Cases: Post-SVR Care and Monitoring

Marion G. Peters, MD
John V. Carbone, MD, Endowed Chair
Professor of Medicine
Chief of Hepatology Research
University of California San Francisco

IAS–USA

ARS Question #1: Which statement is **false**?

1. ALT decreases post SVR
2. Fibroscan can be used to monitor regression of liver disease
3. HCC screening is required for cirrhotic patients post SVR
4. Improvement in systemic diseases (e.g. CVS, DM) occurs post SVR

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ARS Question #2: Which statement about treatment of cirrhotic patients is **false**?

1. DAA Treatment of cirrhotics differs from non cirrhotics
2. All DAAs can be used in decompensated cirrhosis
3. Treatment of cirrhotic patients stops liver decompensation
4. Liver decompensation is best measured by MELD and CPT score
5. MELD and CPT differ in assessment of Liver decompensation

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Case

- 48 yo female with HCV diagnosed 20 years ago
  - IDU, significant alcohol for 15 years, none now
  - Fatigue, loss of energy on disability
  - PH upper GI bleed
- She heard there are new drugs and wants to be treated

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Case Labs

- ALT 44; AST 68; bilirubin 2.7; albumin 3.2;
- INR 1.4; AFP 24.4; creatinine 0.8
- WCC 3,000; Hct 45; platelets 82,000
- HCV RNA 607,509 IU/mL
- HCV genotype 1a

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ARS Question #3: Which statement is **NOT** true?

1. She has cirrhosis
2. She is likely Child's B
3. She can be treated with all oral DAAs
4. She does not have portal hypertension
5. She needs upper endoscopy
6. She needs HCC screening

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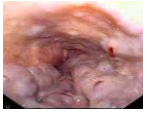
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Diagnosing Cirrhosis – Physical Exam






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Diagnosing Cirrhosis – Labs

EXAM:

Spider nevi, splenomegaly

Most labs not helpful

- 50% Child's A normal
- AST:ALT often >1

Synthetic dysfunction

- Hypoalbuminemia
- Prolonged PT/ INR
- Hyperbilirubinemia

Portal Hypertension

- Thrombocytopenia
- Leukopenia
- Anemia

Renal dysfunction

- Elevated creatinine remember depends on muscle mass

Hyponatremia with ascites

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Case

- 48 yo female with HCV diagnosed 20 years ago
  - IDU, significant alcohol for 15 years, none now
  - Fatigue, loss of energy on disability
- She heard there are new drugs and wants to be treated
- Exam: normal vital signs, spider nevi on shoulders, no ascites or edema, no hepatosplenomegaly

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Case Labs

- ALT 44; AST 68; bilirubin 2.7; albumin 3.1;
- INR 1.4; AFP 24.4; creatinine 0.8
- WCC 3,000; Hct 45; platelets 82,000
- HCV RNA 607,509 IU/mL
- HCV genotype 1a
- How to assess severity?

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Case Labs

- ALT 44; AST 68; bilirubin 2.7; albumin 3.1;
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- WCC 3,000; Hct 45; platelets 82,000
- HCV RNA 607,509 IU/mL
- HCV genotype 1a
- How to assess severity?
  - Child's Pugh Turcotte score
  - MELD

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Child-Pugh-Turcotte Score

Points	1 (normal)	2	3
Hepatic encephalopathy	None	1-2	3-4
Ascites	None	slight	mod
Bilirubin	<2	2-3	>3
Albumin	>3.5	2.8-3.5	<2.8
PT	<4 secs ↑	4-6 secs	>6 secs
or INR	<1.7	1.7-2.3	>2.3

A: 5-6; B: 7-9; C: > 9

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Child-Pugh-Turcotte Score =7

Points	1 (normal)	2	3
Hepatic encephalopathy	None	1-2	3-4
Ascites	None	slight	mod
Bilirubin	<2	2-3	>3
Albumin	>3.5	2.8-3.5	<2.8
PT	<4 secs ↑	4-6 secs	>6 secs
or INR	<1.7	1.7-2.3	>2.3

A: 5-6; B: 7-9; C: > 9

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Model For End Stage Liver Disease

INR 1.4
Bilirubin 2.7 MELD 14
Creatinine 0.8

MELD Formula

The MELD score is calculated using the following formula:

MELD Score = $0.957 \times \text{Log}_e(\text{creatinine mg/dL}) + 0.378 \times \text{Log}_e(\text{bilirubin mg/dL}) + 1.120 \times \text{Log}_e(\text{INR}) + 0.643$[1]

Multiply the score by 10 and round to the nearest whole number.

