Hepatitis C Treatment in Patients with Advanced Fibrosis

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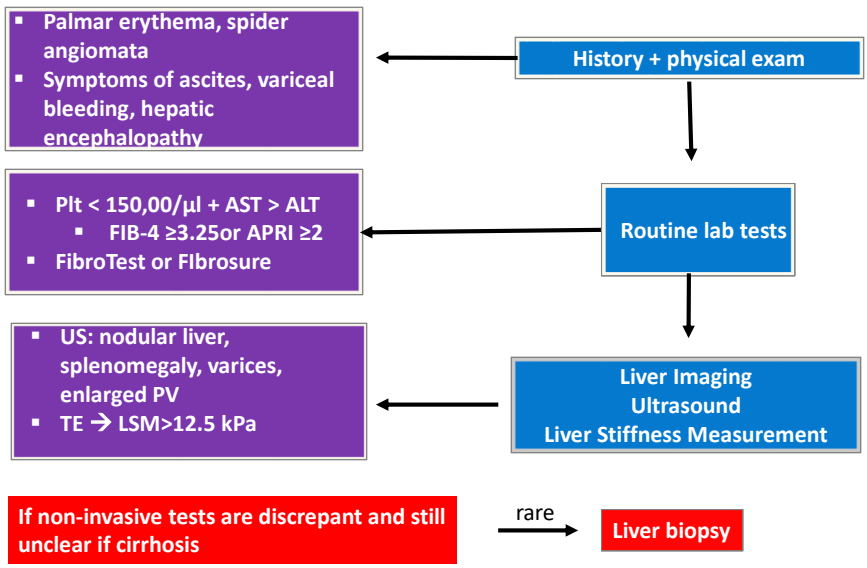
Royalties: Up-to-date

Overview

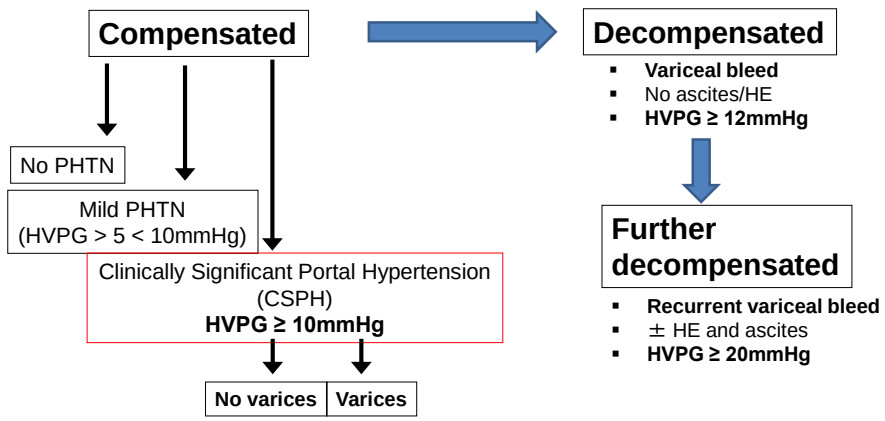
DAA Therapy in Patients with Advanced Fibrosis/Cirrhosis

- Identifying and assessing severity of cirrhosis
  - Liver transplantation: when is it appropriate to consider?
- HCV treatment – unique aspects of decompensated patients
- HCV treatment and HCC
- Post-DAA treatment monitoring in patients with cirrhosis

Establishing if Cirrhosis is Present



Stages of Cirrhosis and Relationship to Portal Hypertension



HVPG: hepatic venous pressure gradient
Normal 0-5 mm Hg

Shung DL and Garcia-Tsao L, Hepatology 2017;65(3):1038

Stage Needs to be Established Prior to Treatment

- **Non-invasive tests to stage liver fibrosis have not been validated in patients after SVR**
  - **Diagnostic accuracy of non-invasive tests after SVR is suboptimal → underestimates fibrosis**
- **Cirrhosis warrants specific surveillance tests**
  - **EGD to assess for varices**
  - **US/CT scan ± AFP to assess for liver cancer every 6 months → should be done pre-treatment**

D'ambrosio, et al., Journal of Hepatology, 2013 and Degasperi, et al. Journal of Hepatology, S60, 2014.

