Invierte en resultados a largo plazo

Advagraf y guías COMMIT

Manuel Rodríguez-Perálvarez

Hospital Universitario Reina Sofía de Córdoba

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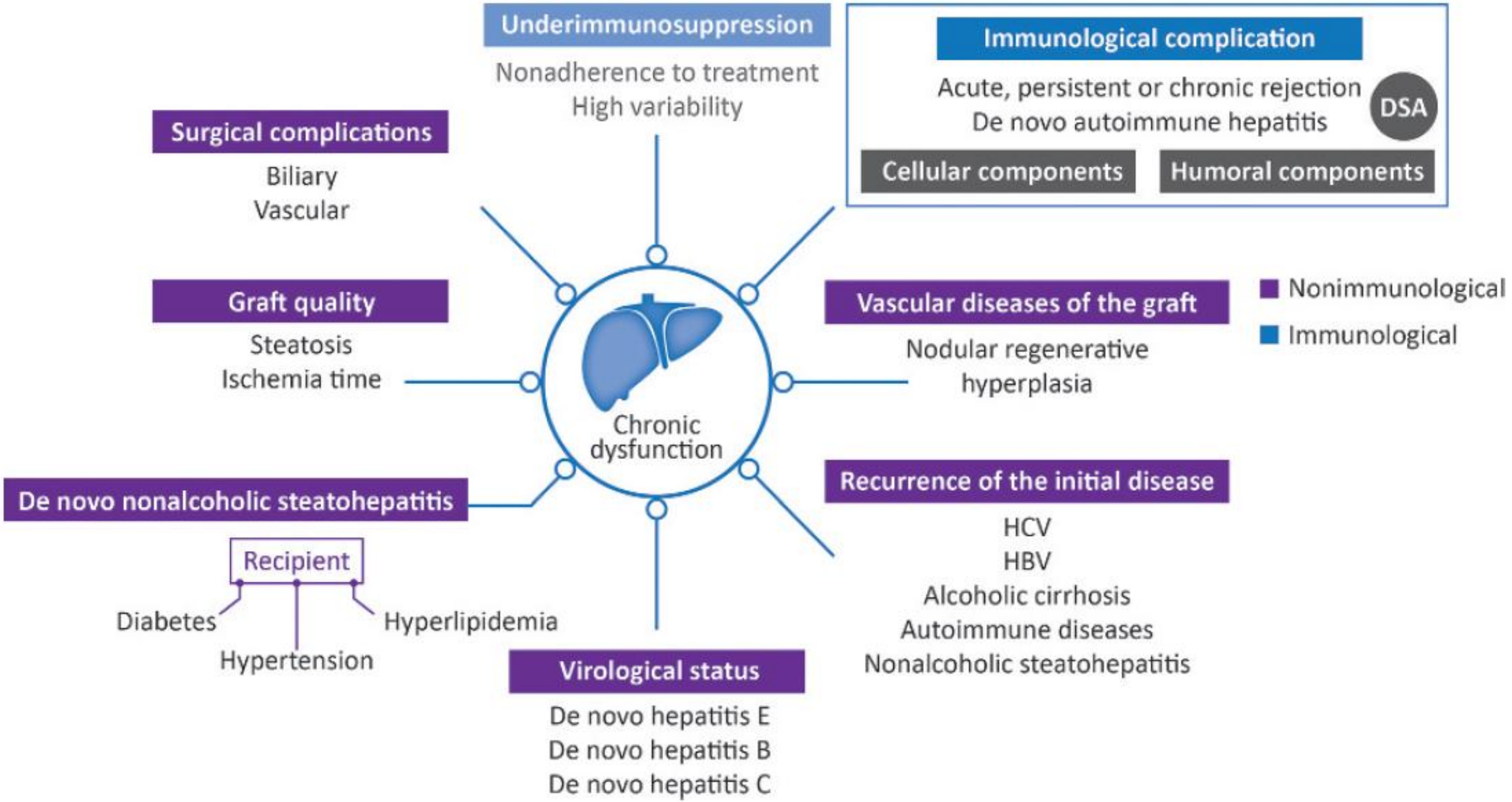
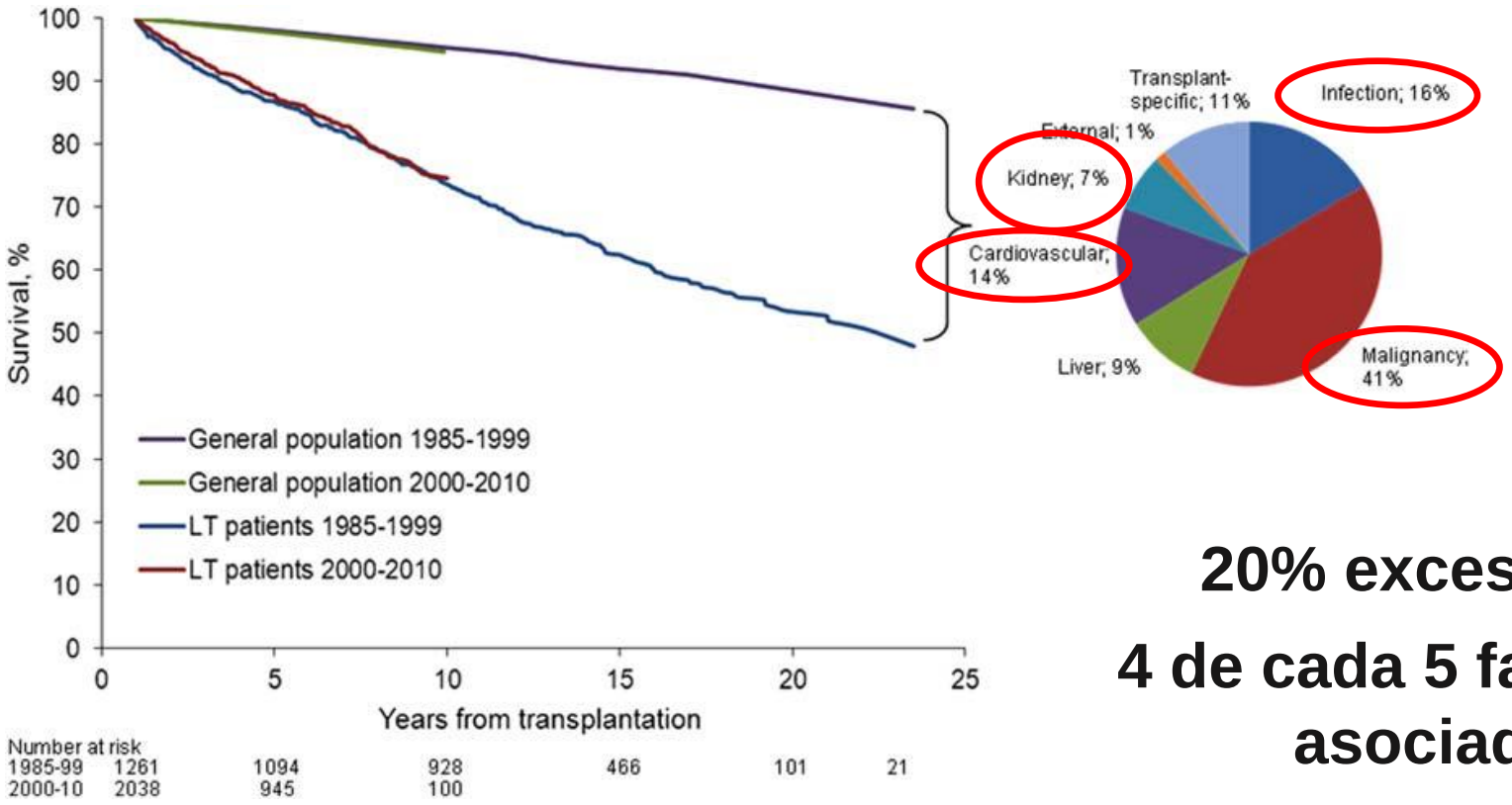