Laboratory values less than 1.0 are set to 1.0 for the purposes of the MELD score calculation.

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Case Labs

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- INR 1.4; AFP 24.4; creatinine 0.8
- WCC 3,000; Hct 45; platelets 82,000
- HCV RNA 607,509 IU/mL
- HCV genotype 1a
- Child's B
- MELD 14

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ARS Question #4: Which is true?

1. She is too far gone for therapy
2. All cause and liver survival is better after SVR
3. HCC will not occur if she has SVR
4. She does not need endoscopy if she has SVR
5. All oral DAAs are not associated with liver decompensation in cirrhotics

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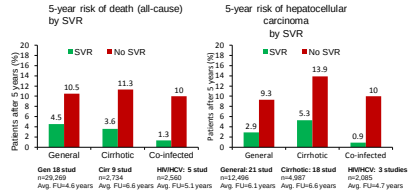
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Effects of SVR on the risk of liver transplant, hepatocellular carcinoma, death and re-infection:
meta analysis, 129 studies, 34,563 patients

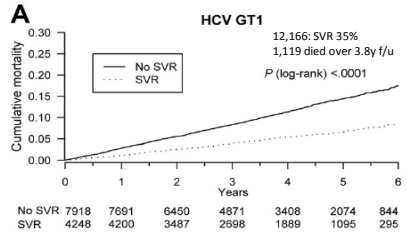


- Benefits may be offset by re-infection over 5 years
  - 0.9% in 'low-risk' persons
  - 8.2% in persons who inject drugs
  - 23.6% in persons coinfected with HIV

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Hill AASLD 2014

HCV SVR and All Cause Mortality



Backus CGH 2011: VAMC 22,942 PEG-IFN/RBV treated 2001-2007: mortality thru 2009

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Recommended and alternative regimens listed by evidence level and alphabetically for: Treatment-Naive Genotype 1a Patients With Compensated Cirrhosis[a]		
RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) for patients without baseline NS5A RASs[b] for elbasvir	12 weeks	I, A
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[c]	12 weeks	I, A
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)	12 weeks	I, A
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, A
ALTERNATIVE	DURATION	RATING
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) with weight-based ribavirin for patients with baseline NS5A RASs[b] for elbasvir	16 weeks	IIa, B

[a] For decompensated cirrhosis, please refer to the appropriate section.
[b] Includes genotype 1a resistance-associated substitutions at amino acid positions 28, 30, 31, or 93 known to confer antiviral resistance.
[c] This is a 3-tablet coformulation. Please refer to the prescribing information.

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Case- treatment

- EGD showed mild portal gastropathy
- Ultrasound reported no HCC, trace ascites
- She was started on 12 weeks of
  - Ledipasvir 90 mg per day
  - Sofosbuvir 400 mg daily

At week 4

- HCV RNA 106 IU/mL

At week 8 HCV RNA <LLOQ

SVR 12

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Case- treatment

- EGD showed mild portal gastropathy
- Ultrasound reported no HCC, trace ascites
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At week 4

- HCV RNA 106 IU/mL

At week 8 HCV RNA <LLOQ

SVR 12

6 months:

- She was complaining of not thinking clearly and swollen ankles
- Ultrasound showed moderate ascites

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HCV treatment in cirrhotics

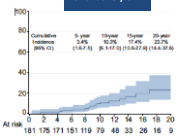
- 5% to 7% of Child's A cirrhotics decompensate per year
- Diagnosis of Child's A, even B cirrhosis may be subtle
- Screen for HCC
- Perform EGD
- Monitor closely on therapy
- Child's B can be treated- OLT back up plan

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Liver-Related Complications Can Occur after Cure in Patients with Advanced Fibrosis

