Simposio de Trasplante Hepático (FUNDIEH-Novartis-Hospital El Cruce)

Recurrencia de la enfermedad original en el injerto

Fernando Cairo
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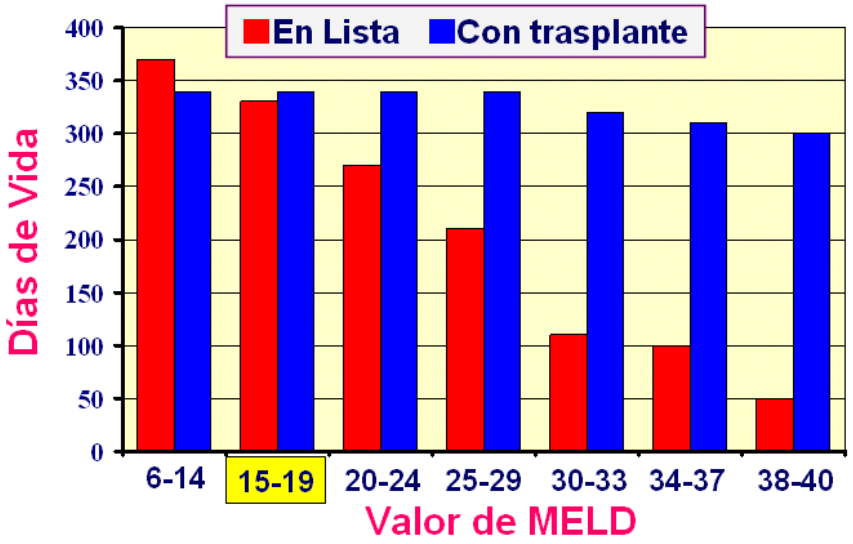
Sobrevida Post-Trasplante Hepático

	Sobrevida del Paciente (%)		
	1 año	5 años	10 años
EEUU (UNOS 1999-08)			
Niños	**92**	**79**	**71**
Adultos	**86**	**70**	**56**
Europa (ELTR 1988-05)	**84**	**73**	**58**
Argentina (incuai)			
Niños (2000-10)	**83**	**76**	**72**
Adultos (2005-15)	**81**	**70**	**58**

UNOS Annual Report (2011); Burra P, Am J Transplant 2010;
Registro Nacional de Trasplante Hepático (2019)

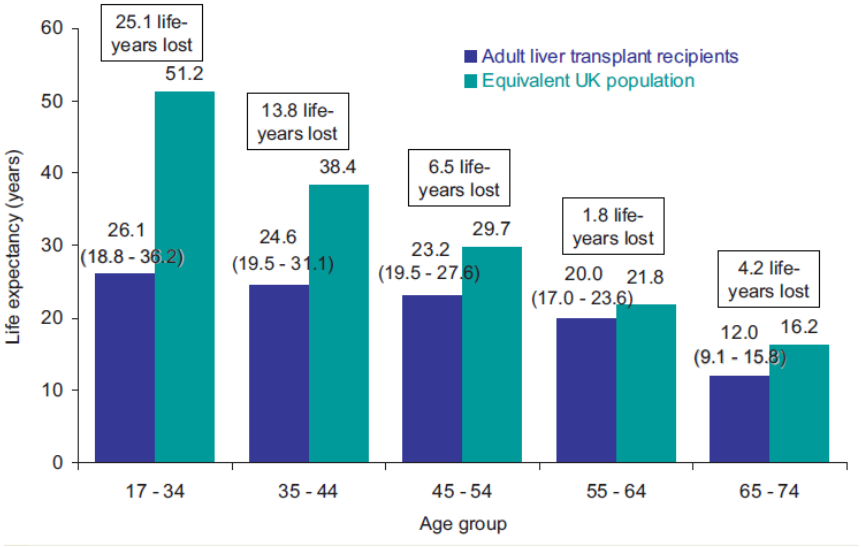
Efectividad: Sobrevida Post-Trasplante

Comparada con candidatos en lista de espera



Freeman R, J Hepatol 2005

Comparada con la población sana

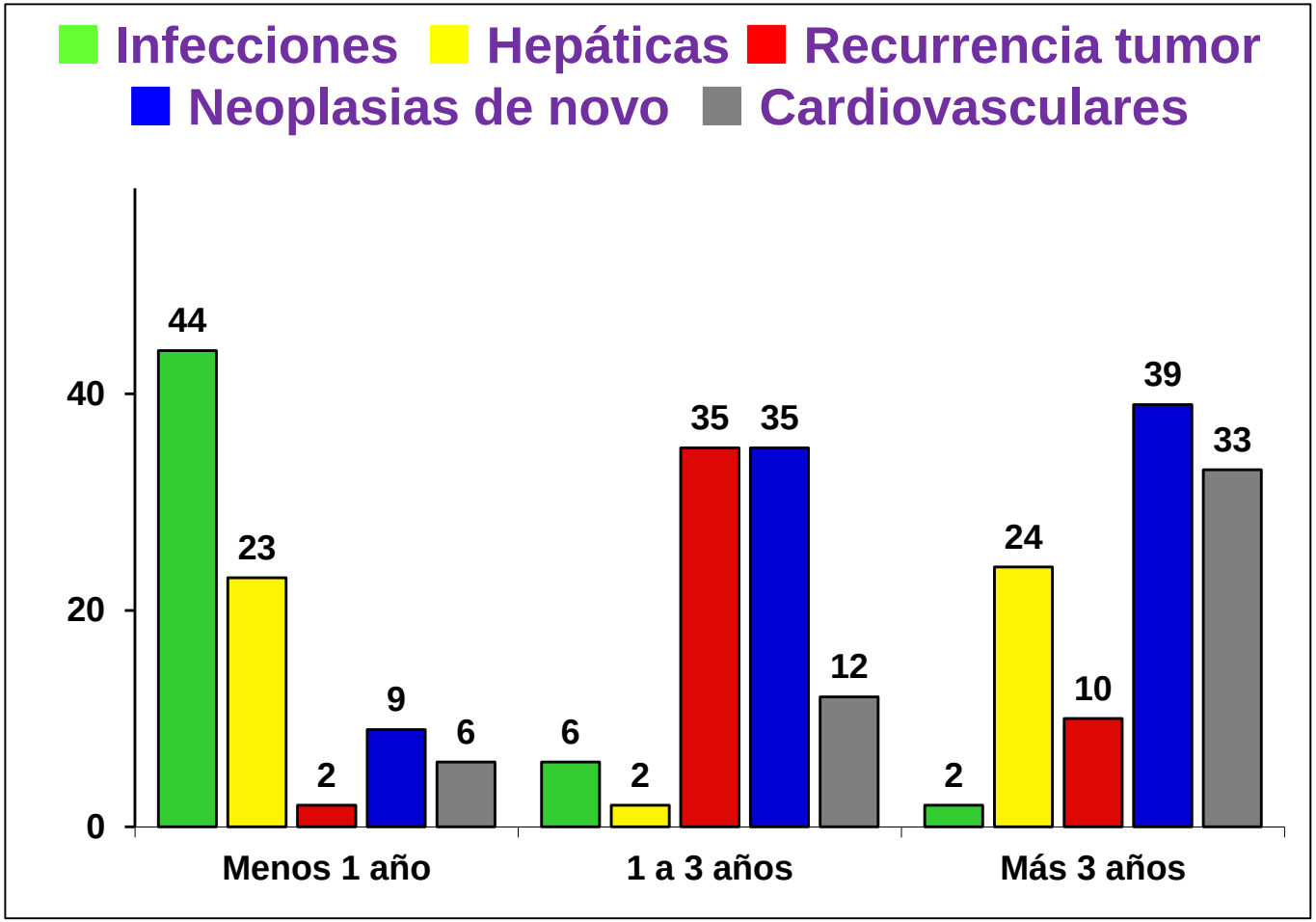


Barber K, Gut 2007

Sobrevida media ➡ <u>22 años</u>

“Pérdida de 7 años de vida con respecto a la población general ~ edad y sexo”

