Akademia Medyczna w Warszawie

Post-liver transplantation management

Klinika Medycyny Transplantacyjnej, Nefrologiii Chorób Wewnętrznych

Instytut Transplantologii

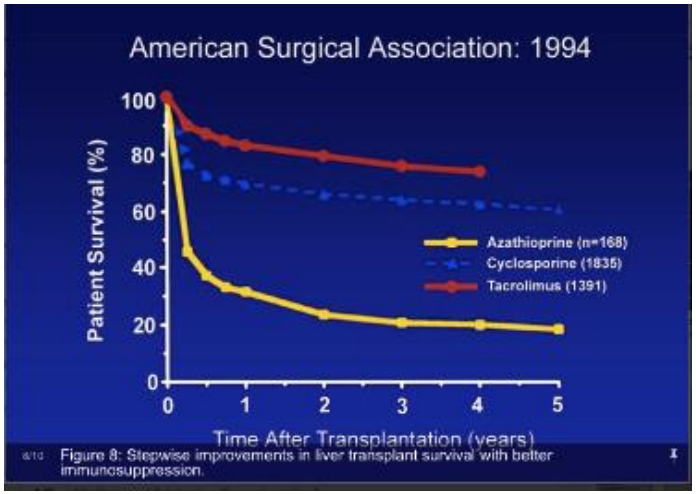
Akademia Medyczna w Warszawie

Rok zał. 1901
SZPITAL DZIECIĄTKA JEZUS

liver transplantation history

•**1963** r, Denver, Profesor **Thomas Starzl** the first trial of liver transplantation

•July **1967** r , the same Profesor make the first with success liver transplantation



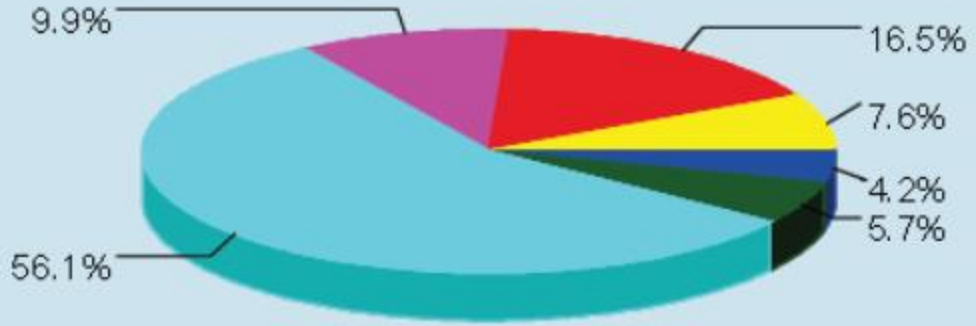
Number of Liver Transplantations per country

137863 Liver Transplantations

4	11	16	29	58	82	88	110
178	283	580	642	751	821	951	1087
1304	1870	2033	2140	2569	2813	3125	3416
4918	5913	15832	18534	21431	22289	23985	

Primary Disease Leading to Liver Transplantation in Europe

N = 119,803 (1988-2015)



Acute hepatic failure : 9048
Cirrhosis : 67208
Cancers : 19756
Metabolic disease : 6870
Cholestatic-Cong disease : 11874
Other disease : 5047

Details of Other Main Diseases :

Other liver diseases-unprecised	2246
Benign liver tumors or Polycystic dis	1658
Budd Chiari	1020
Parasitic disease	91
Hepatopulmonary syndrome	18
TPN-induced cholestasis	11
HIV	1
Microangiopathy	1
Small for size syndrom	1

Indication to liver transplantation - adults

- **cirrhosis:**
  - HBV, HCV infection
  - alcoholic liver disease
  - autoimmune hepatitis
  - PBC, PSC
- **metabolic diseases**(Wilson disease, hemochromatosis, alfha1-antitrypsin deficiency)
- **piorunująca niewydolność wątroby** (drugs liver damage , mushroom poisoning, fulminant hepatitis B, acute Wilson disease decompensation,
- **tumors** (carcinoma hepatocellulare, hepatoblastoma, polycystic, hemangiomas)
- **inne**, np. liver artery thrombosis, Budd Chiari syndrome, HELP, cryptogenic cirrhosis
- transplant liver decompensation

Cirrhosis as Primary Disease in Europe

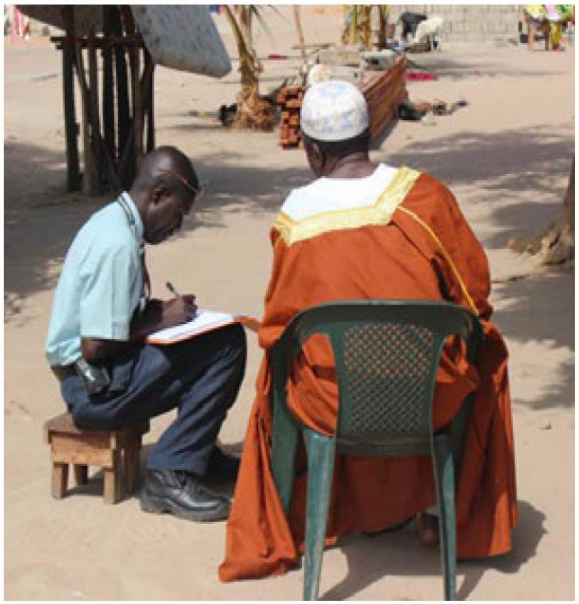
N = 67,208 (1988-2015)

- Alcoholic cirrhosis : 22574
- Cryptogenic (unknown) cirrhosis : 5259
- Primary biliary cirrhosis : 5661
- Viral+Alcoholic cirrhosis : 2617
- Autoimmune Cirrhosis : 2754
- Other cirrhosis : 2619
- Secondary biliary cirrhosis : 909
- Virus related cirrhosis : 24815

Problems

- **disease recurrence**
- vessels complications
  - artery, vena portae, hepatic veins
- bile ducts complications
- chronic kidney disease
- metabolic bone disease
- infections
  - bacterial, fungal, viral
- cardio-vascular disease
  - obesity, type 2 diabetes, lipids abnormalities, hypertension

HBV

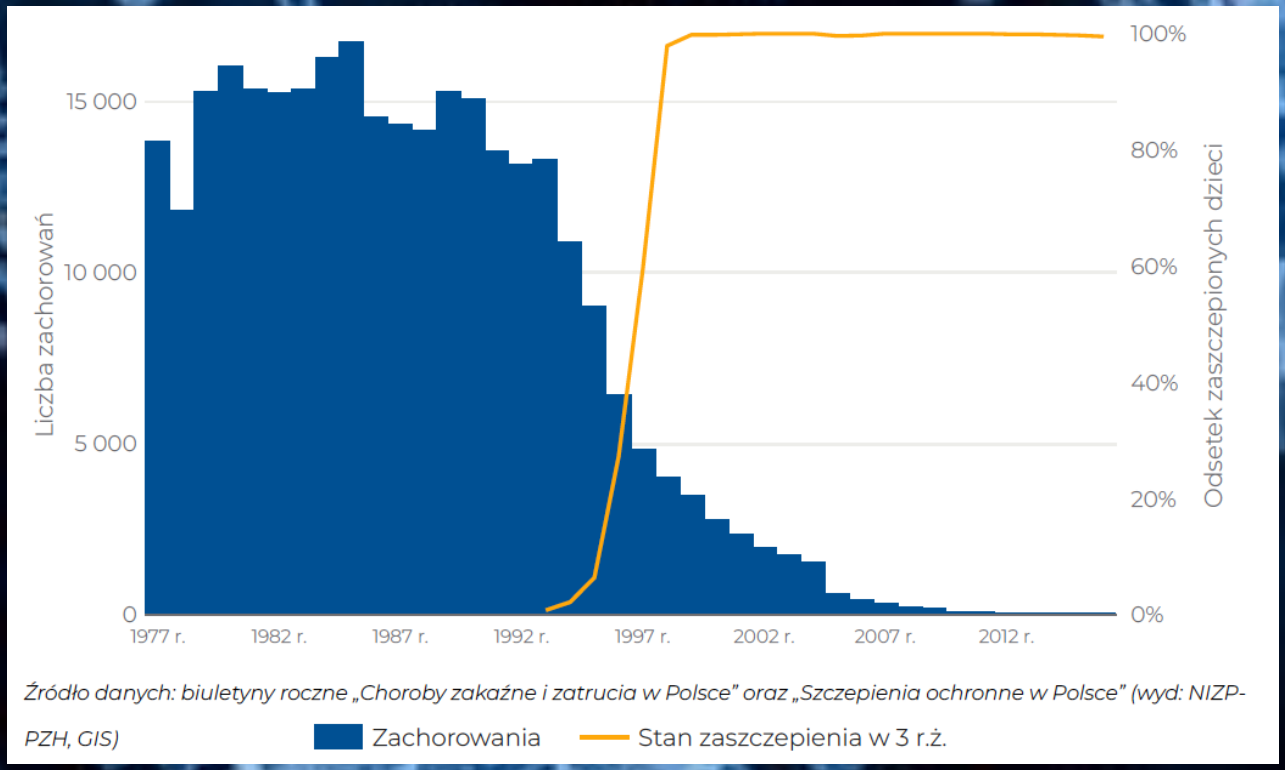


257

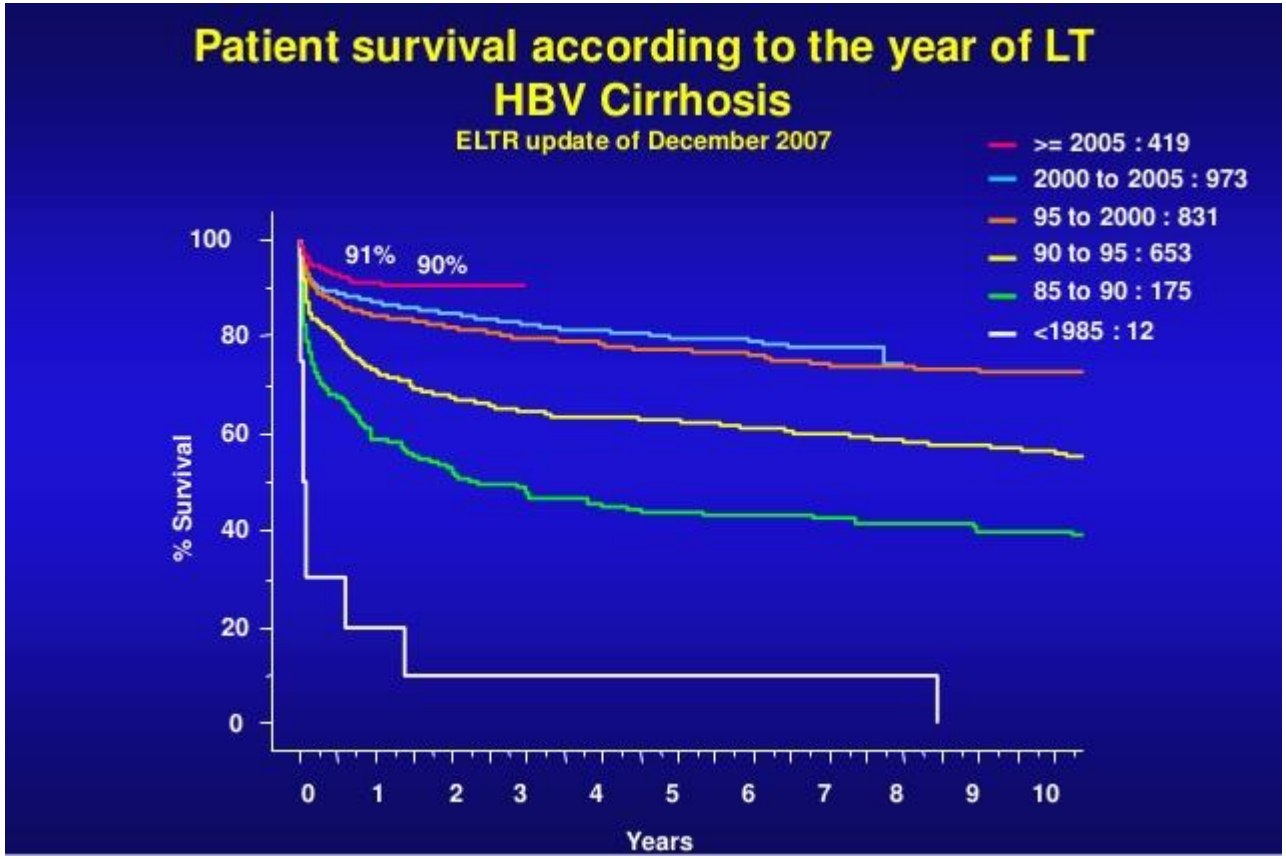
MILLION PERSONS WORLDWIDE ARE LIVING WITH HBV