How to Assess Severity of Cirrhosis?

- **Child-Pugh-Turcotte Class**
  - Albumin, bilirubin, INR, ascites, HE
- **MELD-Na score**
  - Creatinine, bilirubin, INR, Sodium

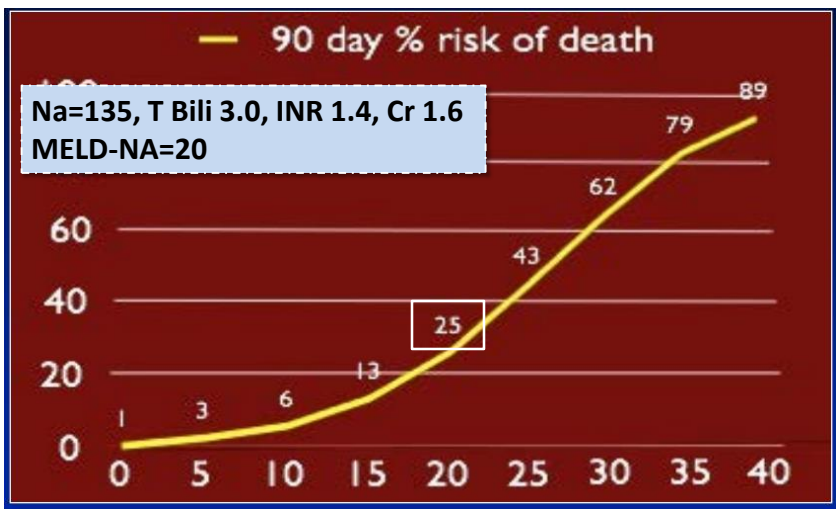
- **Both measures predict short-term mortality**
- **Reflect hepatic reserve (liver synthetic dysfunction and severity of portal HT)**

Calculate Child-Pugh Class

Child-Turcotte-Pugh Classification for Severity of Cirrhosis			
	Points*		
	1	2	3
Encephalopathy	None	Grade 1-2 (or precipitant induced)	Grade 3-4 (or chronic)
Ascites	None	Mild to moderate (diuretic responsive)	Severe (diuretic refractory)
Bilirubin (mg/dL)	< 2	2-3	>3
Albumin (g/dL)	> 3.5	2.8-3.5	<2.8
INR	<1.7	1.7-2.3	>2.3
*Child-Turcotte-Pugh Class obtained by adding score for each parameter (total points)			
Class A = 5 to 6 points (least severe liver disease)			**<5%**
Class B = 7 to 9 points (moderately severe liver disease)			**25%**
Class C = 10 to 15 points (most severe liver disease)			**50%**

1- year post-operative mortality

MELD-Na Score and 90-day Mortality



Wiesner RH, McDiarmid SV, Kamath PS, Edwards EB, Malinchoch M, Kremers WK, et al. MELD and PELD: Application of survivial models to liver allocation. Liver Transpl 2001;7:567-580.

An Important Question to Ask

- **Should liver transplantation be considered?**
  - **MELD ≥12-15**
  - **Any symptoms of decompensation (ascites, HE, varices)**
  - **Liver cancer (if small and confined to liver)**
- **If potentially eligible – hold on treatment**
  - **For many transplant candidates, best option is treating after transplant**
  - **Deferring HCV treatment allows earlier access to transplant (eligible for HCV+ donors)**
  - **Detailed discussion of risks and benefits essential**

DAA Treatment in Patients with Cirrhosis

Importance of Child-Pugh Score

Which Patient with Cirrhosis has the Most DAA Treatment Options?