Causa de Muerte Post-Trasplante Hepático



Herrero JI, Liver Transpl 2009

Recurrencia de la Enfermedad de Base

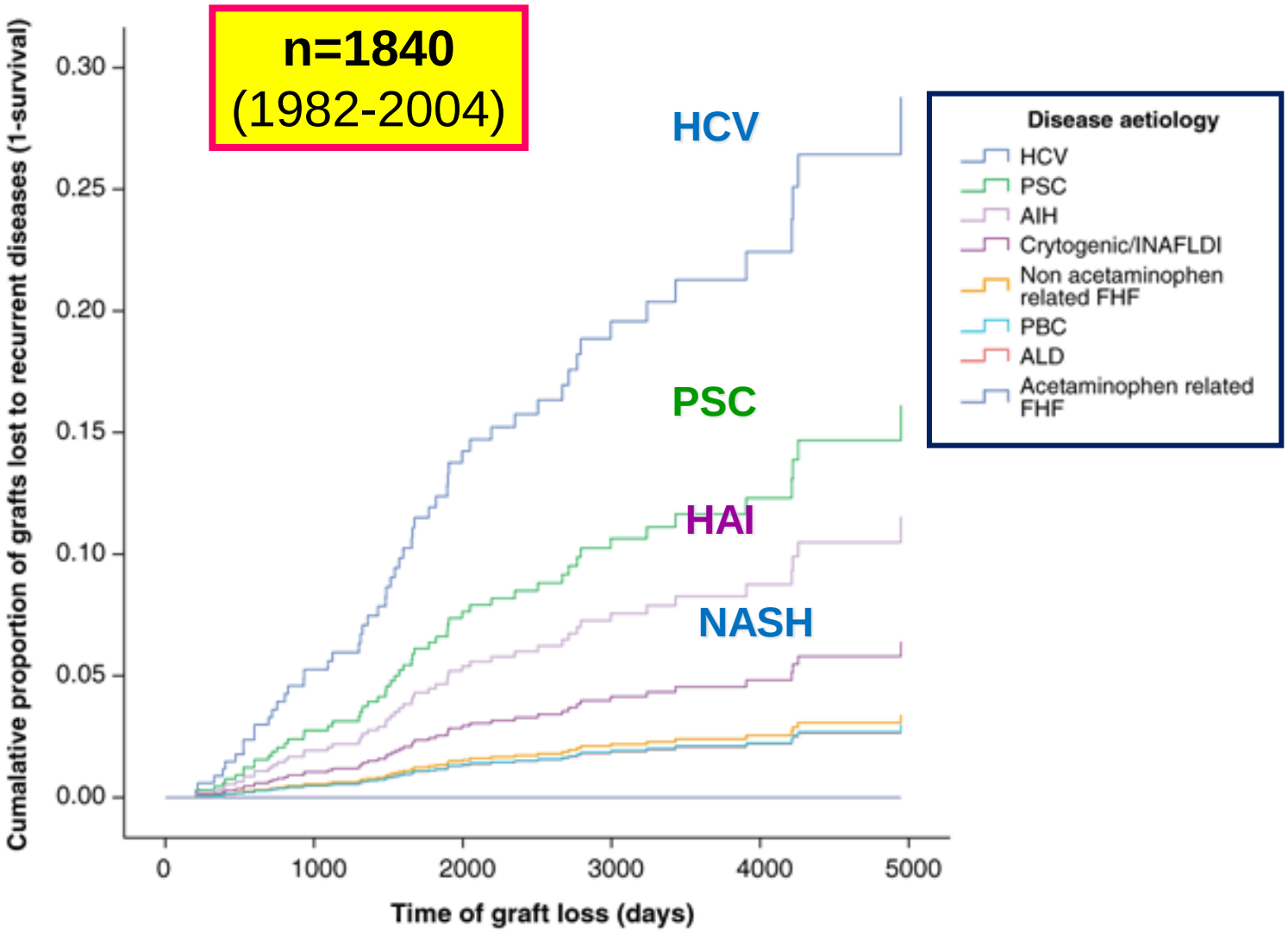
Recurrencia Post-Trasplante Hepático

Universal (90-100%)	Frecuente (20-50%)	Infrecuente (0-10%)
HCV	HAI	HBV
NASH	CBP	HH
	CEP	Wilson
	ALD	ABV

Recurrencia de enfermedad primaria

- Hepatitis C (> 90% de los casos)
- NASH (> 90% de los casos)
- Colangitis biliar primaria (20% a 50%)
- Colangitis esclerosante primaria (20% a 30%)
- Hepatitis autoinmune AIH (20% –30%)
- Hepatitis B (<10%)
- Alcohol (<10%)

Pérdida del Injerto por Recurrencia



Rowe IA, Transpl Int 2008

Historia Natural de la Hepatitis C Post-TH

Recurrencia universal de la infección C

↓

Hepatitis del injerto en el 80-100%

↓

Fibrogénesis acelerada

↓

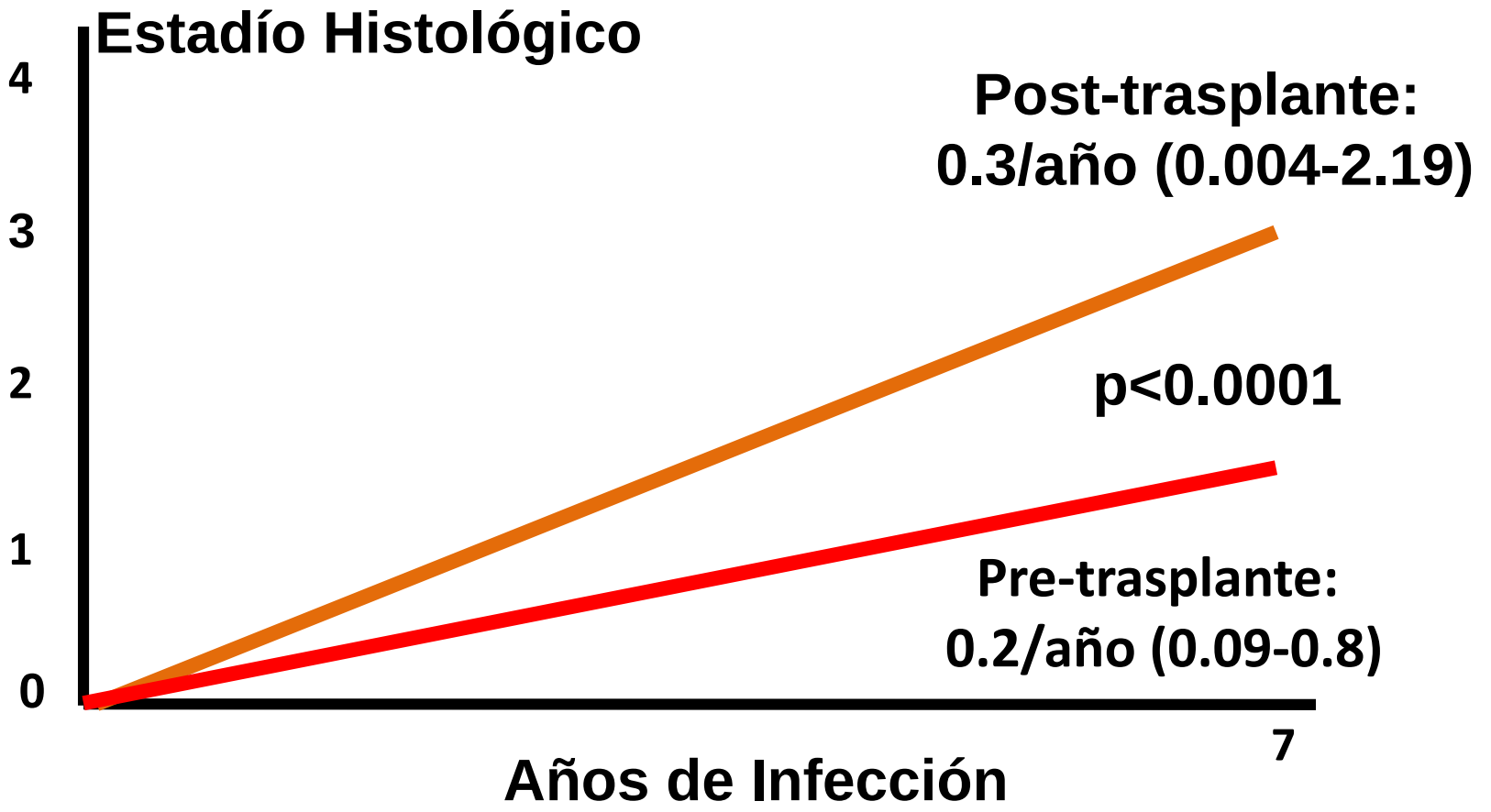
Descompensación acelerada de la cirrosis

↓

Disminución de la sobrevida (injerto y paciente)

