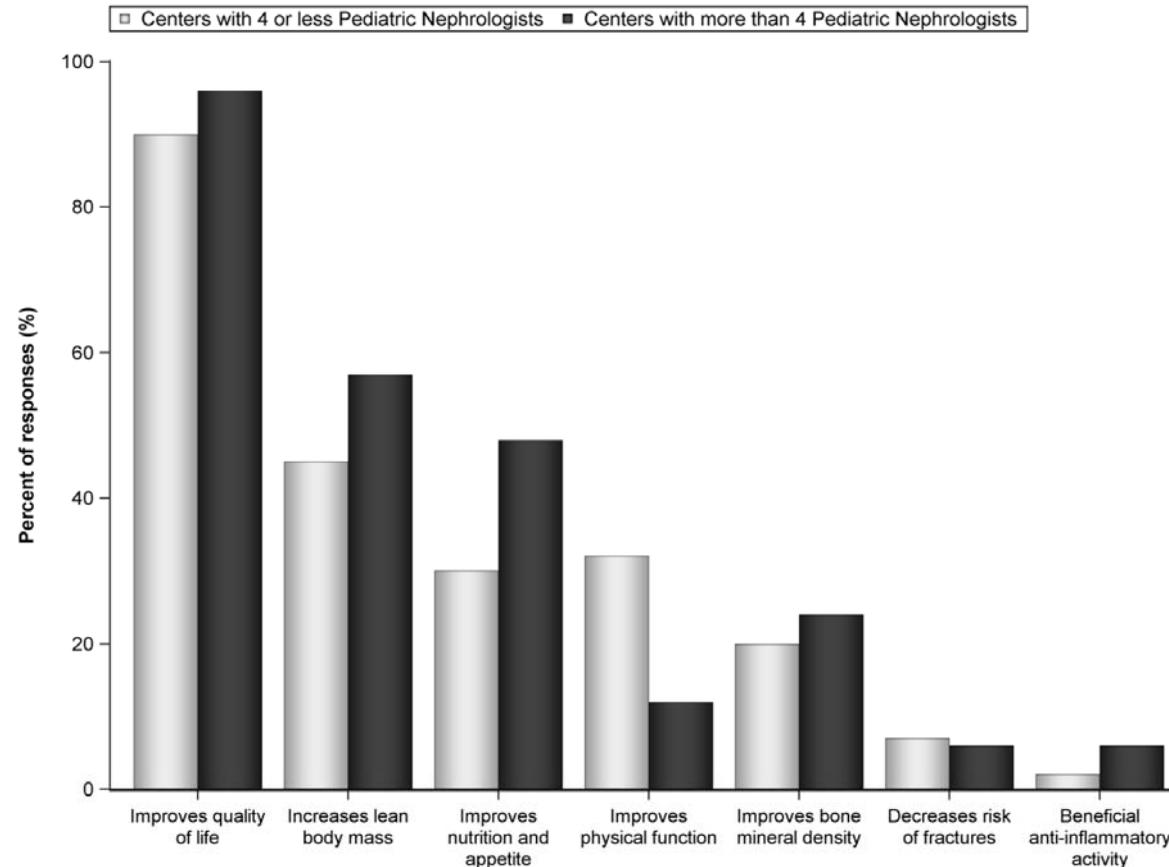
Country	% of rGH use	Eligibility according to short stature (height SDS less than -2)		Eligibility according to national criteria	
		% of patients eligible for rGH	% of eligible patients receiving rGH	% of patients eligible for rGH	% of eligible patients receiving rGH
Belgium	19.9	51.9	29.3	38.9	22.8
Czech Republic	7.7	30.7	10.0	35.7	8.3
Estonia	0.0	20.0	0.0	38.9	0.0
Greece	6.5	48.4	13.3	48.7	11.1
Lithuania ^a	2.1	57.3	2.8	50.6	8.3
The Netherlands	4.0	25.6	6.0	28.8	10.4
Portugal	0.0	34.3	0.0	26.5	3.8
Serbia	4.6	40.8	9.6	35.4	9.5
Slovenia	0.0	53.6	0.0	46.5	0.0
Spain	8.3	29.4	13.7	39.8	9.2
United Kingdom	3.9	45.4	6.6	47.5	5.3
Overall	5.5	38.9	8.9	42.3	7.6

^aAlthough rGH is not reimbursed in Lithuania, a limited number of patients might receive reimbursement from a patient fund and are actually treated with rGH.