- Genotype 1A
- Grade 2-3 varices on EGD
- No ascites or HE
- Na 138, Creatinine 1.2,
- INR 1.5, platelet count 70K
- AST 56, ALT 48, total bilirubin 1.5, albumin 3.6

CPT score =6

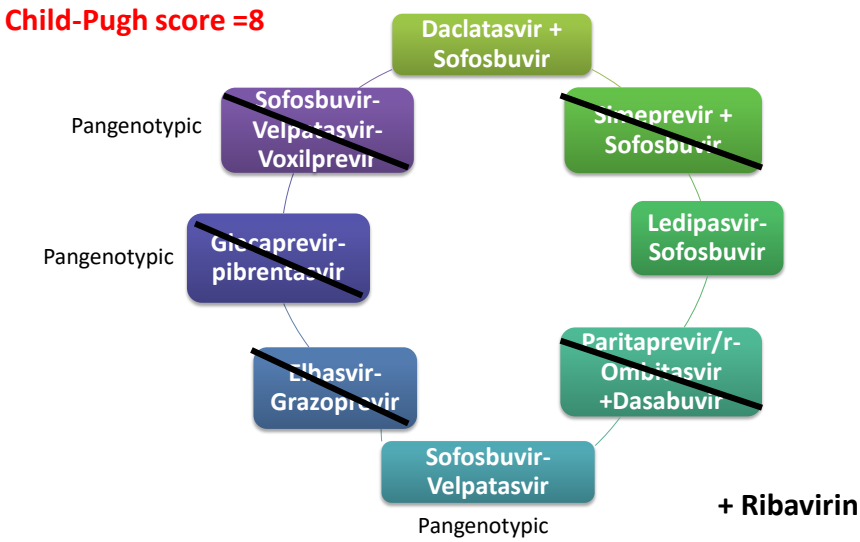
- Genotype 1A
- Grade 1 varices on EGD
- No HE or ascites
- Na 135, Creatinine 0.8
- INR 1.5, platelet count 70K
- AST 56, ALT 48, total bilirubin 2.0, albumin 2.7

CPT score =8

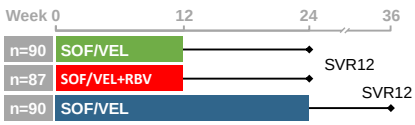
Defining Decompensated Cirrhosis for Treatment Purposes

COMPENSATED	DECOMPENSATED
Childs A **AND** Have NOT experienced any of the following: jaundice, ascites, hepatic encephalopathy or history of variceal hemorrhage	**Childs B or C** **OR** Have experienced one or more of the following: jaundice, ascites, variceal hemorrhage, hepatic encephalopathy

DAA Options for Patients with Cirrhosis

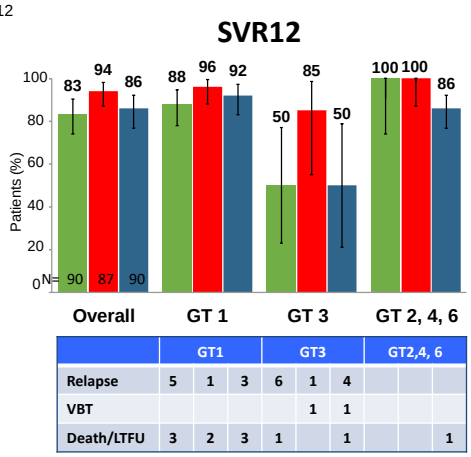


SOF-VEL ± RBV for G1-6 Patients with Child-Pugh B Cirrhosis: The Role of RBV



- **ASTRAL-4**
- **HCV GT 1-6 patients with CPT B cirrhosis**

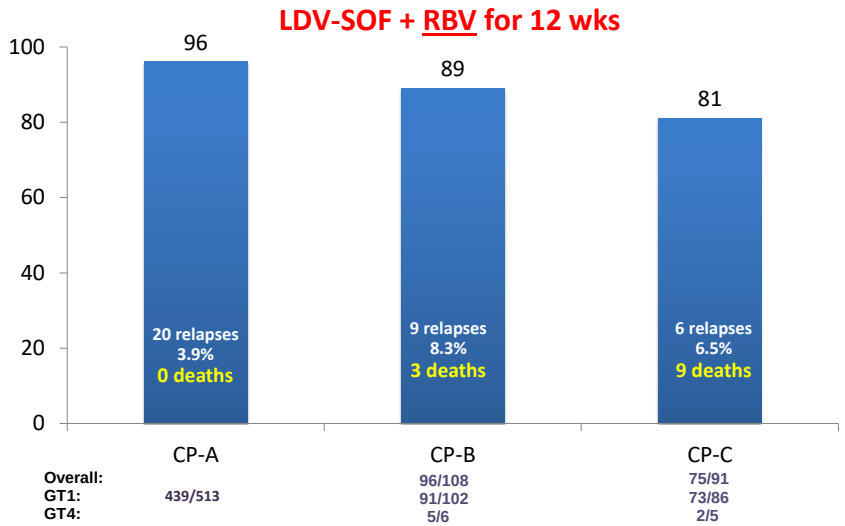
RBV should be included in treatment of all patients with decompensated cirrhosis, especially G3