Neuberger J, et al. Transplantation 2017;101(4S): S1–S56.

Incremento de mortalidad en trasplante hepático

Differences in Long-Term Survival Among Liver Transplant Recipients and the General Population: A Population-Based Nordic Study

HEPATOLOGY
Official Journal of the American Association for the Study of Liver Diseases



20% exceso de mortalidad a 10 años

4 de cada 5 fallecimientos potencialmente asociados a inmunosupresión

Aberg et al. Hepatology 2015 Feb;61(2):668-77

Manejo del tratamiento inmunosupresor ¿Podemos mejorar?

1. Escoger la combinación adecuada de inmunosupresores
2. Evitar el exceso de inmunosupresión
3. Evitar la infra-inmunosupresión y el desarrollo de DSAs
4. Asegurar una correcta adherencia y reducir la variabilidad

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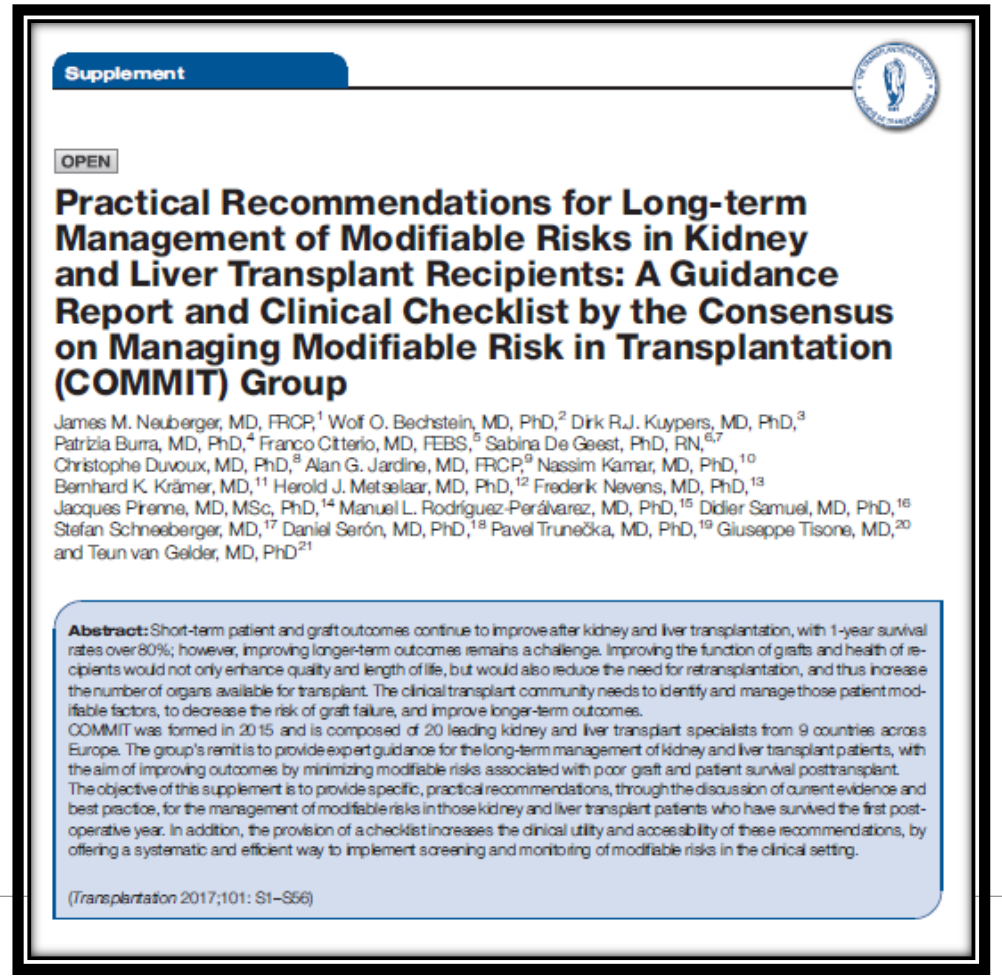
Transformando la evidencia científica en recomendaciones y checklists



Supplement

OPEN

Practical Recommendations for Long-term Management of Modifiable Risks in Kidney and Liver Transplant Recipients: A Guidance Report and Clinical Checklist by the Consensus on Managing Modifiable Risk in Transplantation (COMMIT) Group

James M. Neuberger, MD, FRCP,[1] Wolf O. Bechstein, MD, PhD,[2] Dirk R.J. Kuypers, MD, PhD,[3] Patrizia Burra, MD, PhD,[4] Franco Citterio, MD, FEBS,[5] Sabina De Geest, PhD, RN,[6,7] Christophe Duvoux, MD, PhD,[8] Alan G. Jardine, MD, FRCP,[9] Nassim Kamar, MD, PhD,[10] Bernhard K. Krämer, MD,[11] Herold J. Metselaar, MD, PhD,[12] Frederik Nevens, MD, PhD,[13] Jacques Pirenne, MD, MSc, PhD,[14] Manuel L. Rodríguez-Perálvarez, MD, PhD,[15] Didier Samuel, MD, PhD,[16] Stefan Schneeberger, MD,[17] Daniel Serón, MD, PhD,[18] Pavel Trunečka, MD, PhD,[19] Giuseppe Tisone, MD,[20] and Teun van Gelder, MD, PhD[21]

Abstract: Short-term patient and graft outcomes continue to improve after kidney and liver transplantation, with 1-year survival rates over 80%; however, improving longer-term outcomes remains a challenge. Improving the function of grafts and health of recipients would not only enhance quality and length of life, but would also reduce the need for retransplantation, and thus increase the number of organs available for transplant. The clinical transplant community needs to identify and manage those patient modifiable factors, to decrease the risk of graft failure, and improve longer-term outcomes.
COMMIT was formed in 2015 and is composed of 20 leading kidney and liver transplant specialists from 9 countries across Europe. The group's remit is to provide expert guidance for the long-term management of kidney and liver transplant patients, with the aim of improving outcomes by minimizing modifiable risks associated with poor graft and patient survival posttransplant.
The objective of this supplement is to provide specific, practical recommendations, through the discussion of current evidence and best practice, for the management of modifiable risks in those kidney and liver transplant patients who have survived the first postoperative year. In addition, the provision of a checklist increases the clinical utility and accessibility of these recommendations, by offering a systematic and efficient way to implement screening and monitoring of modifiable risks in the clinical setting.