Progresión de la Fibrosis en Pacientes Trasplantados y no Trasplantados

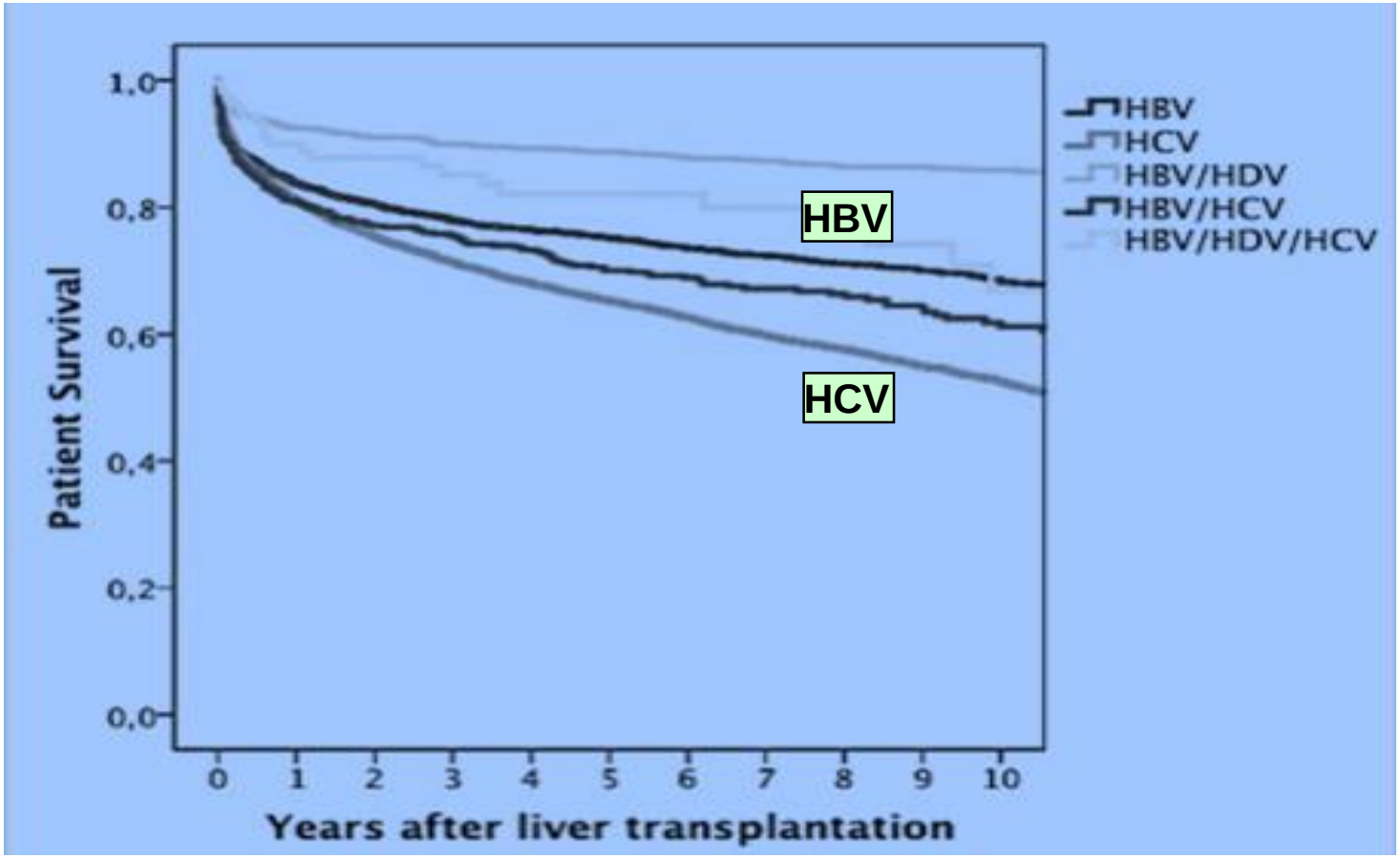
Berenguer M y col (2000)



Intervalo de la infección a la cirrosis	20-40 años en no trasplantados
	9-12 años en trasplantados

Recurrencia del HCV post Tx: Un Problema Mayor

ELTR (N=19.335)



- **30 % cirrosis a 5 años post Tx**
- **Principal causa de mortalidad**

Burra P et al. J Hepatol 2013

Tratamiento de la Hepatitis C Pre- y Post-Trasplante Hepatico

Tratar antes del TxH

- ✓**Evitar el Tx ?, o**
- ✓**Prevenir la recurrencia post Tx**

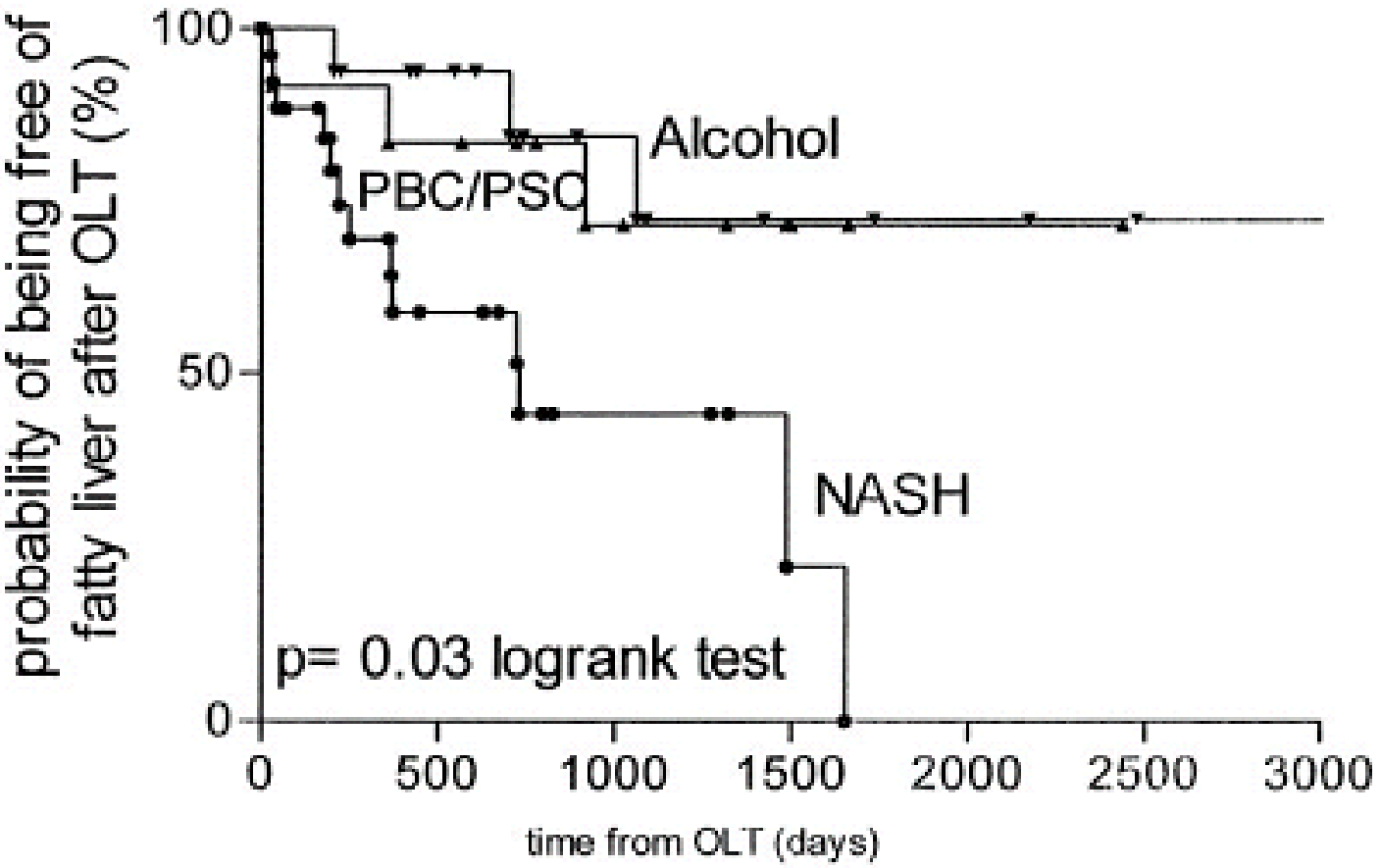
Tratar post TxH

- ✓**Evitar la perdida del injerto**

Todos los pacientes con recurrencia de la infección por VHC después del trasplante deben ser considerados para la terapia (A1)
La hepatitis colestásica o la presencia de fibrosis moderada a extensa o hipertensión portal indican tratamiento antiviral (A1)

Charlton M y col (2015). ILTS Consensus Conference, Chicago May 2016

Desarrollo de Esteatosis Post-Tx



PBC	12	11	7	4	1
NASH	27	11	5	2	0
alcohol	16	13	8	5	4

Contos Liver Transpl 2001

Prevalencia y Severidad de la Recurrencia de NAFLD/NASH Post-Trasplante

Meta-análisis 1864 pac Tx por NASH (recurrencia NAFLD 80-100% - NASH: 3-30%)