World Health Organization

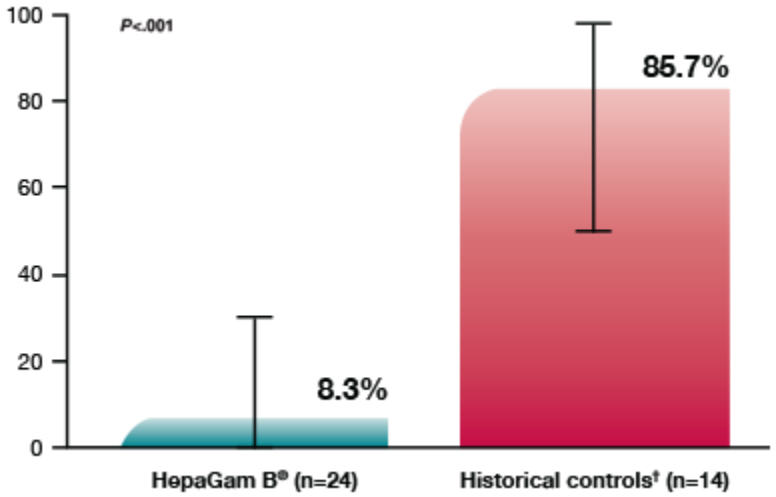
WZW B



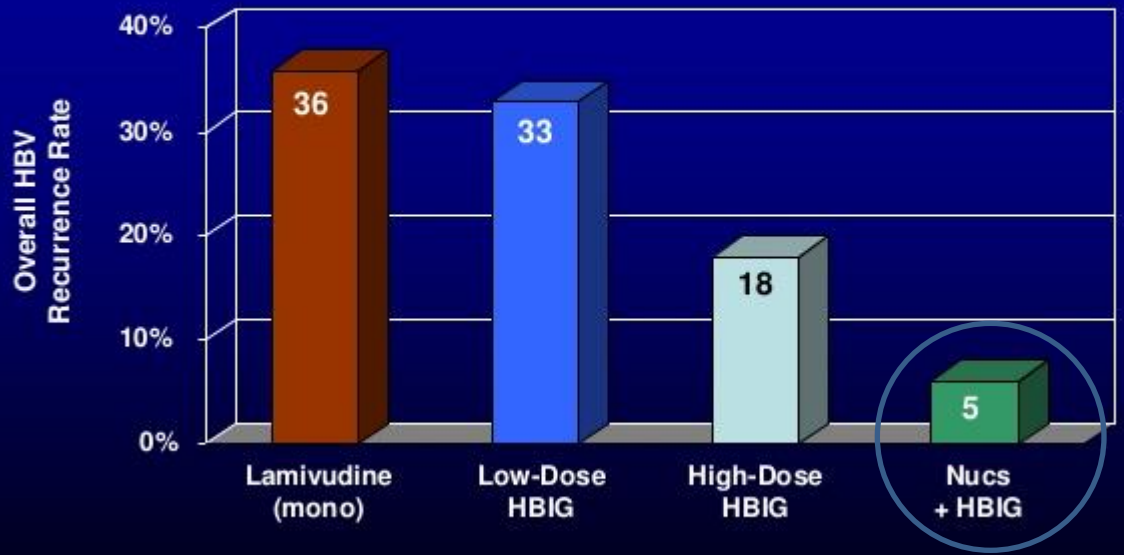
Źródło danych: biuletyny roczne „Choroby zakaźne i zatrucia w Polsce" oraz „Szczepienia ochronne w Polsce" (wyd: NIZP-PZH, GIS)


Patient survival according to the year of LT
HBV Cirrhosis
ELTR update of December 2007
>= 2005 : 419
2000 to 2005 : 973
95 to 2000 : 831
90 to 95 : 653
85 to 90 : 175
<1985 : 12
91%
90%
100
80
60
40
20
0
% Survival
0
1
2
3
4
5
6
7
8
9
10
Years

Proportion of patients with HBV recurrence*



Strategies for Prevention of HBV Recurrence



Adapted from Seehofer D, Berg T. *Transplantation*. 2005;80(1 suppl):S120

How to decrease the risk of HBV reinfection

- HBV DNA 100 – 1000 IU/ml
- **HBV DNA negative before transplantation**

Every patient with HBV infection should be treated before transplantation to make viremia negative if possible

Risk factors of HBV reactivaction

High risk patients

- HBeAg +
- HBeAg – but high HBV DNA level
- patients with drug resitance

Low risk patients

- fuliminant HBV
- co-infection HDV
- low HBV DNA level

AntyHBs globulin as prophylaxis HBV recurrence after liver transplantation

- 10000 U/dose:

One dose during transplantation

week 1: one dose days 1-7

week 2 - 12: one dose every 2 weeks

miesiąc 4 i kontynuacja: one dose monthly

Expected antyHBs first week after transplantation - 500 U/l

First year : **anty HBs 500 U/l high risk group**

100 U/l low risk

HBV recurrence diagnosis

- serum
  - de novo HBsAg +, HBeAg +
  - DNA HBV +
- Liver graft
  - HBsAg +, HBcAg +, DNA HBV +

Prophylaxis and treatment of hepatitis B infection in the setting of liver transplantation

Delia D'Avola and José Ignacio Herrero

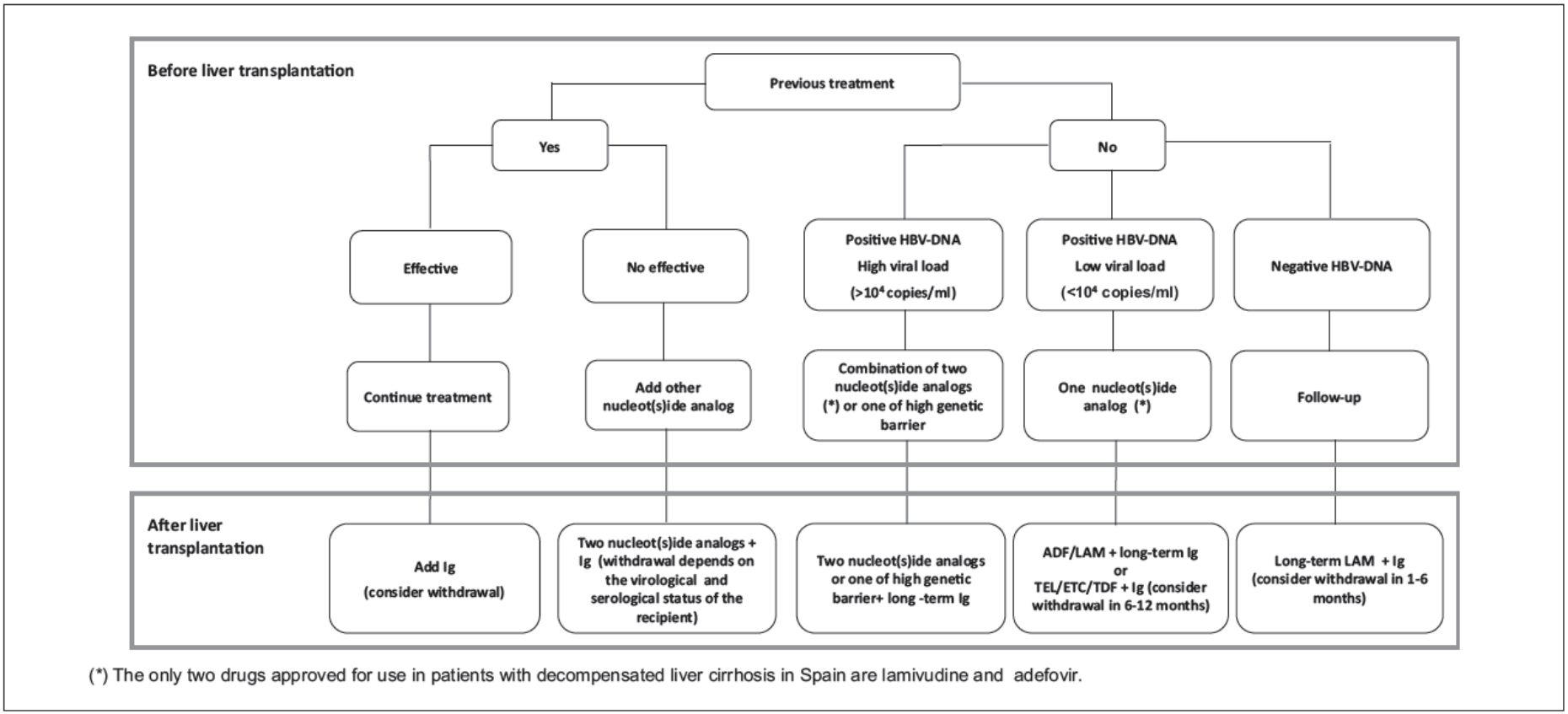


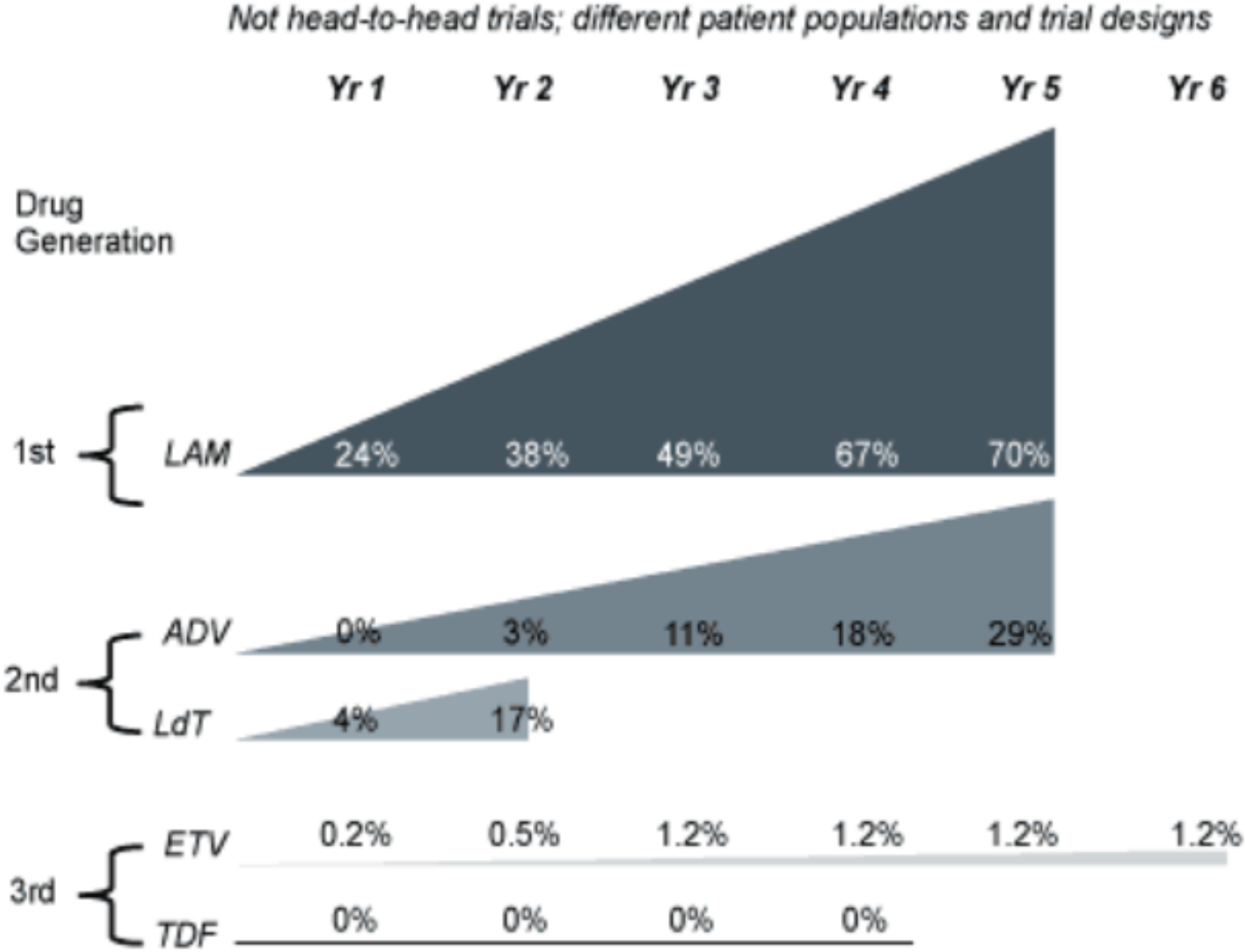
Fig. 1. Proposed prophylactic and treatment protocol of hepatitis B before and after liver transplantation (Ig: anti-hepatitis B hyperimmune immunoglobulin; ADF: adefovir; LAM: lamivudine; TEL: telbivudine; ETC: entecavir; TDF: tenofovir).