	GT1			GT3			GT2,4, 6		
Relapse	5	1	3	6	1	4			
VBT					1	1			
Death/LTFU	3	2	3	1		1			1

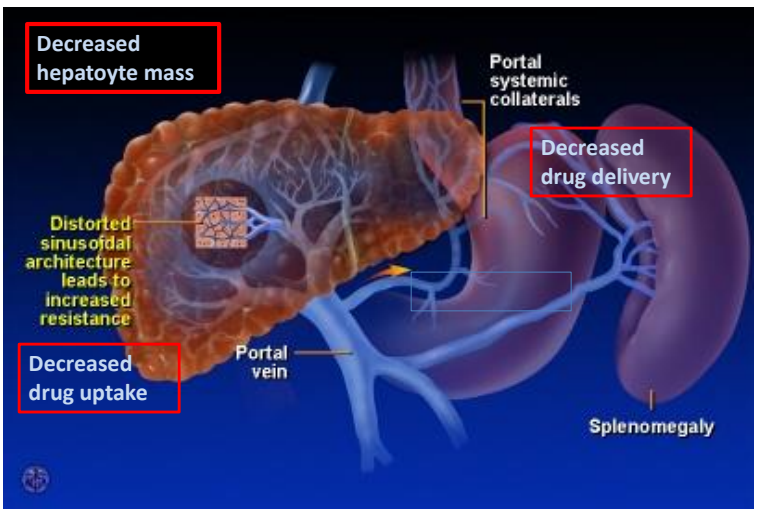
Charlton M, N Engl J Med. 2015;373:2618-28

SVR12 Rates Among Patients with Cirrhosis by Child-Pugh Score



Reddy, RK, Hepatology 2015:62:79-86; Manns M Lancet Infect Dis 2016, Charlton Gastroenterology 2015

Why Higher Rates of Virologic Failure with Advanced Cirrhosis?



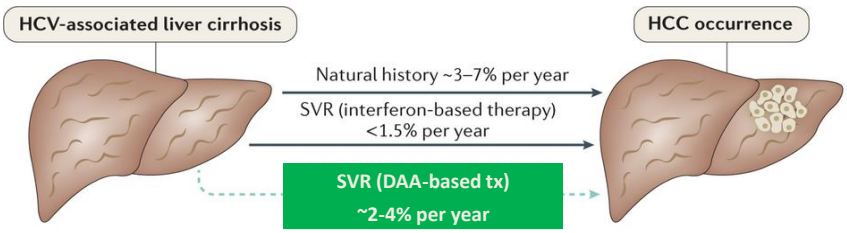
Summary

Unique Aspects of Treating Patients with Decompensated Cirrhosis (CP-B/C)

- Fewer DAA options
  - Protease inhibitor are contraindicated
  - Ribavirin needed to enhance efficacy
- Tolerability and safety need closer scrutiny
  - Ribavirin-associated side effects
  - Risks of worsening decompensation
- Lower rates of SVR
  - Very limited treatment options for those with DAA failure

HCV DAA Therapy and Liver Cancer

Risk of De Novo HCC After DAA Therapy



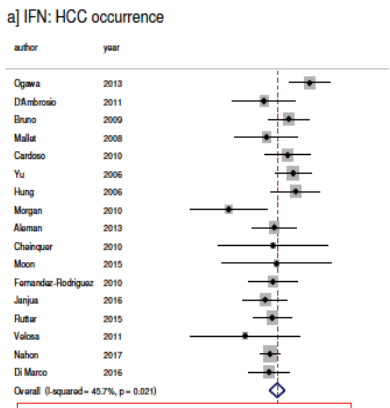
Patients differ in DAA era:

- **Older**
- **More advanced cirrhosis (longer duration of cirrhosis)**
- **Coexistent risks for NAFLD**

Llovet JM, et al. *Nat Rev Gastroenterol Hepatol* 2016;13:561-2

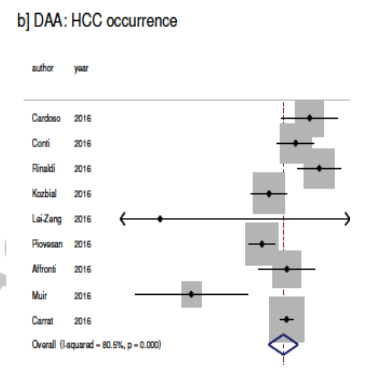
Meta-Analysis of De Novo HCC after IFN and DAA Therapy

5,521 treated in 19 studies from Europe, Asia, SA, NA



1.14/100 person-yrs

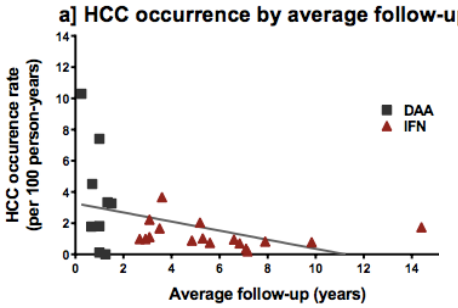
6,002 treated in 7 studies from Europe. 1 Asian



2.96/100 person-yrs

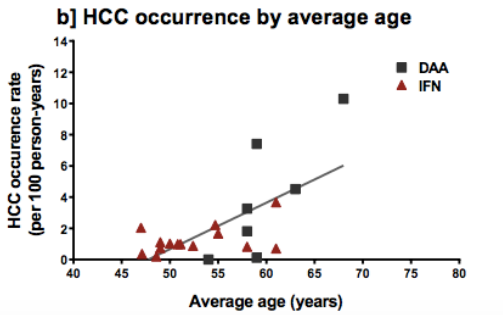
Waziry R, J Hepatol 2017, in press

Effect of Age and Duration of Follow-up on Occurrence of HCC



DAA treated patients have average follow-up which is shorter than IFN-treated patients

DAA treated patients are on average 8 years older than IFN-treated patients



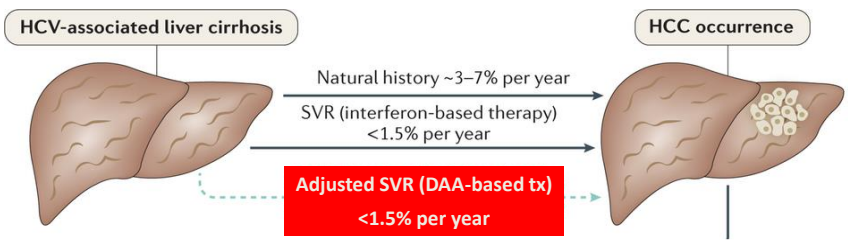
Waziry R, J Hepatol 2017, in press

Risk of De Novo HCC After DAA Therapy

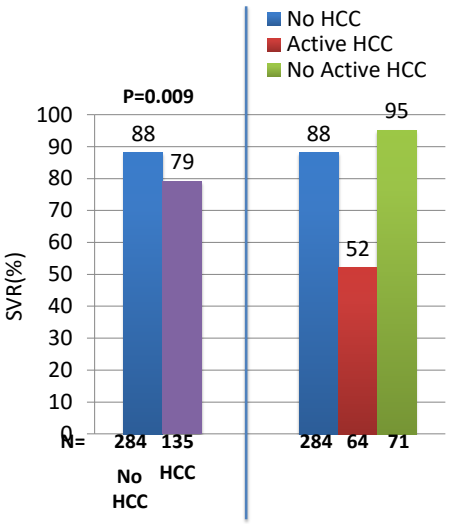
	MULTIVARIATE Analysis	
Variable	**aRR**	**P value**
Treatment		
IFN	**1.00**	**--**
DAA	**0.68**	**0.56**
Avg follow-up	**0.75**	**0.04**
Average age	**1.06**	**0.12**

In meta-regression, adjusting for differences in age and length of follow-up, type of treatment was no longer associated with HCC