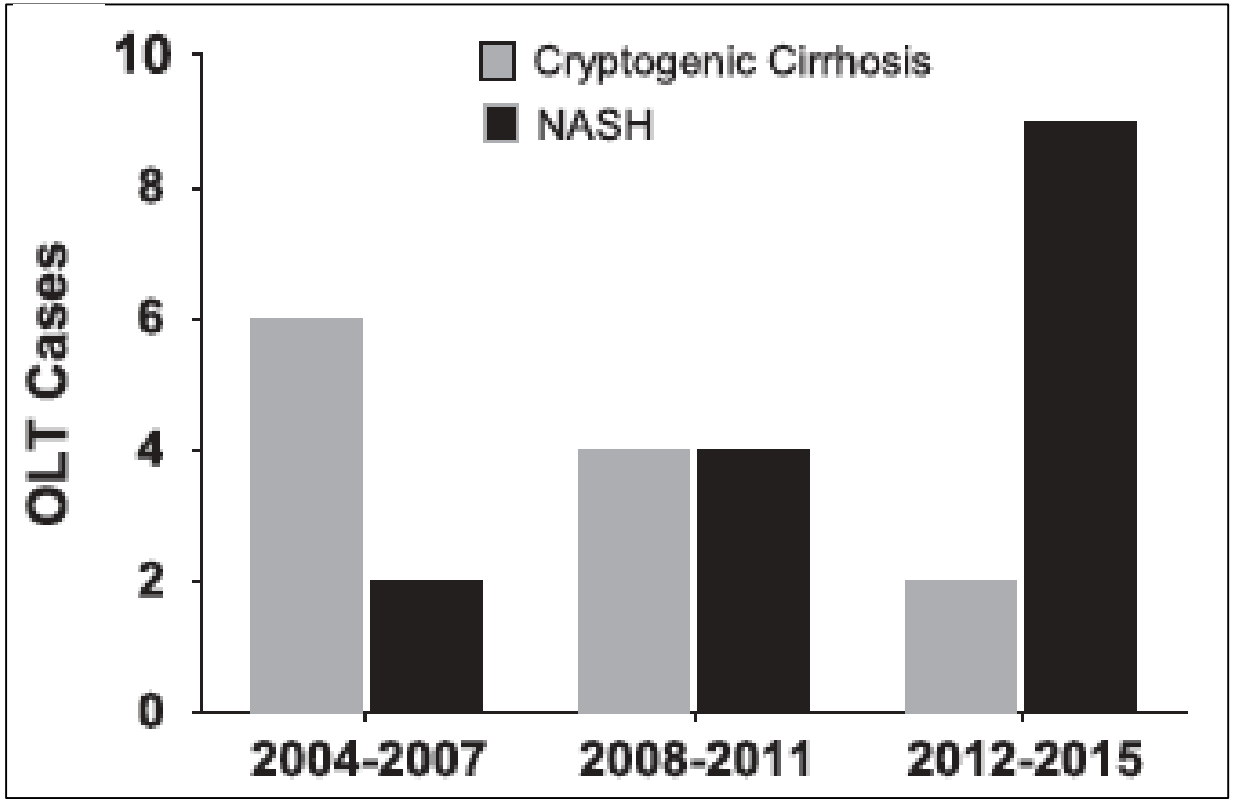
Table 1. Main patterns of analyzed studies about transplanted patients developing NAFLD.

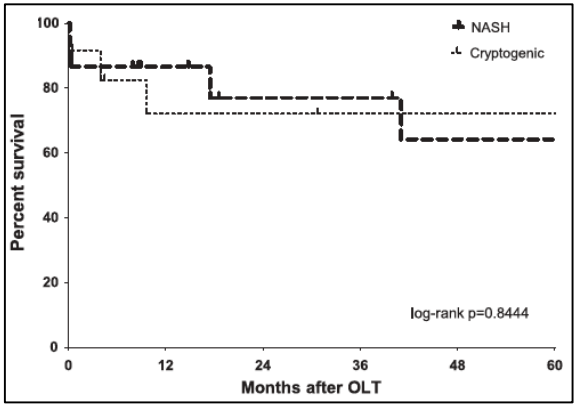
First author, year	Kind of liver disease	Design	Patients (*n*)	Follow-up (months)	Main conclusion
Malik, 2009	Recurrent	Retrospective	98	36	Features of metabolic syndrome were associated with NASH recurrence; at 18 months, 18% of recipients showed severe NASH
Yalamanchili, 2010	Recurrent	Retrospective	257	120	Advanced fibrosis due to NASH recidivism was uncommon; NASH recurrence did not impair survival
Dureja, 2011	Recurrent	Retrospective	88	60	Features of metabolic syndrome were associated with NASH recurrence; 8.8% of recipients showed severe NASH
Sourianarayanane, 2017	Recurrent	Retrospective	185	60	Patients with NASH recurrence showed a slower fibrosis growth than patients with alcohol-related liver disease
Bhagat, 2009	Recurrent	Retrospective	154	6	One-third of recipients showed NASH recurrence; none developed a severe fibrosis
Bhati, 2017	Recurrent	Retrospective	103	180	Recurrent NASH occurred in nearly 88% of transplanted patients; a quarter of recipients developed advanced fibrosis
Contos, 2001	Recurrent	Retrospective	30	60	All patients developed allograft steatosis at 5 years; 3.3% developed severe fibrosis
Dumortier, 2010	*De novo*	Retrospective	599	120	Thirty-one percent of patients developed allograft steatosis; *de novo* NASH was present in 3.8% of cases
Kim, 2014	*De novo*	Retrospective	156	35	NAFLD was present in 27.1% of cases; pre-LT alcoholic cirrhosis, obesity, and preexisting donor graft steatosis were main risk factors
Gitto, 2018	*De novo*	Retrospective	194	120	Posttransplant NAFLD represented a strong cardiovascular risk factor; *de novo* NASH was an independent predictor of long-term mortality

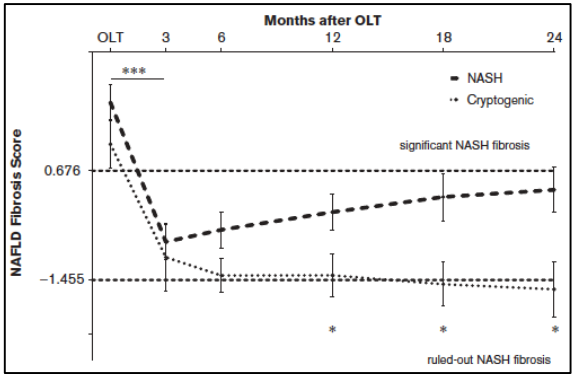
NAFLD: Nonalcoholic fatty liver disease.

Stefano Gitto. Expert Rev Gastroenterol Hepatol. 2019

Prevalencia y Severidad de la Recurrencia de NAFLD/NASH Post-Trasplante







Lukas W Unger. Eur J Gastroenterol Hepatol. 2017

Prevalencia y Severidad de la Recurrencia de NAFLD/NASH Post-Trasplante

103 trasplantes consecutivos por NASH (n=48) o cirrosis criptogénica (n=53) → PBH o elastografía

	Biopsia	Elastografía
Seguimiento	47 meses	75 meses
Esteatosis Severa	88% 18%	87.5% 50%
NASH	41%	-
F0-F1 F3-F4	76.5% 21%	55% 27%

Chandra Bhati, Transplantation. 2017

La Obesidad Como Predictor de Mortalidad Post-Trasplante

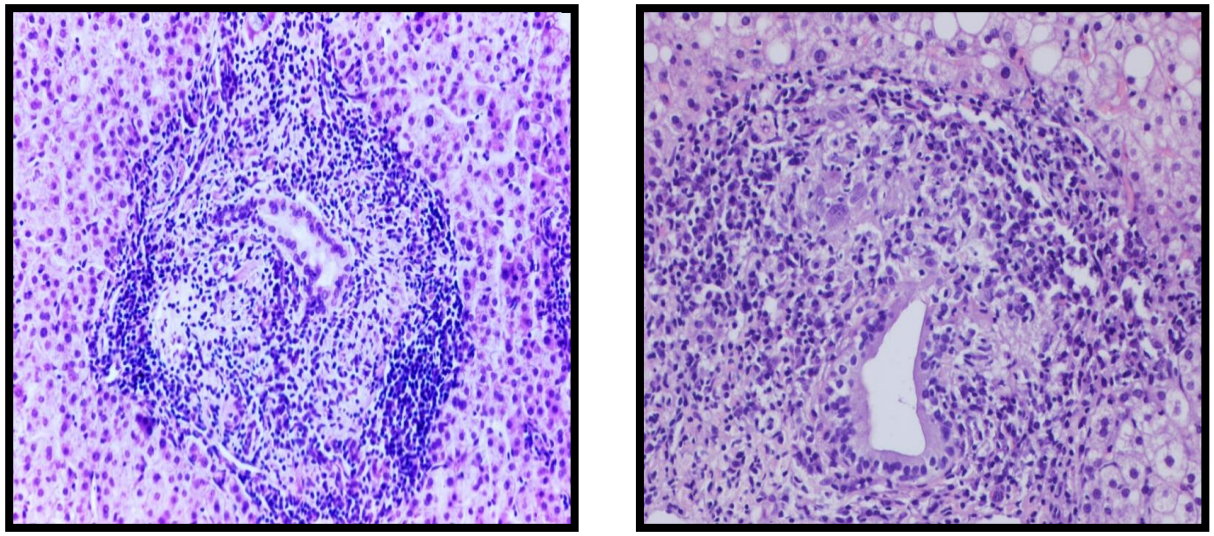
n=18172	No obeso	Sobre-peso	Obeso	Obeso severo	Obeso morbido
BMI	<25	25,1-30	30,1-35	35,1-40	40,1-50
%	46%	33%	14%	5%	2%
DBT	10%	15%	18%	22%	22%
Cirrosis cripto	8%	10%	15 %	18%	18%
Mortalidad 1-5 años	16-44%	14-46%	14-47%	18-51%	22-57%

p<.05

Nair Hepatology 2002

Criterios Diagnósticos de Recurrencia de CBP

- Confirmar la **enfermedad de base** → CBP
- Incremento FA/GGT (**colestasis**) con **persistencia AMA (M2)**
- Descartar otras causas de disfunción del injerto (C-RM y doppler normal)
- **Biopsia** "siempre necesaria" → colangitis granulomatosa o l*esión ductal florida*