(*Transplantation* 2017;101: S1–S56)

commit

2. CARDIO- AND CEREBRO-VASCULAR AND METABOLIC COMPLICATIONS

REVIEW IMMUNOSUPPRESSION

commit CONSENSUS ON MANAGING MODIFIABLE RISK IN TRANSPLANTATION

POST-LIVER TRANSPLANT PATIENT CARE CHECKLIST

This checklist is intended to help the clinician in the management of modifiable risk factors for graft loss in liver transplant patients over 1 year post-transplant and should be used in conjunction with local guidelines.

Patient name:

Patient ID: DOB:

Gender:

Indication for transplant:

Date of transplant:

Type of transplant: (e.g. whole, split, donation after cardiac death, donation after brain death)

Other relevant comorbidities:

CLINICAL VARIABLES

(This checklist is intended to be used in addition to the biochemistry and serology lab report for the patient)

BP: / mmHg

HR: /min Weight: kg

Height: m BMI: kg/m²

Current smoker: Yes No Number per day:

Average alcohol intake: units/week

Medication:

Immunosuppressant doses and levels:

Tacrolimus Cyclosporine Sirolimus

Everolimus Mycophenolate Corticosteroids

Azathioprine

Drug	Level	Corresponding daily dose
	ng/mL	/day
	ng/mL	/day
	ng/mL	/day

Other:

BEFORE YOU SEE THE PATIENT

- Review the patient's immunosuppressive regimen, concomitant medication and over-the-counter medications
- Review immunosuppression serum trough levels over the previous year and identify any significant variation
- Review BMI, BP, fasting plasma glucose and renal function
- Document any known risk factors for non-adherence:
- Each year, consider immunisation status, cardiovascular status, cancer surveillance

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Neuberger J, et al. Transplantation 2017;101(4S): S1–S56.

Manejo del tratamiento inmunosupresor ¿Podemos mejorar?

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4. Asegurar una correcta adherencia y reducir la variabilidad

Guías clínicas y checklists

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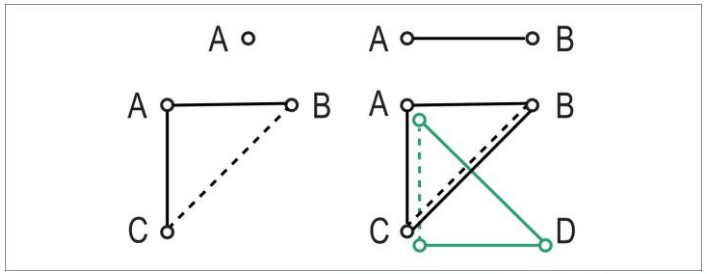
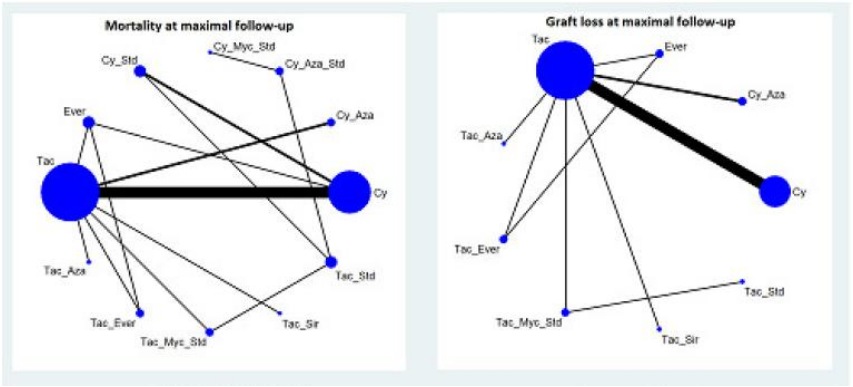
1. Escoger el protocolo adecuado

Maintenance immunosuppression for adults undergoing liver transplantation: a network meta-analysis (Review)

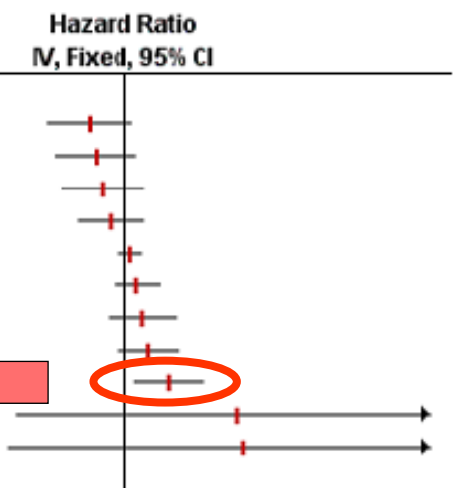
Cochrane Library

Cochrane Database of Systematic Reviews





Study or Subgroup	log[Hazard Ratio]	SE	Hazard Ratio IV, Fixed, 95% CI
1.1.1 Network meta-analysis (fixed-effect model)			
Tac_Aza vs Tac	-0.7823	0.479949	0.46 [0.18, 1.17]
Tac_Myc_Std vs Tac	-0.6684	0.455051	0.51 [0.21, 1.25]
Tac_Std vs Tac	-0.5149	0.469311	0.60 [0.24, 1.50]
Cy_Std vsTac	-0.3356	0.371327	0.71 [0.35, 1.48]
Cy vs Tac	0.1094	0.127985	1.12 [0.87, 1.43]
Cy_Aza vs Tac	0.26	0.25648	1.30 [0.78, 2.14]
Tac_Ever vs Tac	0.3995	0.37977	1.49 [0.71, 3.14]
Ever vs Tac	0.531	0.331554	1.70 [0.89, 3.26]
Tac_Sir vs Tac	0.997	0.394311	2.71 [1.25, 5.87]
Cy_Aza_Std vs Tac	2.543	2.565816	12.72 [0.08, 1942.84]
Cy_Myc_Std vs Tac	2.697	2.723469	14.84 [0.07, 3086.83]



Los regímenes basados en sirolimus se asocian a mayor mortalidad

Rodríguez-Perálvarez et al. Cochrane Database Syst Rev 2017 Mar 31;3:CD011639.