Rev Esp Enferm Dig (Madrid)
Vol. 103. N.° 3, pp. 142-149, 2011

Table 6. Circumstances Where a Certain First-line Anti-HBV Agent May Be Preferred Over Others

Setting	Anti-HBV Agent
Decompensated cirrhosis	• Entecavir preferred • Tenofovir may be appropriate
Renal insufficiency	• Entecavir preferred (with dose modification)
Pregnancy, woman of child-bearing age planning pregnancy in the near term	• Tenofovir preferred
Woman of child-bearing age wishing to eradicate virus prior to pregnancy	• Peginterferon alfa-2a or peginterferon alfa-2b
HIV coinfection	• Tenofovir plus emtricitabine or lamivudine
Younger patients	• Interferon-based therapy

Figure 2. Rates of confirmed antiviral resistance.



ADV, adefovir; ETV, entecavir; LAM, lamivudine; LdT, telbivudine; TDF, tenofovir.

Entecavir	0.5 mg/day PO; 1.0 mg/day for patients with lamivudine refractory/ resistance or decompensated disease	Indefinite	Lactic acidosis, severe hepatomegaly, severe acute exacerbations of hepatitis upon discontinuation	Not recommended for HIV-coinfected patients not receiving HAART; administer on an empty stomach; dose adjustment for renal impairment; not optimal for patients with lamivudine resistance
Tenofovir	300 mg/day PO	Indefinite	Lactic acidosis, severe hepatomegaly, renal insufficiency, Fanconi's syndrome, osteomalacia, decrease in bone mineral density, severe acute exacerbations of hepatitis upon discontinuation	Also active against HIV; do not use as monotherapy in HIV-coinfected patients; dose adjustment for renal impairment; may be less effective in patients resistant to adefovir; monitor creatinine clearance and serum phosphorous on therapy for patients at risk for renal impairment

Management of hepatitis B virus infection after liver transplantation

Miguel Jiménez-Pérez, Rocío González-Grande, José Mostazo Torres, Carolina González Arjona, Francisco Javier Rando-Muñoz

Table 1 Risk of de novo hepatitis B in recipients of anti-HBc-positive organs

Recipient status	Naive	AntiHBc$^+$ AntiHBs$^-$	AntiHBc$^+$ AntiHBs$^+$	AntiHBc$^-$ AntiHBs$^+$
No prophylaxis	> 40%	13%	< 2%	10%
With prophylaxis	12%	< 4%	< 2%	< 2%
	High risk	Intermediate risk	Low risk	Intermediate risk

World J Gastroenterol 2015 November 14; 21(42): 12083-12090

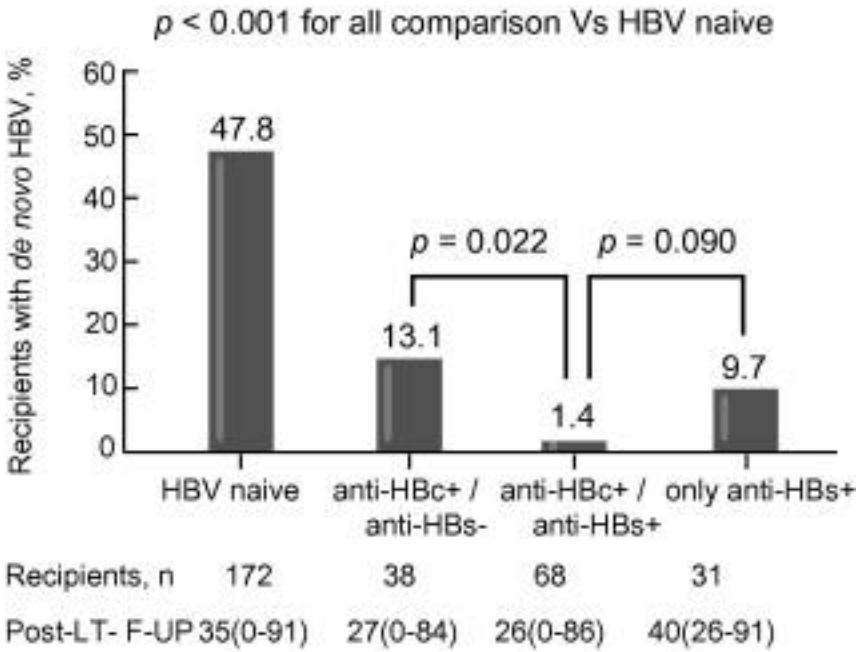


Fig. 1. Risk of de novo hepatitis B virus (HBV) infection in HBsAg-negative recipients who received liver grafts from anti-HBc positive donors and no HBV prophylaxis after liver transplantation (LT) in relation to their HBV serological status before transplant.

Evangelos Cholongitas, George V. Papatheodoridis, Andrew K. Burroughs

Liver grafts from anti-hepatitis B core positive donors: A systematic review

Journal of Hepatology, Volume 52, Issue 2, 2010, 272–279

Table 9. Commonly Encountered Mutations and Susceptibility to Nucleo(s)tide Analogues[Zoulim 2009]

Amino Acid Substitution	Lamivudine	Adefovir	Telbivudine	Entecavir	Tenofovir
Wild type					
M204I					
L180M + M204V					
N236T					
A181T/V					
L180M + M204V/I ± I169T ± V173L ± M250V					
L180M+ M204V/I ± T184G ± S202I/G					

Medium gray, susceptible; light gray, intermediate/reduced susceptibility; dark gray, resistant.

Table 10. Options for Treatment Modification in the Case of a Suboptimal Response Based on Known Data on Cross-Resistance

Nucleo(s)tide Analogue	AASLD Recommendations[Lok 2009]	EASL Recommendations[EASL HBV]
Lamivudine	• Add tenofovir or adefovir • Switch to tenofovir plus emtricitabine	• Switch to tenofovir • Add adefovir if tenofovir not available
Adefovir	• Add lamivudine • Switch to tenofovir plus emtricitabine • Switch to or add entecavir	• Switch to entecavir or tenofovir if patient was nucleos(t)ide analogue naive before adefovir • Switch to tenofovir and add nucleoside analogue if patient had previous lamivudine resistance
Telbivudine	• Add tenofovir or adefovir • Switch to tenofovir plus emtricitabine	• Switch to or add tenofovir • Add adefovir if tenofovir not available
Entecavir	• Switch to tenofovir or tenofovir plus emtricitabine	• ·Switch to or add tenofovir • Add adefovir if tenofovir not available
Tenofovir	• N/A	• Add entecavir, telbivudine, lamivudine, or emtricitabine

N/A, not applicable.