Duclos-Vallee JC, Liver Transpl 2009 – Neuberger J, Liver Transpl 2013

Prevalencia de Recurrencia de Colangitis Biliar Primaria Multicenter International Cohort: The Global PBC Study Group

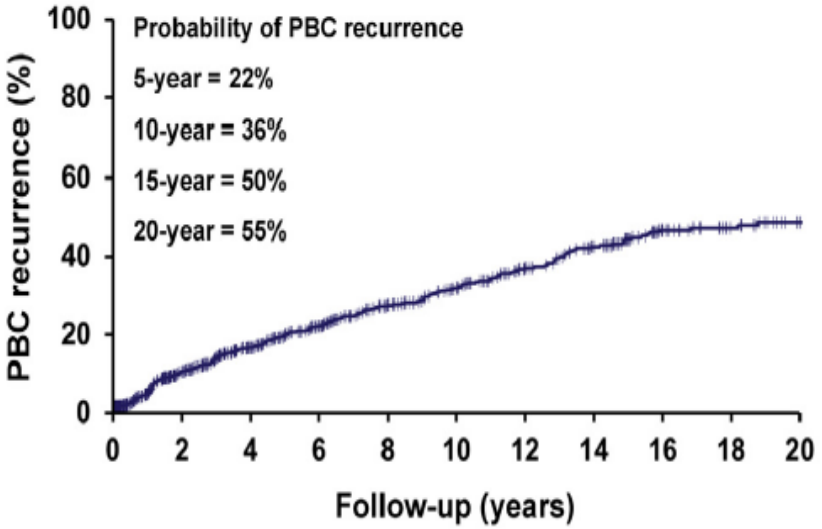
Global PBC Group

785 pts received **Liver Transplant (LT)** due to **Primary Biliary Cholangitis (PBC)**

240 pts developed **Recurrence of PBC**

Risk Factors for rPBC

- **Younger Age** at the time of diagnosis and LT
- **Tacrolimus** use
- **Biochemical Cholestasis** within the first 12 months following LT



Montano-Loza AJ, Gastroenterology 2019

Recurrencia de Colangitis Biliar Primaria: Factores de Riesgo

Global PBC Group

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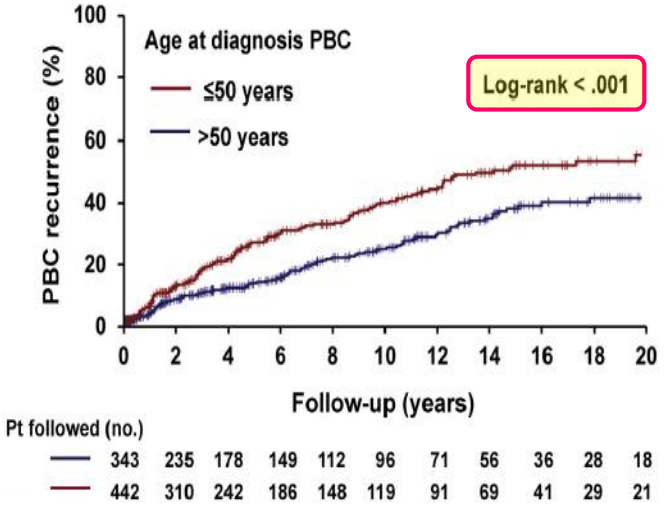

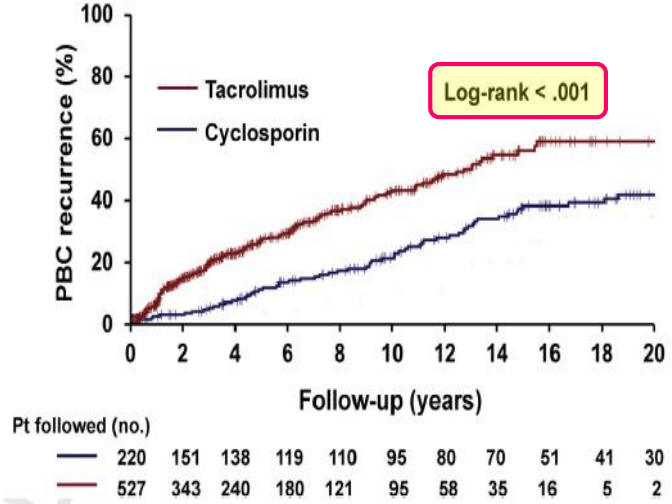

Montano-Loza AJ, Gastroenterology 2019

Recurrencia de Colangitis Biliar Primaria: Impacto en la Sobrevida

Global PBC Group

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→ **240** pts developed **Recurrence of PBC**

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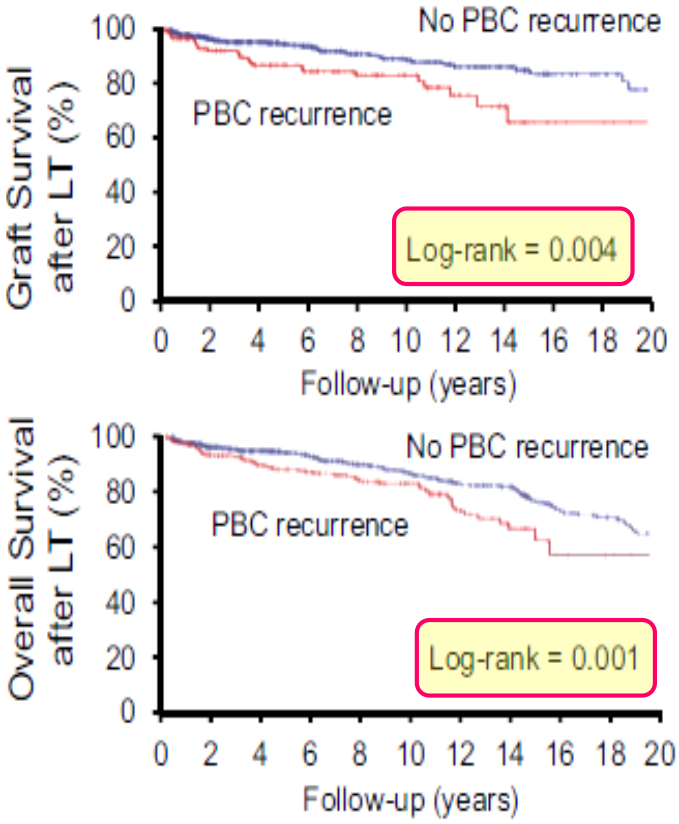


Montano-Loza AJ, Gastroenterology 2019

Criterios Diagnósticos de Recurrencia de CEP

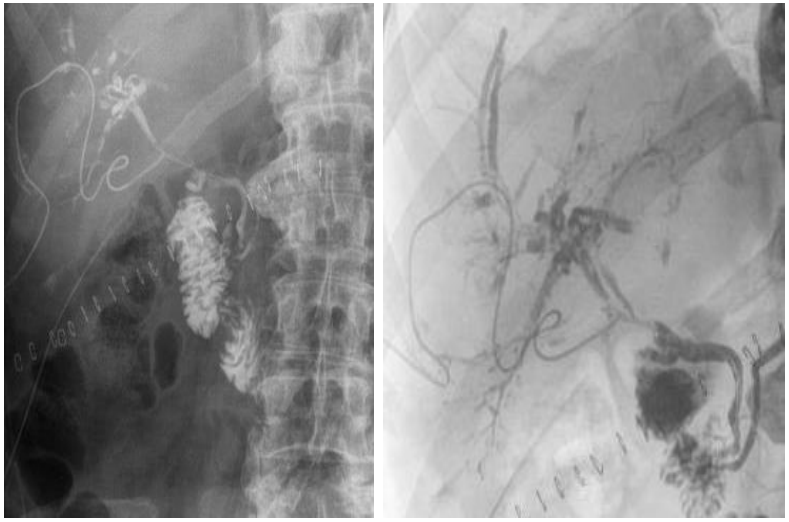
Recurrencia CEP:

- Confirmar el diagnóstico pre-TH de CEP
- Estenosis biliares no-anastomóticas luego de los 90 días post-trasplante hepático
- Descartar otras causas de estenosis biliares no-anastom: isquemia-reperfusión, trombosis arterial, incomp ABO, etc
- Biopsia hepática compatible: colangiopatía fibro-obliteratica