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1. Escoger el protocolo adecuado

Maintenance immunosuppression for adults undergoing liver transplantation: a network meta-analysis (Review)

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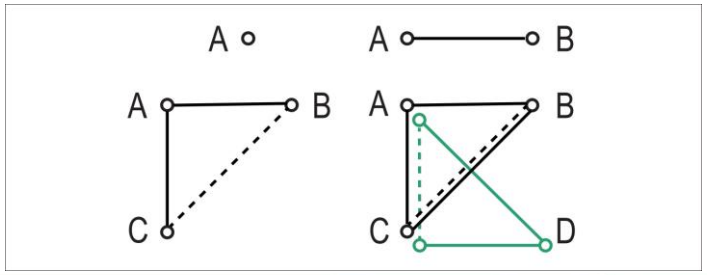
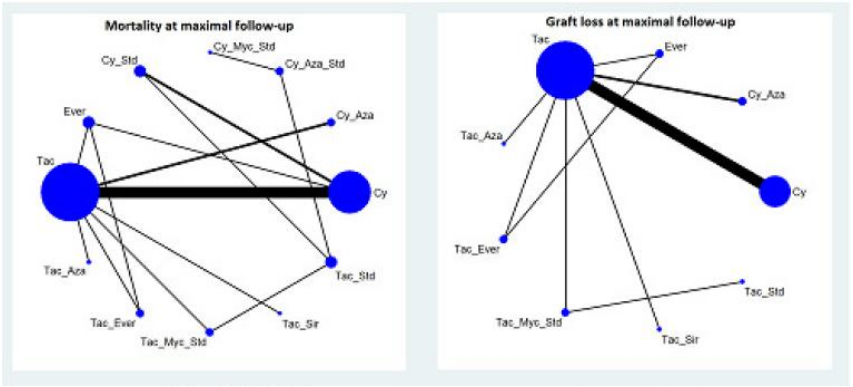
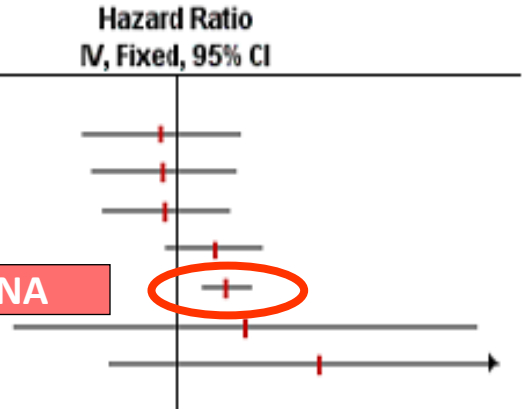




Study or Subgroup	log[Hazard Ratio]	SE	Hazard Ratio IV, Fixed, 95% CI
1.6.1 Network meta-analysis (fixed-effect model)			
Tac_Std vs Tac	-0.3717	0.861735	0.69 [0.13, 3.73]
Tac_Myc_Std vs Tac	-0.3163	0.782908	0.73 [0.16, 3.38]
Tac_Aza vs Tac	-0.2726	0.689796	0.76 [0.20, 2.94]
Cy_Aza vs Tac	0.7954	0.540842	2.22 [0.77, 6.39]
Cy vs Tac	1.05	0.263112	2.86 [1.71, 4.79]
Cy_Aza_Std vs Tac	1.475	2.544643	4.37 [0.03, 640.60]
Tac_Myc vs Tac	3.057	2.306319	21.26 [0.23, 1953.35]



Los regímenes basados en ciclosporina se asociaron a necesidad de retrasplante

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Rodríguez-Perálvarez et al. Cochrane Database Syst Rev 2017 Mar 31;3:CD011639.

TACROLIMUS
Standard of care

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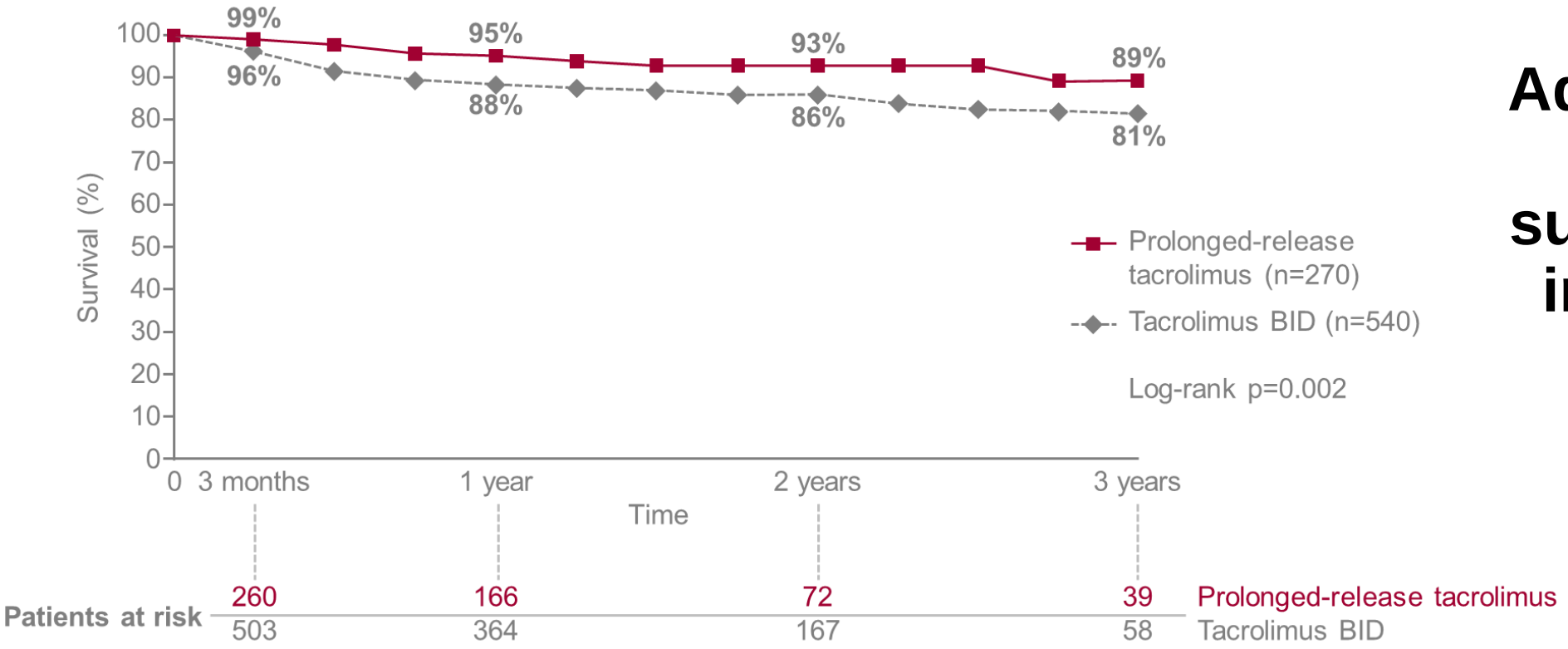
1. Escoger el protocolo adecuado

¿Influye la formulación de tacrolimus?