HCV

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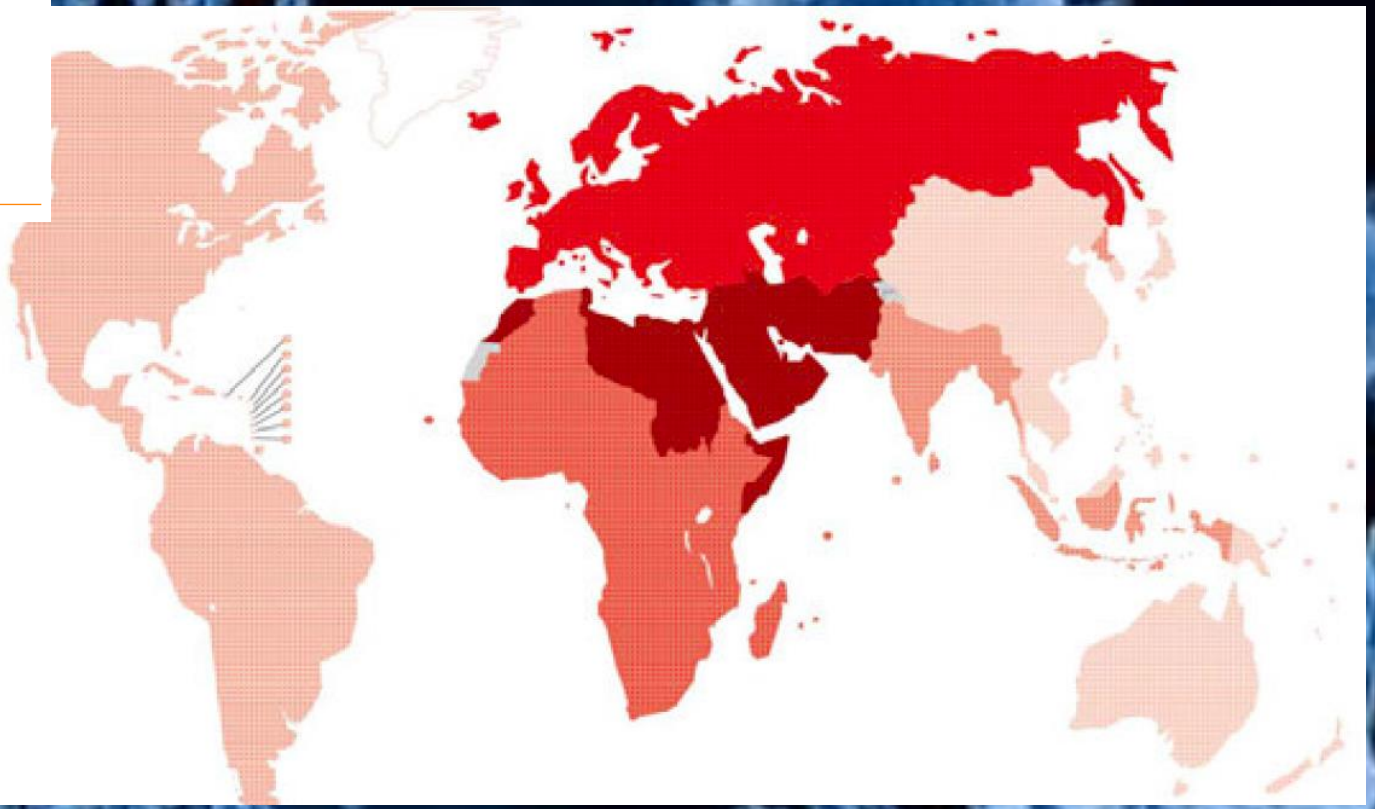
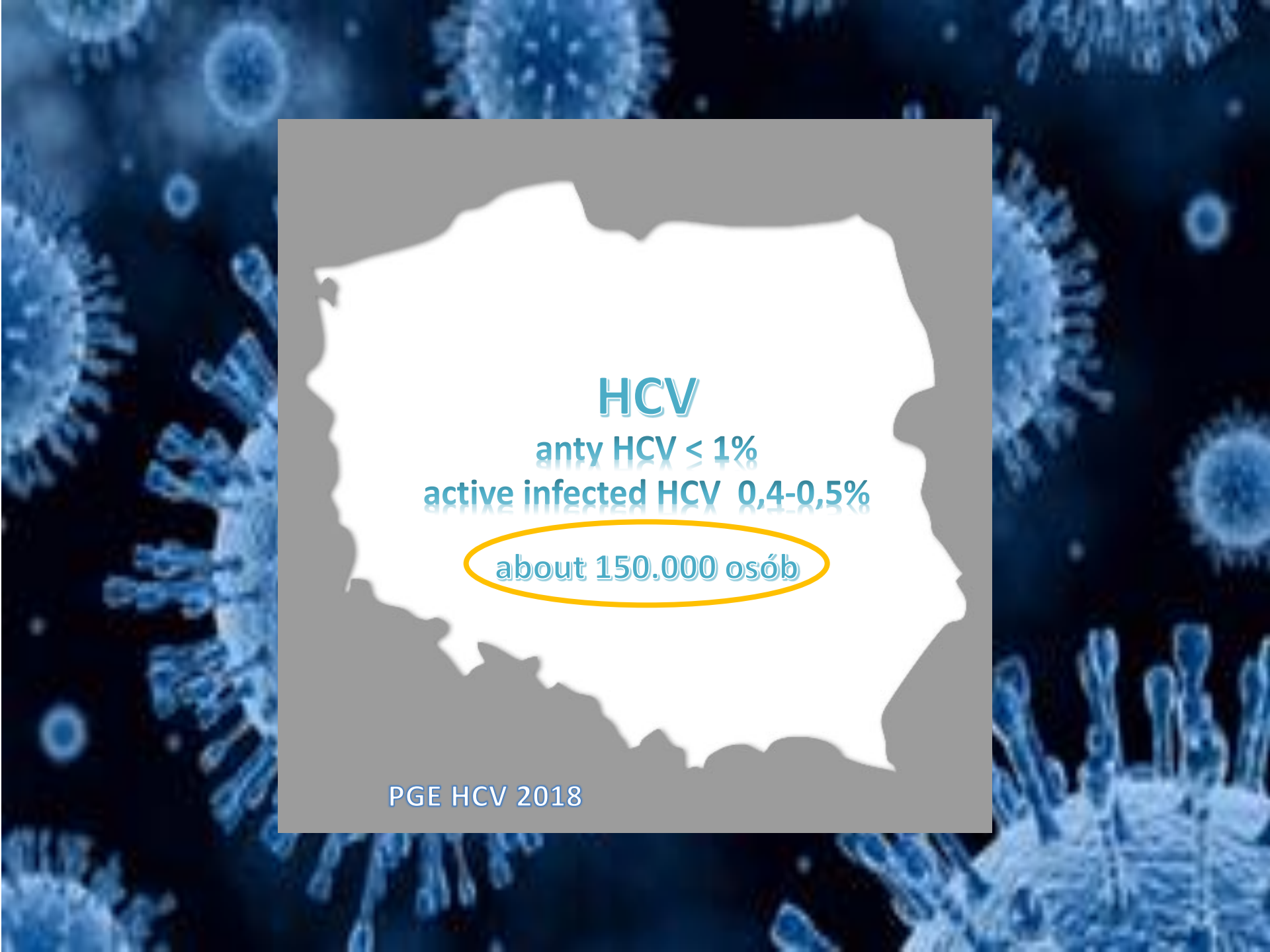
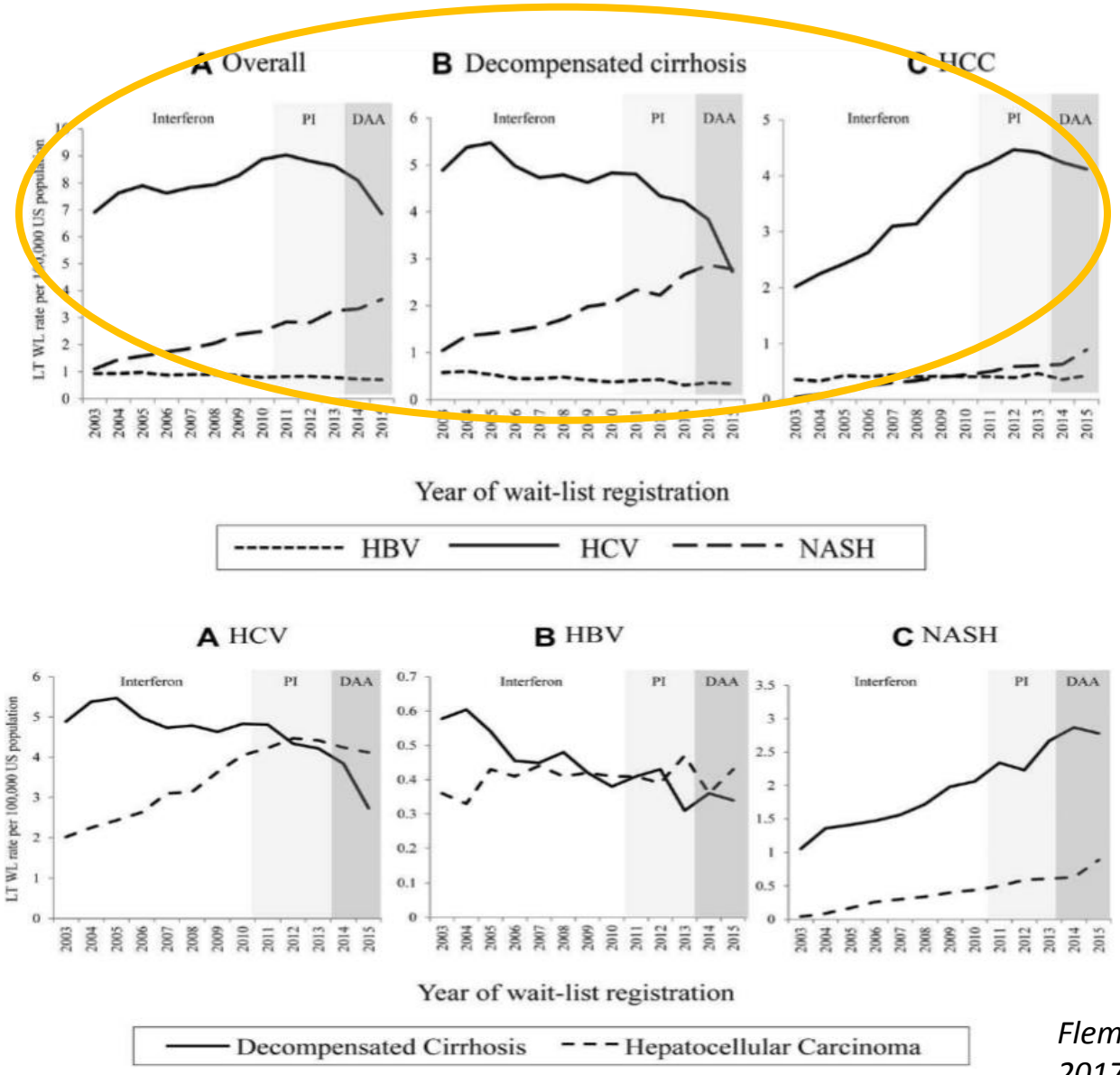
MILLION PERSONS WORLDWIDE ARE LIVING WITH HCV



World Health Organization


HCV
anty HCV < 1%
active infected HCV 0,4-0,5%
about 150.000 osób
PGE HCV 2018

Wpływ terapii DAA na listę oczekujących na przeszczepienie wątroby



Flemming J.A. at al Hepatology 2017,65:3,804-12

Wiremia HCV po OLTx

Faza	RNA HCV	Komentarz
ahepatyczna	↓ 0.5 $\log_{10}$ UI/ml	usunięcie wątroby własnej
reperfuzja	↓	deponowanie w przeszczepie
2 tydzień	↑↑	początek wzrostu
4 miesiąc	↑↑↑	maksymalny wzrost
1 rok	↑↑	10 – 20 krotny wzrost

Management of Hepatitis C Before and After Liver Transplantation in the Era of Rapidly Evolving Therapeutic Advances

Chalermrat Bunchorntavakul[1] and K. Rajender Reddy[2]

Journal of Clinical and Translational Hepatology **2014** vol. 2 | 124–133

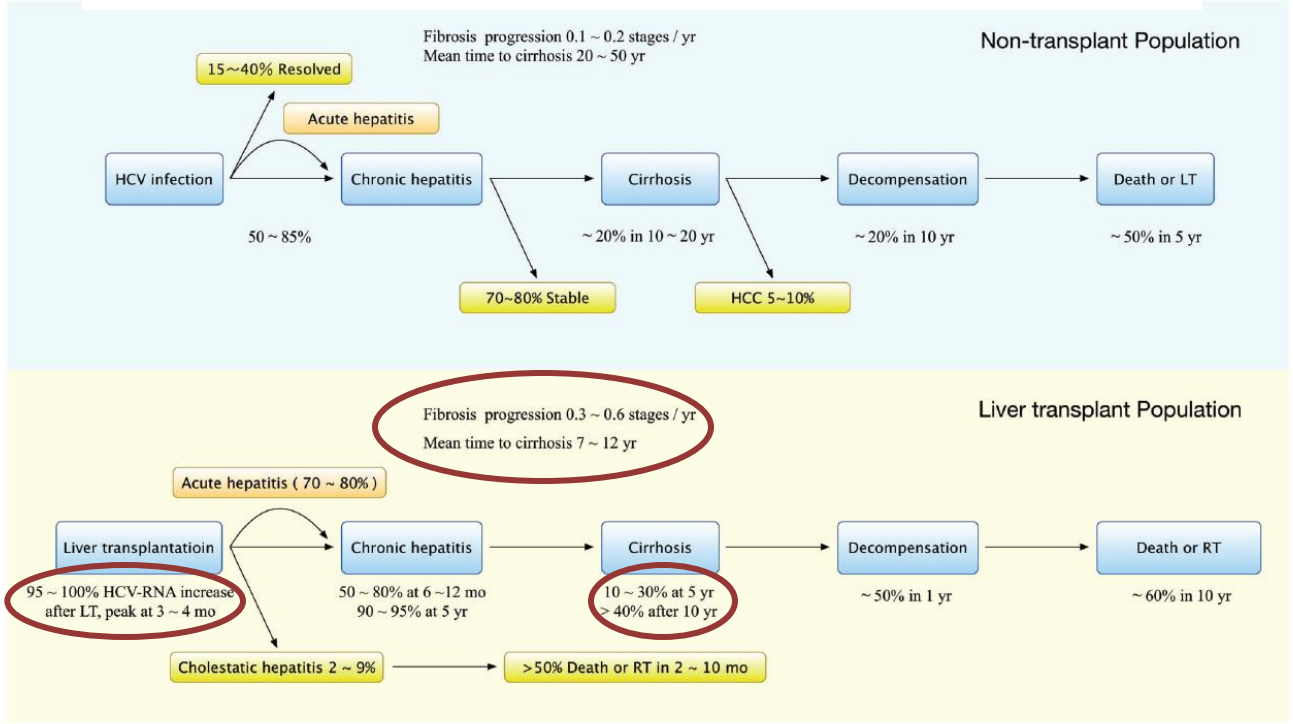
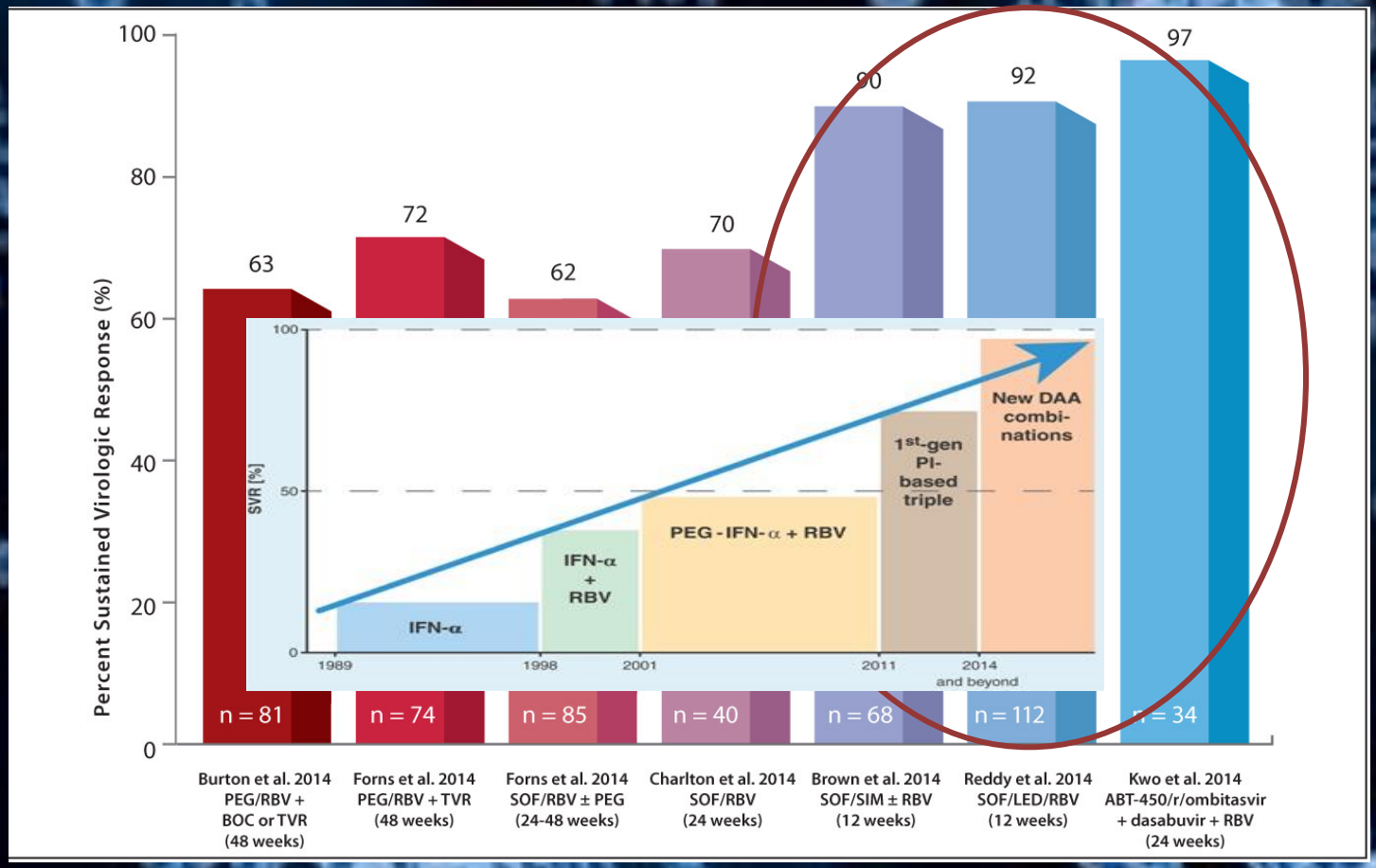