Graziadei IW, Hepatology 1999

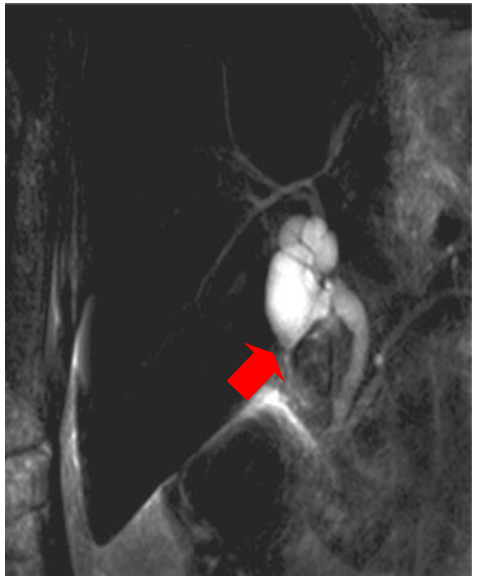
Complicaciones Biliares

Estenosis biliar no anastomótica Colangiopatía Isquémica

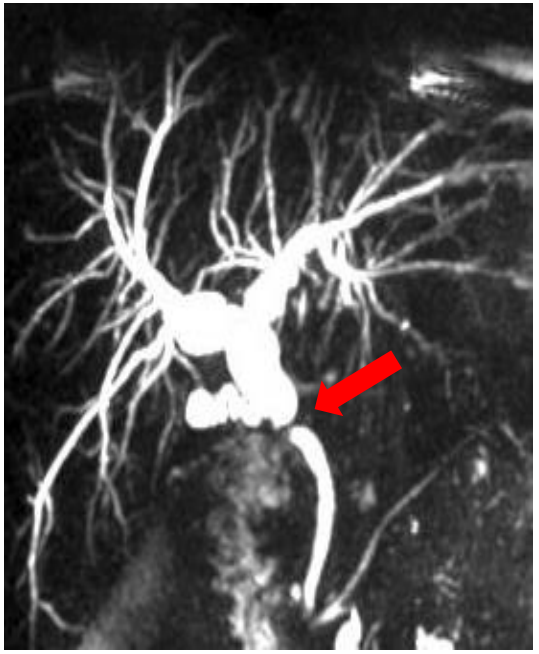


Estenosis biliares múltiples no-anastomóticas (1-6 mes)

Compresión por cistocele



Estenosis anastomótica

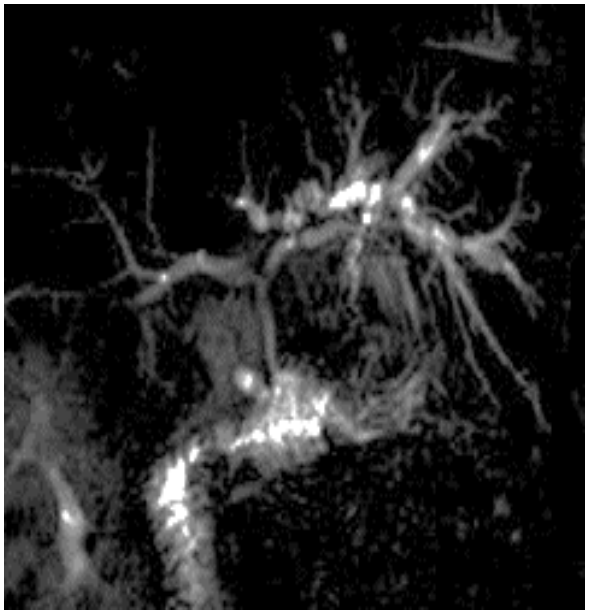


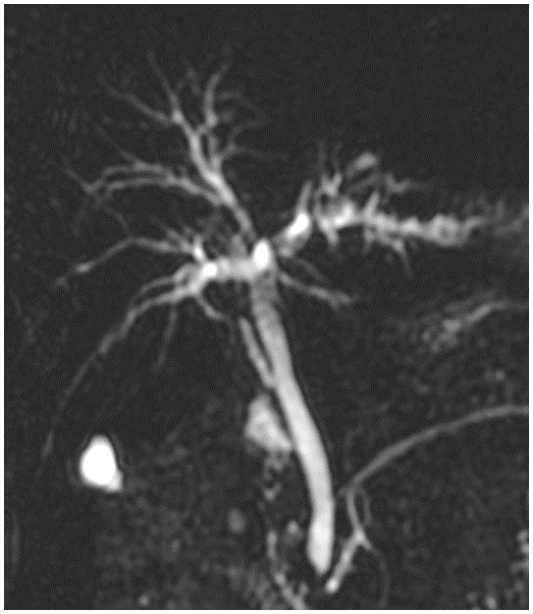
Criterios Diagnósticos de Recurrencia de CEP

Incremento FA/GGT (colestasis) y/o
Episodios de Colangitis Aguda

⬇

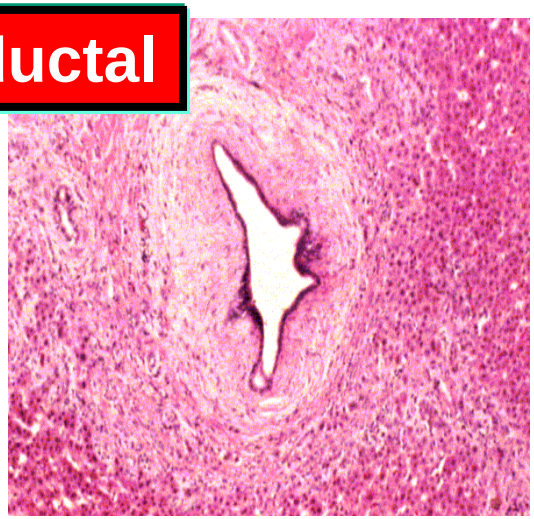
Colangiografía (RM) con múltiples estenosis-dilataciones no anastomóticas

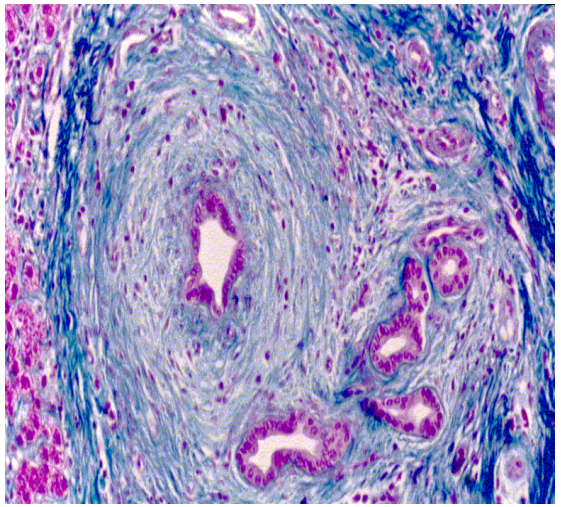




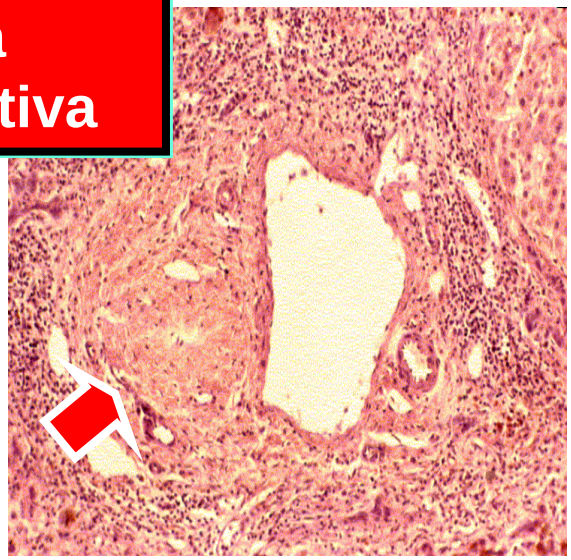
Biopsia Hepática en la Recurrencia de CEP

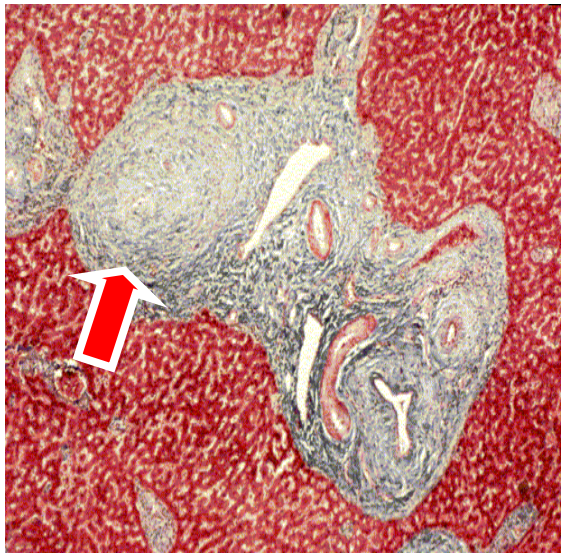
Fibrosis Periductal





Colangiopatía Fibro-obliterativa





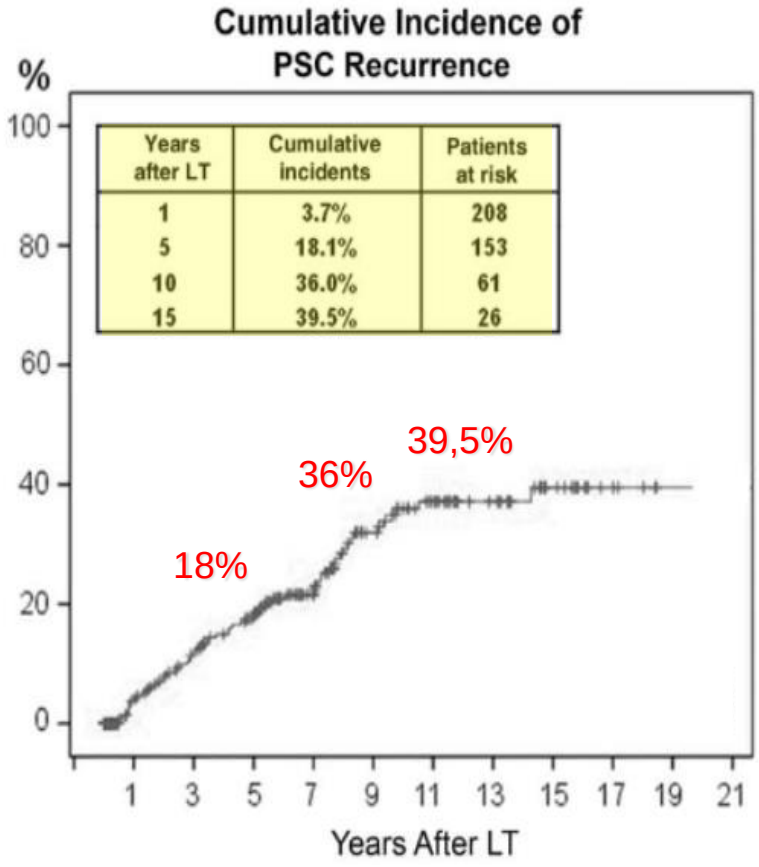
Recurrencia Post-Trasplante Hepático de CEP