Advagraf de novo mejoró la supervivencia del injerto a 3 años

1. Adam R et al. Am J Transplant 2015;15:1267–1282.

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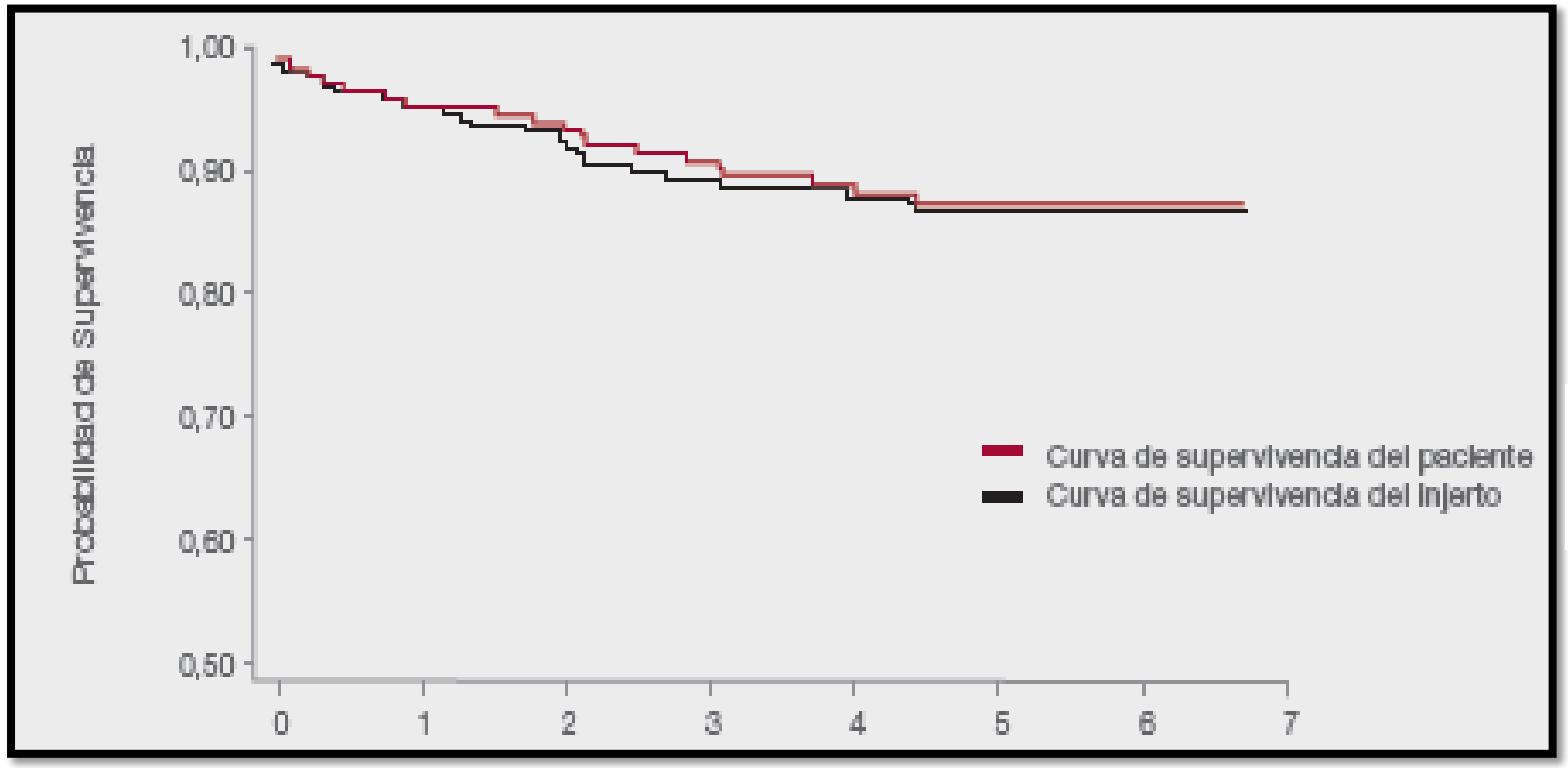
1. Escoger el protocolo adecuado

¿Influye la formulación de tacrolimus?



N=160

La **supervivencia del paciente** a 1, 3 y 5 años fue **96,3%, 91,9%** y **88,3%** respectivamente.

La supervivencia del injerto fue **96,2%, 90,4%** y **87,9%** respectivamente.

Gastaca M et al. Liver Transpl (2016)

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2. Evitar el exceso de inmunosupresión.

Superar niveles de tacrolimus >10ng/mL es contraproducente, sobretodo en el postrasplante precoz

1. Empeora la función renal

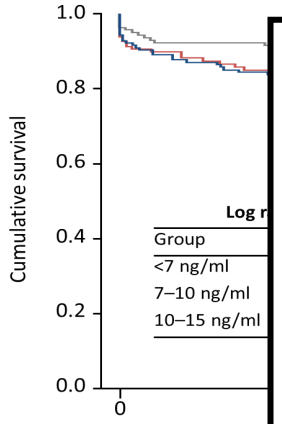
Study or Subgroup	Low trough level Events	Total	Concenti Ev
Boudjema 2011	23	95	
Neuberger 2009	33	336	
Total (95% CI)		431	
Total events	56		

Heterogeneity: Tau² = 0.00; Chi² = 0.59, df = 1 (P = 0.44
Test for overall effect: Z = 4.35 (P < 0.0001)

Figure 8: Forest plot diagram illustrating the ris using reduced (< 10 ng/mL) and conventional (

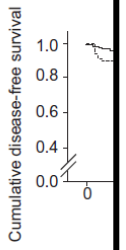
Rodríguez-Perálv

2. Aumenta el riesgo de pérdida injerto



Rodríguez-Perál

3. Mayor recidiva del hepatocarcinoma



HCC recurrence
% (No. at risk)