ALTHOUGH rGH IS NOT REIMBURSED IN LITHUANIA, A LIMITED NUMBER OF PATIENTS MIGHT RECEIVE REIMBURSEMENT FROM A PATIENT FUND AND ARE ACTUALLY TREATED WITH rGH.

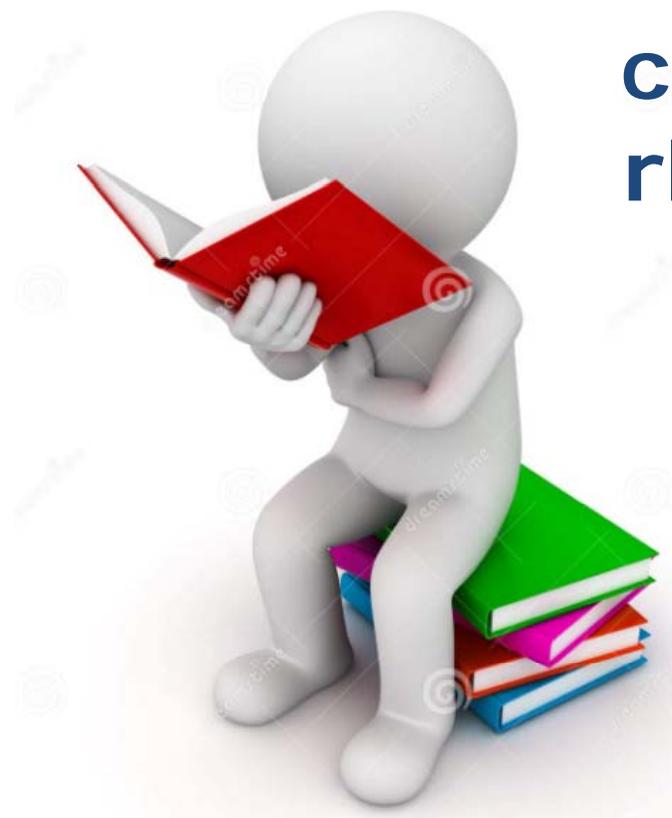
Approach to growth hormone therapy in children with chronic kidney disease varies across North America: the Midwest Pediatric Nephrology Consortium report

Oleh M. Akchurin^{1*}, Amy J. Kogon², Juhi Kumar¹, Christine B. Sethna³, Hoda T. Hammad¹, Paul J. Christos¹, John D. Mahan², Larry A. Greenbaum⁴ and Robert Woroniecki⁵



3 Perceived benefits of growth hormone therapy in children with chronic kidney disease. Total number of participants $n = 73$

**Cual es nuestra experiencia
con el tratamiento con
rhGH en pacientes con
ERC ?**



Experiencia en Hospital de Pediatría J.P.Garrahan

- **Total de pacientes: 1054**
- **Total de paciente tratados con rhGH: 166**
- **Tratamiento completo: 90 pacientes**

Talla inicial: -2.67 ± 0.96 SDS (rango: -4.7 a -0.94)

Talla Final: -1.75 ± 0.84 SDS (rango: -3.3 a 0.84)

- **Tratamiento incompleto: 76 pacientes**
 - a) abandono y/o mala compliance: n:23 (n: 4 pacientes seguimiento otros centros)
 - b) Falta medicación: n: 17
 - c) Eventos durante el tratamiento: 36