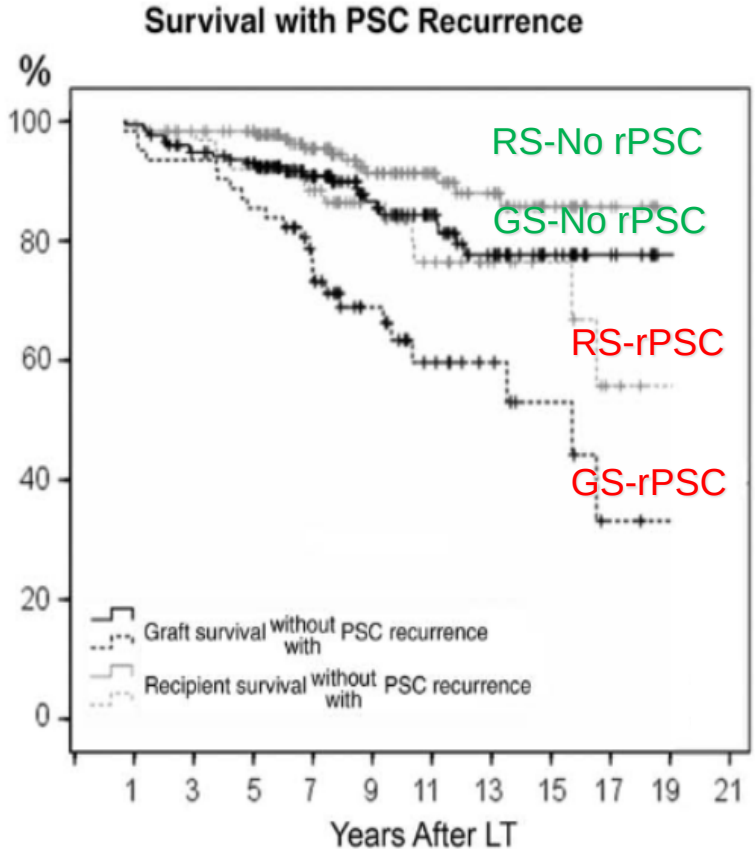
German PSC Study Group

n=335 TH por CEP

1990-2006 → 10 centros Alemania

74% IBD – 39 años – 68% Hombres





Independent risk factors for rPSC: Donor age (>), IBD (CU), INR at LT (MELD)

Hildebrand T, Liver Transpl 2016

Recurrencia Post-Trasplante Hepático de Hepatitis autoinmune (AIH)

Hepatitis autoinmune AIH (20% –30%)

- Diagnóstico pre trasplante
- Biopsia compatible
- Descartar otras causas
- De novo AIH fue reportada en 5%-10% de los niños y 1%-2% receptores adultos
- La tasa de retrasplante es de 8%-23%

Duclos-Vallee JC. Recurrence of autoimmune disease, primary sclerosing cholangitis, primary biliary cirrhosis, and autoimmune hepatitis after liver transplantation. Liver Transpl. 2009;

Recurrencia Post-Trasplante Hepático de Hepatitis autoinmune (AIH)

Recurrent autoimmune hepatitis

Clinical criteria

- History of liver transplantation related to AIH

Serologic findings

- Hypergammaglobulinemia, increased serum IgG levels, and ANA, SMA, or both ANA and SMA

Histological aspects*

-Prominent lymphocytic interface activity with or without plasma cell infiltration
- Acute lobular hepatitis with focal hepatocyte necrosis, acidophil bodies with lymphoplasmacytic cells
- Pseudo-rosetting of hepatocytes, and perivenular lymphoplasmacytic inflammation
- Confluent and bridging necrosis with lymphoplasmacytic infiltration (severe inflammatory activity)

* Features may be less pronounced, absent, or otherwise atypical in part because of concurrent antirejection therapy.

Guido Stirnimann, Recurrent and De Novo Autoimmune Hepatitis. Liver Transpl 2019

Recurrencia Post-Trasplante Hepático de Hepatitis autoinmune (AIH)

Estudios sobre recurrencia HAI *n=283*

PAC → 1998-2016

Preguntas sin respuesta:

- ¿Cuál es la mejor IS?
- ¿Es necesario mantener los esteroides de por vida?
- ¿Se debe indicar azatioprina?

Guido Stirnimann, Recurrent and De Novo Autoimmune Hepatitis. Liver Transpl 2019

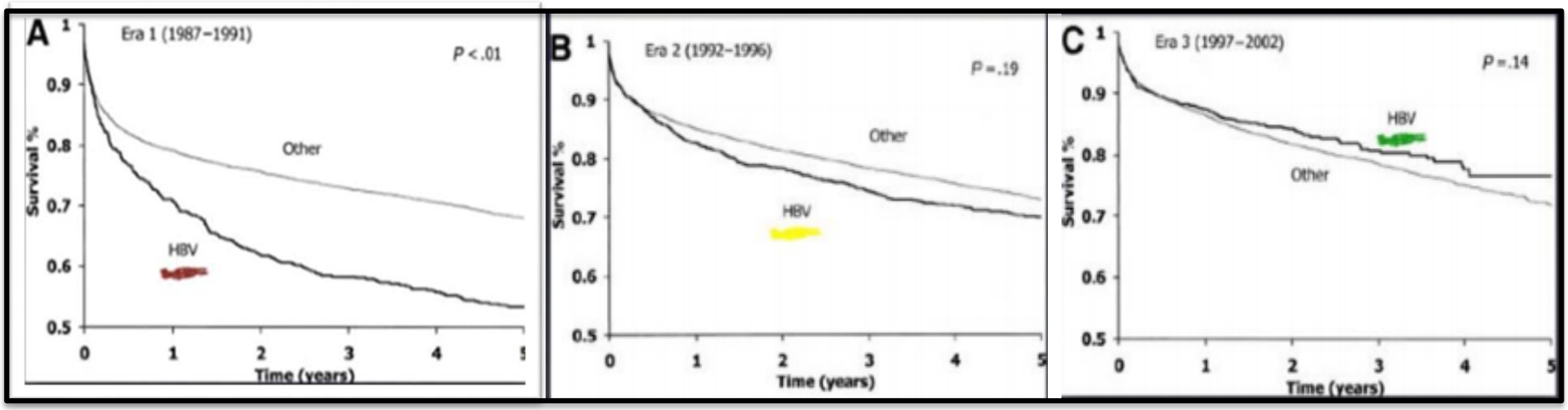
HEPATITIS B y TxH

- La Hepatitis B paso de ser una contraindicacion para trasplante a ser una de las indicaciones con mejor tasa de sobrevida

- La reinfección del injerto por HBV es la principal causa de disminución de la sobrevida del injerto y el paciente

- El uso de HBIG con asociación a análogos nucleos(t)idos en pacientes con HBV sometidos a TxH logra excelentes resultados a largo plazo