High CNI exposure (n = 48
Reduced CNI exposure (n

Rodríguez-Perálva

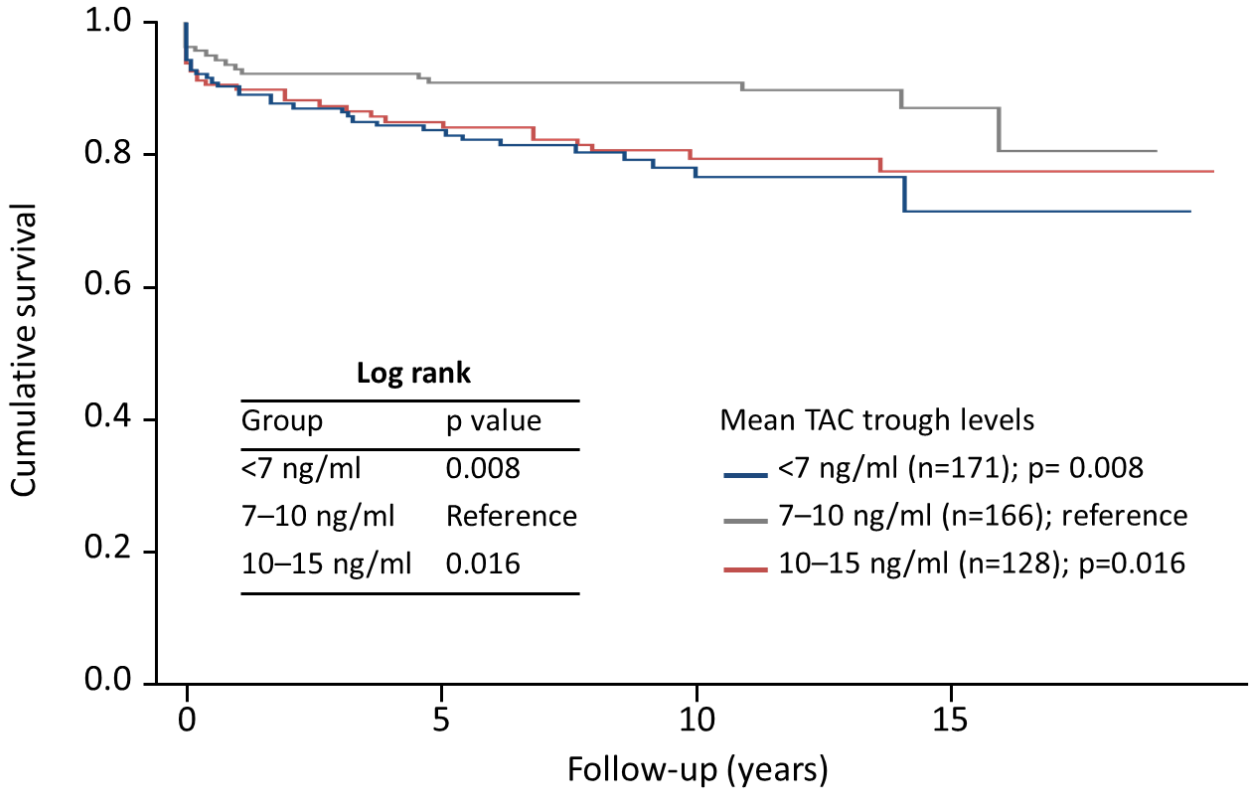
4. Incrementa el riesgo de tumores

Day after LT	Overall population n = 247	No solid cancer n = 204	Solid cancer n = 43	p-Value Wilcoxon
3	12.4	11.8	14.8	0.04
7	10.2	9.8	12	0.03
14	10.5	10.1	12.8	0.001
28	10.7	10.3	12.6	0.001
60	9.6	9.1	11.9	<0.0001
90	9.2	8.9	10.8	0.01
120	8.9	8.6	10.4	0.002
150	8.4	8.3	9.2	0.1
180	8.2	7.9	10	0.001
270	7.6	7	10.5	<0.0001
365	7	6.7	8.6	<0.0001

Carenco et al, Am J Transplant (2014)

3. Evitar infra-inmunosupresión y DSAs

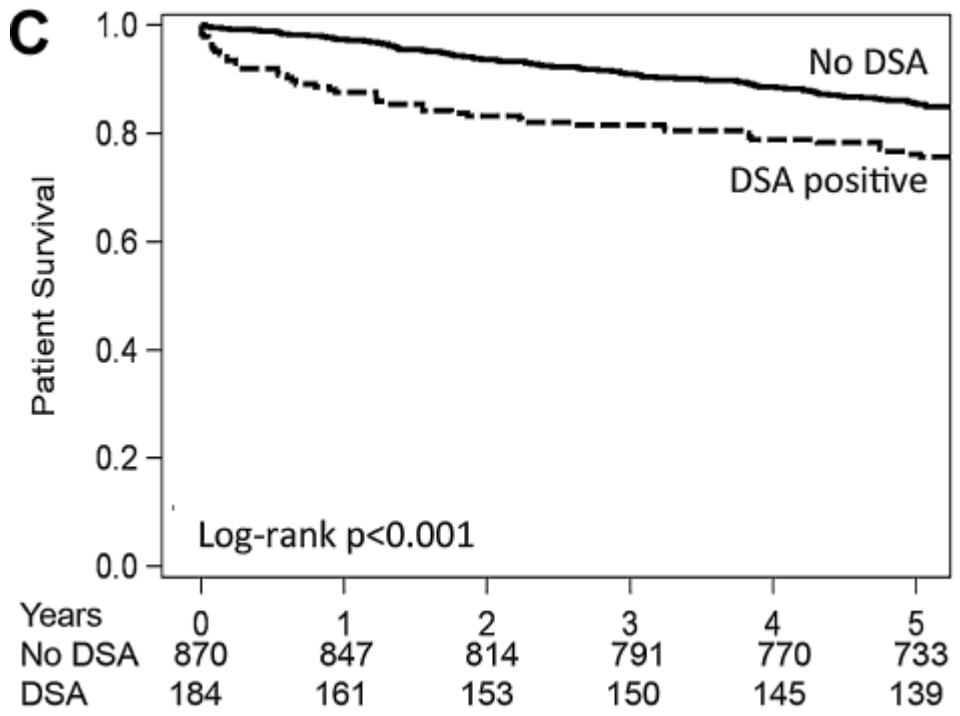
Influencia de los niveles de tacrolimus en el postrasplante precoz sobre la pérdida del injerto

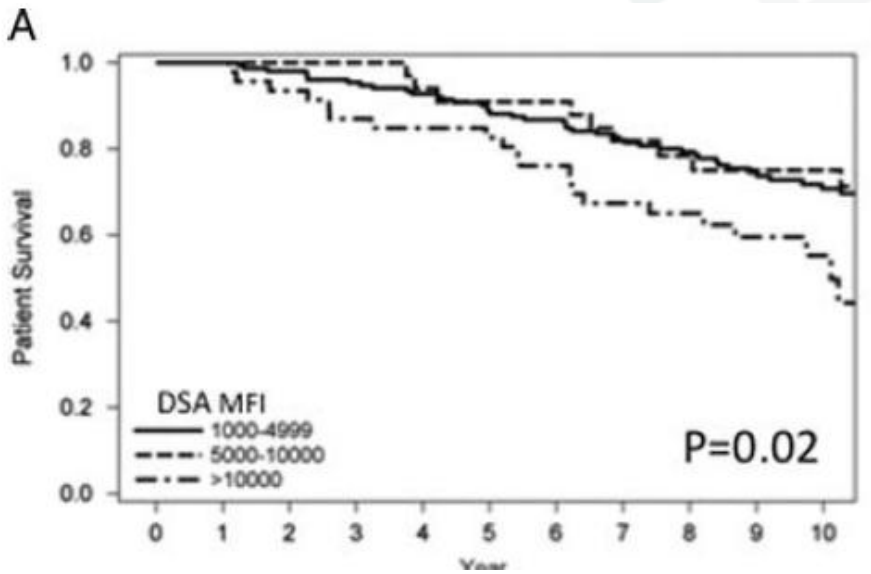


Pacientes estratificados por los niveles medios de tacrolimus en los primeros 15 días post-TH

Rodríguez-Perálvarez M et al. J Hepatol 2013;58(2):262–270.