Fig. 1. Natural history of HCV in non-transplant and liver transplant populations. Abbreviations: HCV, hepatitis C virus; LT, liver transplantation; RT, retransplantation

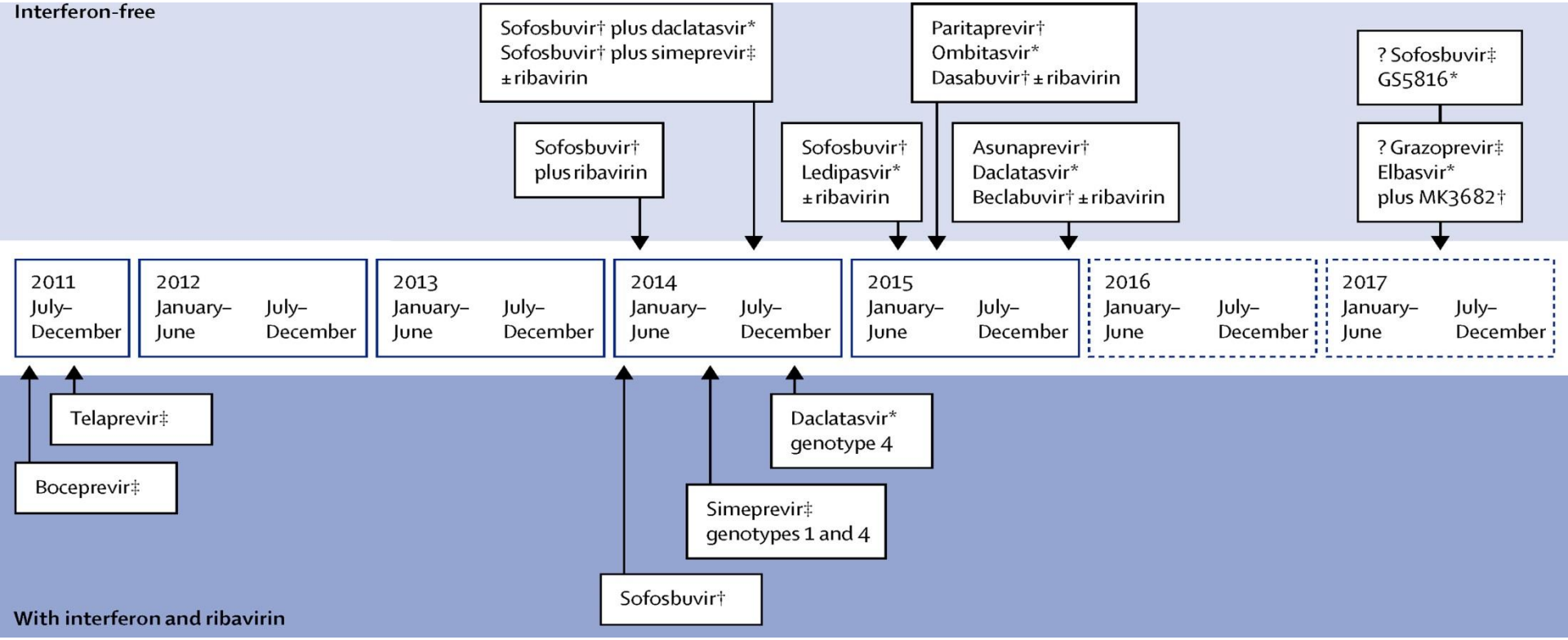
HCV treatment



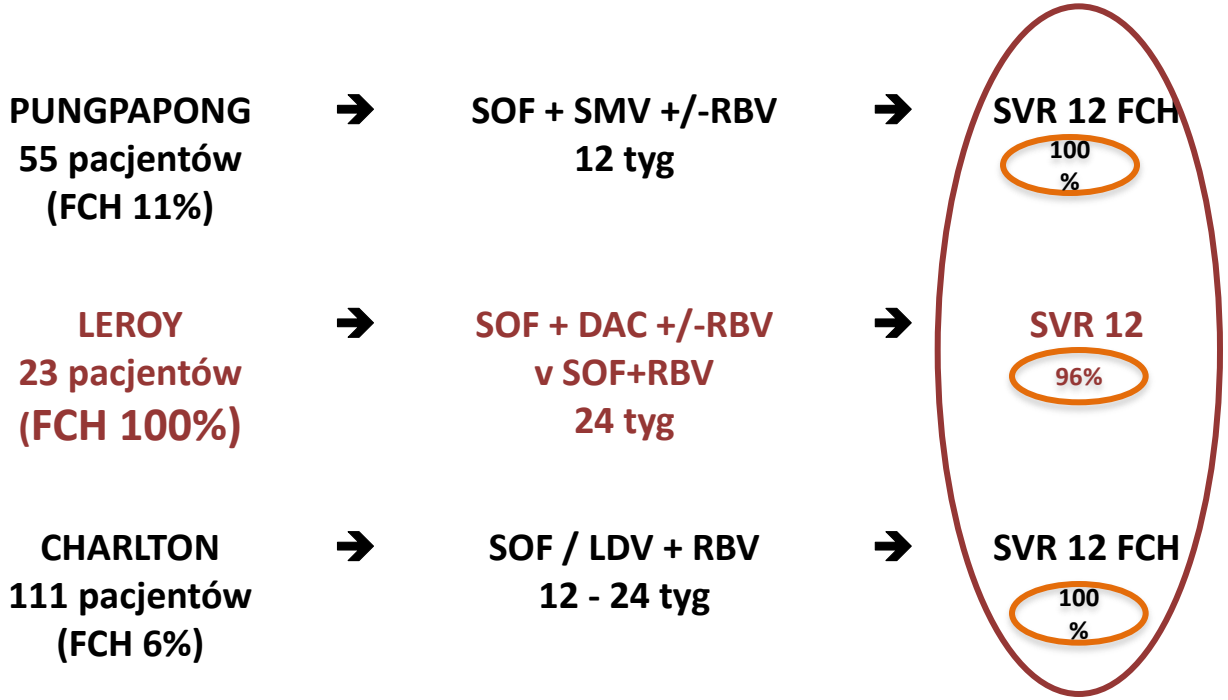
Hepatitis C

Dr Daniel P Webster, FRCPath, Prof Paul Klenerman, FRCPath, Prof Geoffrey M Dusheiko, FRCP

The Lancet Volume 385, Issue 9973, Pages 1124-1135 (March 2015)



The patient after Olt with FCH (genotype 1 i 4)



DAA Interactions With Calcineurin Inhibitors

	Cyclosporine (CSA)	**Tacrolimus** (TAC)
Sofosbuvir (SOF)	4.5-fold ↑ in SOF AUC, but GS-331007 metabolite unchanged; no a priori dose adjustment	No interaction observed; no a priori dose adjustment
Ledipasvir	No data; no a priori dose adjustment	No data; no a priori dose adjustment
Paritaprevir/ritonavir/ombitasvir + dasabuvir (PrOD)	5.8-fold ↑ in CSA AUC; modeling suggest using 1/5 of CSA dose during PrOD treatment, monitor CSA levels and titrate CSA dose as needed	57-fold ↑ in TAC AUC; modeling suggests TAC 0.5 mg every 7 days during PrOD treatment, monitor TAC levels and titrate TAC dose as needed
Elbasvir/grazoprevir (EBR/GZR)	15-fold ↑ in GZR AUC and 2-fold ↑ in EBR AUC; combination is not recommended	43% ↑ in TAC; no a priori dose adjustment
Velpatasvir	No interaction observed; no a priori dose adjustment	No data; no a priori dose adjustment
Glecaprevir/pibrentasvir (GLE/PIB)	5-fold ↑ in GLE AUC with higher doses (400 mg) of CSA; not recommended in patients requiring stable CSA doses >100 mg/day	1.45-fold ↑ in TAC AUC; no a priori dose adjustment, monitor TAC levels and titrate TAC dose as needed
Sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX)	9.4-fold ↑ in VOX AUC; combination is not recommended	No data; no a priori dose adjustment

AUC, area under the curve

AASLD
AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

IDSA
Infectious Diseases Society of America

Pharmacokinetics and Dose Recommendations for Cyclosporine and Tacrolimus When Coadministered With ABT-450, Ombitasvir, and Dasabuvir

P. Badri*, S. Dutta, E. Coakley, D. Cohen, B. Ding, T. Podsadecki, B. Bernstein, W. Awni and R. Menon

AbbVie Inc., North Chicago, IL

Table 3: Projected cyclosporine (CsA) and tacrolimus C_{trough} (C_{24}) values for posttransplant patients who initiate 3D treatment