Trasplante por hepatitis B en EEUU 1987-2002



1987- 1991

Recurrencia severa

1992- 1997

Antivirales+IBHG

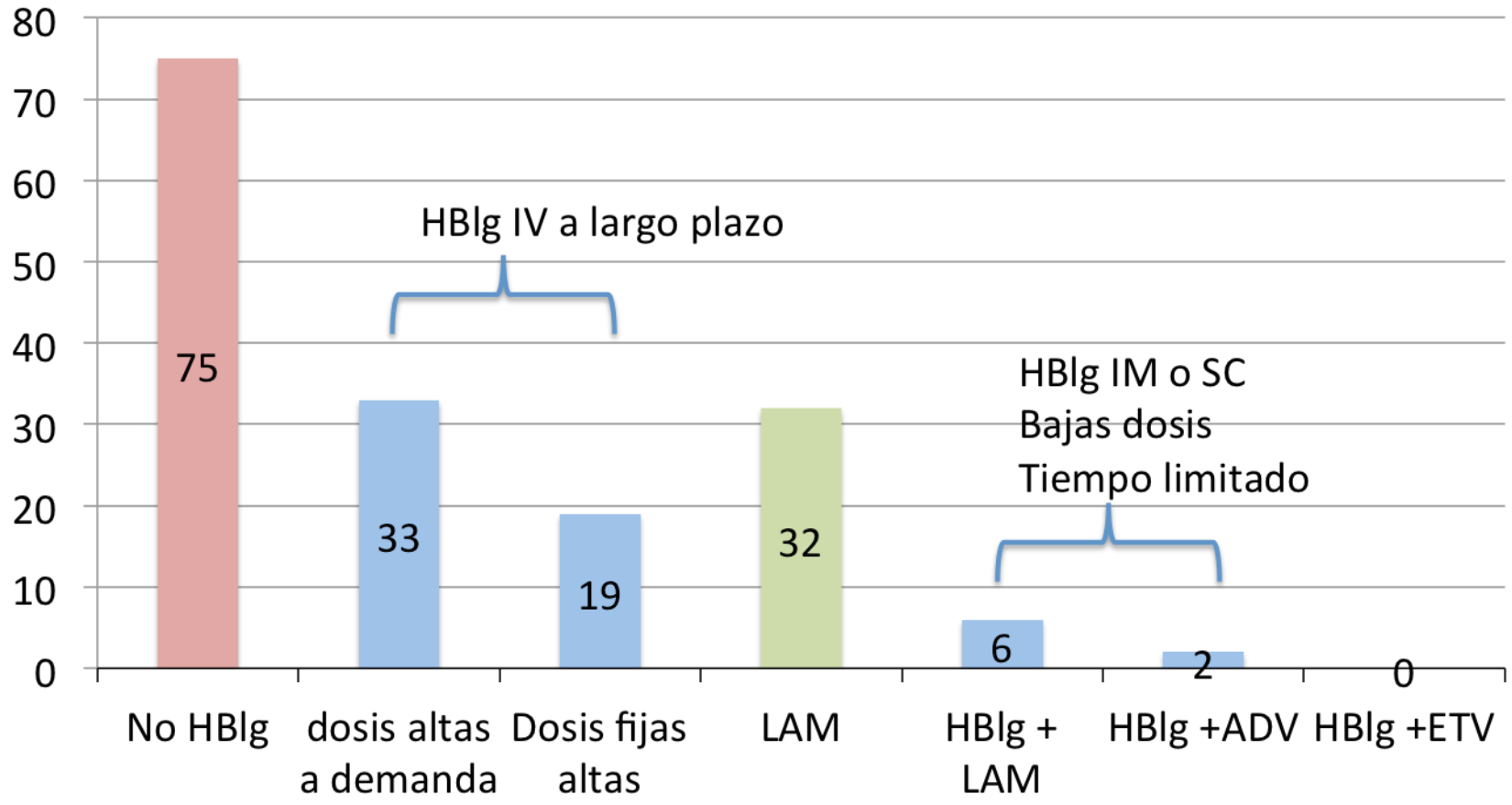
1997- 2003

Supervivencia > 85% a los 5 años del trasplante

Kim R et al. Transplant 2004

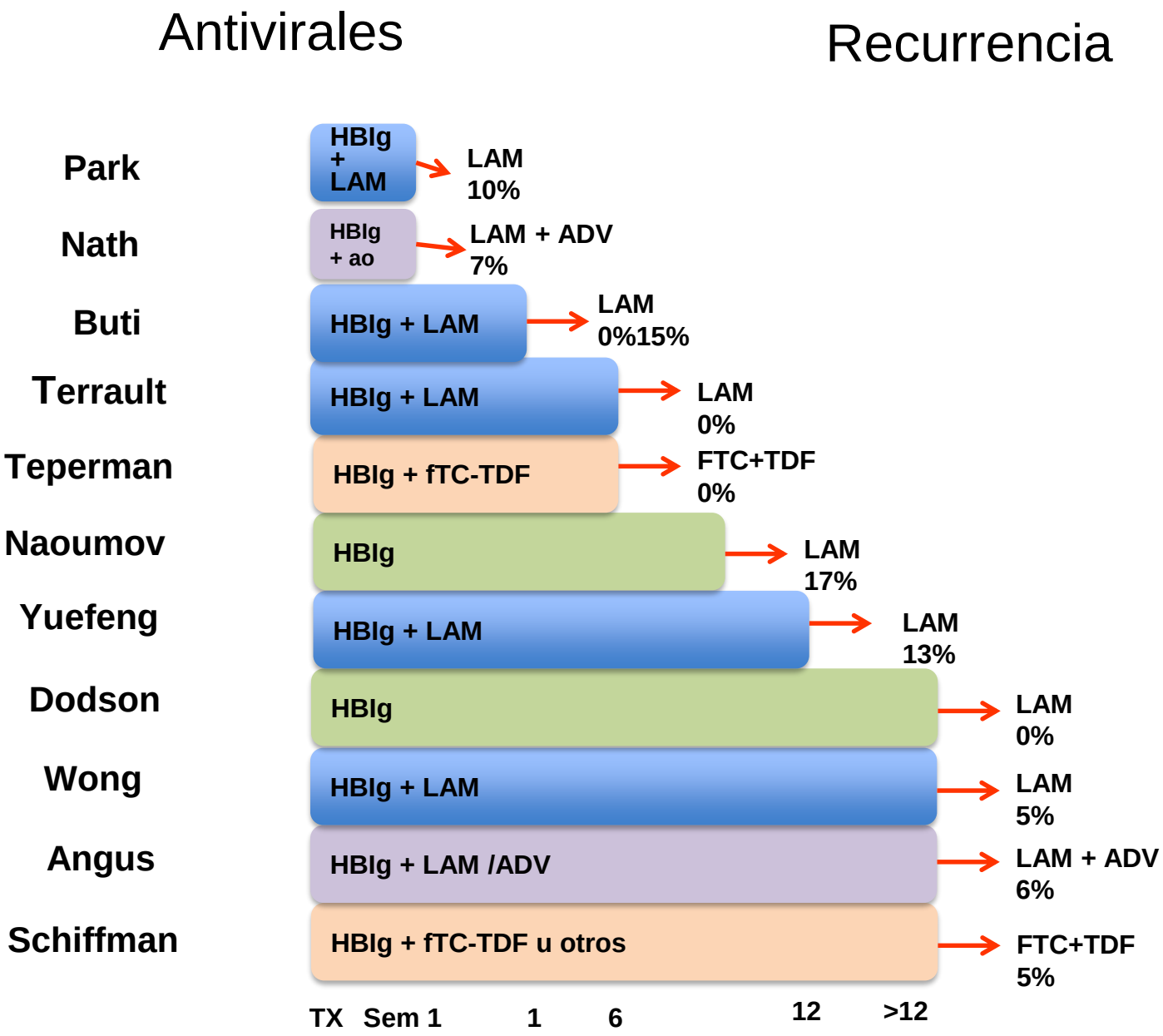
Recurrencia de hepatitis B post trasplante

Reaparición o persistencia de HBsAG en suero



Perillo L 2001, E Cholongitas 2011 , XF XI 2009 Ueda 2012, D Samuel , N Terrenaut

Recurrencia B con IGHB + AO



Recaída de alcohol después de Tx por cirrosis alcohólica

Meta-análisis 995 pac Tx por alcohol: recurrencia anual 4.7% en consumidores de alcohol vs 2.9% en grandes consumidores pre tx.

Author, year	No. of patients	Mean age, years	% Males	Median f/u, years	Number of liver biopsies	% biopsies in relapsers	% biopsies in abstainers
Lucey *et al.* (2009)	50	NA	80	5.3	33	39	61
Pageaux *et al.* (2003)	128	49	81	4.5	93	41	59
Cuadrado *et al.* (2005)	54	49	80	8.3	120	28	72
Faure *et al.* (2012)	206	51	NA	6.8	NA	NA	NA
Rice *et al.* (2013)	300	NA	73	6.5	72	33	67
Egawa *et al.* (2014)	140	NA	63	3.7	73	27	73
Bade and Singal (2014)	117	54	87	7.0	55	22	78
Summary	995	51	77	6	446	32	68

- Relapsers: mayor odds para esteatosis [4.1 (2.4–6.9)]
  esteatohepatitis [4.5 (1.4–14.2)]
  alcoholic hepatitis [9.3 (1.01–85)]
  advanced fibrosis or cirrhosis [8.4 (3.5–20)]
  3-fold more to die at 10 years of follow-up: [3.67 (1.42–9.50)]
- Recurrent alcoholic cirrhosis occurring in 9% of biopsied patients
- Extra-hepatic malignancy, and cardiovascular events were common causes for patient mortality

Alcohol relapse was defined as daily alcohol intake of more than 30 g/ Day. Heavy drinking was defined as more than 14 units per week and/or periods of time with more than 4 units per day

Sudha Kodali . Alcohol and Alcoholism 2018

Recurrencia Post-Trasplante Hepático

1. Prevalencia variable
2. Tratamientos para reducir el daño o recurrencia
3. Es relevante tener presente que mas allá de las recurrencias la mortalidad esta vinculada a enfermedad cardiovascular