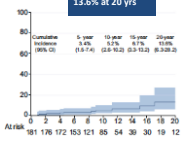
Hepatocellular Carcinoma

10.3% at 10 yrs
23.7% at 20 yrs



Liver Decompensation

5.2% at 10 yrs
13.6% at 20 yrs



CP-A Cirrhosis
IFN-based therapy

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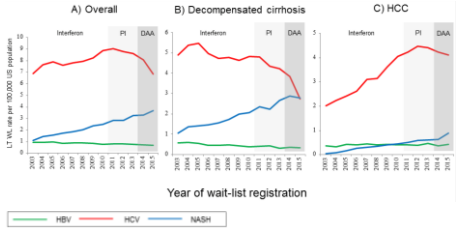
Bruno S. J Hepatol. 2016;64(6):1217-1223

Many Recognized Benefits of HCV Cure

- Reduced mortality
- Reversal of decompensation
- Reduction in HCC
- Reversal of cirrhosis/fibrosis
- Reduced risk of transmission of infection to others

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Sharp Reduction in Transplant Listings for HCV Patients in the DAA Era (2003-2015)



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Flemming J, Terrault NA. Hepatology. 2016

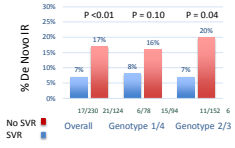
Many Recognized Benefits of HCV Cure

- Reduced mortality
- Reversal of decompensation
- Reduction in HCC
- Reversal of cirrhosis/fibrosis
- Reduced risk of transmission of infection to others
- What about extrahepatic manifestations?

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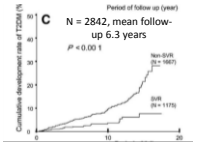
SVR: Prevention of Diabetes/Insulin Resistance

SVR reduced rates of de novo IR when evaluated 24 months later



N = 384, 71% nonadvanced fibrosis
HOMA-IR done pre- and 24 mos post-treatment

SVR reduces incidence of type 2 diabetes* by ~60%



Period of follow-up post-SVR

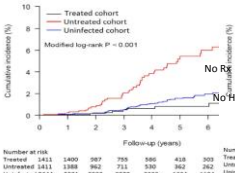
***Independent of age, cirrhosis and prediabetes at baseline**

Arase Y, et al. Hepatology. 2009

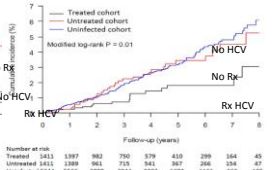
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HCV Therapy Is Associated with Better Renal, Cardiovascular Outcomes in Diabetic Patients

End-stage Renal Disease (3 cohorts)
Cumulative Incidence (% over time)



Ischemic Stroke (3 cohorts)



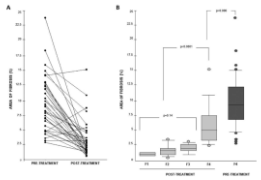
HCV Rx HR (95% CI) 0.16 for ESRD, 0.53 for ischemic stroke, and 0.64 for ACS

Hsu YC, et al. Hepatology. 2014

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HCV Cure: Paired Biopsy Studies
Morphometric Analysis of Fibrosis

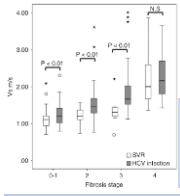
- Follow-up CP-A patients treated with IFN-based therapy and achieved SVR
- Biopsy done a median of 61 mos (range, 48-104) post-SVR



Area of fibrosis decreased in 89%, increased in 8% and unchanged in 3%

D'Ambrosio R. Hepatology. 2012;56:532-43

Liver Stiffness Values Require Different Thresholds to Stage Fibrosis after Cure



Paired liver biopsy and liver stiffness measurement using acoustic radiation force impulse (ARFI) elastography:

- N = 121 with SVR (5.9 y post-cure)
- N = 215 with chronic HCV

- LS values lower in SVR vs chronic HCV for each stage of fibrosis
- Higher ARFI with higher ALT
- Lower ARFI with longer time from cure