	C_{trough} before 3D treatment[1] (ng/mL)	C_{trough} during 3D treatment (ng/mL)
CsA dose	**250 mg BID (500 mg daily)**	**100 mg QD (1/5th total daily dose)**
	70–90	90–120
	100–120	100–120
Tacrolimus dose	**2 mg (BID)**	**0.5 mg every 7 days**
	5–7	6–12
	8–10	8–12
	2 mg (BID)	**0.5 mg every 14 days**
	5–7	3–4
	8–10	3–6
	2 mg (BID)	**0.2 mg[2] every 72 h**
	5–7	5–8
	8–10	8–9

Use of direct-acting antiviral agents in hepatitis C virus- infected liver transplant candidates

Chiranjeevi Gadiparthi *World J Gastroenterol* 2018 January 21; 24(3): 315-322

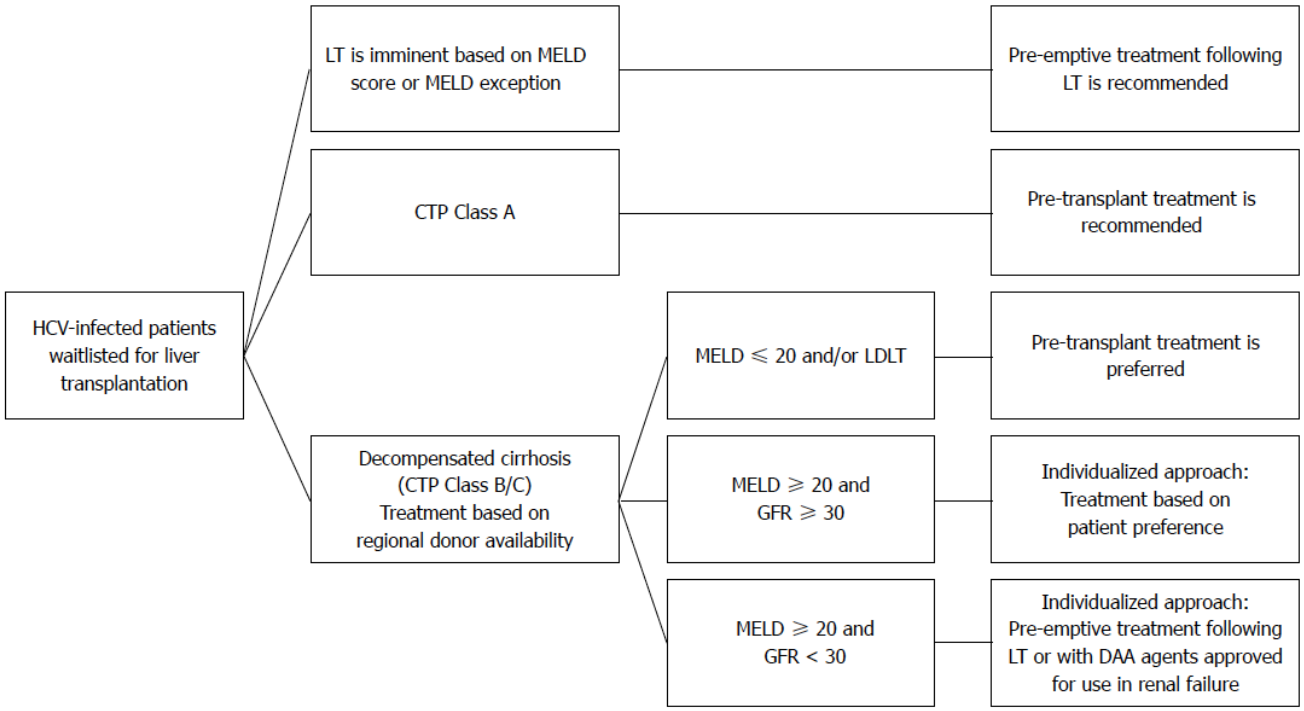


Figure 1 A pragmatic treatment approach in hepatitis C virus-infected liver transplant candidates. HCV: Hepatitis C virus; MELD: Model for End-Stage Liver Disease; LT: Liver transplantation; CTP: Child-Turcotte-Pugh; GFR: Glomerular filtration rate; LDLT: Living donor liver transplantation.

Recommended regimens listed by evidence level and alphabetically for:

Treatment-Naive and -Experienced Patients With Genotype 1, 4, 5, or 6 Infection in the Allograft Without Cirrhosis

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[a]	12 weeks	I, A
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) with weight-based ribavirin	12 weeks	I, A

Recommended regimen for:

Treatment-Naive and -Experienced Patients With Genotype 1, 4, 5, or 6 Infection in the Allograft With Compensated Cirrhosis

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) with weight-based ribavirin for 12 weeks	12 weeks	I, A

Recommended regimen for:

Treatment-Naive and -Experienced Patients With Genotype 1, 4, 5, or 6 Infection in the Allograft and Decompensated Cirrhosis[a]

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) with low initial dose of ribavirin (600 mg, increase as tolerated)	12 weeks	I, B

[a] Includes CTP class B and class C patients.

AASLD 2018

Recommended regimens listed by evidence level and alphabetically for:

Treatment-Naive and -Experienced Patients With Genotype 2 or 3 Infection in the Allograft Without Cirrhosis

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[a]	12 weeks	I, A
Daily daclatasvir (60 mg)[b] plus sofosbuvir (400 mg) with low initial dose of ribavirin (600 mg, increase as tolerated)	12 weeks	II, A

Recommended and alternative regimens listed by evidence level and alphabetically for:

Treatment-Naive and -Experienced Patients With Genotype 2 or 3 Infection in the Allograft With Compensated Cirrhosis

RECOMMENDED	DURATION	RATING
Daily daclatasvir (60 mg)[a] plus sofosbuvir (400 mg) with low initial dose of ribavirin (600 mg, increase as tolerated)	12 weeks	II, A

ALTERNATIVE	DURATION	RATING
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[b]	12 weeks	II, C
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) with weight-based ribavirin	12 weeks	II, C

[a] The dose of daclatasvir may need to be increased or decreased when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretroviral therapy.
[b] This is a 3-tablet coformulation. Please refer to the prescribing information.

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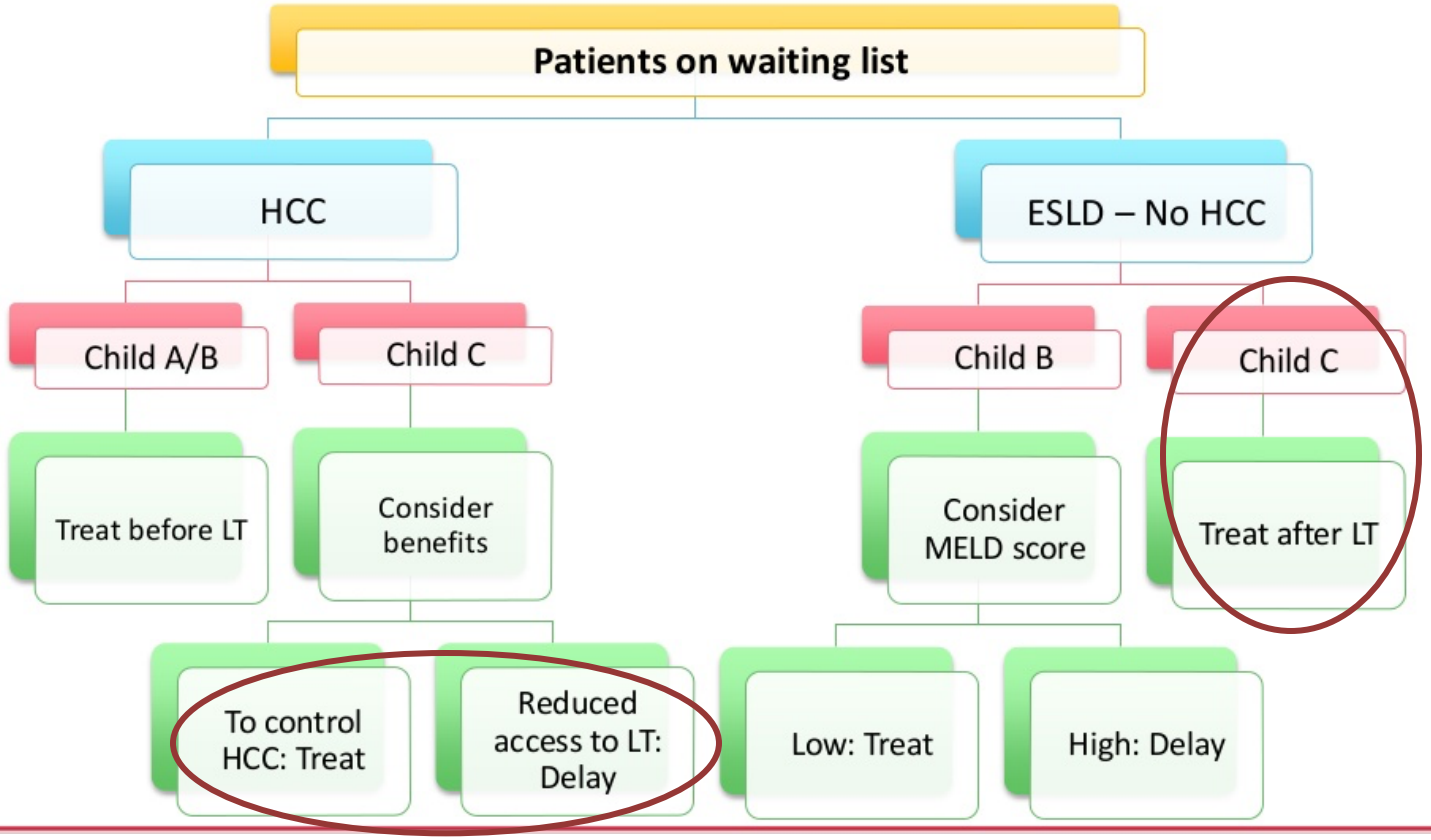
Conclusion 3: Management Proposal
Treatment with DAA Before or After LT



Didier Samuel Centre Hepatobiliaire Hopital Paul Brousse Villejuif France

Pros and Cons: Usage of organs from donors infected with hepatitis C virus – Revision in the direct-acting antiviral era

Audrey Coilly, Didier Samuel*

Journal of Hepatology **2016** vol. 64 | 226–231

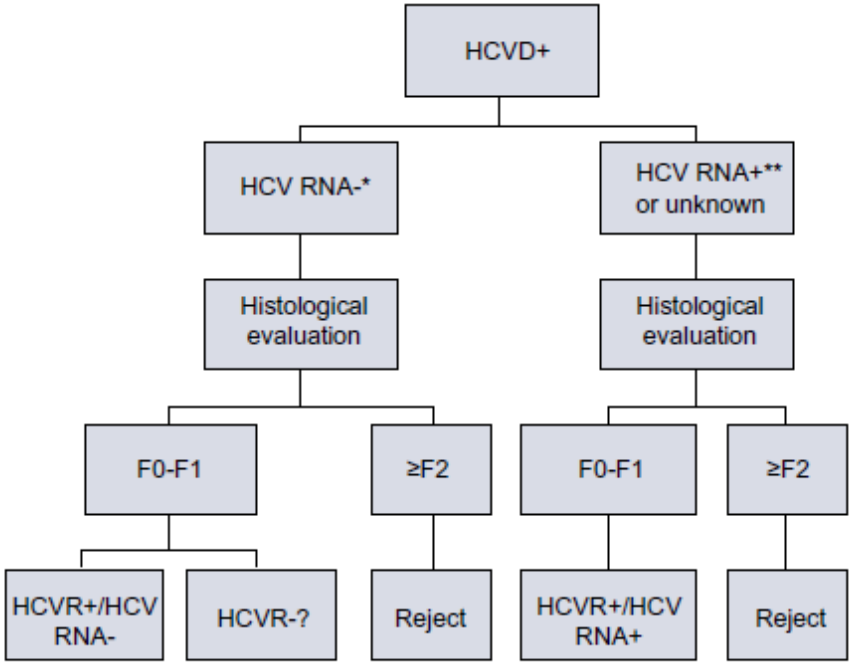


Fig. 1. Proposal to accept grafts from HCV infected donors. *Negativity of HCV RNA should be known, as determination at the time of harvesting is mostly technically impossible. **When known before harvesting, donors with genotype 3 or resistant virus should not be used.