DAA and IFN risks NOT different



SVR Rates Reduced in Patients with HCV and "Active" HCC



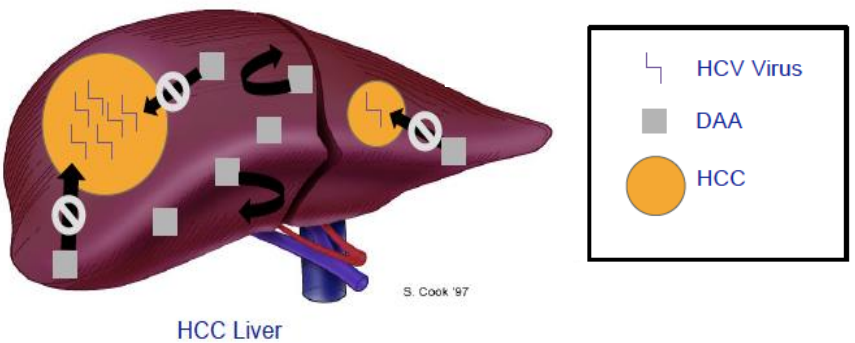
Predictors of DAA Treatment Failure

Covariates	OR	95% CI	P Value
Inadequate regimen	2.85	1.32-6.16	0.008
Active tumor	**8.49**	**3.90-18.49**	**<0.001**
Platelet count	0.99	0.99-1.0	0.09

Adjusted for age, sex, race, CPT class, genotype and anti-HBc

Prenner S et al, J Hepatology, 2017, in press

Why Higher Rates of Virologic Failure in Patients with HCC?



HCC Liver

Prenner S et al, J Hepatology, 2017, in press

Summary

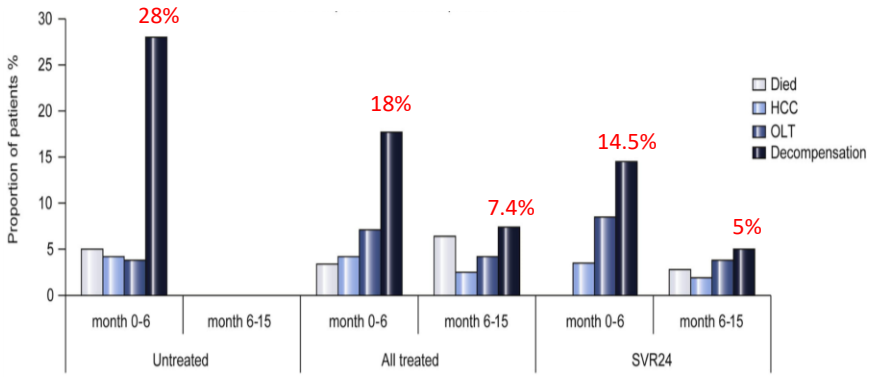
HCC and DAA Therapy

- Treatment with DAAs does not appear to increase the risk of de novo HCC
  - Higher rates reported in DAA era reflect older patient population with more advanced cirrhosis
- SVR rates are lower in patients with HCC
  - If possible, wait until after HCC is treated then treat HCV
- Curative therapy available for small HCCs → importance of surveillance to detect early

Management of Patients with Advanced Fibrosis After the Cure

DAA Therapy Reduces But Does Not Eliminate Risk of Liver Complications

Decompensated cirrhosis treated with DAA therapy
N=406 treated
N=261 untreated

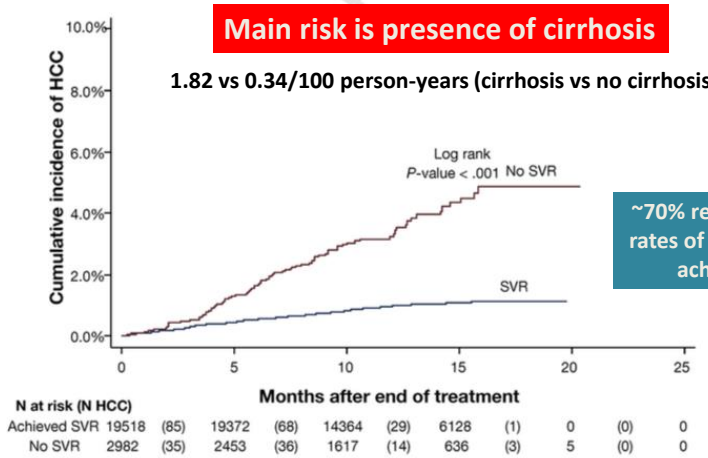


Cheung et al., J Hepatology 2016 Oct 65(4) 741-7

Risk of HCC in Patients Treated with DAA Therapy

Main risk is presence of cirrhosis

1.82 vs 0.34/100 person-years (cirrhosis vs no cirrhosis)