New cut-offs to defined stage in patients with SVR are needed

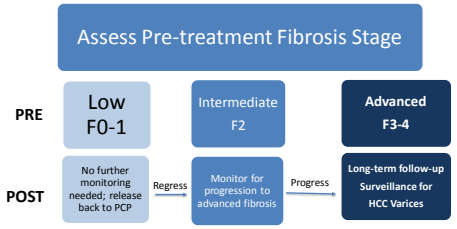
Tachi Y. APT. 2016;44:346-55

Noninvasive Testing after SVR

- Noninvasive tests to stage liver fibrosis have not been validated in patients after SVR
- Risk of underestimating severity of fibrosis by relying on post-SVR test results (APRI, FIB-4, LSM)
- Pending additional studies, management of patients must be based on PRE-treatment fibrosis staging
- Elastography evaluation post-SVR more useful to assess for progression than regression

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

Post-cure Follow-up and Fibrosis Stage



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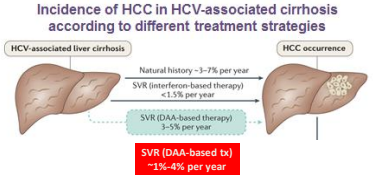
Variceal Surveillance after Cure

- All patients with pre-rx cirrhosis should have screening EGD
  - Cannot use TE <20 kPa and platelets >150,000/mL to identify patients at low risk post SVR
- If baseline EGD is negative for varices
  - If no ongoing liver injury – EGD every 3 years
  - Unclear if/when to stop surveillance if 2-3 negative EGDs
- If small varices at baseline
  - If no ongoing liver injury – EGD every 2 years
  - Unclear if can stop if no progression by several serial EGDs
- If worsening portal hypertension (by radiology or clinical)
  - Repeat EGD

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Garcia-Tsao G, et al. Hepatology. 2017;65:310-335 Jacobson I. Gastroenterology 2017

HCC Surveillance after HCV Cure



- Higher HCC incidence than with IFN-therapy reflecting treatment of older patients with more advanced cirrhosis (who have higher risk for HCC)

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

Predictors of HCC post HCV SVR- IFN

33,005 VA patients; 10,827 SVR 100 new HCC cases

Incidence rate of
No SVR 1.32% per year
SVR to IFN-based Rx 0.33% per year

	OR (CI)	P value
DM	1.80 (1.2-2.9)	0.005
Hispanic vs Cauc	2.3 (1.1-4.8)	0.03
Cirrhosis at SVR	**6.69 (4.3-10.4)**	**<0.0001**
Alcohol	1.68 (1.08-2.60)	0.02
Age 55-64 y	2.04 (1.3-3.2)	0.002
Age >65	**4.51 (2.0-10.4)**	**0.004**

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El-Serag. Hepatology. 2016

Liver-related Health Problems after Cure

Prevention of NAFLD MS

- Optimize weight
- Prevent/treat diabetes
- Treat dyslipidemia

Coffee: >3 cups per day associated with lower risk of progression

Cannabis Use

- Non-daily use

Safe levels of alcohol

- None if advanced fibrosis

Caution with herbals/supplements

- Awareness of potential for hepatotoxicity



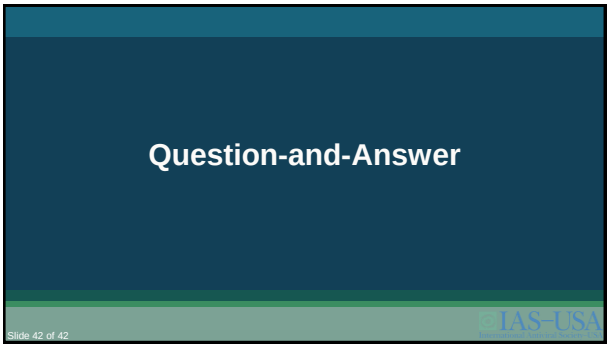
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Terrault & Hassanein. J Hepatol. 2016
Jacobson I. Gastroenterology. 2017;Mar 23

Summary

- Many benefits of HCV cure: liver and non-liver
- Those with F3/4 pre-SVR need HCC monitoring post-SVR
- Need to stage fibrosis pretreatment to optimally monitor post-cure
- Concurrent alcohol or fatty liver places patients at risk for future cirrhosis
  - Monitor for fibrosis progression in these patients
- Counsel healthy liver practices for all
- Monitor for reinfection in at-risk patients

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Question-and-Answer
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