3. Evitar infra-inmunosupresión y DSAs





Description	Year 1 DSA MFI	N
Year 5 DSA MFI	Number	132
	<1000	35
	1000-4999	56
	5000-10 000	23
	>10 000	18

O'Leary et al, Transplantation, (2017); O'Leary et al, Am J Transplant (2015)

Perseguir niveles de tacrolimus entre 6 y 10 ng/mL en el primer mes post-TH, reduciendo posteriormente entre 4 y 8 ng/mL en la fase de mantenimiento. (Nivel 1).

Niveles valle más reducidos podrían ser aceptables si tacrolimus se combina con MMF, inhibidores de MTOR o inducción con basiliximab. (Nivel 2).

Se debe evitar la infra-inmunosupresión, entendida como niveles inferiores a 6ng/mL en ausencia de otros agentes inmunosupresores. (Nivel 1)

Los corticoides pueden ser suspendidos de forma segura en los primeros 6 meses post-trasplante. (Nivel 1)

El cribado de DSAs se recomienda antes de una minimización agresiva de la inmunosupresión (Nivel 4) o ante un fallo del injerto de causa no aclarada (Nivel 5).

Los niveles recomendados en este consenso se basan en opiniones de experto y revisión de la literatura. Pueden ser diferentes a los de ficha técnica del producto.

Neuberger J, et al. Transplantation 2017;101(4S): S1–S56.

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4. Asegurar adherencia y reducir variabilidad

- La pobre adherencia al tratamiento inmunosupresor aumenta el riesgo de rechazo agudo y potencialmente podría provocar la pérdida del injerto[1,2]

Long-term graft survival in patients with high and low adherence to treatment, measured as standard deviation (SD) in tacrolimus blood levels 6–18 months after transplant (N=228; p=0.04)[1]

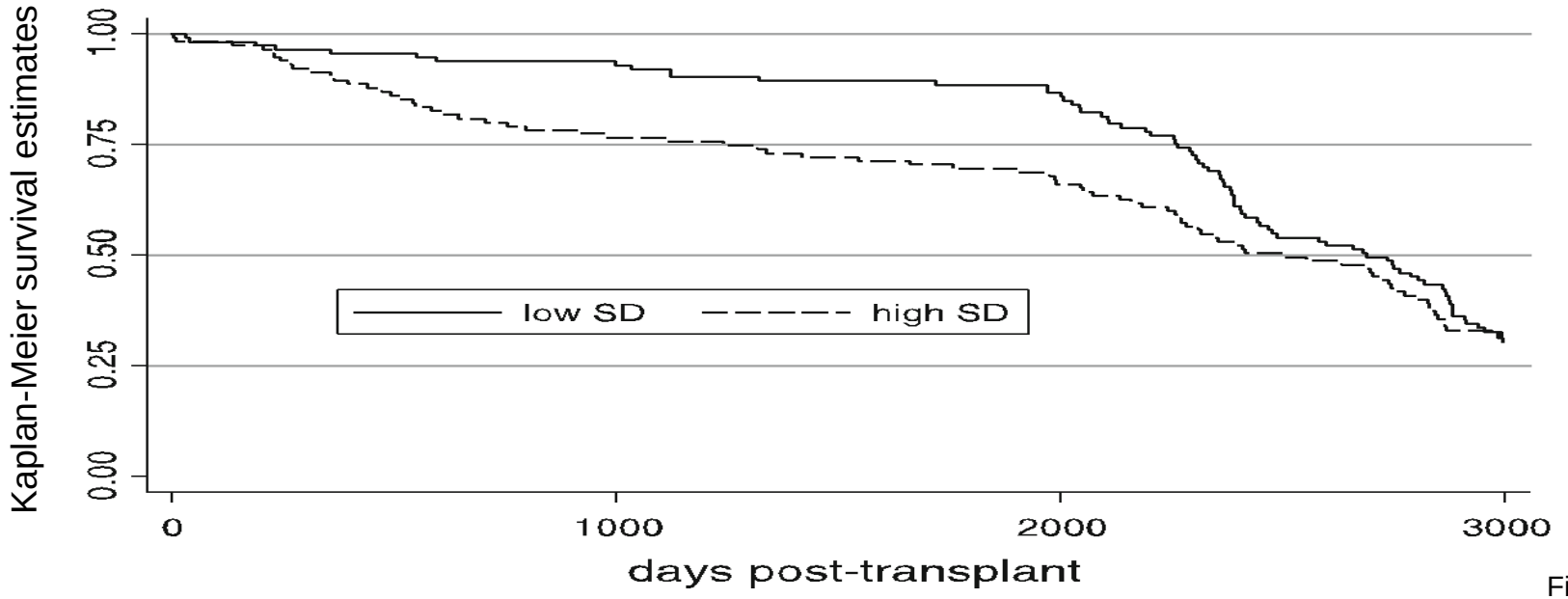
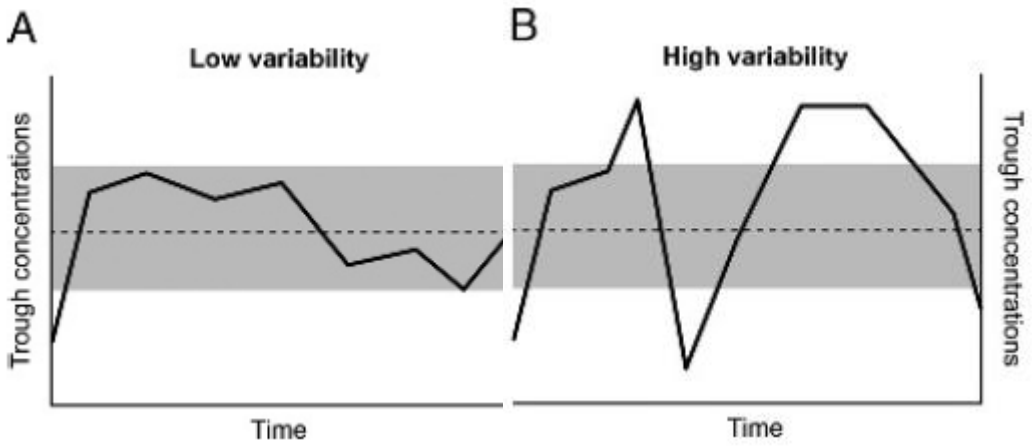


Figure adapted from Lieber et al, 2013[1]