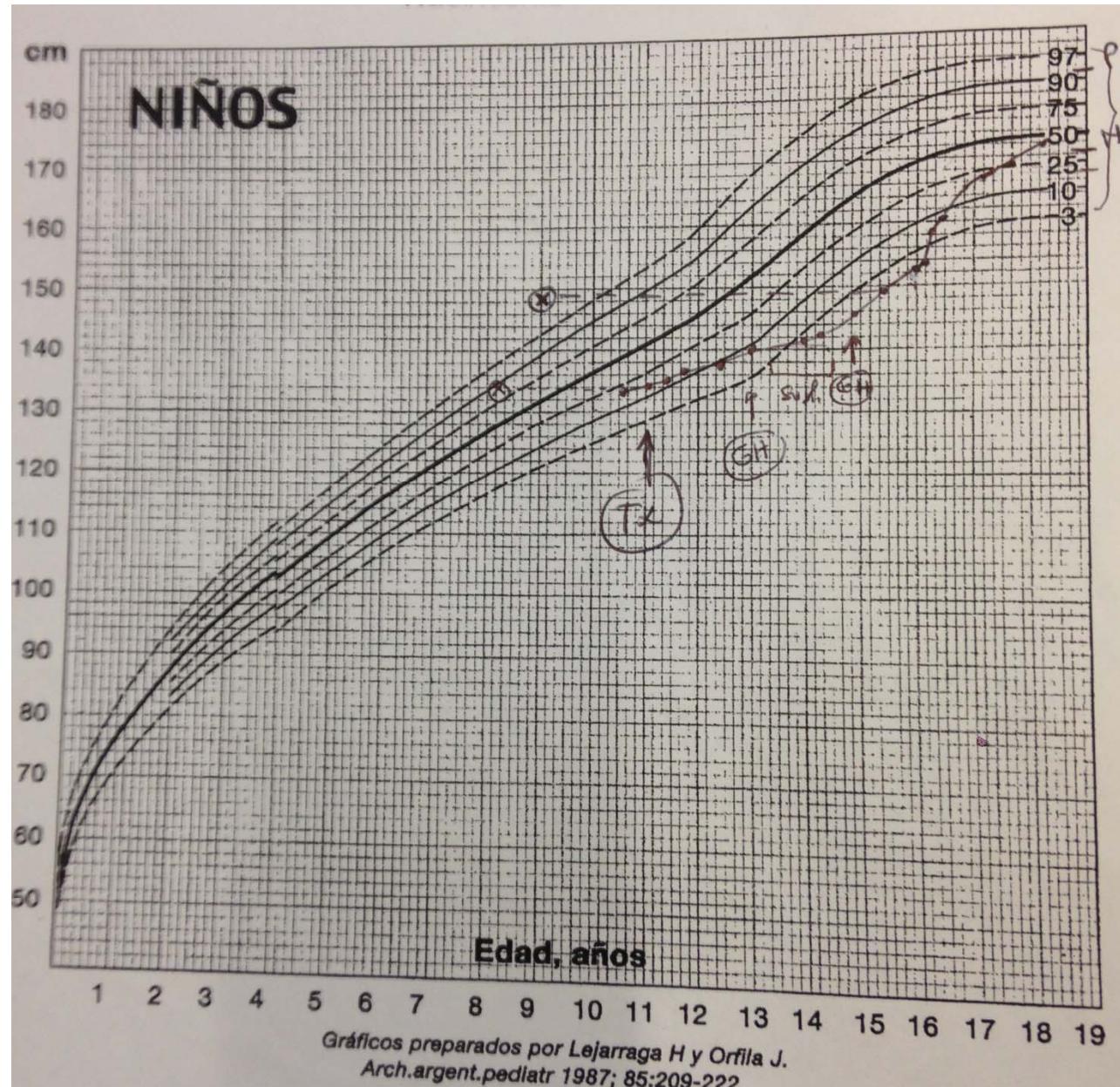
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Experiencia en Hospital de Pediatría J.P.Garrahan