- about %% HCV + donors
- **Transmission risk, if HCV PCR + donor**
  100% liver recipients
  48% heart recipients
  25% kidney recipients
- viral genotype domination?
- hist-pat - > 80% HCV + donors with liver fibrosis F≥2.
- the risk of high fibrosis progresion

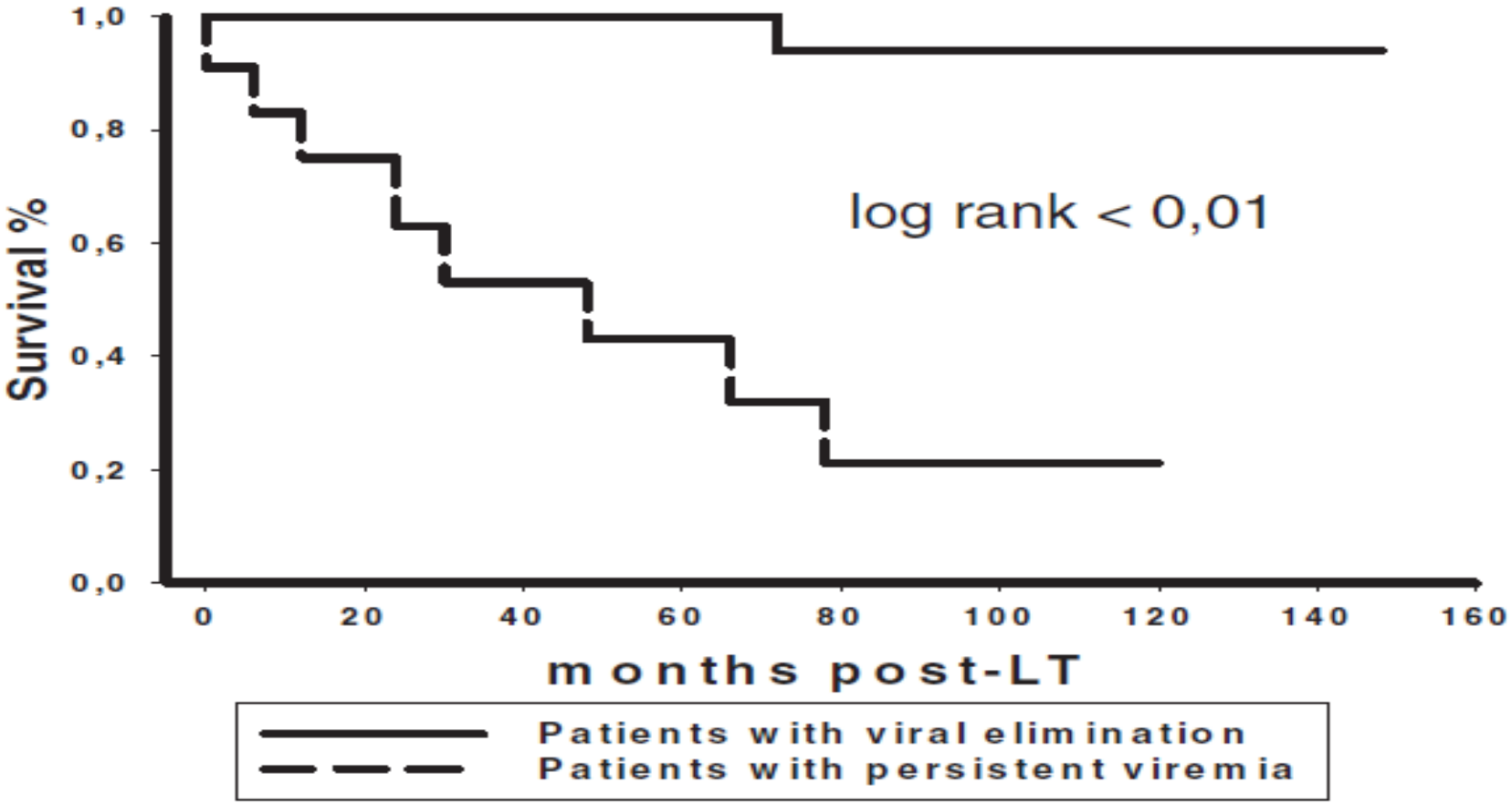


FIGURE 1. Clearance of serum HCV RNA resulted in significantly improved long-term survival.

One Standard Drink
= 14 grams of pure alcohol

1 can of regular beer
330ml
5% alc.

1 glass of wine
120 ml
12% alc.

1 shotglass of spirit
30 ml
40% alc.

2.5 shotglasses of sake
75 ml
18% alc.

Risk of liver cirrhosis

- **60-80 g/dobę** pure alcohol for 10 years - men
- **20 g/dobę – women**

- 6-41% liver cirrhosis

Chronic kidney disease

- calcineurin inhibitors toxicity
- old age
- low basal GFR and GN
- history of acute kidney failure
- diabetes, hypertension
- chronic HCV
- GFR < 30 ml/min./1.73 m^2
  - 3–years 14 %
  - 5–years 19 %

(~ 37.000 recipients)

- GFR < 15 ml/min./1.73 m^2
  - 10–years 4.2 – 9.5 %

Acute kidney injury

- **25-50% (serum creatinine elevation > 25-50% or ≥ 0,5 mg/dl with diuresis reduction)**

- **risk factors**: kidney injury before liver transplantation, **hepato-renal syndrome 34% (25% typ 1 i 9% typ 2),** ↑BMI, M, calcineurin inhibitors toxicity, sepsis, hypovolemic ATN- esophagus varices bleeding, diuretics side effects, lactulose diarrhea, NLPZ, nephrotoxic antibiotics,

- **3-4 x elevation in death risk in 30 days after operation**
- **2 x long hospitalisation time (39 vs 73 days)**

- **prophylaxis-** variceal obliteration, SBP/antibiotic treatment, liquid balance, albumin, nourishment
- renal replacement therapy

Chronic kidney disease

- **30-90%** (CKD) / **renal replacement thepary** **2-5%** /year
- CNI nephrotoxicity 73%(↓GFR o 30-35% first weeks of treatment), hepato-renal syndrome 7%, FSGS 7%,
- **Risk factors:** kidney injury before liver transplantation, **hepato-renal syndrome ,** ↑BMI, M, calcineurin inhibitors toxicity, sepsis, diabetes, hypertension
- **complication:** cardio-cavsular disease, hospitalisation, 4 x death risk
- **combined liver/kidney transplantation - indications** ESRD (GFR < 30 ml/min i albuminuria > 3 g/dobę) or HD (AKI z HD > 6 weeks)

Hepato-renal sydrome (HRS)

- The hepatorenal syndrome is one of many potential causes of acute kidney injury in patients with acute or chronic liver disease. Affected patients usually have **portal hypertension due to cirrhosis**, severe alcoholic hepatitis, or (less often) metastatic tumors, but can also have fulminant hepatic failure from any caus. The hepatorenal syndrome represents the end-stage of a sequence of **reductions in renal perfusion induced** by increasingly severe hepatic injury. The hepatorenal syndrome is a **diagnosis of exclusion** and is associated with a poor prognosis.

- International Club Of Ascites www.icascites.org

- **Type 1 hepatorenal syndrome** –is the more serious type; it is defined as at least a twofold increase in serum creatinine (reflecting a 50 percent reduction in creatinine clearance) to a level greater than 2.5 mg/dL (221 micromol/L) during a period of less than two weeks. At the time of diagnosis, some patients with type 1 hepatorenal syndrome have a urine output less than 400 to 500 mL per day
- ●**Type 2 hepatorenal syndrome** –is defined as renal impairment that is less severe than that observed with type 1 disease. The major clinical feature in patients with type 2 hepatorenal syndrome is ascites that is resistant to diuretics.

Hepato-renal sydrome (HRS)

PATHOGENESIS **Arterial vasodilatation** in the splanchnic circulation, which is triggered by portal hypertension, appears to play a central role in the hemodynamic changes and the decline in renal function in cirrhosis. The presumed mechanism is **increased production or activity of vasodilators**.

CLINICAL PRESENTATION

- a progressive rise in serum creatinine
- an often normal urine sediment
- no or minimal proteinuria (less than 500 mg per day)
- a very low rate of sodium excretion (ie, urine sodium concentration less than 10 mEq/L)
- oliguria

TREATMENT

improvement of liver function from recovery of alcoholic hepatitis, treatment of decompensated hepatitis B with effective antiviral therapy, recovery from acute hepatic failure, or liver transplantation

In patients with hepatorenal syndrome who are **critically ill**, we suggest initial treatment with norepinephrine in combination with albumin. Norepinephrine is given intravenously as a continuous infusion (0.5 to 3 mg/hr) with the goal of raising the mean arterial pressure by 10 mmHg, and albumin is given for at least two days as an intravenous bolus (1 g/kg per day [100 g maximum]). Intravenous vasopressin may also be effective, starting at 0.01 units/min and titrating upward as needed to raise the mean arterial pressure as noted below

PBC

- EASL *Recommendations*

42. EASL recommends considering patients for transplant assessment when they present with complications of cirrhosis, markers of disease severity (*e.g.* persistent elevated bilirubin values [50 μmol/L or 3 mg/dl] or MELD >15), or severe medically resistant pruritus. EASL recommends that listing for transplantation should follow local (usually national) guidelines (**II-2**, **1**).

43. EASL suggests that in patients with proven or likely recurrent PBC post liver transplant, the use of UDCA is safe and can improve liver biochemistry (**II-2**, **2**).

PBC

- Risk recurennce
  - 5 years 8–18 %
  - 10 years 22–30 %

    (Pittsburgh, 421 biorców; Birmingham 400 biorców)
- 5-year patient survival rates of 80–85%
- recurrent PBC infrequently leads to graft loss and current evidence does not suggest an impact on graft or patient survival after transplantation
- treatment with UDCA lowers liver enzymes and may lower the incidence of recurrent PBC
- **diagnosis**
  - biopsy +
  - ALP, bilirubin –
  - AMA – (AMA persists after liver transplantation)

PBC reccurence - criteria

- Liver transplantation due to PBC
- persistant AMA or antyM2 in serum (10% patients with AMA -negative reccurence PBC)
- biopsy
- exclusion: AR, chronic rejection, bile duct complications, cholangitis, vessel complications, drug toxicity, viral infection

Treatment

- UDCA improves liver biochemistries and may delay histologic progression of recurrent PBC
- patients on UDCA post liver transplantation appear to have lower recurrence rates compared with patients who did not receive UDCA post transplant (21% versus 62%;
- After liver transplantation, pruritus improves, sicca syndrome is unchanged, bone disease worsens initially and then improves, and AMA may persist or reappear but does not signal the recurrence of PBC. Fatigue improves in a subset of patients with PBC, but moderate to severe fatigue continues to affect nearly half of patients 2 years after liver transplantation.