1. Lieber SR et al. Dig Dis Sci 2013;58:824–834; 2. Burra P et al. Liver Transplant 2011;17:760–770.

Variabilidad intra-paciente en la exposición a tacrolimus



Absorción I. delgado

Unido a hematíes/albúmina

Metabolismo hepático/intestinal

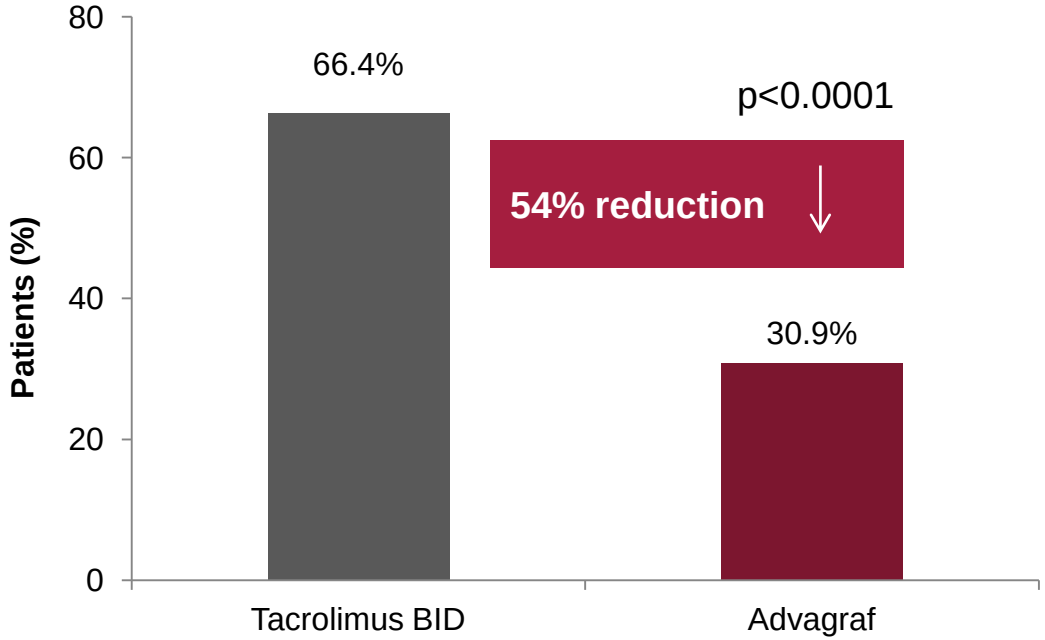
Eliminación biliar

	Factors
Nonmodifiable	• Pharmacogenetics: polymorphisms in CYP3A genes • Circadian rhythm of tacrolimus exposure
Slightly modifiable	• Nonadherence • Gastrointestinal events (diarrhea, vomiting) • Any clinical situation motivating liver graft dysfunction • Low serum proteins (hypoalbuminemia) • Anemia
Highly modifiable	• Food (dietary fat content, grapefruit juice, pomelo) • Drug–drug interactions: antifungals, antivirals, other immunosuppressants, and other drugs • Herbal products • Uncontrolled generic substitution

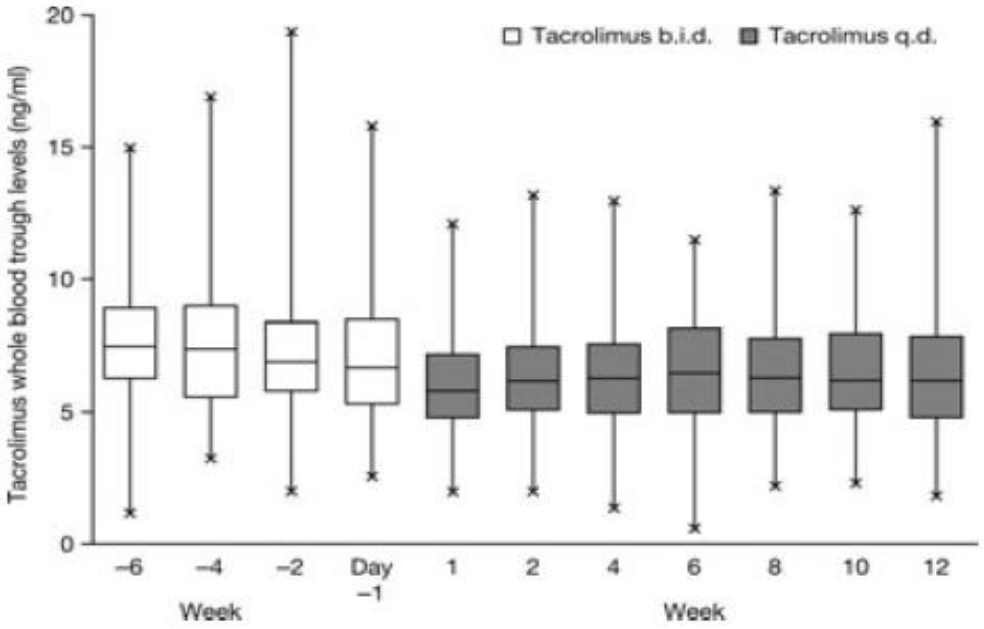
- 1. Shuker N et al. Transplant Rev. 2015;29:78-84; 2. Neuberger J, et al. Transplantation 2017;101(4S): S1–S56.

Advagraf mejora la adherencia y disminuye la variabilidad intra-paciente

- La tasa de pobre adherencia se redujo a la mitad tras la conversión a Advagraf[1]



- La conversión a advagraf se asocia a menor variabilidad y niveles valle más constantes[2]



1. Beckebaum S et al. Transplant Int 2011;24:666–675.

2. Sańko-Resmer J et al. Transplant Int 2012:25:282–293.

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La adherencia al tratamiento debe ser evaluada en cada revisión clínica tras el trasplante hepático. (Nivel 1)

Los niveles del ICN deben medirse cada 2-3 días en las primeras dos semanas, semanalmente hasta el día 30, mensualmente hasta el sexto mes y cada 3 meses en adelante. (Nivel 5)

La aparición de factores de riesgo de variabilidad debe motivar una monitorización más intensiva de niveles valle para un ajuste de dosis si fuese preciso. (Nivel 4)

En pacientes con variabilidad documentada, la conversión a una formulación de liberación prolongada de tacrolimus puede ser de utilidad. (Nivel 2)

En pacientes con rechazo agudo histológicamente demostrado y niveles en rango terapéutico se debe evitar un aumento brusco de la dosis de tacrolimus. (Nivel 5).

Los niveles recomendados en este consenso se basan en opiniones de experto y revisión de la literatura. Pueden ser diferentes a los de ficha técnica del producto.

Neuberger J, et al. Transplantation 2017;101(4S): S1–S56.

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CONCLUSIONES

- Los pacientes sometidos a trasplante hepático tienen una expectativa de vida más corta que la población general.
- La supervivencia a largo plazo está condicionada por el uso crónico de inmunosupresores.
- Un manejo más refinado del tratamiento inmunosupresor podría mejorar el pronóstico de los pacientes.
- El uso de guías clínicas y *checklists* ayuda a implementar pequeños cambios en nuestra práctica habitual, los cuales podrían resultar en un gran impacto pronóstico en el paciente.