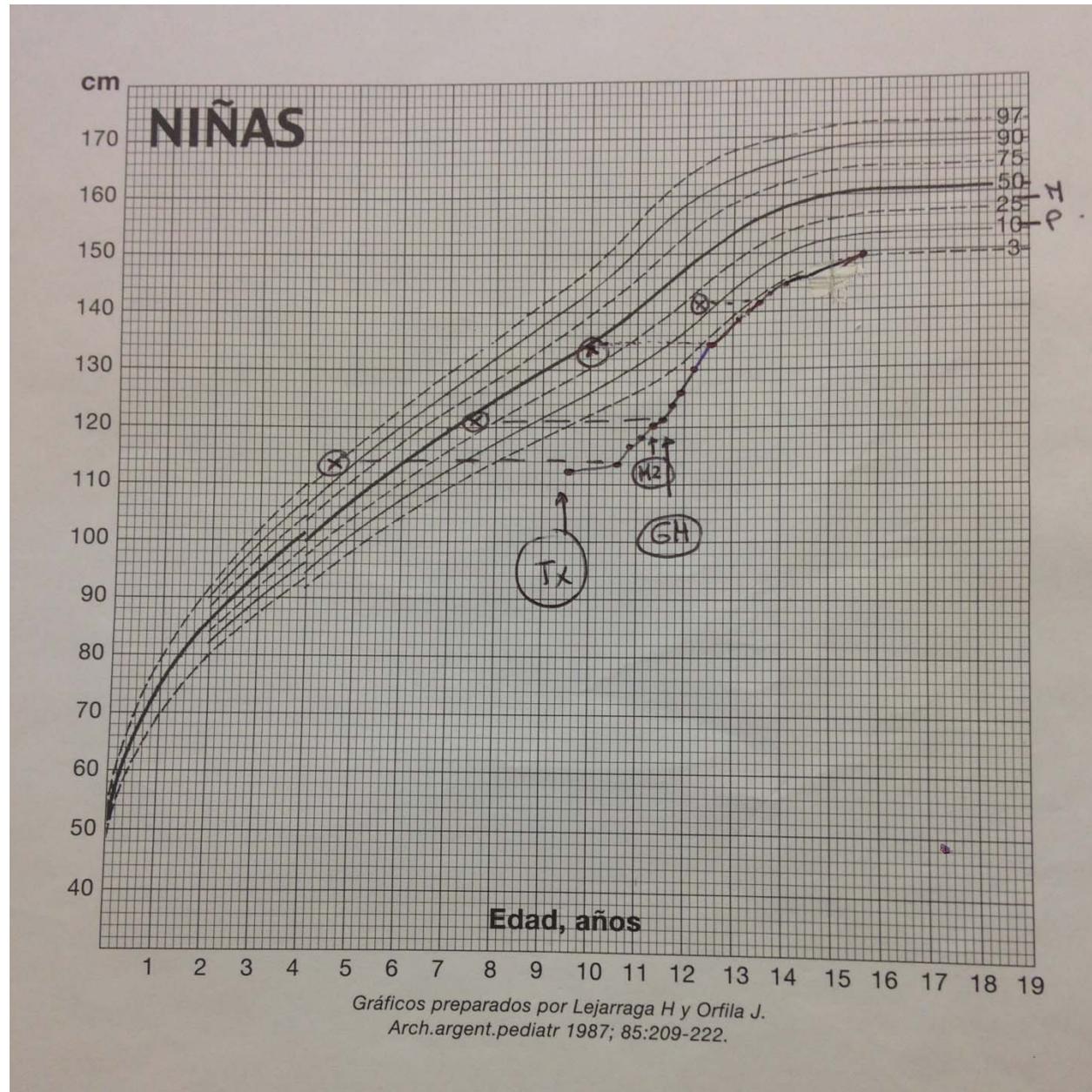
Eventos durante el tratamiento con rhGh	n (pacientes)
Trasplante renal	13
Alteración Metabolismo Hidrocarbonado	7 (4.21%)
Enfermedad Linfoproliferativa	4 (2.4%)
Rechazos	4 (2.4%)
Hipertensión endocraneana benigna	3 (1.8%)
Epifisiolísis	1 (0.6%)
DBT	1 (0.6%)
Otros	3 (1.8%)