~70% reduction in rates of HCC if SVR achieved

39% had cirrhosis

Kanwal F, Gastroenterology 2017

Predictors of HCC in Patients Achieving SVR

Those most consistently reported across studies:

Categories	Specifics
Patient	Older age
[Viral]	Genotype 3
Disease-related	Cirrhosis* Lower platelet count
Comorbidities	Diabetes Alcohol use

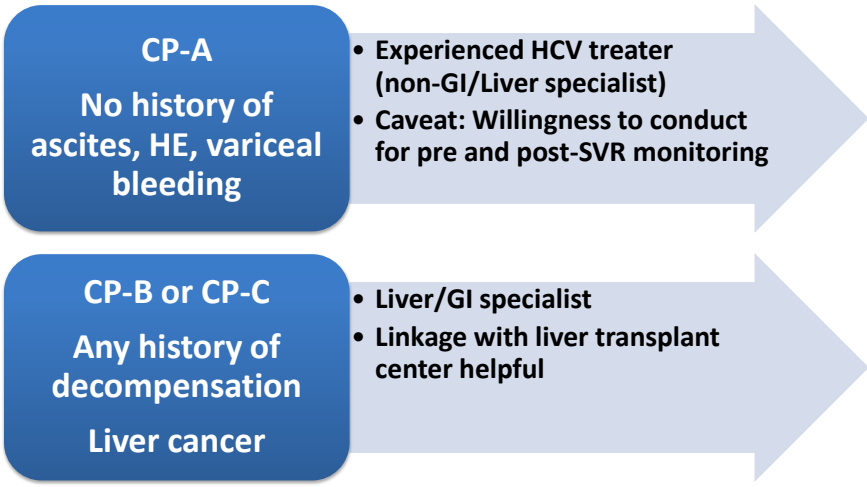
***Variably defined: APRI≥2, FIB-4 ≥3.25, elastography, biopsy**

Chang, KC, J Antimicrob Chemoth 2012; Huang C, J Hepatol 2014; Toyoda H, J Gastroenterol Hepatol 2015; El-Serag, Hepatology, 2016; Nirei K Int J Med Sci 2017; Tada T, Hematology Res 2016; vanderMeer A,J Hepatol 2016; Hayashi T, Infect Agent Cancer. 2016 Feb 24;11:9; Nahon P, Gastroenterology 2017 Jan;152(1):142-156.e2

Monitoring Required Post-SVR in Patients with Advanced Fibrosis

At Risk For	Monitor With	Frequency
Variceal bleeding	EGD screening	Yearly if decompensated
		Every 2-3 years if compensated
Liver cancer	Ultrasound + AFP	Every 6 months
New onset decompensation	MELD and clinical evaluation	Every 6 months if compensated
		Every 1-3 months if decompensated

Suggested Triage of Patients with Cirrhosis



Reasons to Triage Patients with CP-B/C Cirrhosis to Specialists

- Liver complications can occur before, during and after treatment
- Liver transplantation needs to be considered
  - Timing of HCV treatment influenced by whether patient is on list or not
- Fewer drug options, greater risk of toxicity
- Long-term follow-up for liver complications needs even after SVR
  - Especially risk of HCC

Summary

Treatment of HCV in Patients with Advanced Fibrosis

- Establish if cirrhosis present pre-treatment; determine severity using Child-Pugh score and MELD
- Treatment of decompensated patients quite different from compensated
- Risk of HCC is not increased by treatment with DAA but risk for HCC persists after cure
- Long-term follow-up for liver-related complications is essential

Thank- you!

San Francisco Cable Car