Liver transplantation AIH

- AIH is the indication for liver transplantation (LT) in approximately 2%-3% of pediatric and 4%-6% of adult recipients in the United States and Europe
- Untreated patients have a 10-year survival of <30%,69-73 and treatment failure requiring
- LT is often associated with the HLA genotype DRB1*03
- LT for AIH is very successful with 5-year and 10-year patient survivals of approximately 75%.
- A combination of prednisone and a calcineurin inhibitor (tacrolimus more frequently than cyclosporine) is the most common immunosuppression regimen after LT

AIH after liver transplantation

- Recurrent AIH in transplant allografts occurs in approximately 30% of adult and pediatric patients (range 12%-46%) with an average time to recurrence of 4.6 years
- The incidence increases with time after LT and accelerates after discontinuation of steroids

Diagnostic criteria for recurrence include:

- (1) elevation of serum AST or ALT levels;
- (2) persistence of autoantibodies;
- (3) hypergammaglobulinemia and/or elevation of IgG level;
- (4) compatible histopathological findings;
- (5) exclusion of alternative etiologies;
- (6) responsiveness to steroids

AIH Recommendations:

- Recurrent AIH should be treated with prednisone and azathioprine in adjusted doses to suppress serum AST or ALT levels or increased doses of corticosteroids and optimization of calcineurin inhibitor levels (preferably, tacrolimus). (Class, IIa, Level C)

- Continued inability to normalize the serum AST or ALT levels following recurrent disease justifies the addition of mycophenolate (2 g daily) to the regimen of corticosteroids and calcineurin inhibitor. (Class, IIa, Level C)

- If treatment response continues to be inadequate in recurrent disease, tacrolimus should be replaced with cyclosporine or the calcineurin inhibitors replaced with sirolimus. (Class IIa, Level C)
-
- Retransplantation must be considered for patients with refractory recurrent AIH that is progressing to allograft loss.

PSC Liver Transplantation

Unique liver transplant indications for patients with PSC include
-intractable pruritus
-recurrent
-bacterial cholangitis
-Cholangiocarcinoma

Liver transplantation for PSC is highly successful with **five-year survival** rates of approximately **85%** in patients receiving deceased donor allograft

Disease **recurrence occurs in 20%-25%, after 5-10 years** in patients, from the transplant procedure

Other risk factors for non-anastomotic biliary strictures must be excluded before concluding the patient has recurrent PSC;
These non-PSC risk factors for non-anastomotic biliary strictures include:
donation after cardiac death,prolonged graft ischemic time, ABO blood group incompatibility, hepatic artery thrombosis, CMV infection, chronic rejection, and early onset biliary strictures occurring within 3 months of the transplant procedure

Reported risk factors for recurrent PSC following liver transplantation include:

- active IBD with a need for corticosteroid therapy
- presence of an intact colon,
- male sex,
- presence of CCA prior to liver transplantation
- History of acute cellular rejection

There is no established medical therapy for recurrent PSC following liver transplantation and is similar to management of other liver transplant recipients

Hepato-Biliary Cancer as Primary Disease in Europe

N = 19,754 (1988-2015)

Carcinoma biliary tract : 376
Cholangiocellular carcinoma : 500
Hepatocellular carcinoma : 17252
Metastases : 612
Other cancers : 1014

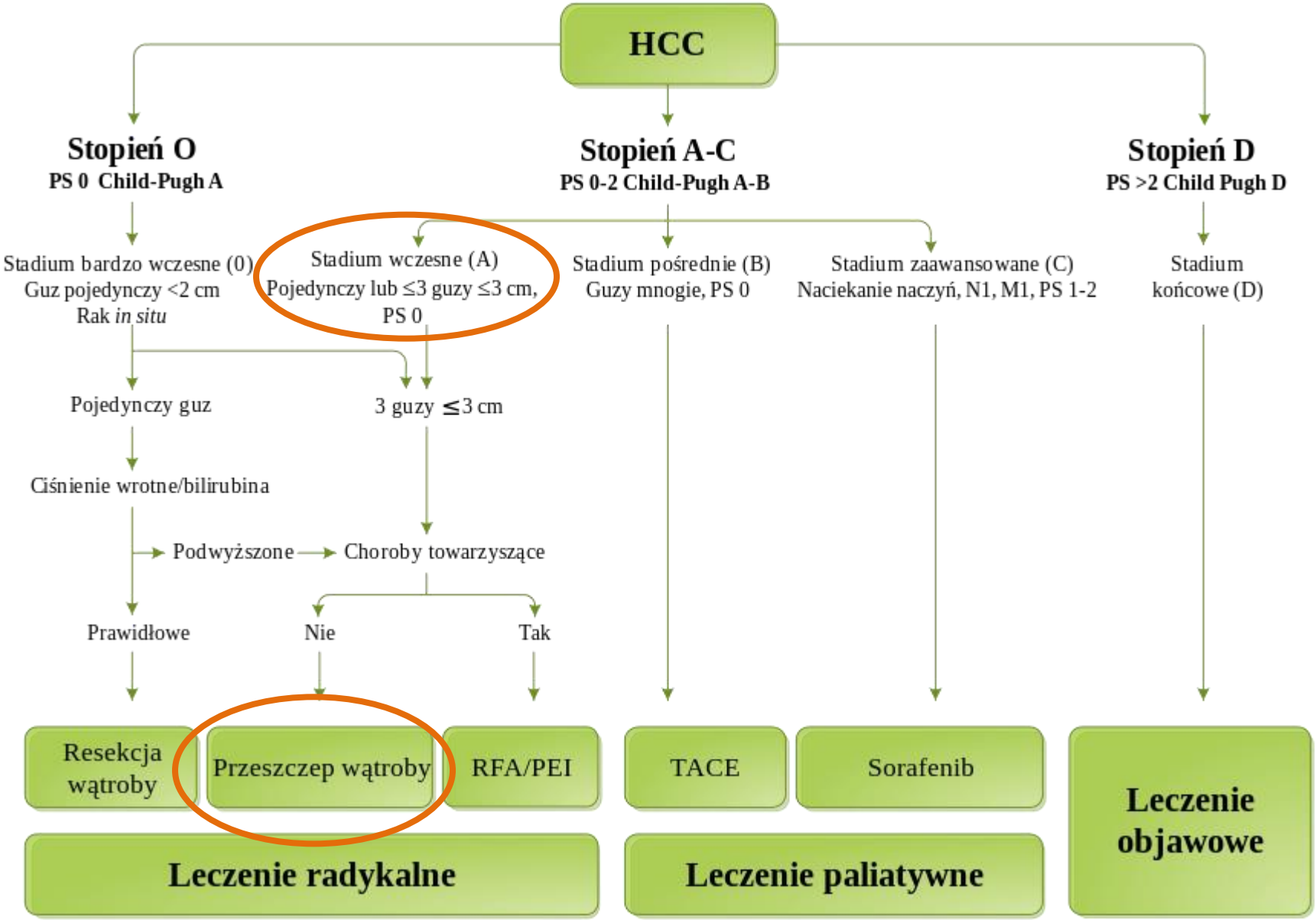
HCC

Liver transplantation achieves excellent results in patients with limited tumour load.

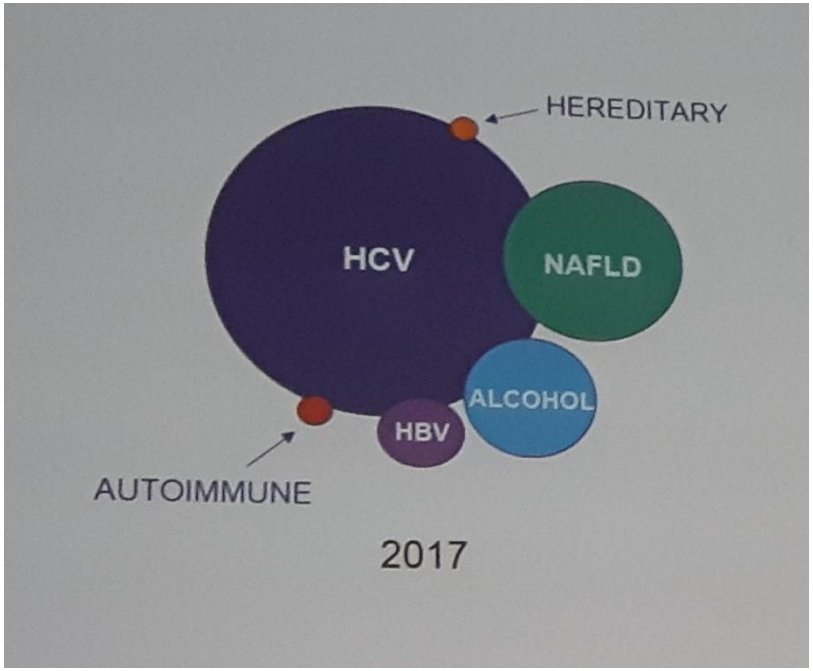
Patients with **solitary HCC of less than 5 cm** or with up to **three nodules of less than 3** cm (the Milan criteria) have **a 5-year survival of 70% after liver transplantation, with recurrence in less than 10%.**

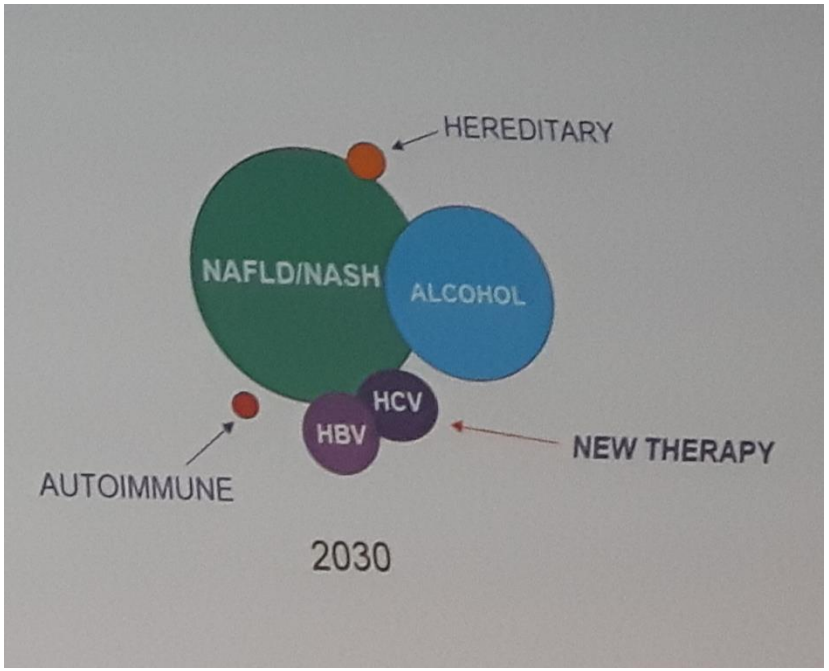
HCC

- The main concern after liver transplantation for HCC **is the risk of tumour recurrence, which occurs in 8–20% of recipients**
- HCC recurrence is usually seen **within the first 2 years after liver** transplantation, and is associated with a median **survival of less than 1 year (IQR 7–18 months) from the time of diagnosis**.
- post-transplant monitoring may include **6–12-monthly contrast-enhanced** CT or MRI imaging and **α -fetoprotein measurements**
- there is currently insufficient evidence from clinical trials to base a recommendation for choosing the type or dose of immunosuppression therapy to influence the incidence of HCC recurrence or its prognosis;
- based on current evidence, **no recommendation can be made on the use of mTOR inhibitors to reduce the risk of HCC recurrence outside clinical trials.**


HCC
Stopień O
PS 0 Child-Pugh A
Stopień A-C
PS 0-2 Child-Pugh A-B
Stopień D
PS >2 Child Pugh D
Stadium bardzo wczesne (0)
Guz pojedynczy <2 cm
Rak in situ
Stadium wczesne (A)
Pojedynczy lub ≤3 guzy ≤3 cm,
PS 0
Stadium pośrednie (B)
Guzy mnogie, PS 0
Stadium zaawansowane (C)
Naciekanie naczyń, N1, M1, PS 1-2
Stadium końcowe (D)
Pojedynczy guz
3 guzy ≤3 cm
Ciśnienie wrotne/bilirubina
Podwyższone
Choroby towarzyszące
Prawidłowe
Nie
Tak
Resekcja wątroby
Przeszczep wątroby
RFA/PEI
TACE
Sorafenib
Leczenie objawowe
Leczenie radykalne
Leczenie paliatywne

Liver transplantation- indication today / tomorrow





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http://www.aphc.info/wp-content/uploads/2017/02/BELLENTANI_Paris_30_Jan_2017_Epidemiology_of_NASH.pdf
(accessed May 2017)

NAFLD: non-alcoholic fatty liver disease; NASH: non-alcoholic steatohepatitis


Dziękuję