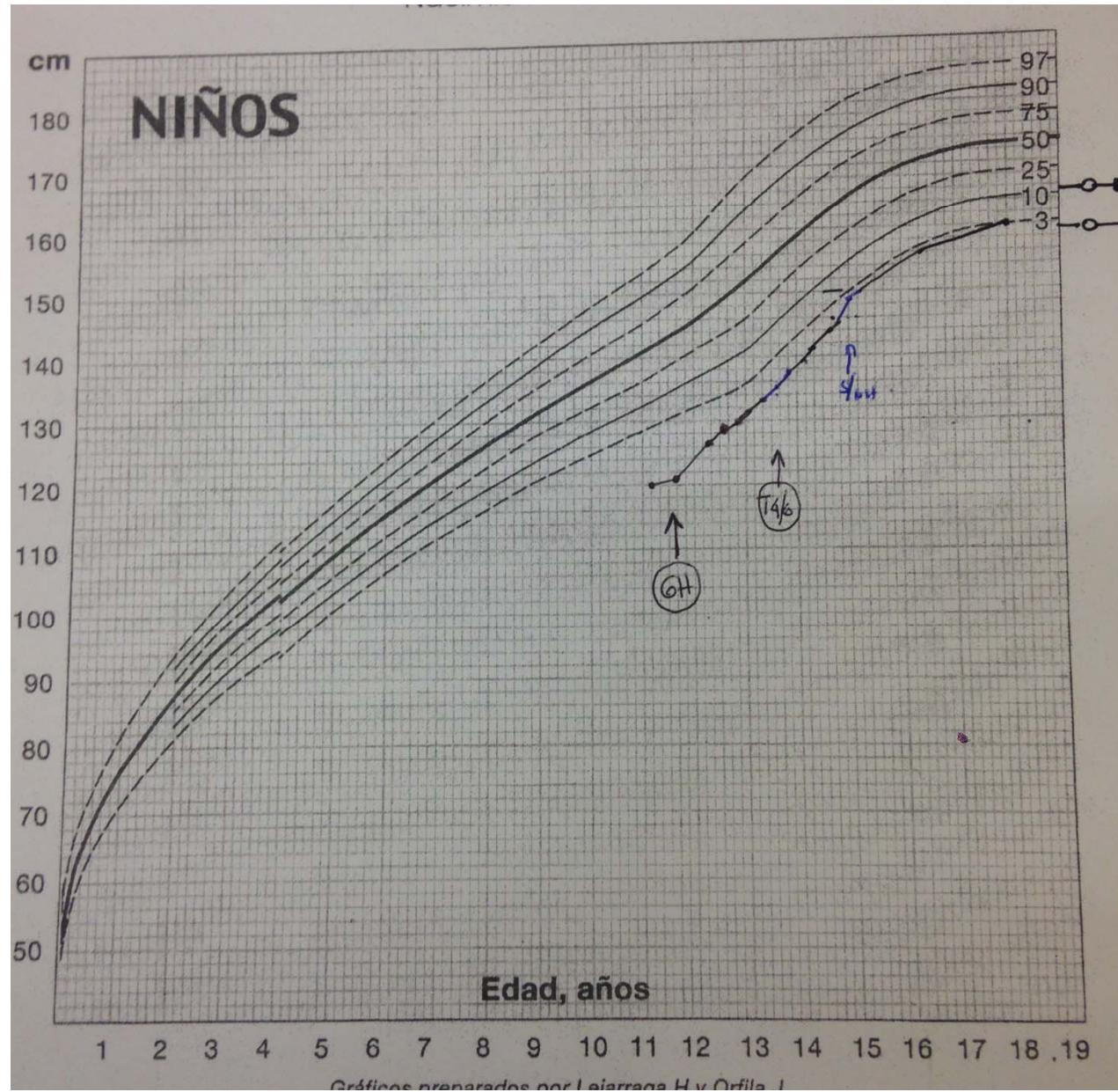
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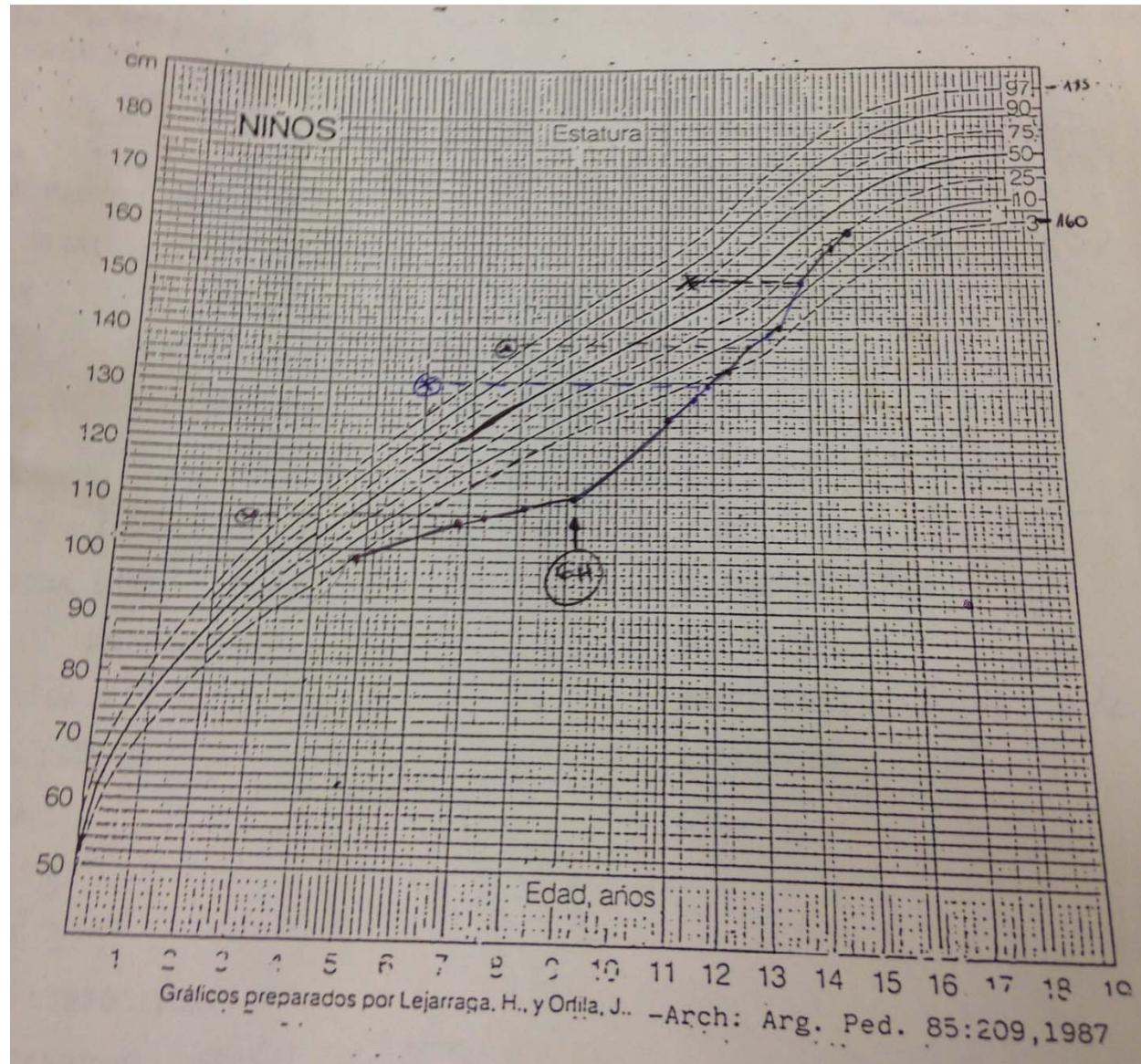
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Conclusión

**Evidencias científicas
Experiencia**



**Mejor calidad de vida
Disminución morbilidad**

**Aplicación al paciente
Desarrollar estrategias de evaluación y seguimiento
Desarrollar guías y concesos médicos
Ampliar la evidencia científica**

Conclusión



Muchas Gracias !



Por un niño sano
en un mundo mejor



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